AB SCIENCE WEBCONFERENCE

MASITINIB IN INDOLENT SYSTEMIC MASTOCYTOSIS

20 November 2019

Disclaimer

This presentation, together with the material set forth herein, does not constitute an offer of securities for sale nor the solicitation of an offer to purchase securities in any jurisdiction. Distribution of such presentation in certain jurisdiction may constitute a breach of applicable laws and regulation.

This document is solely for your information on a confidential basis and may not be reproduced, redistributed or sent, in whole or in part, to any other person, including by email or by any other means of electronic communication. In particular, neither this document nor any copy of it may be taken, transmitted or distributed, directly or indirectly, in the United States, Canada, Japan or Australia. The distribution of this document in other jurisdictions may be restricted by law and persons into whose possession this document comes should make themselves aware of the existence of, and observe, any such restrictions.

Neither the Company, nor any of its advisors and representatives may accept any responsibility for any loss or damage incurred by the use of this document or the information set forth herein. Neither the Company, nor any of its advisors and representatives takes any undertaking nor guarantees, whether explicitly or tacitly, the accuracy or the completeness of the information set forth herein. Neither this document, nor any part of it, shall form the basis of, or be relied upon in connection with, any contract or commitment whatsoever.

In particular, in France, any decision to purchase such securities shall rely solely on the documents that have been reviewed by the Autorité des Marchés Financiers (the "AMF") and/or published by the Company.

This document does not constitute an offer to purchase any financial instruments in the United States. Securities mentioned in this document have not been and will not be registered under the Securities Act of 1933, as amended (the "Securities Act") and may not be offered or sold in the United States absent registration or an exemption from the registration requirements of the Securities Act. The Company does not intend to register any offering in all or in part or to make a public offer of securities in the United States.

This document contains information on the objectives of the Company along with some projections and forward-looking statements. The reader's attention is drawn to the fact that these objectives may not be fulfilled, and the forecasts or information provided may prove erroneous, and the Company is not required to update such information. Past performance is no guide to future performance and persons needing advice should consult an independent financial adviser.

By attending this presentation or reading this document, you agree to be bound by the limitations set out above.

AGENDA

- Introduction of participating experts
- Current results with masitinib in ISM
- Design of confirmatory study and pathway to registration
- Experts' Opinions
- Q&A

Presenting KOL

Participating Experts in Mastocytosis

Cem AKIN, MD, PhD
Dr. Akin is currently a Professor of Allergy and Immunology in the Department of Internal Medicine at the University of Michigan. He is co-chair of the steering committee of the American Initiative in Mast Cell Diseases (AIM).

Michel AROCK, PharmD, PhD
Dr. Arock is professor of physiology and hematology at the Ecole Normale Supérieure of Paris-Saclay and is currently heading the Functional Unit for Biological Emergencies within the Hospital Pitié-Salpêtrière Charles-Foix in Paris. He has conducted researches on the physiology of mast cells and on the pathophysiology and treatment of mastocytosis for many years. He has also co-authored more than 180 publications referenced in Medline and is currently the Chair (2015-2020) of the European Competence Network on Mastocytosis (ECNM).

Mariana CASTELLS, MD, PhD
Mariana Castells is a Professor at Harvard Medical School. She is a clinician/teacher/researcher at the Brigham and Women's Hospital Rheumatology, Immunology and Allergy Division serving as Director of Drug Hypersensitivity and Rapid Desensitization Center and the Director of the Mastocytosis Center. The Brigham and Women's Hospital BWH Mastocytosis Center in Boston is pioneer in basic, translational and clinical research in mast cell disorders. It is a multidisciplinary center providing excellence in care and innovations in treatment. In 2005, Dr. Castells was the founding Chair of the Task Force on Mast Cell Disorders of the American Academy of Allergy, Asthma and Immunology. Dr. Castells is a member of the American Initiative in Mast Cell Diseases (AIM) Organizing Committee and a member of the Medical Advisory Board of The Mastocytosis Society (TMS).

Oliver HERMINE, MD, PhD
Olivier Hermine is Professor of Hematology at Paris V-René Descartes University, Chief of adults Hematology staff at Hospital Necker (Paris), member of the French *Académie des Sciences* and author of 365 international publications. He is founder and coordinator of the reference center of mastocytosis (CEREMAST). He is member of the Medical Advisory Board of The Mastocytosis Society (TMS), a US nonprofit organization dedicated to supporting patients affected by mastocytosis or mast cell activation diseases. Olivier Hermine is also co-founder of AB Science and head of its scientific committee.

Masitinib positioning

The planned indication for masitinib is indolent or smouldering systemic mastocytosis, which are the most prevalent forms of mastocytosis.

Category	Disease according to WHO classification	% patients	Characteristics	Symptoms	Masitinib scope
Symptomatic disease	**Cutaneous mastocytosis (CM)**	≈ 30%	Urticaria pigmentosa	Primarily mild to moderate	Not in scope
	Systemic mastocytosis (SM) ▪ Indolent SM (ISM) ▪ Smouldering SM (SSM)	≈ 60%	Gastrointestinal, skin, muscle (inflammatory symptoms) and neurology symptoms	Mild/ Moderate/ Severe	In scope
Aggressive disease	▪ SM with associated hematologic neoplasm (AHN) ▪ Aggressive SM (ASM) ▪ Mast cell leukemia (MCL)	≈5-10%	Cancer: mast cell proliferation and organ failure	Not applicable	Not in scope
	Mast cell sarcoma	< 2%			

Indolent or Smouldering Systemic Mastocytosis

Patient with Indolent SM experience multiple symptoms, which can be severe and considered for some patients as not tolerable. Cognitive impairment and depression are prominent features of the disease.

Symptom	Rank	Controls	Patients	P-value
		Severe or intolerable disability[d]	Severe or intolerable disability[d]	Severe or intolerable disability[d]
Psychological impact	1	1 (1%)	120 (33%)	*<0.0001*
Asthenia	2	3 (3%)	102 (28%)	*<0.0001*
Pruritus	3	3 (3%)	82 (23%)	*<0.0001*
Food allergy/intolerance	4	0 (0%)	97 (27%)	*<0.0001*
Erythemateous crisis	5	1 (1%)	69 (19%)	*<0.0001*
Muscle and joint pain, cramps	6	3 (3%)	71 (20%)	*0.0002*
Pollakiuria	7	6 (7%)	64 (18%)	*0.0098*
Drug allergy	8	0 (0%)	70 (19%)	*<0.0001*
Aerophagia/eructation	9	1 (1%)	62 (17%)	*<0.0001*
Dyspnea/bronchoreactivity	10	3 (3%)	94 (26%)	*<0.0001*
Headache	11	4 (4%)	48 (13%)	*0.0190*
Bone pain	12	0 (0%)	65 (18%)	*<0.0001*
Reduced sexual relations	13	4 (4%)	65 (18%)	*0.0014*
Epigastric pain	14	2 (2%)	40 (11%)	*0.0100*
Ocular discomfort	15	1 (1%)	55 (15%)	*0.0003*
Memory loss	16	0 (0%)	34 (9%)	*0.0025*
Tinnitus	17	1 (1%)	47 (13%)	*0.0011*

Hermine et al. PLoS One. 2008. Case-control cohort study of patients' perceptions of disability in mastocytosis..

Masitinib profile

Masitinib is a selective kinase inhibitor that targets mast cells and macrophages/microglia.

Masitinib targets mast cells

- Masitinib is a potent and selective inhibitor of mast cells
  - Wild-type mast cells through c-Kit
  - D816V activated mast cells through Lyn and Fyn kinases.

Masitinib targets macrophages/microglia

- Masitinib is a potent and selective inhibitor of Macrophage Colony Stimulating Factor Receptor 1 (MCSFR-1)

Masitinib is highly selective

- Masitinib does not inhibit ABL, Flt3, SRC, and VEGFR
- Masitinib high kinase selectivity limits the risk of off-target toxicity[1,2] such as cardiac toxicity or opportunistic infections

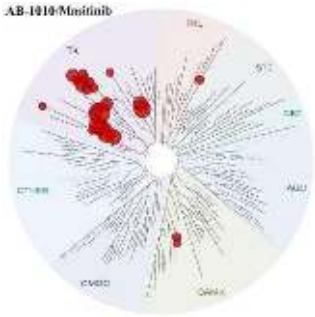
Masitinib is orally administered

- Tablet in 2 dosage forms
- Morning and evening intake

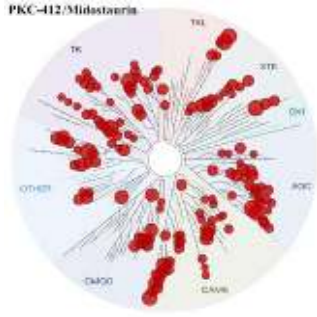
Kinase inhibition profile of masitinib

Cellular Target	Molecular Target	IC_{50} [nM]	Kd [µM]
Mast cells	KIT wild-type (WT)	200	0.008
	FYN	240	0.14
	LYN	225	0.061
	D816V KIT (exon 11)	5,000	
Microglia	MCSFR-1	90	0.0076

Masitinib



Midostaurin



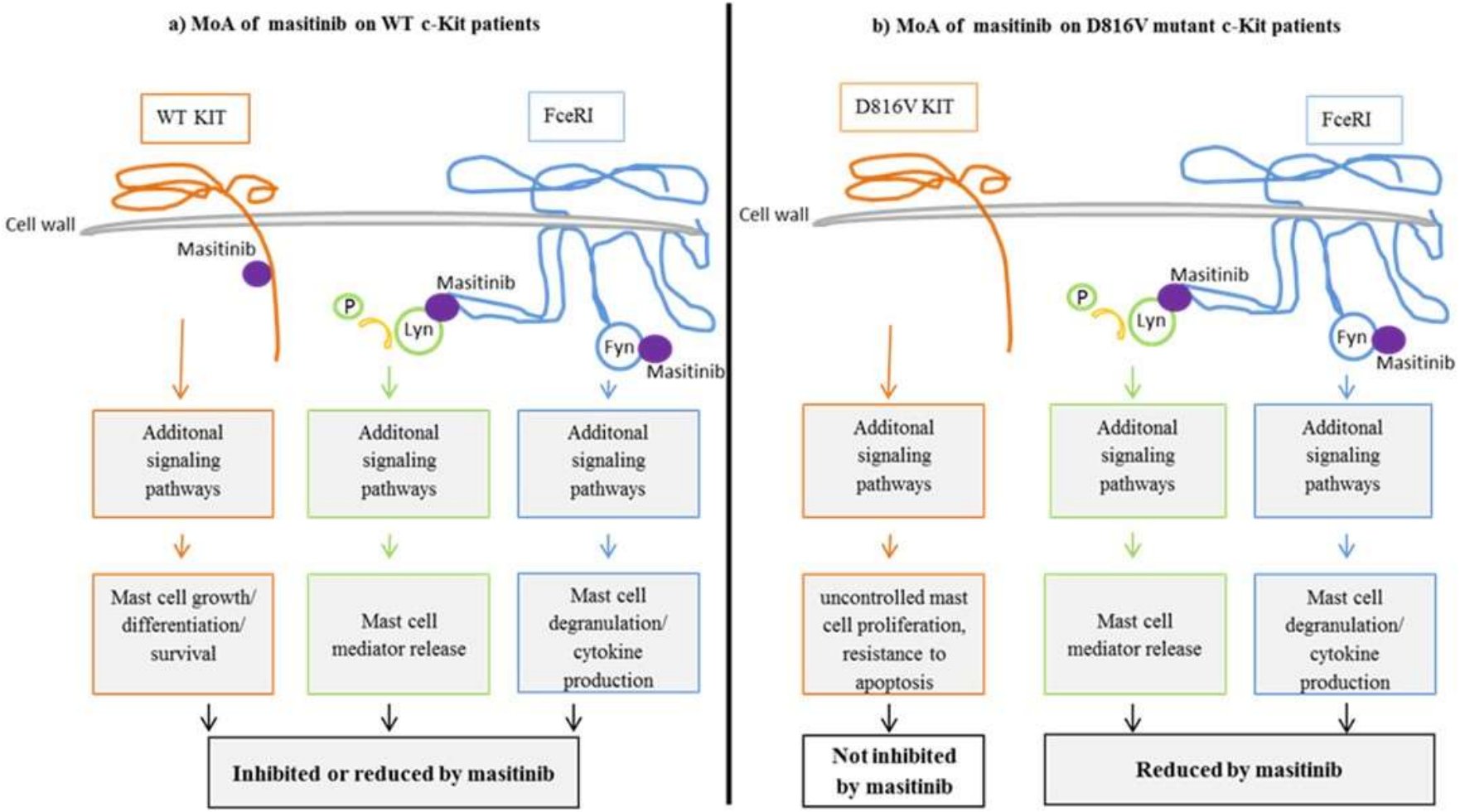
Notes

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

Masitinib profile

Masitinib inhibits mast cells, regardless of c-Kit mutation status, through inhibition of c-Kit, Lyn and Fyn kinases.

Illustration of masitinib MoA in mastocytosis



The c-Kit receptor is primarily responsible for mast cell growth, differentiation and survival with mast cell mediator release being initiated through the integration of downstream signaling pathways of c-Kit and FcεRI. D816V mutant c-Kit receptors result in uncontrolled mast cell proliferation and resistance to apoptosis. Masitinib inhibits WT c-Kit, Lyn and Fyn. In WT c-Kit mast cells (panel a) masitinib directly inhibits mast cell activation via inhibition of WT c-Kit, while mast cell mediator release and cytokine production are inhibited through targeting of Lyn and Fyn. In D816V mutant c-Kit mast cells (panel b) masitinib inhibits mast cell degranulation and cytokine production via Lyn and Fyn inhibition.

Masitinib safety database

The safety profile of masitinib is sufficiently understood with over 6,000 patients enrolled in clinical studies.

Patient exposure as of February 2018*

	Safety population	Patients exposed for at least (months)	
	All	**> 6**	> 12
Healthy Volunteers subjects	114	0	0
Non Oncology subjects	2 992	1 594	1 001
Oncology subjects	2 926	632	271
Total	**6 032**	**2 226**	**1 272**
ICH E1 Guidance (registration on non-life threatening diseases)		300 - 600	100

Safety population defined as enrolled patients with at least one documented intake of study drug (Masitinib, placebo, or comparator). All doses
** : Annual safety database cut-off date for the release of the Investigator Brochure. Next cut-off date : February 2019*

ISM – Clinical Development

The clinical program in mastocytosis is comprised of 2 proof of concept studies (*one published)*, one phase 3 study (*published*), and one phase 3 confirmatory study.

Phase	Design	Population	Primary endpoint	Patient target	Study status	Related publications
2a	Prospective, open-label, 2-parallel group study	Patients with mastocytosis with handicap and bearing activating point mutations in the phosphotransferase domain of c-Kit (D816V)	Masitinib efficacy on 2 out of these 4 variables : Pruritius, Flush, Hamilton score and Fatigue Impact Scale	21	Study completed	-
2a	Open-label, 2-parallel group study	Patients with systemic indolent mastocytosis with handicap and not bearing activating point mutations in the phosphotransferase domain of c-Kit (D816V)	Masitinib efficacy on Pruritius, Flush, Pollakyuria, Number of stools, QLQ-C30 score and Hamilton Score	25	Study completed	Paul, 2010
3	Prospective, double-blind, 2-parallel group study	Patients with documented smouldering or indolent systemic mastocytosis with severe handicap	Cumulative response by handicap (Pruritius, Flush, Hamilton score and Fatigue Impact Scale). Response on a handicap is defined as an improvement ≥ 75%	135	Study completed	Lortholary, 2017 (The Lancet)
3 confirmatory	Prospective, double-blind, 2-parallel group study	Patients with documented smouldering or indolent systemic mastocytosis with severe handicap	Cumulative response by handicap (Pruritius, Flush, Hamilton score and Fatigue Impact Scale). Response on a handicap is defined as an improvement ≥ 75%	150	To be initiated	

ISM – Proof of concept studies

Clinical proof of concept has been established both in patients with and without D816V c-Kit mutation.

Phase 2
patients not bearing activating point mutations in the phosphotransferase domain of c-Kit (D816V) (n=21 patients, single arm)

Change from baseline % at week 12

Flush (per day)	-64%
Pruritus	-36%
Depression (HAMD-17)	-43%
Fatigue	Not assessed

Phase 2
patients bearing activating point mutations in the phosphotransferase domain of c-Kit (D816V) (n=25 patients, single arm)

Change from baseline % at week 12

	Baseline symptoms		***MSQ at week 21 to 22***	***MAS2 at week 21 to 22***
	≥ Moderate	**≥ Severe**		
Flush (per day)	-60%	-74%	*-38%*	*-57%*
Pruritus	-45%	-45%	*-49%*	*-53%*
Depression (HAMD-17)	-43%	-49%	*n/a*	*n/a*
Fatigue (Fatigue Impact Scale)	-38%	-30%	*-47%*	*-22%*

Phase 1 AK002
(N = 11 ISM patients)
Baseline symptoms
≥ Moderate

MSQ: Mastocytosis Questionnaire
MAS2 : Mastocytosis activity and symptom severity questionnaire

ISM – Proof of concept studies

The majority of patients in phase 2 chose to remain on masitinib over the long term, and some have been treated for up to 7 years.

Duration of treatment exposure with masitinib in indolent systemic mastocytosis (Pooled phase 2; n=46 patients)

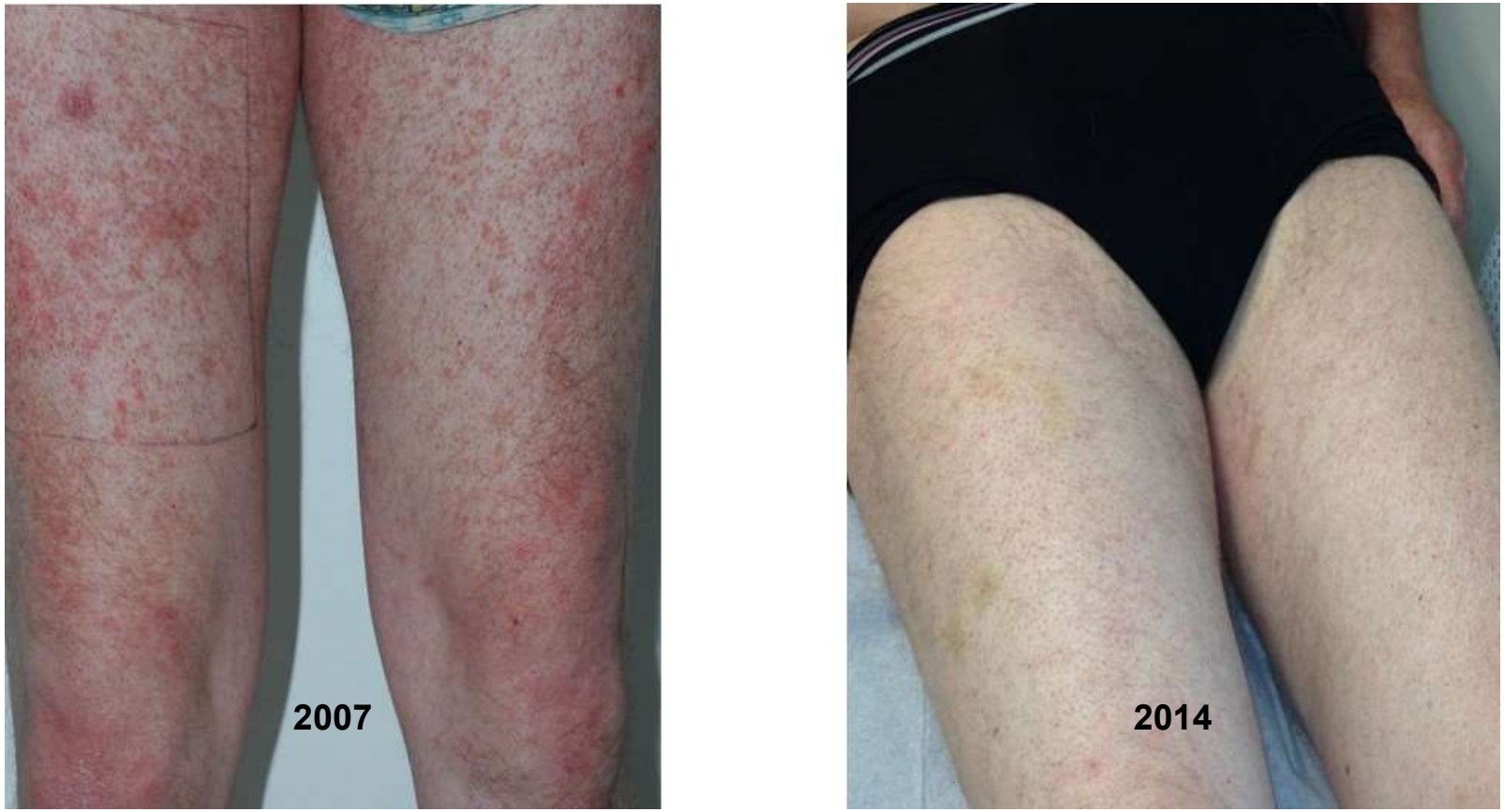
Exposure to treatment	Patients in extension phase ; N=31 (67.4%)
≥ 12 months	19 (61.3%)
≥ 24 months	13 (41.9%)
≥ 36 months	11 (35.5%)
≥ 48 months	10 (32.3%)
≥ 50 months	10 (32.3%)
≥ 62 months	8 (**25.8%**)

- Long term follow up data of two phase 2 studies showed that two-thirds of the patients decided to enroll in the extension phase of the study
- **61% patients were treated for more than 1 year and 25% were still receiving masitinib after 5 years.**

ISM – Proof of concept studies

Masitinib also had an effect on mast cells in the skin, as shown by the reduction in urticaria pigmentosa.

Cutaneous effects of masitinib treatment in a male patient before (2007) and after (2014) continuous masitinib therapy (Study AB06013).

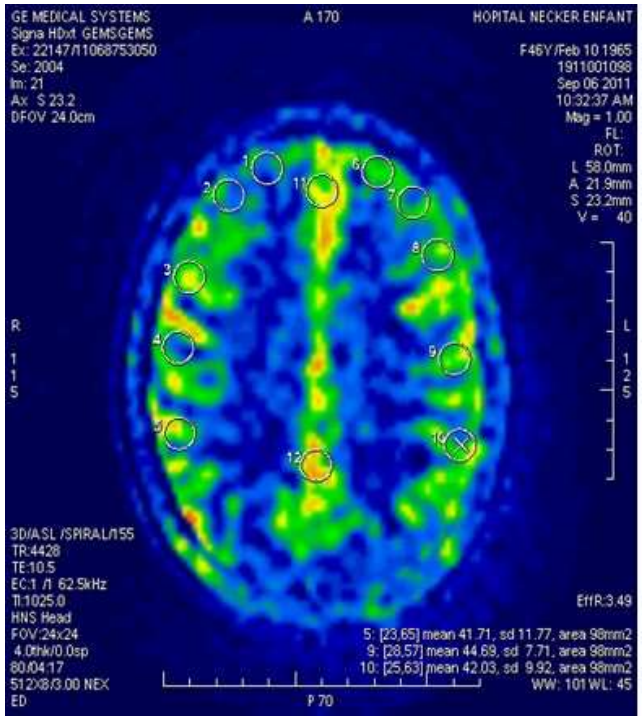


ISM – Proof of concept studies

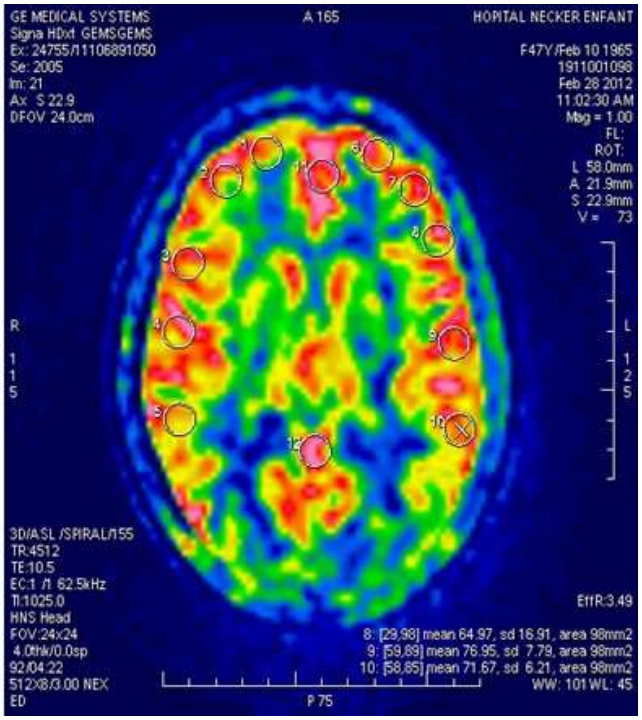
Preliminary evidence suggest that masitinib may be able to reverse cerebral hypoperfusion in mastocytosis patient, correlating with improved cognitive function.

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

A



B



Functional disorders associated with mastocytosis do not appear in conventional MRI but do appear on MRI measuring cerebral blood flow.

ISM – Phase 3 study

The first phase 3 study (AB06006) evaluated masitinib versus placebo in 135 patients with ISM and severe symptoms at baseline.

- **Study Design :**
  - Blinded, placebo controlled, masitinib versus placebo,
  - Randomization 1:1
  - Masitinib 6 mg/kg/day
  - 135 patients with ISM
- **To be evaluable, patients had to have at least one severe symptom (handicap) at baseline**

  A handicap was defined as a baseline symptom above predefined severity threshold
  - Pruritus score : ≥ 9
  - Number of flushes per week : ≥ 8
  - Depression (HAMD-17) score : ≥ 19
  - Asthenia (FIS) total score : ≥ 75
- **Patients had to be unresponsive to optimal symptomatic treatment**
- **Primary analysis: Number of cumulative responses on 4 handicaps [W8 – W24]**
  - Response :
    - Decrease of ≥75% in any 4 handicap
    - 5 assessments at w8, w12, w16, w20, w24
  - Calculation
    - Patients can have between 1 and 4 handicaps at baseline
    - Therefore a patient can score for 1 to 4 responses at each timepoint
  - The primary endpoint presented for each treatment arm the number of actual responses divided by the total of theoretical responses
- **Statistical calculation of the p-value is based on the GEE (generalized estimating equation) model** that takes into consideration correlation across variables and across time so that valid inferences can be assured. Missing data = failure

ISM – Phase 3 study

Pre-specified primary and secondary analyses on symptoms were positive and supported efficacy based on odds ratio.

AB06006 – Analyses based on symptoms (n=135 ISM patients with severe symptoms)

		Masitinib	Placebo	p-value	Odds ratio
Primary Analysis	**4H75%** Cumulative 75% response rate on baseline symptoms among **pruritus, flushes, depression, asthenia**	18.7%	7.4%	0.0076	**3.63**
Secondary Analyses	**3H75%** Cumulative 75% response rate on baseline symptoms among **pruritus, flushes, depression**	24.7%	9.8%	0.0071	**3.06**
	2H75% Cumulative 75% response rate on baseline symptoms among **pruritus or flushes**	27.2%	10.7%	0.038	**2.63**
	Pruritus 75% Cumulative 75% response rate on **pruritus**	22.0%	7.3%	0.032	**3.13**

Cumulative response based on the generalized estimating equation model with missing data considered as failure. Longitudinal analysis with respect to symptoms as opposed to patient response rate at a single point in time.
Response rates expressed as ratio of sum of actual responses between weeks 8 and 24 divided by the total number of possible responses over the same treatment period.
4H75% = cumulative response in severe symptoms present at baseline among the four :pruritus, flushes, depression, asthenia.
3H75% = cumulative response in severe symptoms present at baseline among the three: pruritus, flushes, depression.
2H75% = cumulative response in severe symptoms present at baseline among the two: pruritus, flushes.
NOTE that in *Lancet* article these endpoints use the nomenclature 4R75% etc, R standing for 'response', a term preferred over 'Handicap'.

ISM – Phase 3 study

Masitinib also demonstrated significant activity on objective markers of mast cell activation and burden.

AB06006 – Analyses based on objective endpoints

	Masitinib	Placebo	p-value
Tryptase - Patients with baseline tryptase ≥20 µg/L	46	44	0.0001
Average relative change from baseline Mean±SD	-18.0 ± 21.4	2.2 ± 26.9	
Urticaria Pigmentosa (UP) - Patients with baseline UP	33	36	0.0210
Average relative change from baseline in the Body Surface Area (BSA) covered by UP (Wallace correction)	-12.34 ± 26.41	15.91 ± 59.79	
Darier's sign – Number of patients (baseline)	37	37	0.0187
Response rate for Darier's sign disappearance (Yes/No) in patients with "Darier's sign" at baseline	18.92%	2.70%	

ISM – Phase 3 study

The most frequent severe adverse events were related to gastrointestinal disorders and skin cutaneous disorders. No life-threatening toxicities occurred.

AB06006 – All severe AEs during 24-week treatment period with at least one event in the masitinib treatment-arm

SOC / Preferred Term	Masitinib (N=70)	Placebo (N=63)
Blood and lymphatic syst. disorders	5 (7·1%)	5 (7·9%)
Neutropenia	3 (4·3%)	1 (1·6%)
Febrile neutropenia	1 (1·4%)	0 (0·0%)
Leukocytosis	1 (1·4%)	2 (3·2%)
Lymphadenopathy	1 (1·4%)	0 (0·0%)
Cardiac disorders	1 (1·4%)	0 (0·0%)
Palpitations	1 (1·4%)	0 (0·0%)
Eye disorders	1 (1·4%)	0 (0·0%)
Eyelid oedema	1 (1·4%)	0 (0·0%)
Gastrointestinal disorders	12 (17·1%)	3 (4·8%)
Diarrhoea	8 (11·4%)	1 (1·6%)
Nausea	2 (2·9%)	1 (1·6%)
Aphthous stomatitis	1 (1·4%)	0 (0·0%)
Glossitis	1 (1·4%)	0 (0·0%)
Haemorrhoids	1 (1·4%)	0 (0·0%)
Irritable bowel syndrome	1 (1·4%)	0 (0·0%)
Rectal spasm	1 (1·4%)	0 (0·0%)
General disorders and administration site conditions	6 (8·6%)	2 (3·2%)
Asthenia	4 (5·7%)	1 (1·6%)
Pyrexia	2 (2·9%)	0 (0·0%)
Chills	1 (1·4%)	0 (0·0%)
Face oedema	1 (1·4%)	0 (0·0%)
Localised oedema	1 (1·4%)	0 (0·0%)
Oedema peripheral	1 (1·4%)	0 (0·0%)
Hepatobiliary disorders	1 (1·4%)	0 (0·0%)
Cholestasis	1 (1·4%)	0 (0·0%)
Immune system disorders	1 (1·4%)	1 (1·6%)
Allergic oedema	1 (1·4%)	0 (0·0%)

SOC / Preferred Term	Masitinib (N=70)	Placebo (N=63)
Infections and infestations	3 (4·3%)	1 (1·6%)
Hand-foot-and-mouth disease	1 (1·4%)	0 (0·0%)
Pharyngitis	1 (1·4%)	0 (0·0%)
Viral infection	1 (1·4%)	0 (0·0%)
Investigations	7 (10·0%)	8 (12·7%)
Neutrophil count decreased	2 (2·9%)	1 (1·6%)
Alanine aminotransferase increased	1 (1·4%)	0 (0·0%)
Aspartate aminotransferase increased	1 (1·4%)	0 (0·0%)
Blood alkaline phosphatase increased	1 (1·4%)	0 (0·0%)
Blood phosphorus decreased	1 (1·4%)	0 (0·0%)
Gamma-glutamyltransferase increased	1 (1·4%)	0 (0·0%)
Investigation	1 (1·4%)	0 (0·0%)
Lymphocyte count increased	1 (1·4%)	0 (0·0%)
White blood cell count increased	1 (1·4%)	0 (0·0%)
Musculoskeletal and connective tissue disorders	4 (5·7%)	2 (3·2%)
Intervertebral disc protrusion	1 (1·4%)	0 (0·0%)
Muscle spasms	1 (1·4%)	0 (0·0%)
Osteoarthritis	1 (1·4%)	0 (0·0%)
Pain in extremity	1 (1·4%)	0 (0·0%)
Neoplasms benign, malignant and unspecified	1 (1·4%)	1 (1·6%)
Bladder cancer	1 (1·4%)	0 (0·0%)

SOC / Preferred Term	Masitinib (N=70)	Placebo (N=63)
Nervous system disorders	3 (4·3%)	3 (4·8%)
Headache	3 (4·3%)	3 (4·8%)
Psychiatric disorders	1 (1·4%)	0 (0·0%)
Depression	1 (1·4%)	0 (0·0%)
Reproductive system and breast disorders	1 (1·4%)	0 (0·0%)
Genital lesion	1 (1·4%)	0 (0·0%)
Respiratory, thoracic and mediastinal disorders	2 (2·9%)	1 (1·6%)
Dyspnoea	1 (1·4%)	0 (0·0%)
Pneumothorax	1 (1·4%)	0 (0·0%)
Skin and subcutaneous tissue disorders	11 (15·7%)	2 (3·2%)
Rash	4 (5·7%)	0 (0·0%)
Pruritus	3 (4·3%)	1 (1·6%)
Drug eruption	1 (1·4%)	0 (0·0%)
Erythema multiforme	1 (1·4%)	0 (0·0%)
Palmar-plantar erythrodysaesthesia syndrome	1 (1·4%)	0 (0·0%)
Urticaria	1 (1·4%)	0 (0·0%)
Vascular disorders	1 (1·4%)	0 (0·0%)
Flushing	1 (1·4%)	0 (0·0%)

ISM – Phase 3 study

Results from this phase 3 study were published in *The Lancet in 2017*.

Lancet (London, England)
Author Manuscript HHS Public Access

Masitinib for treatment of severely symptomatic indolent systemic mastocytosis: a randomised, placebo-controlled, phase 3 study

Olivier Lortholary, Marie Olivia Chandesris, [...], and Olivier Hermine

Additional article information

Associated Data

- Supplementary Materials

Summary

Background

Indolent systemic mastocytosis, including the subvariant of smouldering systemic mastocytosis, is a lifelong condition associated with reduced quality of life. Masitinib inhibits KIT and LYN kinases that are involved in indolent systemic mastocytosis pathogenesis. We aimed to assess safety and efficacy of masitinib versus placebo in severely symptomatic patients who were unresponsive to optimal symptomatic treatments.

Methods

In this randomised, double-blind, placebo-controlled, phase 3 study, we enrolled adults (aged 18–75 years) with indolent or smouldering systemic mastocytosis, according to WHO classification or documented mastocytosis based on histological criteria, at 50 centres in 15 countries. We excluded patients with cutaneous or non-severe systemic mastocytosis after a protocol amendment. Patients were centrally randomised (1:1) to receive either oral masitinib (6 mg/kg per day over 24 weeks with possible extension) or matched placebo with minimisation according to severe symptoms. The primary endpoint was cumulative response (>75% improvement from baseline within weeks 8–24) in at least one severe baseline symptom from the following: pruritus score of 9 or more, eight or more flushes per week, Hamilton Rating Scale for Depression of 19 or more, or Fatigue Impact Scale of 75 or more. We assessed treatment effect using repeated measures methodology for rare diseases via the generalised estimating equation model in a modified intention-to-treat population, including all participants assigned to treatment minus those who withdrew due to a non-treatment-related cause. We assessed safety in all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, number NCT00814073.

Findings

Between Feb 19, 2009, and July 15, 2015, 135 patients were randomly assigned to masitinib (n=71) or placebo (n=64). By 24 weeks, masitinib was associated with a cumulative response of 18·7% in the primary endpoint (122·6 responses of 656·5 possible responses [weighted generalised estimating equation]) compared with 7·4% for placebo (48·9 of 656·5; difference

ISM – Phase 3 confirmatory study design

Three optimizations of the phase 3 confirmatory study have been implemented based on the first phase 3 and are increasing the probability of success of the study.

DESIGN

- **Double blind, placebo controlled, randomized 1:1**
  - Masitinib titration up to 6.0 mg/kg/day
  - Placebo titration up to 6.0 mg/kg/day
- **Main Inclusion Criteria**
  - Smouldering or Indolent Mastocytosis
  - Severe symptoms at baseline : Pruritus score ≥ 9 and/or Flushes per week ≥ 8 and/or HAMD-score ≥ 19
  - Optimal symptomatic treatment failure of his/her handicap
- **Enrolment:** 140 patients
  - Masitinib arm : 70 patients
  - Placebo arm : 70 patients
- **Primary endpoint:**
  - Cumulative 75% response rate on baseline severe symptoms/handicaps among (pruritus, flush, depression)
  - Response on a handicap is defined as an improvement ≥ 75% for pruritus, flushes and depression.
- **Treatment duration :** 24 weeks

OPTIMIZATIONS FROM PREVIOUS PHASE 2/3

- **Dose Titration**
  - In previous study, starting dose of 6 mg/kg/day without titration
  - This led to 20% treatment discontinuation, with discontinuation equal to treatment failure in the analysis
  - With dose titration from 3.0 to 4.5 and then 6.0 mg over two months period, marginal discontinuation rate
- **Recording of rescue therapy**
  - In previous study, patients could take rescue treatment in case of worsening of symptoms, which favored the placebo arm
  - In new study, rescue treatment is equal to treatment failure in the analysis
- **Run-in period**
  - In previous study, there was no run-in to ensure that patients were taking optimal symptomatic treatment at screening
  - In new study, one-month run-in period to control failure to symptomatic treatment

ISM – Phase 3 confirmatory study regulatory status

The phase 3 confirmatory study is being initiated and patient enrolment is expected to be initiated in Q1 2020.

- **Europe**
  - Design reviewed through 2 scientific advices plus input from registration dossier
  - Protocol approved in France (ANSM) and other European countries
- **USA**
  - Design reviewed through 1 scientific advices plus once recent interaction
  - IND approval expected in Q1 2020

ISM – Phase 3 confirmatory study timelines

The confirmatory study is expected to be completed early 2022.

- **Start date: Q1 2020**
- **Patient enrolment: 18 months**
  - Enrolment : 140 patients
  - Identified sites : 30 sites, only hematology centers
  - Average enrolment : around 5 patients per site over 18 months
- **Protocol period: 6 months**
- **Phase 3 completion : Q1 2022**

Masitinib Intellectual Property

Masitinib IP rights are secured up to 2031 in the US and potentially 2036 in Europe in ISM.

Protection	Item	Duration of protection	Status
Orphan drug status	Masitinib has been granted orphan drug designation by both EMA and FDA for ISM	Exclusivity of 7 years for FDA and 10 years for EMA	Delivered
Phase 2/3 'Method of use' patents	Systemic mastocytosis (severe)	Until 2031 in the USA Until 2036 outside USA	Delivered Pending

Mariana CASTELLS, MD, PhD

- **About Mariana Castells**
  - Professor at Harvard Medical School. She is a clinician/teacher/researcher at the Brigham and Women's Hospital Rheumatology, Immunology and Allergy Division serving as Director of Drug Hypersensitivity and Rapid Desensitization Center and the Director of the Mastocytosis Center.
  - Founding Chair in 2005 of the Task Force on Mast Cell Disorders of the American Academy of Allergy, Asthma and Immunology.
  - Member of the American Initiative in Mast Cell Diseases (AIM) Organizing Committee
  - Member of the Medical Advisory Board of The Mastocytosis Society (TMS).

- **Role in masitinib program**
  - Willing to participate in AB15003 confirmatory study.

Mariana Castells

There is a high unmet medical need for patients with indolent forms of systemic mastocytosis.

- **About the Brigham and Women's Hospital (BWH) Mastocytosis Center in Boston**
  - The BWH Mastocytosis Center in Boston is pioneer in basic , translational and clinical research in mast cell disorders. It is a multidisciplinary center providing excellence in care and innovations in treatment.
  - The center provides diagnosis, management and treatment options for over 2000 mastocytosis patients of which 80 % are adults and 20% are children.
  - The BWH Mastocytosis Center has a majority of patients with Indolent Systemic Mastocytosis suffering from symptoms of mast cell activation and for whom there has been no new options for the last 20 years.

- **ISM remain a high unmet medical need**
  - The quality of life of patients with mastocytosis is overall severally affected
  - Patients suffer from itching, flushing , nausea, diarrhea, brain fog , anxiety and acute episodes of anaphylaxis among other debilitating symptoms
  - Patients remain uncontrolled despite conventional symptomatic treatments
  - Use of new therapeutic options requires a balanced approach with careful evaluation of potential benefits and side effects

Mariana Castells

Masitinib has a benefit and toxicity profile which sets it apart from other current tyrosine kinase , with a more favorable benefit ratio and with great potential to improve the quality of life of ISM patients.

- **Key differentiating factors with masitinib**
  - Safety profile
    - No apparent long-term cumulative toxicity
    - No vascular toxicity
  - Impact on neurological symptoms
    - Patients complain first about neurological symptoms
  - Impact on neurological symptoms
    - Proven efficacy on neurological symptoms
    - Proven efficacy on flush and pruritus

- **Confirmatory phase 3 with masitinib**
  - The most important goal of the BWH Mastocytosis Center is to help alleviate the suffering of patients with mastocytosis , from skin, gastroenterological, neurological and psychiatric symptoms
  - Masitinib is the leading program in ISM and a viable approach to this goal.
  - BWH Mastocytosis Center intends to participate to the confirmatory study once the IND is opened

Cem AKIN, MD, PhD

- **About Cem Akin**
  - Professor of Allergy and Immunology in the Department of Internal Medicine at the University of Michigan.
  - Co-chair of the steering committee of the American Initiative in Mast Cell Diseases (AIM).
  - Member of the Scientific Advisory Board of ECNM.
  - Consultancy agreements with Novartis and Blueprint.
  - Receive research support from Blueprint.

- **Role in masitinib program**
  - Involved as a consultant in early development program of masitinib.
  - Willing to participate in AB15003 confirmatory study once the IND is opened.

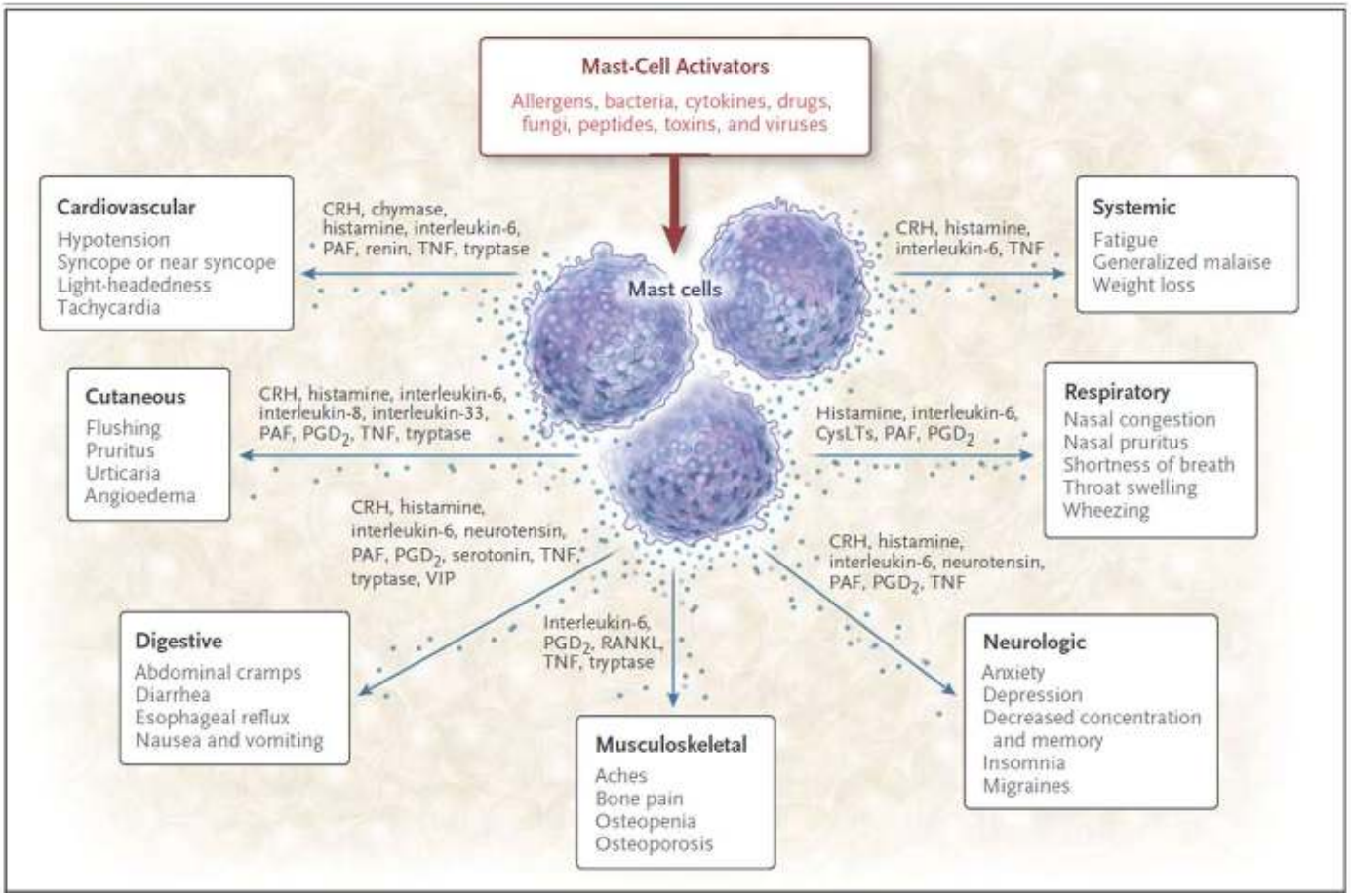
Cem Akin

Masitinib is currently the only drug in phase 3 for a claim on indolent systemic mastocytosis.

Main Forms of mastocytosis	Drug	Sponsor	Target	Status	Differentiating point
Aggressive Mastocytosis	Midostaurin	Novartis	Multi-kinase	Registered	Not competing with masitinib
	Avapritinib	Blueprint Medicines	Kit 816	Phase 2	
	DCC-2618	Deciphera Pharmaceuticals	Multi-kinase	Phase 1	
Indolent or Smouldering Systemic Mastocytosis	Masitinib	AB Science	Kit, Lyn, Fyn	Phase 3	First positive phase 3 study in this label
	Avapritinib	Blueprint Medicines	Multi-kinase	Phase 2	Effects on mast cell activation are not known As per Blueprint Investigator Brochure, which is publicly available: ▪ 3 cases of intracranial bleeding (1 case of cerebral hemorrhage and 2 cases of subdural hematoma) were reported ▪ Cognitive effects (cognitive disorder, confused state, disturbance in attention, memory impairment, mental impairment, personality change, speech disorder) have occurred in about 30% of patients
	AK002	Allakos	Antibody targeting Siglec-8	Phase 1	

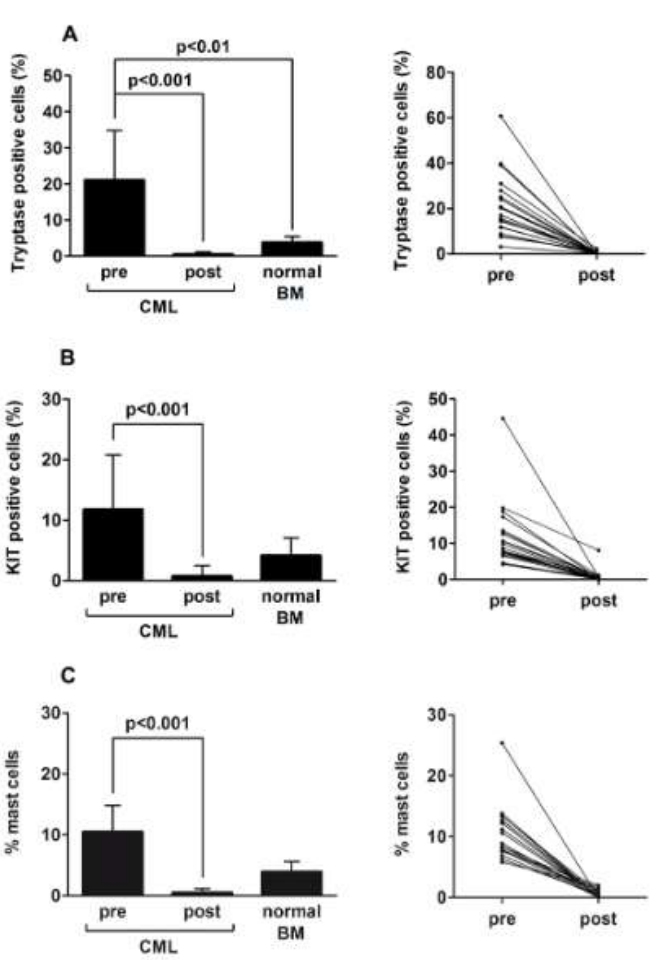
Activation of mast cells leads to degranulation and secretion of numerous mediators that are thought to contribute to the multiple symptoms observed in patients.

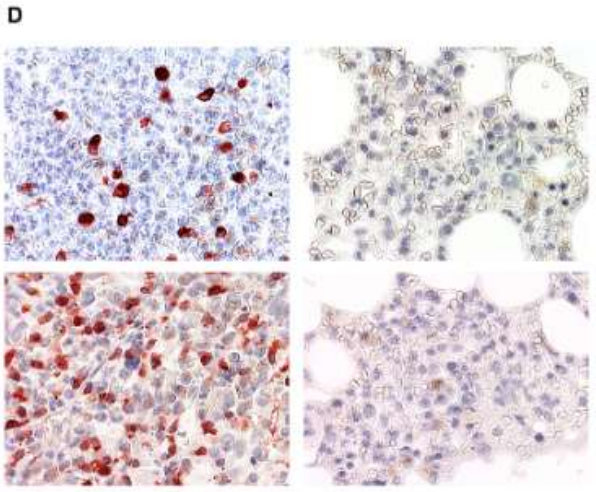
Clinically Relevant Mediators Released from Mast Cells and Putative Effects



Theoharides T., Valent P., Akin C., NEJM 2015. Mast Cells, Mastocytosis, and Related Disorders

KIT-targeting drug imatinib suppresses mast cell production in vitro and in vivo. However, drug-induced mast cell depletion is not accompanied by adverse clinical event.





Imatinib induces mast cell deficiency in the bone marrow of patients with CML. Bone marrow (BM) biopsy material was obtained from patients with CML (n=23) at diagnosis and at the time of major or complete molecular response and at least 2 years on therapy with imatinib (400 mg/day).

Serial sections were prepared from paraffin-embedded BM specimens and stained with antibodies against tryptase (A) and against KIT (B) by indirect immunohistochemistry as well as by Giemsa-staining (C). D: Examples of BM sections stained for tryptase (upper panels) and KIT (lower panels) at diagnosis (upper and lower left panels) and at the time of re-investigation (upper and lower right panels) by indirect immunohistochemistry

Valent P. et al, Oncotarget 2014. Long-term treatment with imatinib results in profound mast cell deficiency in Ph+ chronic myeloid leukemia

Masitinib demonstrated a positive benefit risk balance in a large controlled study.

- **Clinically relevant efficacy on key severe symptoms**
  - Efficacy on depression and asthenia
  - Efficacy on flush and pruritus
  - Response based on 75% reduction of severity of symptoms

- **Favorable safety profile**
  - Most frequent AEs occurring at treatment start (rash, diarrhea, nausea) can be managed by judicious dose-escalation in the first two months of treatment
  - Favorable long-term safety profile, which is key as patient need life-long treatment

- **There is enough evidence in my opinion to support the use of masitinib in the treatment of ISM with severe symptoms**

Michel AROCK, PharmD, PhD

- **About Michel Arock**
  - Professor of physiology and hematology at the Ecole Normale Supérieure of Paris-Saclay and is currently heading the Functional Unit for Biological Emergencies within the Hospital Pitié-Salpêtrière Charles-Foix in Paris.
  - Conducted research on the physiology of mast cells and on the pathophysiology and treatment of mastocytosis for many years.
  - Co-authored more than 180 publications referenced in Medline
  - Currently the Chair (2015-2020) of the European Competence Network on Mastocytosis (ECNM).

- **Role in masitinib program**
  - Member of IDMC of AB15003 confirmatory study.

Michel Arock

For patients with ISM/SSM, the need is to reduce symptoms, which can be severe.

- Mastocytosis can be categorized into cutaneous mastocytosis (CM; mainly children, but some adults have also pure CM) and systemic mastocytosis (SM) and other internal organs, involving the bone marrow.
- SM can be further categorized into indolent SM (ISM), smoldering SM (SSM) and advanced SM (ASM, SM-AHN, MCL). In most patients with SM, the skin is also involved.
- While Advanced SM therapy is usually based on cytoreductive treatments (Cladribine, Midostaurin), treatment of ISM and SSM.
- Indeed the major clinical signs and symptoms observed in ISM and SSM are related to the excessive release of inflammatory/allergic mediators by accumulated mast cells (mast cell mediator-related symptoms; MCMS).
- These MCMS, responsible for severe handicap in the patients, comprise among others: pruritus, flushing, GI-tract symptoms, neuropsychiatric symptoms (depression, brain fog, others), bone pain, etc…
- These MCMS are usually more or less controlled/attenuated by antimediator therapy (anti-histamines, anti-leukotrienes, corticoids, etc…).
- However in a significant proportion of ISM/SSM patients, classical anti-mediator therapy fail to improve severe handicap.

Patients with ISM/SSM receive multiple conventional symptomatic treatments, which are in most cases unable to reduce symptomatology.

Treatment	Symptoms
Selective serotonin reuptake inhibitors (SSRIs)	Depression
H1 Antagonists	Pruritus, flush and sometimes GI pains
H2 Antagonists	Essentially GI pains
Aspirin	Flush, tachycardia (but may cause vascular collapse)
Corticoids	Local treatment of cutaneous lesions, ascites, malabsorption, GI cramps
Cromoglycate disodium	Non-specific mediator release symptoms
Leukotrienes receptor blocker	Respiratory manifestations
Epinephrine	Hypotension
Biphosphonates	Bone pain and bone loss
Ketamine , substance P inhibitors, SSRI	Pain
Anti-IgE antibody *(off label)*	Anaphylaxis and symptoms

Michel Arock

Therefore, there is an urgent need of new drugs able to significantly improve severe symptoms in ISM/SSM and devoid of significant adverse effects.

- Among the new drugs, the most promising are tyrosine kinase inhibitors (TKIs).
- However, Midostaurin and Avapritinib, two TKIs active in advanced categories of SM, have demonstrated numerous side effects, sometimes life-threatening, not compatible with their use in classical therapy-resistant ISM/SSM patients.
- Masitinib is a TKI which targets KIT wild-type and, interestingly Lyn and Fyn, all being clearly involved in the release of mediators by mast cells in mastocytosis.
- Masitinib has already been proved as highly efficacious on severely handicapped ISM/SSM patients in two well-conducted phases IIa and one phase III. Numerous patients remain on masitinib for years without exhibiting significant adverse effects.
- We, at the European Competence Network (ECNM), the largest network of experts working in the field of mastocytosis, strongly believe that Masitinib, thanks to its selectivity on mast cell activation and absence significant side effects, is the perfect drug to control severe handicaps in symptomatic ISM/SSM patients.
- We, at the ECNM, support and encourage AB Science to initiate as soon as possible a confirmatory Phase III in severely handicapped ISM/SSM patients and we strongly hope that the results of this Phase III will soon lead to the registration of the drug.

Q& A

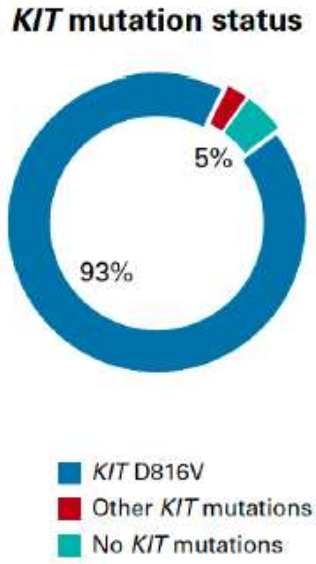
APPENDICES

Mastocytosis

Mastocytosis is a set of diseases characterized by an abnormal accumulation of mast cells in one or more organ systems. The disease is primarily driven by the KIT D816V mutation.

WHO Classification of mastocytosis (2016)

Cutaneous mastocytosis (CM)	≈ 30%	
Systemic mastocytosis (SM) ▪ Indolent SM (ISM) ▪ Smouldering SM (SSM)	≈ 60%	Symptomatic forms (debilitating disease)
▪ SM with associated hematologic neoplasm (AHN) ▪ Aggressive SM (ASM) ▪ Mast cell leukemia (MCL)	≈5-10%	Aggressive forms (Life-threatening disease)
Mast cell sarcoma	< 2%	

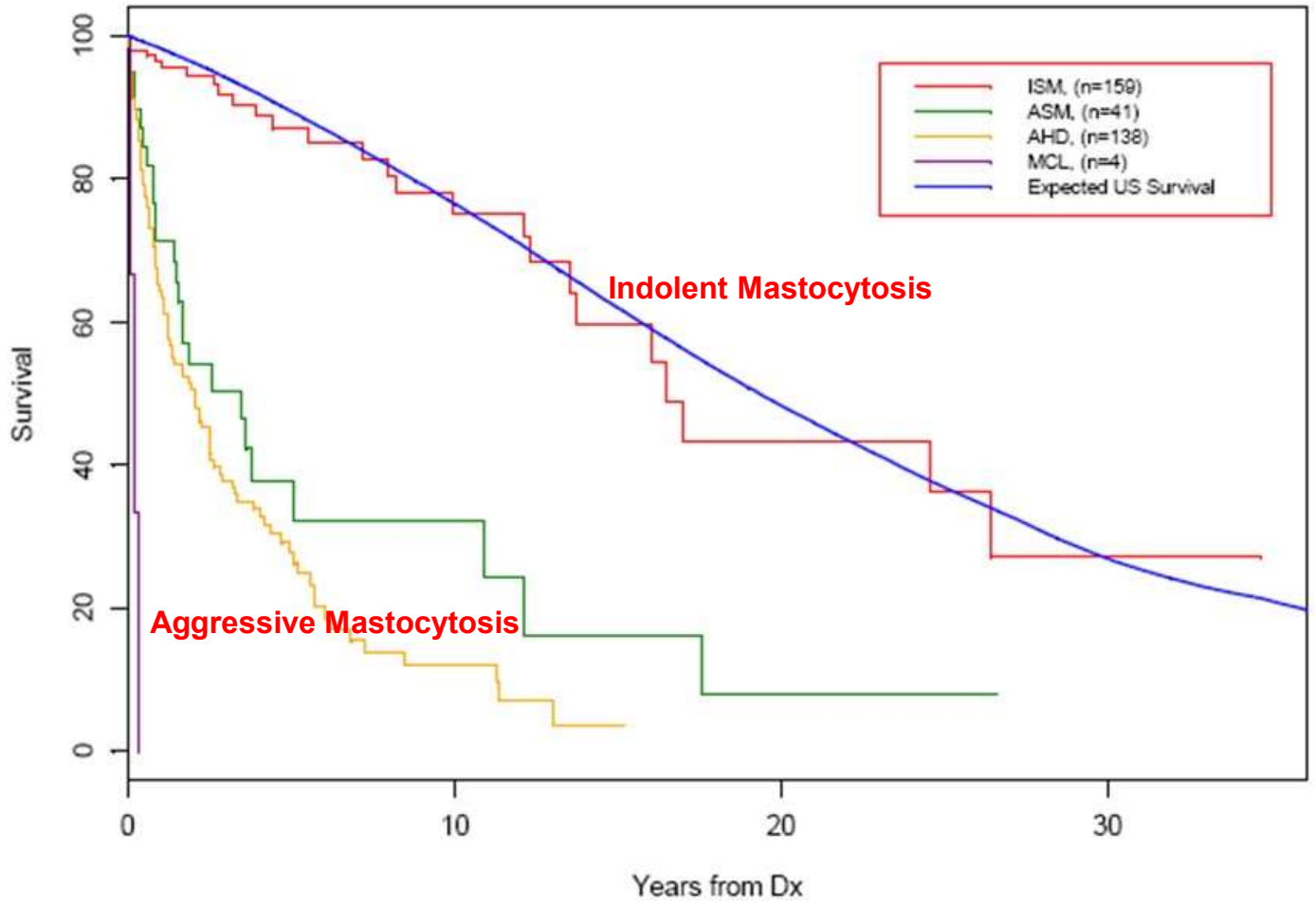


Jawhar et al., Leukemia 2016; 30:136-143
Jawhar *et al.*, JCO 2019

Mastocytosis

Patients with Indolent SM have a (nearly) normal life expectancy, while patients with aggressive mastocytosis have a median overall survival of approximately four years.

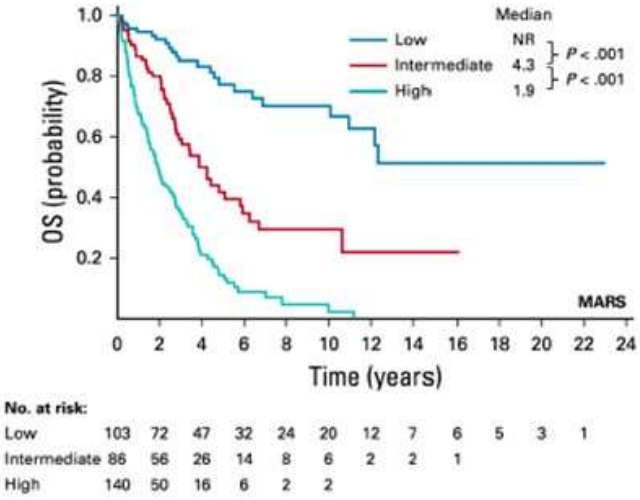
Kaplan Meier Survival for systemic mastocytosis patients classified by type



Lim KH et al. Blood 2009. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors.

Aggressive Mastocytosis

Aggressive mastocytosis can be stratified, based on MARS clinical and molecular criteria, in three risk-groups, each requiring different therapeutic options, and for which masitinib is not a candidate.



- How can you implement all these scores in our daily routine?
- How should we treat the individual patient within the various risk-groups?
- No evidence to make a decision – no prospective and even little retrospective data.

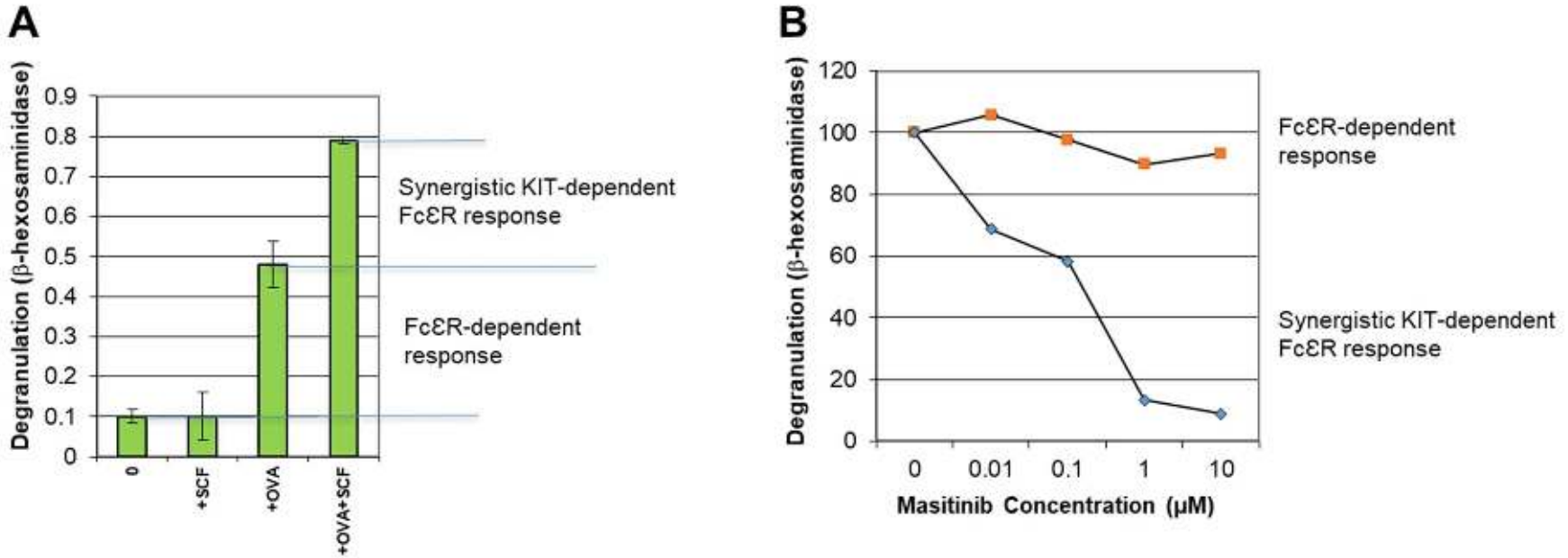
- **Low-risk:**
  - Mostly associated with absence of HMR (S/A/R)
  - First-line treatment:
    - Midostaurin – likelihood to response is high[1]
  - Second-line: clinical trial (e.g. Avaprintib)
  - Probably no allogeneic SCT (in first line)
- **Intermediate-risk:**
  - Clinical trial (e.g. Avapritinib)
  - Midostaurin + Cladribine (simultaneously? sequentially?)
- **High-risk:**
  - Mostly associated with presence of HMR (S/A/R) and AHN
  - Clinical trial (e.g. Avapritinib)
  - Midostaurin ± Cladribine ± AHN targeted compounds
  - Allogeneic SCT at best response

Jawhar et al., Blood 2017. Jawhar et al., JCO 2019

Masitinib profile

Masitinib inhibits mast cell hyper-activation in a manner that is independent of mutant-KIT (D816V) signaling pathways and which demonstrates cytostatic, disease-modifying properties.

Masitinib potently inhibits degranulation in a model of mast cell hyperactivation. Reduction of mast cell mediator release/availability in the tissue microenvironment, including SCF, will impact on the disease's underlying pathophysiology.



A) Degranulation of rat RBL-2H3 mast cells under different conditions (increasing degranulation indicated by greater concentration of the β-hexosaminidase release). The signaling pathways of FcεR and c-KIT are stimulated by ovalbumin (OVA) and SCF (stem cell factor), respectively. These are independent from one another but synergize when stimulated concomitantly (as observed by the KIT-dependent FcεR response).

B) Masitinib exerts simultaneous inhibition of these pathways via its activity against Lyn/Fyn and c-KIT, respectively. Masitinib treatment of hyper-activated mast cells produced a modest inhibition of the FcεR-dependent response (relative to degranulation in absence of masitinib) and a near total inhibition of the synergistic KIT-dependent FcεR degranulation response.
(RBL-2H3 is mutated on D817V, equivalent of human D816V in rat, and therefore model of systemic mastocytosis).

ISM – Phase 3 study

Similar efficacy was reported in patients with D816V mutation.

AB06006 – Analyses based on symptoms (n= 116 ISM patients with severe symptoms)

		Masitinib	Placebo	p-value	Odds ratio
Subgroup analysis in patients with D816V mutation	**4H75%** Cumulative 75% response rate on baseline symptoms among **pruritus or flushes or depression or asthenia**	20.2%	7.4%	0.0316	**4.45**
	3H75% Cumulative 75% response rate on baseline symptoms among **pruritus or flushes or depression**	26.6%	9.9%	0.0051	**3.36**
	2H75% Cumulative 75% response rate on baseline symptoms among **pruritus or flushes**	28.8%	10.6%	0.0342	**2.80**

ISM – Phase 3 study

Clinical relevance of the results is supported by patient response analysis.

AB06006 – Analyses based on patient response

- **Patient response on at least one handicap is positive**

Patient response rate 4H: Number of patients having response (≥75%) on at least 1 handicap

Overall W8-W24 – Pearson Chi-Square			
Masitinib (n=67)	Placebo (n=62)	**Diff.**	p-value
40.3%	24.2%	**16.1%**	0.0062

- **Patient response on each handicap is positive**

Patient response rate 4H: Number of patients having response (≥75%) on all their baseline handicaps

Overall W8-W24 – Pearson Chi-Square			
Masitinib (n=67)	Placebo (n=62)	**Diff.**	p-value
16.4%	1.6%	**14.8%**	0.0038

- **Patient response regardless of the number of baseline handicaps is positive**

Response rate 4H: Number of patients having response (≥75%) for each handicap

	Overall W8-W24		
	Masitinib	Placebo	**Diff.**
Patient having 2 handicaps at baseline	21.0% (n=19)	0.0% (n=25)	**21.0%**
Patient having 3 handicaps at baseline	12.5% (n=16)	0.0% (n=18)	**12.5%**
Patient having 4 handicaps at baseline	16.7% (n=6)	0.0% (n=3)	**16.7%**

A handicap was defined as a baseline symptom above predefined severity threshold

ISM – Phase 3 study

The pre-specified primary analysis based on 4H75% endpoint and the GEE model is most appropriate to demonstrate the clinical relevance of masitinib in the claimed indication.

- **The composite endpoint selected, although complex, was the most appropriate for the disease**

Key parameters	Choice	Validation
Selected symptoms	▪ Key symptoms of the disease ▪ Measurable symptoms based on validated scales	▪ FDA recommended to use symptoms for which a validated scale is available ▪ Flush and pruritus: choice of endpoints validated through scientific advice ▪ Depression: Prevalent symptom validated in the literature • Hermine 2008: 63% of patients particularly suffer from depression • Moura 2011: 64% of patients • Jennings 2014: Ranked n°1 for continual burden of extreme severity symptoms • Siebenhaar 2016: Representative symptoms include tired during the day, and anxiety and depression
Baseline severity threshold	Severe symptoms to justify benefit / risk balance	▪ Validated by EMA scientific advice (EMA/CHMP/H/SA/573/2/FU/2/2011/PA/SME/II)
Response threshold	Deep response (≥75%) to guarantee relevant benefit	▪ Validated by EMA scientific advice (EMA/CHMP/H/SA/573/2/FU/2/2011/PA/SME/II)
Timepoint for efficacy assessment	Repeated measure on patient*handicap allowing the measure of the change over time in the burden of symptoms	Validated by literature (Magliacane, 2014) to capture fluctuation of symptoms ▪ High inter-individual and intra-individual variability associated with the symptoms ▪ The occurrence, persistence and severity of each symptom can fluctuate over time for any given individual, as well as from person to person

- **Analysis based on GEE model**
  - Application of EMA guidance (CHMP/EWP/83561/2005) on clinical trials in small populations
  - GEE adjusts for correlation between treatment, visits, and symptoms and does not inflate responses

ISM – Targeted population

Adult population with indolent systemic mastocytosis is estimated to be around 65,000 in the USA and in the EU.

	Europe	US
Population (’000)	500 000[1]	320 000[1]
Mastocytosis with Symptoms (ISM-SY[4])	1/10,000[2]	
Adult population	78%[3]	
Potential Patients, adults with ISM-SY	**40,000**	**25,000**

1. https://data.worldbank.org/indicator/SP.POP.TOTL and https://ec.europa.eu/eurostat/web/population-demography-migration-projections/population-data/main-tables
2. Cohen SS, Skovbo S, Vestergaard H, et al. Epidemiology of systemic mastocytosis in Denmark. Br J Haematol 2014; 166: 521-8.
3. Population Division, U.S. Census Bureau.
4. Theoharides T., Valent P., Akin C., NEJM 2015. Mast Cells, Mastocytosis, and Related Disorders

Commercialization

AB Science is ideally positioned to commercialize masitinib in mastocytosis in case of registration.

No Competition	In severe systemic mastocytosis in adults ▪ No registered drug ▪ No drug in phase 3 clinical development
Ease of Market Access	▪ Network of physician specialists already structured in Europe, with ECNM Network of patients already structured through national patient associations in the main countries (France, Germany, Spain, UK, NL, USA, etc…) ▪ Founders of AB Science are also founders of the French patient association AFIRMM with over 2,500 patients identified ▪ Close relationship developed between AB Science and patients association and Key Opinion Leaders over the past 10 years ▪ High demand from patients
Greater profitability	▪ AB Science retains 100% of the right on the molecule since no license has been granted ▪ Limited number of centers worldwide already identified, requiring a limited salesforce ▪ Orphan Drug Status designation granted to masitinib by both at EMA and FDA, granting respectively 10 and 7 years exclusivity