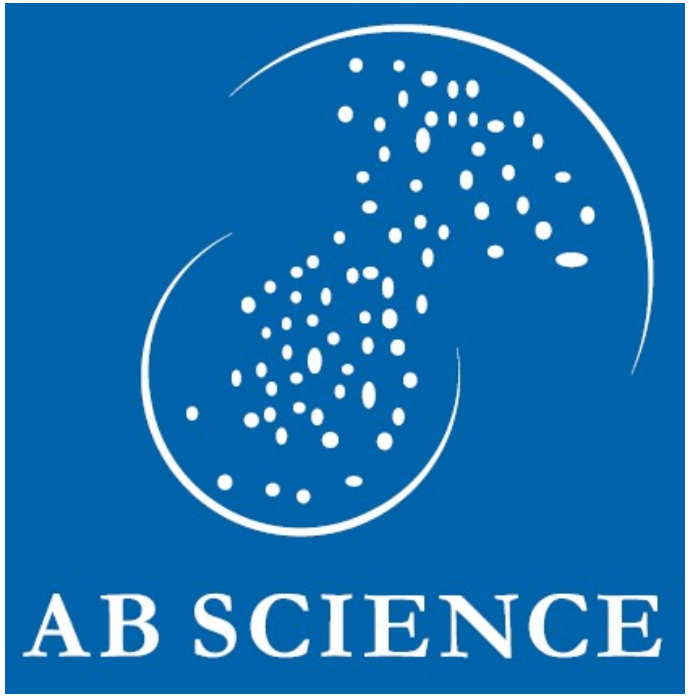

AB SCIENCE WEBCONFERENCE

MASITINIB IN SEVERE ASTHMA UNCONTROLLED BY ORAL COTICOSTEROIDS

02 December 2019

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AGENDA

- Introduction of participating experts
- Overview of masitinib clinical results
- Masitinib positioning
- Q&A

Participants

Asthma Experts

Pascal CHANEZ, MD, PhD
APHM and Aix Marseille University at Marseille France

Lavinia DAVIDESCU, MD, PhD
Faculty of Medicine and Pharmacy, University of Oradea - Romania.

Elliot ISRAEL, MD
Brigham and Women's Hospital (BWH) – Boston - USA

AB Science Management and Scientific Committee

Alain MOUSSY, MBA
Co-founder and Chief Executive Officer.

Laurent GUY, MBA
Chief Financial Officer

Oliver HERMINE, MD, PhD
Chief Scientific Officer and Caiman of Scientific Committee

Masitinib profile

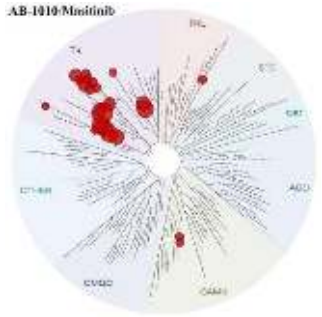
Masitinib is a selective kinase inhibitor that targets mast cells and macrophages/microglia. It is orally administered.

- **Masitinib targets mast cells**
  - Masitinib is a potent and selective inhibitor of mast cells, through the inhibition of c-Kit, 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
Microglia	MCSFR-1	90	0.0076

Masitinib



Notes

1 Dubreuil 2009, PLoSONE.4(9):e7258; AB Science

2 Davis 2011, Nat Biotechnol; 29(11):1046

Scientific Rationale

Masitinib is a *first in class* drug in asthma, selectively targeting mast cells.

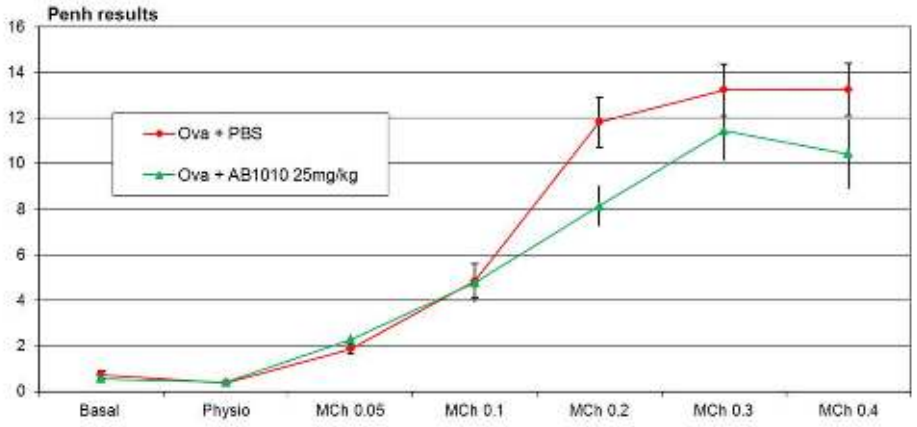
- **Mast cells are involved in allergic and anaphylactic reactions.**
- **Mast cells are involved in inflammatory diseases** [1]**.**
  - Mast cells are activated by triggers leading to selective release of pro-inflammatory mediators
- **Mast cells play an important role not only in immediate hypersensitivity and late phase inflammation but also in tissue remodeling of the airways** [2]**.**
  - Mediators such as tryptase and cytokines from MCs can modulate Airway Smooth Muscle (ASM) cell function.
  - Infiltration of ASM by mast cells (MCs) is associated with the disordered airway function.
  - Increase in Airway Smooth Muscle (ASM) mass is recognized as one of the most important factors related to AHR and to the severity of asthma.
  - Persistent airway hyper-responsiveness (AHR) is associated with airway remodeling.
  - MCs were found to contribute to the development of multiple features of chronic asthma in MC-deficient mice.
- **Mast cells play a key role in the development of late airway hyper-responsiveness (AHR) also through liberation of TNF-alpha** [3]**.**

[1] Theoharides TC et al. The critical role of mast cells in allergy and inflammation. Ann N Y Acad Sci. 2006 1088:78-99.
[2] Okayama Y et al. Role of mast cells in airway remodeling. Curr Opin Immunol. 2007 19(6):687-93
[3] Kim YS et al. Eur J Immunol. 2007 37(4):1107-15

Scientific Rationale

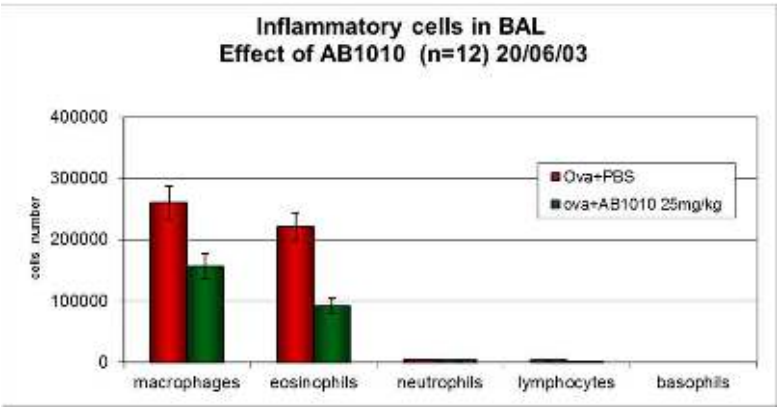
Masitinib activity has been established in asthma mouse model.

Effect of masitinib on the bronchoconstriction measured by Penh in AHR



Masitinib induces in asthma mouse model a significant decrease of airway hyper-responsiveness

Effect of masitinib on the number inflammatory cells measured by eosinophils in BAL of mice



Masitinib induces in asthma mouse model a significant decrease of eosinophils recruitment

Effect of treatment with AB1010 at 25mg/Kg by gavage 1 time per day for a period of 5 days on ovalbumin-sensitized mice (n=11)
The sensitisation of mice with ovalbumin (50µg) by intraperitonal injection on days 1 and 7 followed by intranasal challenges with ovalbumin (10µg) every day from days 18 to 21 induced the 2 major components of the asthmatic airways an allergic inflammation with recruitment of eosinophils and the airway hyperresponsiveness. To reduce the asthma symptoms, the AB1010 treatment started on days 17 to 21.On day 22, airway hyperresponsiveness (AHR) was measured by the enhanced pause (Penh) in the whole body plethysmograph, which is a widely used measurement for AHR. The bronchoconstrictive response was evaluated as the response to a concentration-dependent methacholine aerosol exposure. The infiltration of inflammatory cells has been assessed by histological determination in the bronchoalveolar lavage fluid (BAL).

Clinical Development

The development program in asthma is comprised of one proof of concept study, one positive phase 3 study is severe asthma uncontrolled by oral corticosteroids (OCS), and one on-going phase 3 study is severe asthma uncontrolled by inhaled corticosteroids (ICS).

Phase	Study code	Design	Population	Primary endpoint	Patient target	IDMC recommendation	Study status	Related publications
2a	AB04026 (NCT00842270)	Double-blind, placebo-controlled, parallel-group study	Patients with severe corticosteroid dependent asthma	Change from baseline in corticosteroids doses, after 4 months of treatment	44	NA	Study completed	Humbert M, Chanez P, 2009
3	AB07015 (NCT01449162)	Prospective, double-blind, placebo-controlled, 2-parallel groups study	Patients with severe asthma **uncontrolled with oral corticosteroids (OCS)**	Severe Asthma exacerbation rate adjusted on the available person-time (time to end of treatment)	420	Continuation of the study without resampling option (based on interim analysis and safety data)	Study completed	-
3	AB14001 (NCT03771040)	Prospective, double-blind, placebo-controlled, 2-parallel groups study	Patients with severe asthma uncontrolled with **high dose of inhaled corticosteroids (ICS) and with elevated eosinophil levels**	Severe Asthma exacerbation rate adjusted on the available person-time (time to end of treatment)	347	Continuation of the study (based on safety data)	Recruitment completed	-

Clinical Development

The proof of concept has been validated through a corticosteroid weaning clinical study in patients with severe asthma uncontrolled with oral corticosteroids.

- **Reduction in asthma exacerbation rate.**
  - -38% in the ITT population.
  - -70% in patients with baseline daily prednisone >15 mg.
- **Patients could be weaned from oral corticosteroids (OCS).**
  - OCS was decreased between Week 4 and Week 16.
  - 32% treated patients with baseline daily prednisone >15 mg weaned with masitinib, versus 0% in placebo.
- **The overall safety was acceptable.**
- **The study achieved its objectives with a limited sample population (n=44), warranting further evaluation of masitinib in asthma.**

Allergy. 2009 Aug;64(8):1194-201. Masitinib, a c-kit/PDGF receptor tyrosine kinase inhibitor, improves disease control in severe corticosteroid-dependent asthmatics. Humbert M, Chanez P.

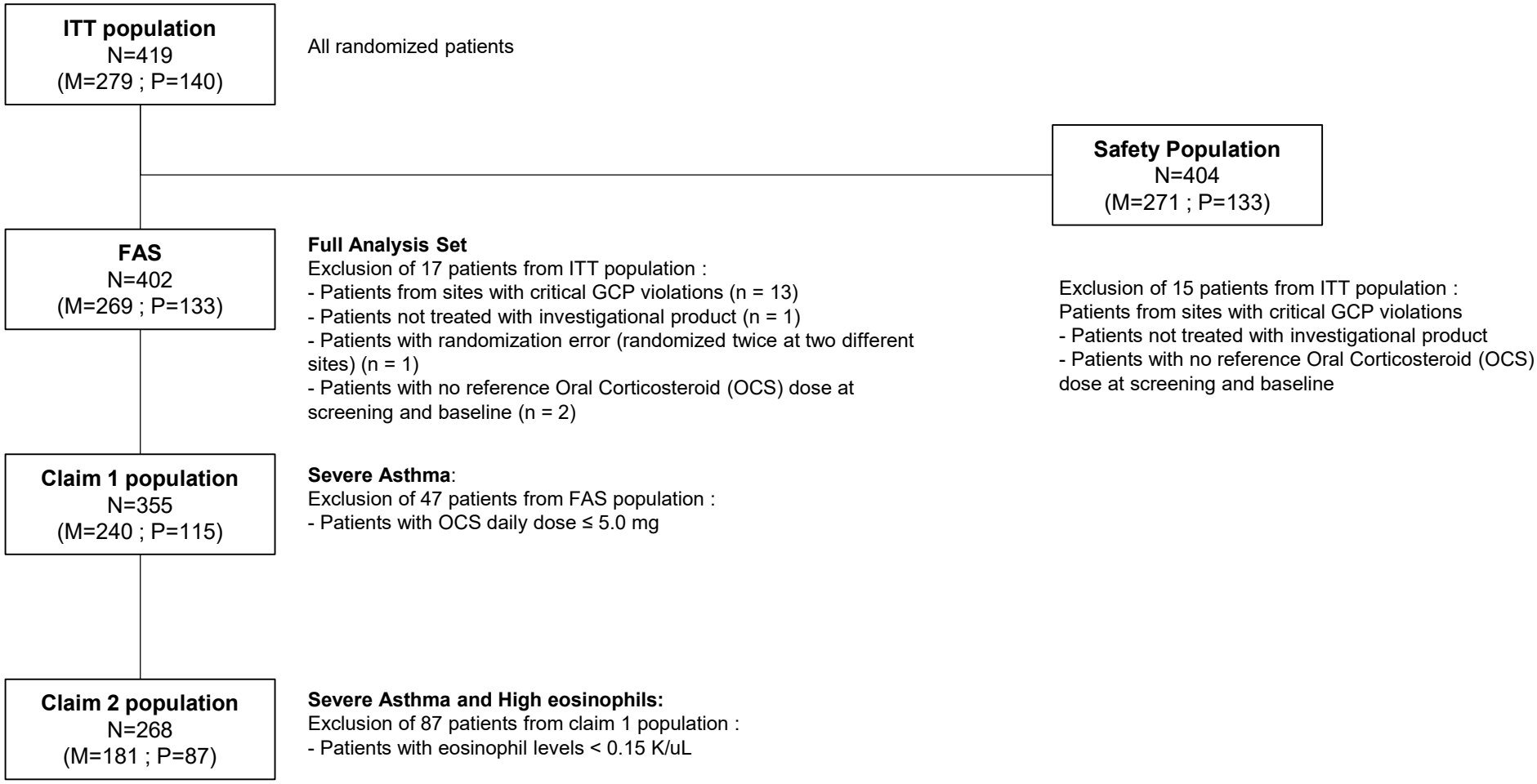
Phase 2/3 study - Design

Study AB07015 evaluated masitinib 6.0 mg/kg/day in patients treated with severe asthma uncontrolled by OCS.

- **Double blind, placebo controlled, randomized 2:1**
- **Main Inclusion Criteria**
  - Oral corticosteroids (OCS) dose ≥ 7.5 mg daily for at least 3 months prior to screening visit.
  - Patient with history of severe asthma ≥ 1 year.
    - baseline FEV1 ≥35 to <80% of the predicted normal value.
    - at least 2 asthma exacerbations within one year prior to screening visit.
  - Both high (≥ 150K/uL) and low (<150K/uL) eosinophils.
- **Multicenters study**
  - EU countries: Czech Republic, France, Germany, Greece, Hungary, Poland, Romania; Slovakia, Spain
  - Non EU countries: Algeria, Argentina, Bulgaria, India, South Africa, Taiwan, Thailand, Tunisia, Ukraine
- **Primary analysis:** Study powered to detect 33% reduction on severe asthma exacerbation in severe asthma population (Claim 1)
- **Primary endpoint**
  - Number of severe asthma exacerbations divided by the time under treatment for the overall protocol period.
  - 0verall protocol period = main protocol period (from baseline to week 36 time point) + extension period (after the week 36, patients could continue treatment in their original treatment arm without unblinding).
  - Severe asthma exacerbation rate defined as asthma worsening that requires an increase from stable maintenance dose of corticosteroids for at least three days and /or hospitalization because of Asthma.
- **Secondary endpoints:**
  - Severe and Moderate asthma exacerbations. Moderate exacerbation defined as asthma deterioration in symptoms, increase in rescue medication use, lasting for 2 or more days and requiring a change in asthma treatment.
  - Quality of life : Asthma Control Questionnaire (ACQ), Use of rescue medication for asthma.
  - Respiratory functions : Forced Expiratory Volume (FEV1), Forced Vital Capacity (FVC).

Phase 2/3 study – Disposition of patients

The Primary analysis was pre-specified in the claim 1 (severe asthma population). A sequential analysis was pre-specified for the claim 2 (severe asthma and high eosinophils). ITT and FAS population were analyzed for sensitivity.



Phase 2/3 study - Efficacy

The pre-specified primary analysis in the severe asthma population (claim 1) demonstrated a statistically significant reduction in severe asthma exacerbations.

AB07015 - Severe Exacerbation Rate – Claim 1 (Severe Asthma)

N	Average Exposure (Months)		Yearly Exacerbation Rate		Estimate adjusted with covariates	Reduction in Severe Exacerbation	95% CI	p-Value
	Masitinib	Placebo	Masitinib	Placebo				
355 (M=240 ; P=115)	**13.7**	**13.8**	**0.34**	**0.48**	**0.65**	**35%**	**(0.47, 0.90)**	**0.0103**

- **Primary analysis is positive and detected a 35% statistically significant difference in severe exacerbation rate between masitinib and placebo.**
- **Duration of exposure was well balanced between the treatment arms.**

Phase 2/3 study - Efficacy

The sensitivity analyses in ITT and FAS populations were also statistically significant, indicating that the results are consistent and robust.

AB07015 - Severe Exacerbation Rate – Sensitivity analyses of population

N	Average Exposure (Months)		Yearly Exacerbation Rate		Estimate adjusted with covariates	Reduction in Severe Exacerbation	95% CI	p-Value
	Masitinib	Placebo	Masitinib	Placebo				
Full Analysis Set (FAS)								
402 (M=269 ; P=133)	13.2	13.1	0.34	0.45	0.67	33%	(0.49, 0.92)	0.0145
Intent To Treat (ITT)								
419 (M=181 ; P=87)	13.1	12.8	0.34	0.44	0.67	33%	(0.49, 0.93)	0.0156

- **There was not impact of patient with daily OCS intake <7.5 mg.**

Phase 2/3 study - Efficacy

There was a center effect, with greater efficacy in the EU countries (**-51% reduction** in severe asthma exacerbations, **p=0.0038**).

AB07015 - Severe Exacerbation Rate – Sensitivity analyses in EU countries

N	Average Exposure (Months)		Yearly Exacerbation Rate		Estimate adjusted with covariates	Reduction in Severe Exacerbation	95% CI	p-Value
	Masitinib	Placebo	Masitinib	Placebo				
Claim 1 (Severe Asthma)								
123 (M=83 ; P=40)	**13.2**	**11.4**	**0.48**	**0.90**	**0.49**	**51%**	**(0.30, 0.79)**	**0.0038**
Full Analysis Set (FAS)								
148 (M=98 ; P=50)	13.0	10.7	0.47	0.81	0.51	49%	(0.32, 0.81)	0.0044

- **In EU countries, the reduction in severe asthma exacerbations was greater than 50% and comparable to the reduction observe with biologic drugs**
- **In EU countries, yearly exacerbation rate in the placebo arm was more in line with the expectations (0.90 as compared with 0.48 when considering all countries),**
- **Suggesting that Non EU countries enrolled a different and less severe population, with disease controlled by rigorous follow-up in the context of the clinical trial.**

Phase 2/3 study - Efficacy

The pre-specified analysis in the severe asthma with high eosinophils (≥150K/uL) population (claim 2) also demonstrated a statistically significant reduction in severe asthma exacerbations.

AB07015 - Severe Exacerbation Rate – Claim 2 (Severe Asthma with high eosinophils ≥ 150K/uL)

N	Average Exposure (Months)		Yearly Exacerbation Rate		Estimate adjusted with covariates	Reduction in Severe Exacerbation	95% CI	p-Value
	Masitinib	Placebo	Masitinib	Placebo				
268 (M=181 ; P=87)	13.2	13.4	0.34	0.51	0.62	38%	(0.42, 0.91)	0.0156

- **In the claim 2 population, the study detected a 38% statistically significant difference in severe exacerbation rate between masitinib and placebo.**
- **Duration of exposure was well balanced between the treatment arms.**

Phase 2/3 study - Safety

The study demonstrated an acceptable safety profile for the targeted population.

AB07015 - Overall Summary of Adverse Events (AEs) - Safety Population

	Masitinib (N = 271) n (%)	Placebo (N = 133) n (%) m
At least one AE	226 (83.4)	109 (82.0)
At least one serious AE (non-fatal)*	48 (17.7)	22 (16.5)
At least one severe AE	130 (48.0)	61 (45.9)

- **The occurrence of adverse events (AEs) and serious adverse events (SAEs) was comparable between masitinib and placebo.**

** Four fatal SAEs were reported(1.1% with masitinib and 0.8% with placebo), all reviewed by the IDMC and non related to treatment.*

Phase 2/3 study – Discussion

Study AB07015 demonstrated efficacy in a difficult to treat population, with 100% of patients receiving high dose OCS maintenance therapy and not restricted to high eosinophils.

- **Enrolment of a different population from other asthma trials**
  - Oral corticosteroids (OCS) without weaning:
    - Patient remained on OCS treatment.
    - This is not a OCS weaning study with decrease of OCS at the start of the study.
  - Eosinophils level
    - Study included both high (≥150K/uL) and low (<150K/uL) eosinophils.
    - Definition of thresholds for high eosinophils (≥150K/uL) is low compared to other studies (≥300K/uL).
- **Reduction in severe asthma exacerbation rate**
  - -35% overall and -51% in EU countries, without restriction to high eosinophils
  - Evaluated over a long period of time of around 13.7 months, well balanced between treatment arms.
- **There was a center effect**
  - In EU countries, comparable efficacy (-51% exacerbations) as other studies with biologics
  - In EU countries, exacerbation rate in placebo arm was in line with the expectations (0.90)
  - In all countries, exacerbation rate in placebo arm was low (0.48), when considering all countries, suggesting that Non-EU countries enrolled a different and less severe population, with disease controlled by rigorous follow-up in the context of the clinical trial.

Lavinia DAVIDESCU, MD, PhD

❖ **About Lavinia Davidescu**

- Assistant Professor at the Faculty of Medicine and Pharmacy, University of Oradea.
- President of Rare Disease Section of Romanian Pneumology Society, member in the boarding Committee of the Romanian Society of Pneumology.

❖ **Role in masitinib program**

- Coordinating investigator of masitinib study AB07015 in severe asthma uncontrolled with oral corticosteroids.
- Willing to take an active role in masitinib program in severe asthma.

Lavinia Davidescu

Masitinib generated positive results with a favorable safety profile.

- **Masitinib is *first in class* based on a new mechanism of action**
  - First positive large phase 2/3 with a tyrosine kinase inhibitor
  - First positive large phase 2/3 with mast cells as a therapeutic target
- **Efficacy is demonstrated in the general population of asthma population**
  - Not restricted to allergic asthma (High IgE)
  - Not restricted to high eosinophils
- **Advantageous mode of administration**
  - Orally administered
  - Likely to have better compliance
- **Favorable safety profile**
  - No anaphylaxis
  - No opportunistic infection
- **This study warrants confirmatory study**

Pascal CHANEZ, MD, PhD

About Pascal Chanez

- Professor of Respiratory Medicine at the APHM and Aix Marseille University at Marseille France.
- Coordinator of a research group at INSERM-CNRS on the role of bronchial epithelium in inflammation and environmental aggression in severe bronchial diseases.
- Head of a clinical research group investigating new innovative treatments for severe asthma and COPD.
- Author or co-author of more than 300 peer reviewed articles, reviews and monographs.
- Editor of the European Respiratory Journal, of the Journal of allergy and clinical Immunology.
- Clinical and research interests are devoted to a better understanding of the mechanisms of severe asthma and COPD with a special focus on combining clinical and biological findings to identify new specific biomarkers and therapies.

Role in masitinib program

- Lead investigator with M. Humbert of proof of concept study with masitinib (published in *Allergy* journal).
- Investigator in AB07105 study.
- Willing to take an active role for future steps of masitinib program in severe asthma.

Pascal Chanez

The clinical data are encouraging and we can be optimistic about the future development of masitinib in asthma.

- **The clinical data are supported by a strong and validated mechanism of action**
  - Activation of mucosal mast cells releases broncho constrictor mediators and induce airway hyper responsiveness by interaction with smooth muscle.
  - The airway remodeling leads to permanent alterations in the airway architecture.
- **The clinical data are encouraging and one can be optimistic about the future development of masitinib in asthma**
  - Significant reduction in asthma exacerbations in difficult to treat severe asthma patients that required oral corticosteroid maintenance treatment.
  - In the EU, the reduction of asthma exacerbation and the placebo effect were comparable to other studies with biologics
  - The reduction of asthma exacerbation was sustained over a long period of time (≥13 months).
  - The safety profile is good based on available data.
- **There is a positive signal and positioning for masitinib in a landscape that as changed dramatically in the past years**
  - Masitinib is the first drug targeting mast cells and has a distinctive and relevant mechanism of action.
  - Masitinib can be positioned in patients insufficiently controlled by biologics, in single agent or in combination

Elliot ISRAEL, MD

- **About Elliot Israel**
  - Director of clinical research in the Pulmonary and Critical Care Medicine Division and an associate physician at Brigham and Women's Hospital (BWH).
  - Professor of medicine at Harvard Medical School.
  - Research interests include therapeutic interventions to alter asthmatic airway hyperactivity and the role of arachidonic acid metabolites in airway narrowing.
  - Author of over 200 peer-reviewed publications
  - Currently leads a team researching novel asthma treatments funded by the National Institutes of Health.
  - Recipient of the HMS Daniel D. Federman Outstanding Clinical Educator Award and named one of "Boston's best in Pulmonary Medicine" by Boston Magazine.

- **Role in masitinib program**
  - Willing to take an active role in masitinib program in severe asthma.

Elliot Israel

The mechanism of action of masitinib is highly relevant for severe asthma and masitinib could potentially address the unmet needs that remains in asthma despite the recent major improvements in this disease.

- **There is still a need for alternative therapies in asthma despite the major progress achieved in the recent years**
  - None of the drugs prevented most exacerbations requiring systemic corticosteroids.
  - 33% to 50% of patients are in failure to anti-interleukin therapies.
  - Lack of long-term safety and effectiveness data at this time.
  - Eosinophils are part of the immune response to parasitic infections. It is unknown if the therapies that decrease eosinophil counts will affect patients' ability to fight such infections.

- **C-KIT dependent processes and mast cells contribute to the pathobiologic basis of severe asthma**
  - Masitinib proved to blunts airway inflammation and improves associated lung mechanics in a feline model of chronic allergic asthma (*Int Arch Allergy Immunol*. 2012;158(4):369-74).
  - In patients with severe asthma, c-kit inhibition proved to decrease airway hyperresponsiveness, mast-cell counts, and tryptase release (*N Engl J Med*. 2017 May 18;376(20):1911-1920).

- **Masitinib demonstrated long-term efficacy in severe asthma uncontrolled by OCS and with Eosinophils ≤300K/uL**

- **Masitinib can be position**
  - In addition to positioning proposed by Pascal Chanez, or
  - In low eosinophils, defined as <150K/uL or ≤300K/uL, or
  - In the "*vulnerable zone*" of anti-interleukin therapies, i.e. severe asthma uncontrolled by high dose inhaled corticosteroids and with Eosinophils ≥150K/uL and ≤300K/uL.

Key differentiating factors

Masitinib has a unique positioning in severe asthma, in terms of administration, mechanism, targeted population, use of OCS and eosinophil count in population studied.

		Key Differentiating factors			
		Administration	**Mechanism of action**	**Severe asthma phenotype**	**%OCS use in trial pop. (note *)**
	Masitinib	**Oral**	**Mast-cells**	**All**	**100%**
FDA approved therapies	**Omalizumab** (**Xolair**, Genentech)	Subcutaneous	Anti-IgE	Allergic	0% to 22%
	Mepolizumab (**Nucala**, GSK)	Subcutaneous	Anti-IL-5	High eosinophils	24% to 31%
	Reslizumab (**Cinqair**, Teva)	Intravenous infusion	Anti-IL-5	High eosinophils	17%
	Benralizumab (**Fasenra**, AstraZeneca)	Subcutaneous	Anti-IL-5Rα	High eosinophils	-
	Dupilumab (**Dupixent**, Sanofi/Regeneron)	Subcutaneous self-administered	Anti-IL-4Rα	High eosinophils	0%

Note *: In phase 3 studies excluding the Oral Corticosteroids (OCS) targeted weaning studies.

Source : For Masitinib, AB Science. For other drugs, ©Institute for Clinical and Economic Review, 2018. Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks

Positioning in severe asthma

Masitinib has several strategic positioning opportunities in severe asthma, complementary to biologics strategies.

Options	Masitinib	Eosinophil Count (cells/µL)	Positioning
Severe asthma insufficiently controlled by biologics	**In single agent**	**>300**	After biologics
	in combination with biologics	**>300**	After biologics
Severe asthma in the "Vulnerable" zone of biologics	**In single agent**	**≥150 and ≤300**	First Line
Severe asthma not in type 2 inflammatory phenotypes	**In single agent**	**≤300**	First Line
	In single agent	**≤150**	First Line

Intellectual Property

Masitinib IP rights are secured up to 2032 in severe asthma uncontrolled by OCS.

Protection	Item	Duration of protection	Status
Phase 2/3 'Method of use' patents	Asthma (severe)	Until 2032	Delivered

Q&A