AB SCIENCE

Emerging pharmaceutical company
in targeted therapies

MASITINIB IN SEVERE ASTHMA UNCONTROLLED BY ORAL CORTICOSTEROID

2 DECEMBER 2014

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Definition of Severe Asthma Uncontrolled by Oral Corticosteroïd

Masitinib data in Severe Asthma Uncontrolled by Oral Corticosteroïd

Questions

ASTHMA POPULATION

Asthma ranges from intermittent disease with no impact on normal activities to severe disease with permanent symptoms and extreme alteration of normal activities.

GINA Classification of Asthma severity

	Intermittent	Persistent			
	Step 1	Mild Step 2	Moderate Step 3	Step 4	**Severe Step 5**
Symptoms	≤ 2 days/week	> 2 days/week not daily	Daily	Daily	**Throughout the day**
Impact on normal activity	None	Minor	Some	Some	**Extreme**
Treatment	SABA	Low dose inhaled corticosteroid	Low dose inhaled corticosteroid + LABA	Medium/High dose inhaled corticosteroid + LABA	**High dose inhaled corticosteroid + LABA + oral corticosteroid** **Consider Omalizumab for patients having allergic asthma**
Distribution	80%				**20%**

SABA: short-acting beta2-agonist ; LABA: long-acting beta2-agonist
GINA : Global Initiative for Asthma

Not yet under development
Asthma uncontrolled by medium or high dose inhaled corticosteroid

Current Study AB07015
Severe asthma uncontrolled with oral corticosteroid

http://www.nhlbi.nih.gov/files/docs/guidelines/asthgdln.pdf

POPULATIONS WITH SEVERE ASTHMA UNCONTROLLED WITH OCS AND ICS

Population with severe asthma uncontrolled by oral corticosteroid is around 70,000 in the USA and in the EU, while the population with asthma uncontrolled by high-dose inhaled corticosteroids is 20 times larger, estimated at 1,5000,000 patients.

	Adult patient with asthma uncontrolled by high-dose inhaled corticosteroid	Adults with severe asthma uncontrolled by Oral Corticosteroid
Asthma Prevalence :	10% of population [1] (≈ 70,000,000)	10% of adult population (≈ 70,000,000)
Target population	≈ 2.2% of asthma patients [2] (20% severe x 20% uncontrolled x 55% confirmed diagnosis)	> 1/1000 asthmatic patients[3]
Potential Patients in EU/USA	**≈ 1,500,000** (Prevalence x target population less adults with severe asthma uncontrolled by OCS)	**≈ 70,000**

1. Prevalence ranges from 7% (France, Germany) to 11% (USA) and 18% (UK). Average 10%. Rising incidence
2. 20% of asthma patients have asthma,requiring high dose inhaled or oral corticosteroids
   20% of these asthma patients are uncontrolled
   Only 55% of patients initially suspected of having asthma uncontrolled by high dose ICS or OCS receive a confirmed diagnosis
3. Absolute resistance to corticosteroids is very rare, with a prevalence of less than 1 per 1000 asthmatics

1. Respir Med. 2006 Jul;100(7):1139-51. Epub 2006 May 18.
2. J Investig Allergol Clin Immunol 2012; Vol. 22(7): 460-475
3. Barnes PJ, Adcock IM. Steroid resistance in asthma. QJM. 1995;88: 455-68

HIGH UNMET MEDICAL NEED

Uncontrolled severe asthma is a condition with high unmet medical need.

- **Severe asthma uncontrolled by oral corticosteroids (OCS)**
  - No drug registered in this population only
  - Huge impact on quality of life
    - Major reduction in lung function (between 35% and 80% of predicted normal measured by forced expiratory volume-FEV_1)
    - Restrictions on activities of daily living, work absenteeism
    - Nighttime awakening several times a week
    - Frequent exacerbations and greater risk of life-threatening asthma exacerbations
- **Severe asthma uncontrolled by high dose inhaled corticosteroids (ICS)**
  - Impaired quality of life
  - Omalizymab (Xolair) targets only allergic severe asthma uncontrolled by high-dose ICS or OCS, which account for 50% asthmatic patients in these two categories[2]
  - There are resistance or failure to Xolair, which are also candidates to masitinib

1. Respir Med. 2006 Jul;100(7):1139-51. Epub 2006 May 18.
2. Eur Respir J, 22 (2003), pp. 470–477

Definition of Uncontrolled Severe Asthma

Masitinib data in asthma

Questions

STUDY RATIONALE

The involvement of mast cells in asthma is well established in key publications.

- **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 remodelling of the airways [2]**
  - Mediators such as tryptase and cytokines from MCs can modulate 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 remodelling.
  - 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 remodelling. Curr Opin Immunol. 2007 19(6):687-93
[3] Kim YS et al. Eur J Immunol. 2007 37(4):1107-15

STUDY RATIONALE

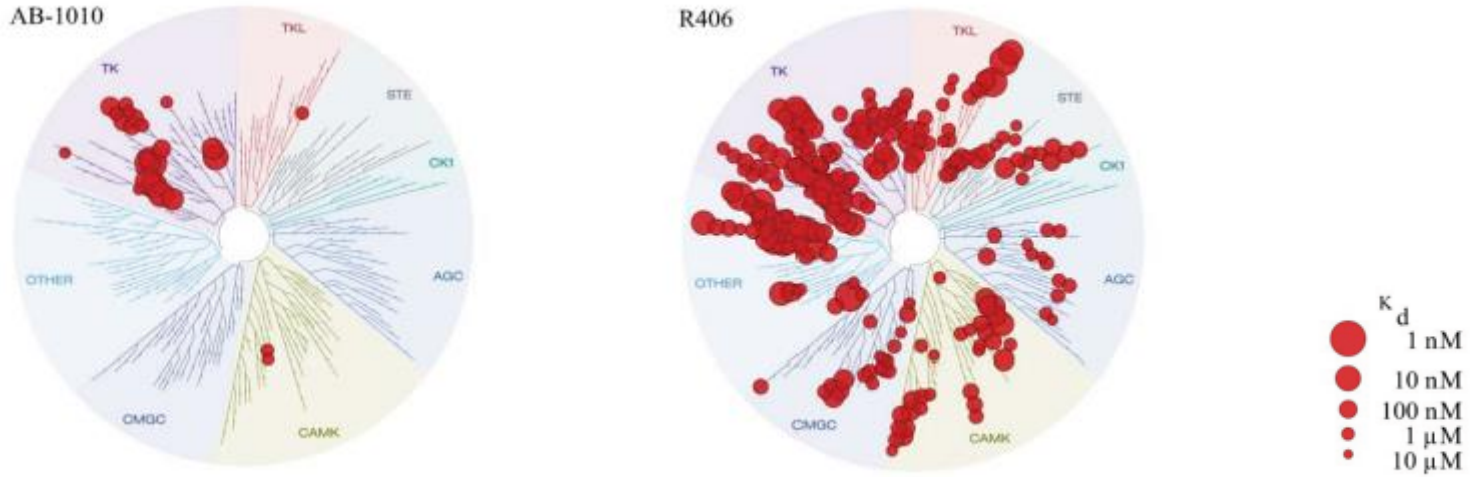
Masitinib has been designed to be a selective blocker of mast cells (through c-kit, Lyn and Fyn tyrosine kinases) and is well profiled for asthma.

Masitinib potency

Target / IC50 [µM]	Enzymatic Assay
c-KIT Wild type	0.02
FYN	0.24
LYN	0.225

Masitinib selectivity : masitinib is among the most selective TKIs [Davis et al, 2011]

Kinome interaction maps for masitinib (AB1010) versus Fostamatinib (R406)



Mast Cell Inhibitor **Published as SYK inhibitor**

1. PLoS One. 2009 Sep 30;4(9):e7258. doi: 10.1371/journal.pone.0007258.
2. Nat Biotechnol. 2011 Oct 30;29(11):1046-51. doi: 10.1038/nbt.1990.

CLINICAL DATA

Proof of concept has been established with masitinib in uncontrolled severe asthma, in particular in patients treated with high dose of oral corticosteroid.

Efficacy results in uncontrolled severe asthma

(Phase 2 ; n=44 patients, with 25 patients taking daily >15 mg OCS)

Change of dose of OCS (in patients > 15mg of OCS at baseline)

	Masitinib (N=19)	Placebo (N=6)
Absolute change between W4 and W16		
Mean ± Std	-14 ± 14	-7 ± 16
Median	-15	-8
Min ; Max	-40 ; 20	-25 ; 20
% change between W4 and W16		
Mean ± Std	-52 ± 53	-28 ± 47
Median	-65	-38
Min ; Max	-100 ; 100	-83 ; 50
Patients weaned at W16	6 (31.6 %)	0 (0.0 %)

Exacerbation rate (in patients > 15mg of OCS at baseline)

	Masitinib (N=19)	Placebo (N=6)
Exacerbation rate per month	0.23	0.37
% reduction	-37.8%	
Nb exacerbation per patient	0.6	0.9

Control of symptoms (in patients > 15mg of OCS at baseline)

	Masitinib (N=19)	Placebo (N=6)
Improvement from baseline in Asthma Control Questionnaire		
6 item ACQ	+35%	+6%
7 item ACQ	+42%	+8%

OCS : Oral corticosteroids

PREVIOUS CLINICAL DATA

These phase 2 results have been published in the Journal of Allergy.

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, de Blay F, Garcia G, Prud'homme A, Leroyer C, Magnan A, Tunon-de-Lara JM, Pison C, Aubier M, Charpin D, Vachier I, Purohit A, Gineste P, Bader T, Moussy A, Hermine O, Chanez P.

Université Paris-Sud 11, Service de Pneumologie et Réanimation Respiratoire, Hôpital Antoine-Béclère, Assistance Publique des Hôpitaux de Paris, 157 rue de la Porte de Trivaux, Clamart 92140, France.

BACKGROUND: Masitinib is a tyrosine kinase inhibitor targeting stem cell factor receptor (c-kit) and platelet-derived growth factor (PDGF) receptor, which are expressed on several cell types including mast cells and bronchial structural cells, respectively. We hypothesized that c-kit and PDGF receptor inhibition may decrease bronchial inflammation and interfere with airway remodeling, which are crucial features of severe asthma. OBJECTIVES: The primary endpoint was the percent change from baseline in oral corticosteroids after 16 weeks of treatment. Change in asthma control (asthma control questionnaire), exacerbation rate, pulmonary function tests, rescue medication requirement and safety were secondary endpoints. METHODS: A 16-week randomized, dose-ranging (3, 4.5, and 6 mg/kg/day), placebo-controlled study was undertaken in 44 patients with severe corticosteroid-dependent asthma who remained poorly controlled despite optimal asthma management. RESULTS: At 16 weeks of treatment, a comparable reduction in oral corticosteroids was achieved with masitinib and placebo (median reduction of -78% and -57% in the masitinib and placebo arms, respectively). Despite this similar reduction, the Asthma Control Questionnaire score was significantly better in the masitinib arm as compared to placebo with a reduction by 0.99 unit at week 16 ($P < 0.001$) vs 0.43 unit in the placebo arm. Masitinib therapy was associated with more transient skin rash and edema. CONCLUSIONS: Masitinib, a c-kit and PDGF-receptor tyrosine kinase inhibitor, may represent an innovative avenue of treatment in corticosteroid-dependent asthma. These preliminary results warrant further long-term clinical studies in severe asthma

PMID: 19614621 [PubMed - in process]

PHASE 3 AB07015 DESIGN IN SEVERE ASTHMA UNCONTROLLED BY OCS

Phase 3 AB07015 design

Study design	▪ Severe Persistent Asthma treated with oral corticosteroids ▪ Blinded ▪ Masitinib 6 mg/kg versus placebo ▪ Randomization 2:1
Selection of patients with severe asthma	▪ oral corticosteroids daily dose ≥ 7.5 mg ▪ Patient with history of severe asthma ≥ 1 year
Primary analysis	▪ Severe asthma exacerbation rate
Recruitment	▪ 340 patients randomised in two groups

PHASE 3 AB07015 UPDATE IN SEVERE ASTHMA UNCONTROLLED BY OCS

Phase 3 study AB07015 passed successfully a futility test, which is a significant milestone because this indication is an unmet medical need.

- **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 the study primary analysis : frequency of severe asthma exacerbation
  - 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
- **Significant milestone**
  - The indication is a high unmet medical need
  - No knowledge of non futile phase 3 in patients with severe asthma uncontrolled with oral corticosteroid allergic and non allergic

NEW DEVELOPMENT – SEVERE ASTHMA UNCONTROLLED WITH HIGH-DOSE ICS

On the basis of the non-futility of study AB0715 in severe asthma uncontrolled by oral corticosteroid, AB Science has decided to initiate a phase 3 in patients with severe asthma uncontrolled by high-dose inhaled corticosteroid.

Masitinib in severe Asthma uncontrolled by high-dose inhaled corticosteroid.

- Phase 3
- Sites identified, already participating to phase 3 in severe asthma uncontrolled by OCS
- Scientific advice obtained in 2014 from EMA
- Initiation planned in 2015
- Fast recruitment expected : Prevalence 20 times higher than for patients in study AB07015 in patients uncontrolled by OCS

ASTHMA POSITIONING

Masitinib has a unique positioning in asthma.

	Masitinib	Dupilumab	Omalizumab (Xolair®)
Target	▪ Mast cells ▪ Upsteam in asthma process	▪ IL-13 and IL-4	▪ IgE
Administration	▪ Oral	▪ Injectable	▪ Injectable
Asthma Label according to GIINA • **Severe asthma Step 5** • **Severe asthma Step 4 high dose ICS** • **Step 4 medium dose ICS**	 ▪ Yes ▪ Yes ▪ No	 ▪ No ▪ Yes ▪ Yes	 ▪ Allergic only (50%) ▪ Allergic only (50%) ▪ No

- Severe asthma Step 5 :
  - Masitinib is the only drug that will provide efficacy data in patients with allergic and non allergic severe asthma uncontrolled with OCS.
  - Masitinib will also address the need of patients with non-allergic severe asthma and unresponsive to Xolair.
- Severe asthma Step 4 high dose ICS :
  - Masitinib will provide efficacy data in patients with allergic and non allergic severe asthma step 4 high dose ICS.
  - Dupilumab has a broaden label in patients uncontrolled by medium or high dose ICS, which is not exclusively severe asthma

NEW DEVELOPMENT - COPD

A development of masitinib is also initiated in COPD with a phase 2.

Masitinib in chronic obstructive pulmonary disease (COPD)

- Phase 2, double-blind, placebo-controlled
- Primary efficacy criteria : Absolute change from baseline (W0) in the 6-minutes walking distance test at Week 24
- Sites identified, already participating to phase 3 in severe asthma uncontrolled by OCS
- Although different, asthma and COPD are two converging diseases[1]
  - Similar structural alterations can develop in both diseases as a consequence of chronic inflammatory tissue injury, especially in the most severe cases.
  - Inflammation and tissue remodeling is present in both diseases
  - COPD with airway remodeling is a severe phenotype and part of the overlap between COPD and asthma
- High unmet medical: only symptomatic treatment available (Spiromax)
- COPD is currently the fifth-leading cause of death worldwide with still-growing prevalence, causing around 400,000 deaths in USA and EU in 2005

1. Kim 2010, Overlap Between Asthma and COPD: Where the Two Diseases Converge. Allergy Asthma Immunol Res. 2010 Oct;2(4):209-14. doi: 10.4168/aair.2010.2.4.209.)

MASITINIB SAFETY DATABASE

The safety database of masitinib is adequate to support registration in severe asthma uncontrolled by oral corticosteroid or high-dose inhaled corticosteroid.

Number of Patients enrolled in masitinib clinical studies

	Total
Asthma*	> 300
Non-oncology indications **	1,500
TOTAL**	**3,000**

* Status upon completion of phase 3 study ; ** current status

Duration of patients exposure to masitinib at registration

	Masitinib	ICH guideline[1]
Overall patient exposure	> 1,500	1,500
Treated for 6 months	> 600	300-600
Treated for 12 months	> 300	100

1. http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4068B1_09_ICH-E1A-Guidelines.pdf

IP PROTECTION

IP rights for masitinib are secured in severe asthma until 2028 and potentially until 2032.

Protection		Duration of protection
Patent on Composition of matter and PTE	▪ Composition of matter has been file and delivered and will be further extended until 2028 through patent tem extension (PTE).	Until 2028
Synthesis process patent	▪ A further protection until 2028 has been achieved through synthesis'process' patent already granted.	Until 2028
Phase 2 patents	▪ Patent filed in February 2012 on treatment of severe persistent asthma with masitinib	Until 2032
Pediatric investigation plan (PIP)	▪ A further 6 months exclusivity can be granted in case on implementation of a PIP, as will be the case for masitinib in severe asthma	6 months exclusivity

Definition of Uncontrolled Severe Asthma

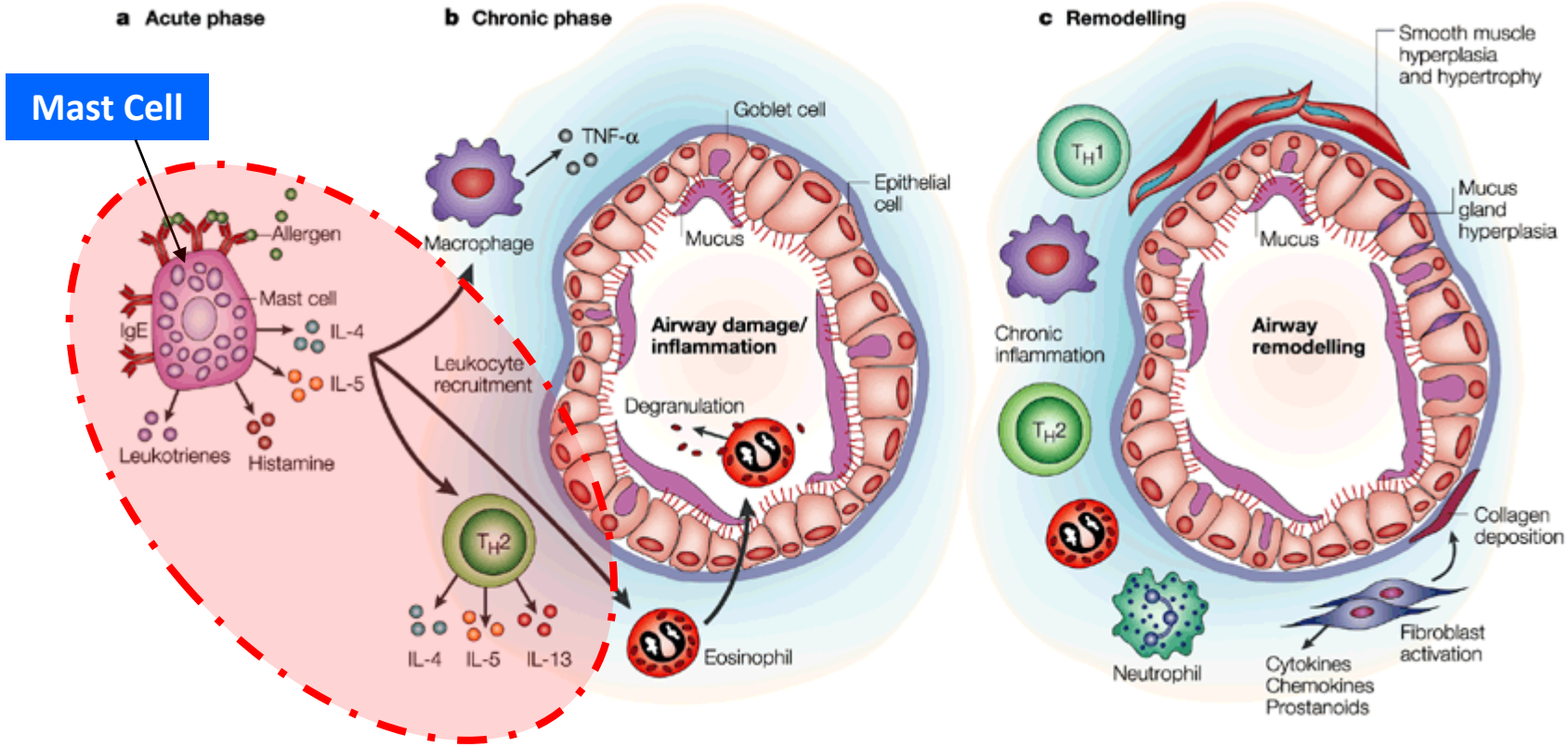
Masitinib data in asthma

Questions

Appendix

ASTHMA – ROLE OF MAST CELLS

Activation of mucosal mast cells releases bronchoconstrictor mediators and induce airway hyper responsiveness by interaction with smooth muscle.



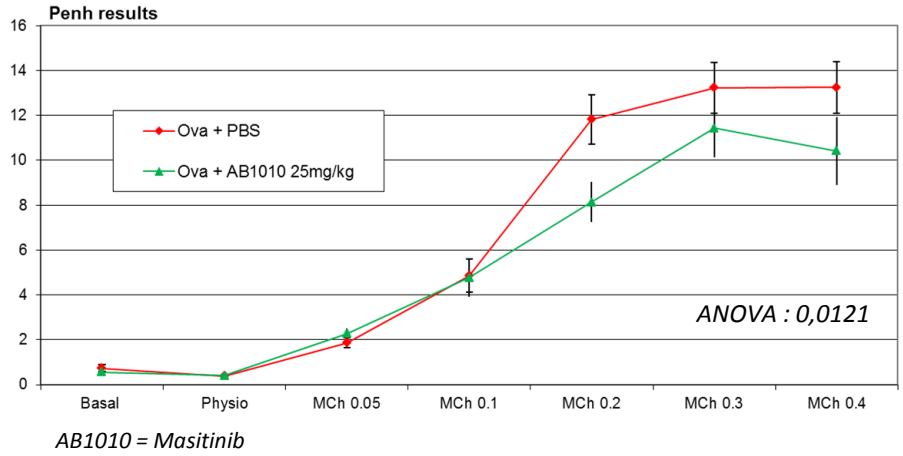
a. Acute phase : Mast cells release pro-inflammatory cytokines and mediators (Histamine, IL-4, IL-5), leading to acute bronchoconstriction and airway obstruction
b. Chronic inflammation : Activation of T helper (T_H) 2 cells and macrophages, and recruitment and degranulation of eosinophils. The changes in the airway cause airflow obstruction and an increase in airway responsiveness.
c. Airway remodelling leading to permanent alterations in the airway architecture

James E. Gern & William W. Busse
Nature Reviews Immunology **2**, 132-138 (February 2002)
doi:10.1038/nri725

ASTHMA - STUDY RATIONALE

Masitinib treatment in an asthma mouse model induce a significant decrease of airway hyper-responsiveness and eosinophils recruitment

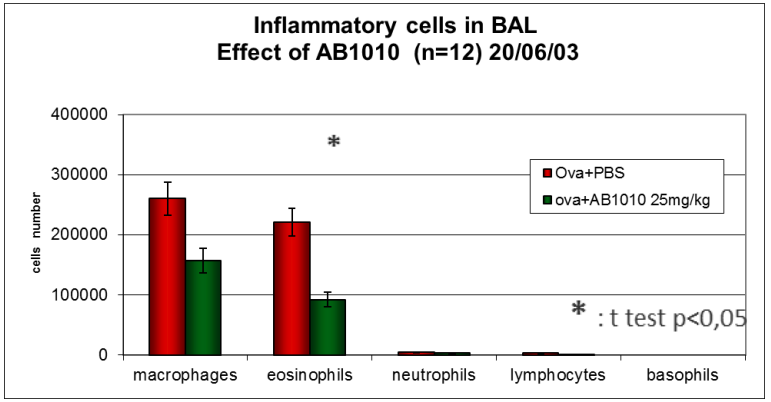
Effect of masitinib on the bronchoconstriction measured by Penh in AHR



AB1010 = Masitinib

***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).