Asthme allergique: vers une meilleure compréhension et une optimisation de la prise en charge

Symposium ALK

ALLER2A

L'allergologue, spécialiste de la tolérance

Lyon le 16/12/2017

Gilles Devouassoux

Service de Pneumologie, Hôpital de la Croix-Rousse
Hospices Civils de Lyon
Faculté de Médecine Lyon Sud Charles Mérieux
&EA 7426

Liens d'intérêt

Consultancy: Novartis Pharma, Astra-Zeneca, GSK, Boehringer Ingelheim, Mundi Pharma, Vivisol, Sanofi, Chiesi, ALK, Teva

Participation to medical meeting: GSK, Astra-Zeneca, Novartis Pharma, Chiesi, MSD, Takeda, AGIR à dom, Orkyn, Mundi Pharma, ALK, Stallergène, Boehringer Ingelheim, Teva

Clinical trial (investigator): GSK, ALK, Novartis Pharma, Boehringer-Ingelheim, Vitalair, AB Science, Amgen, Lilly, Astra-Zeneca, Sanofi, Roche, Teva

Research grants: GSK, Novartis Pharma, MSD, Chiesi, AGIR à dom.

Adults and adolescents (12 years and older)			
Drug	**Daily dose (mcg)**		
	Low	Medium	High
Beclometasone dipropionate (CFC)*	200–500	>500–1000	>1000
Beclometasone dipropionate (HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (HFA)	80–160	>160–320	>320
Fluticasone propionate(DPI)	100–250	>250–500	>500
Fluticasone propionate (HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000

GINA 2016

Diagnosis
Symptom control & risk factors (including lung function)
Inhaler technique & adherence
Patient preference

ASSESS

Asthma medications
Non-pharmacological strategies
Treat modifiable risk factors

ADJUST TREATMENT

REVIEW

Symptoms
Exacerbations
Side-effects
Patient satisfaction
Lung function

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER CHOICE	Low dose ICS		Low dose ICS/LABA*	Med/high ICS/LABA	Refer for add-on treatment e.g. anti-IgE *(Box 3-14)*
Other controller options	*Consider low dose ICS*	*Leukotriene receptor antagonists (LTRA) Low dose theophylline**	*Med/high dose ICS Low dose ICS+LTRA (or + theoph*)*	*High dose ICS+LTRA (or + theoph*)*	*Add low dose OCS*
RELIEVER	As-needed short-acting beta$_2$-agonist (SABA)		As-needed SABA or low dose ICS/formoterol**		

STUDY PROTOCOL | OPEN ACCESS | OPEN PEER REVIEW

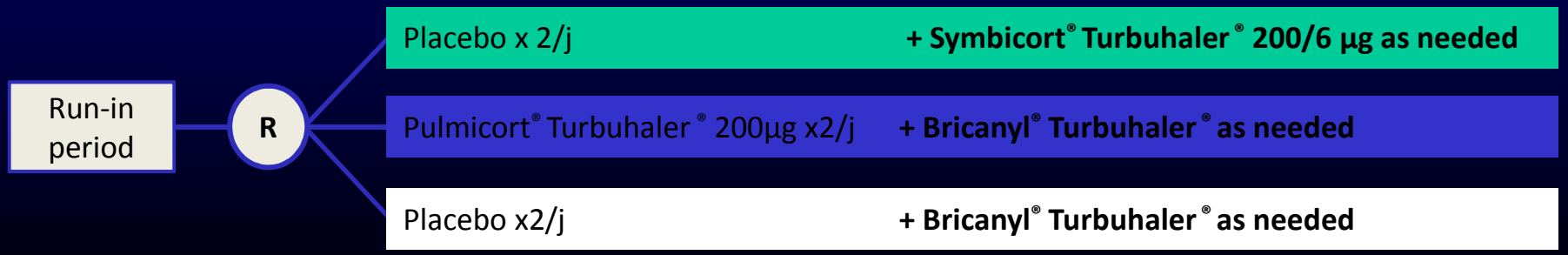
The SYGMA programme of phase 3 trials to evaluate the efficacy and safety of budesonide/formoterol given 'as needed' in mild asthma: study protocols for two randomised controlled trials

Paul M. O'Byrne ✉, J. Mark FitzGerald, Nanshan Zhong, Eric Bateman, Peter J. Barnes, Christina Keen, Gun Almqvist, Kristine Pemberton, Carin Jorup, Stefan Ivanov and Helen K. Reddel

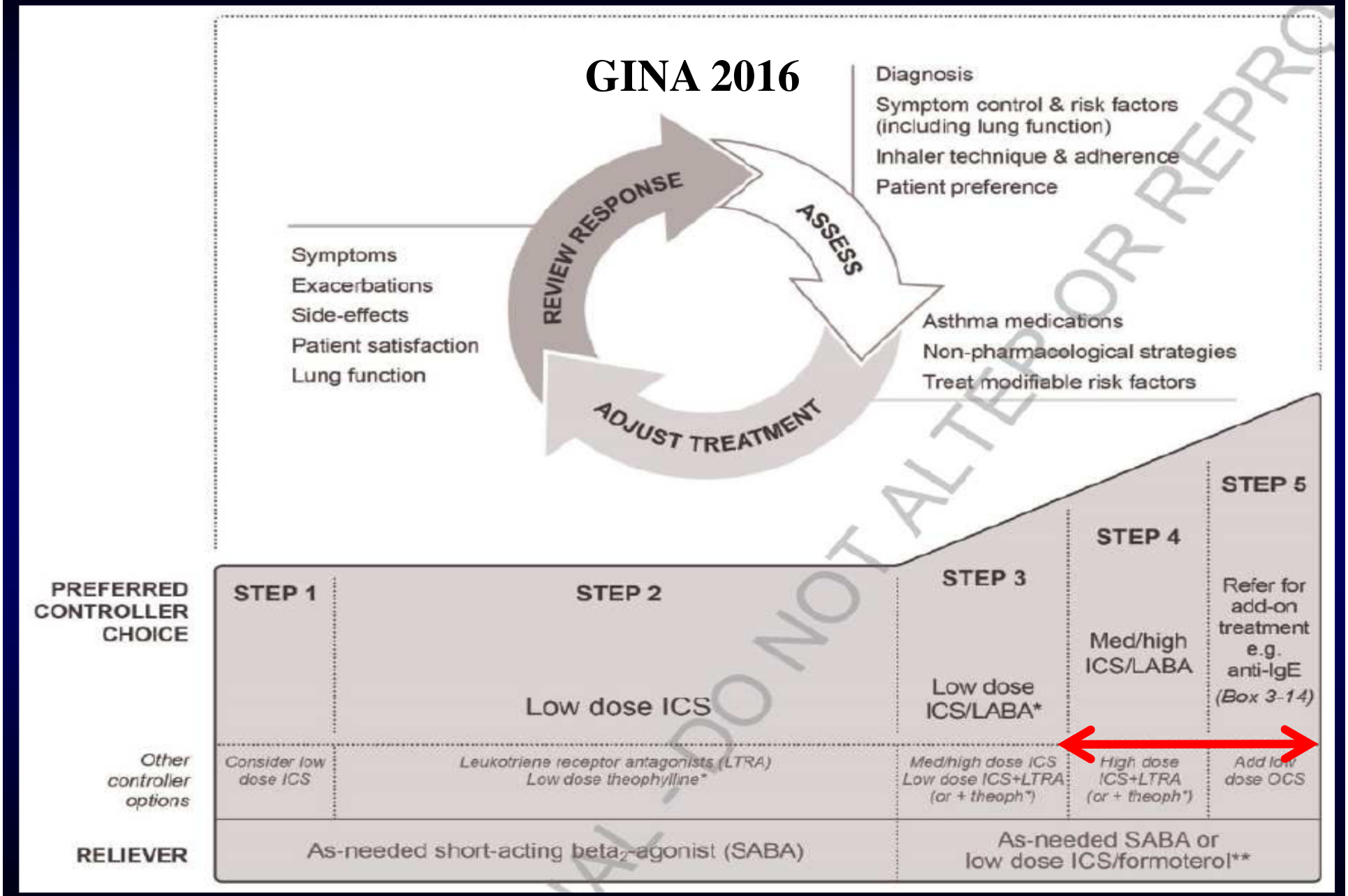
Trials 2017 18:12 | https://doi.org/10.1186/s13063-016-1731-4

Received: 21 March 2016 | **Accepted:** 28 November 2016 | **Published:** 10 January 2017

3,750 patients aged ≥12 years with asthma in need of low-dose ICS
Carried out in approx. 18 countries



GINA 2016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As-needed SABA or low dose ICS/formoterol**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma

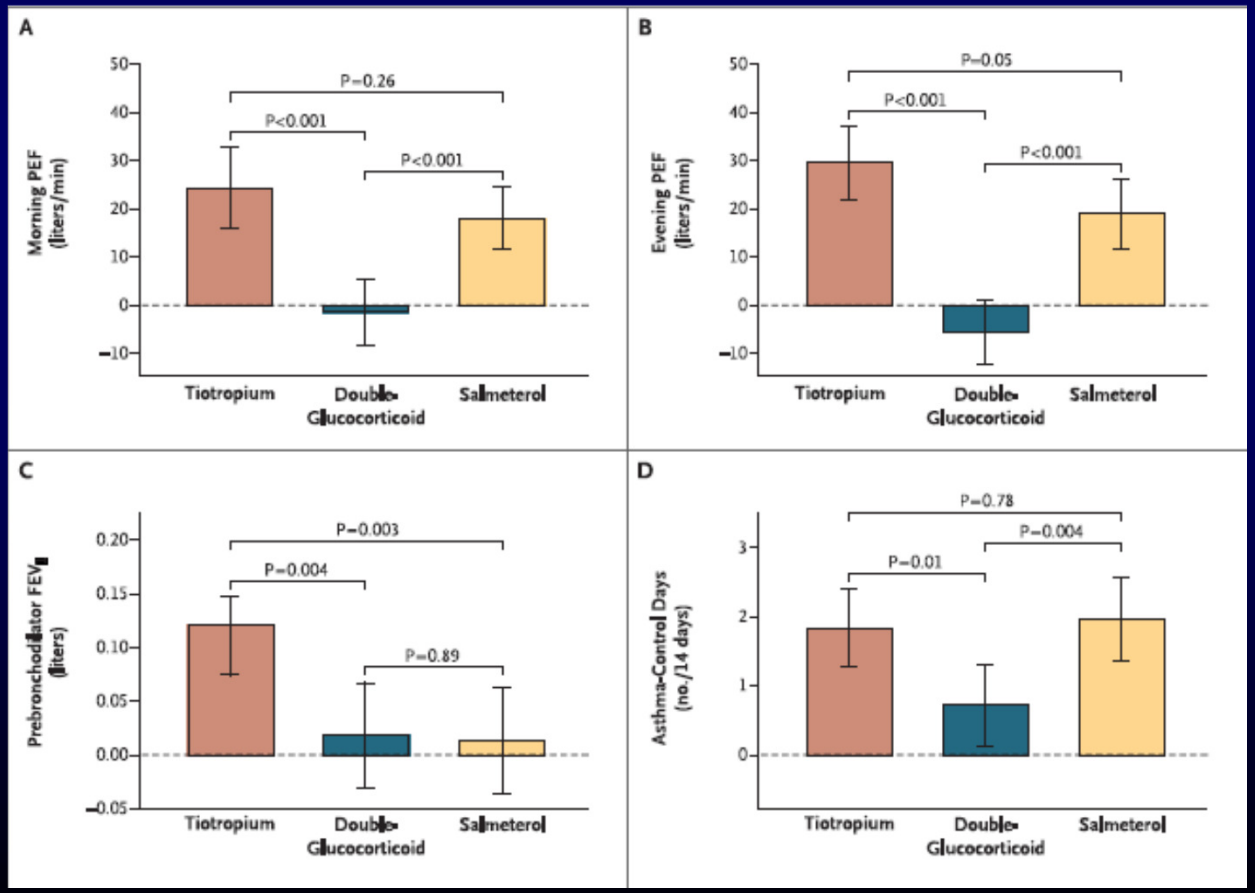
Stephen P. Peters, M.D., Ph.D., Susan J. Kunselman, M.A., Nikolina Icitovic, M.A.S., Wendy C. Moore, M.D., Rodolfo Pascual, M.D., Bill T. Ameredes, Ph.D., Homer A. Boushey, M.D., William J. Calhoun, M.D., Mario Castro, M.D., Reuben M. Cherniack, M.D., Timothy Craig, D.O., Loren Denlinger, M.D., Ph.D., Linda L. Engle, B.S., Emily A. DiMango, M.D., John V. Fahy, M.D., Elliot Israel, M.D., Nizar Jarjour, M.D., Shamsah D. Kazani, M.D., Monica Kraft, M.D., Stephen C. Lazarus, M.D., Robert F. Lemanske, Jr., M.D., Njira Lugogo, M.D., Richard J. Martin, M.D., Deborah A. Meyers, Ph.D., Joe Ramsdell, M.D., Christine A. Sorkness, Pharm.D., E. Rand Sutherland, M.D., Stanley J. Szefler, M.D., Stephen I. Wasserman, M.D., Michael J. Walter, M.D., Michael E. Wechsler, M.D., Vernon M. Chinchilli, Ph.D., and Eugene R. Bleecker, M.D., for the National Heart, Lung, and Blood Institute Asthma Clinical Research Network

METHODS

In a three-way, double-blind, triple-dummy crossover trial involving 210 patients with asthma, we evaluated the addition of tiotropium bromide (a long-acting anticholinergic agent approved for the treatment of chronic obstructive pulmonary disease but not asthma) to an inhaled glucocorticoid, as compared with a doubling of the dose of the inhaled glucocorticoid (primary superiority comparison) or the addition of the LABA salmeterol (secondary noninferiority comparison).

CONCLUSIONS

When added to an inhaled glucocorticoid, tiotropium improved symptoms and lung function in patients with inadequately controlled asthma. Its effects appeared to be equivalent to those with the addition of salmeterol. (Funded by the National Heart, Lung, and Blood Institute; ClinicalTrials.gov number, NCT00565266.)

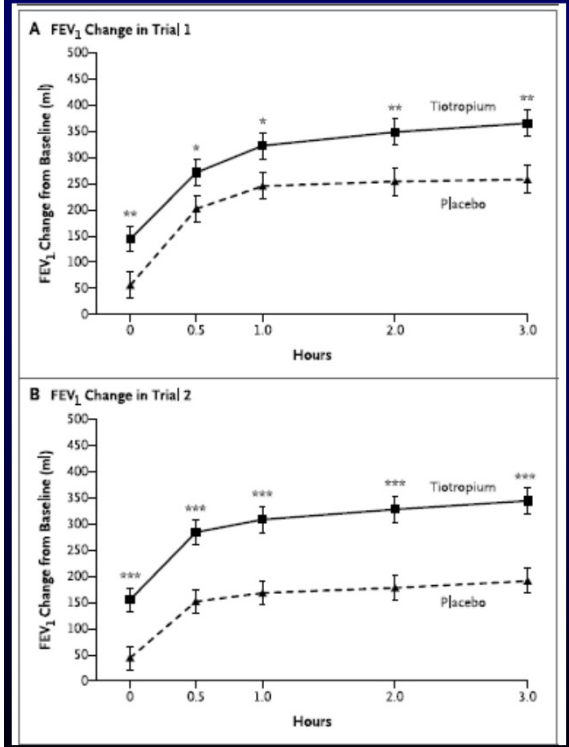


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

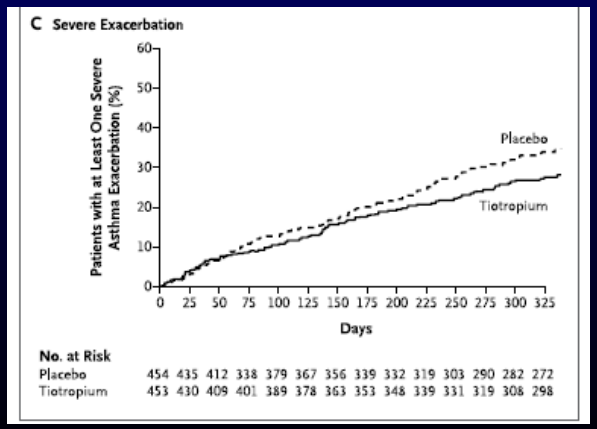
Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy

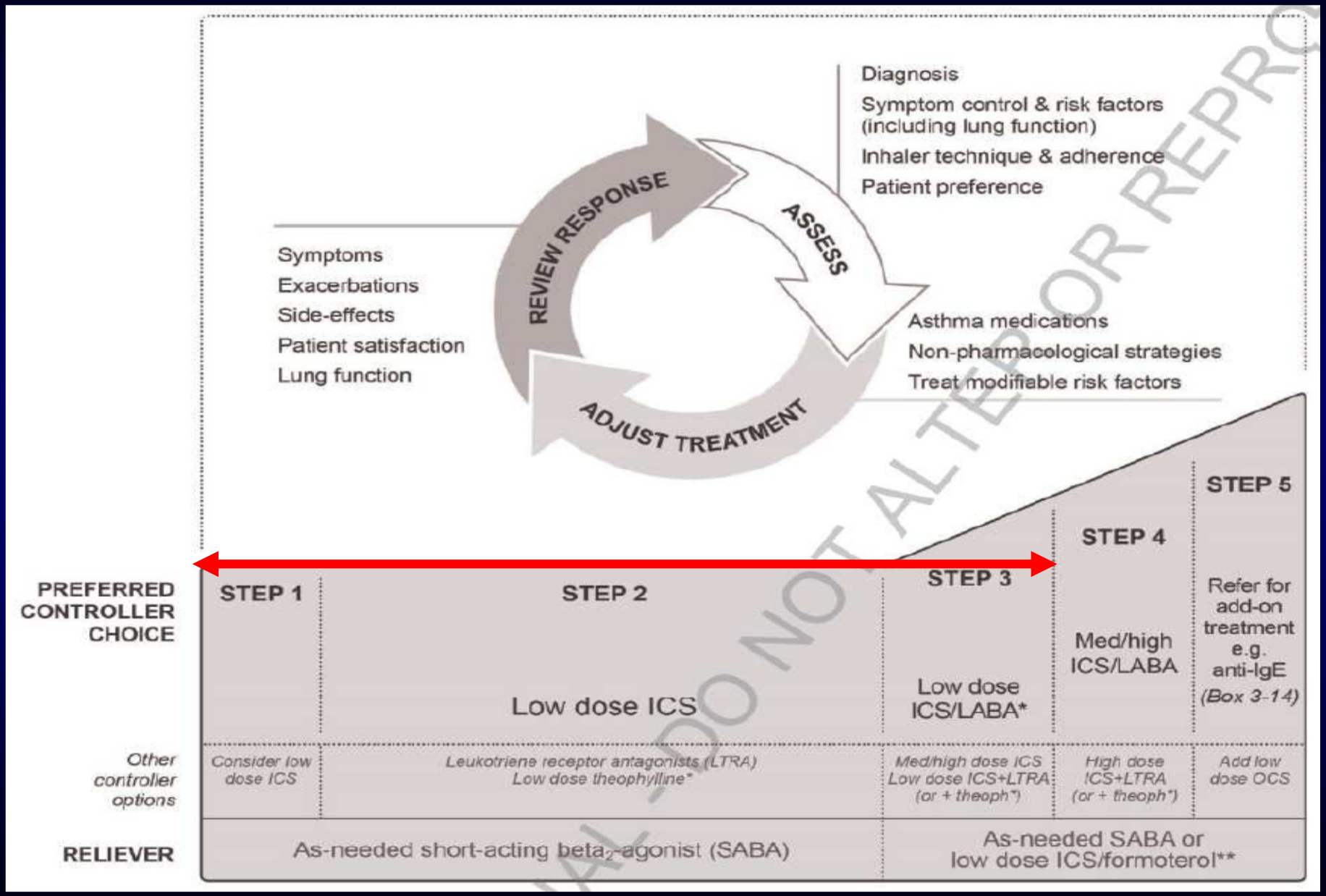
Huib A.M. Kerstjens, M.D., Michael Engel, M.D., Ronald Dahl, M.D., Pierluigi Paggiaro, M.D., Ekkehard Beck, M.D., Mark Vandewalker, M.D., Ralf Sigmund, Dipl.Math., Wolfgang Seibold, M.D., Petra Moroni-Zentgraf, M.D., and Eric D. Bateman, M.D.



METHODS

In two replicate, randomized, controlled trials involving 912 patients with asthma who were receiving inhaled glucocorticoids and LABAs, we compared the effect on lung function and exacerbations of adding tiotropium (a total dose of 5 μg) or placebo, both delivered by a soft-mist inhaler once daily for 48 weeks. All the patients were symptomatic, had a post-bronchodilator forced expiratory volume in 1 second (FEV_1) of 80% or less of the predicted value, and had a history of at least one severe exacerbation in the previous year.

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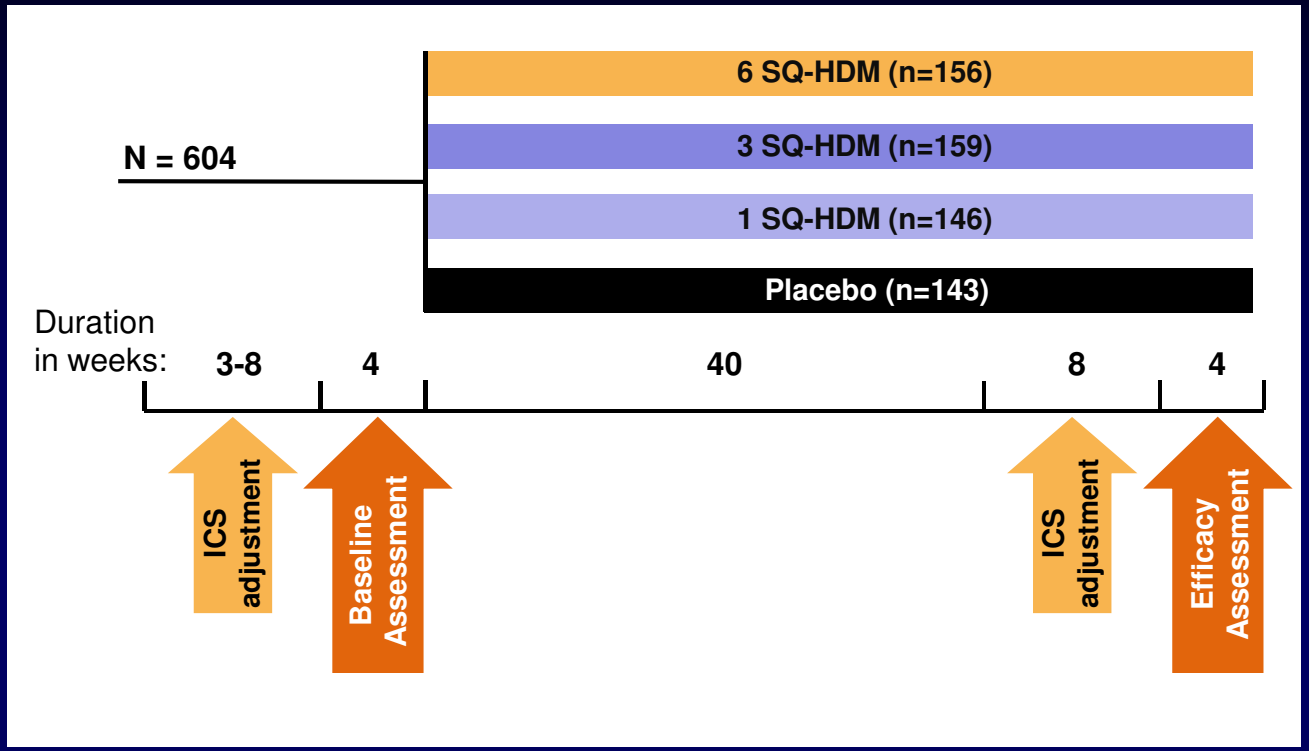
MT-02 Trial design Phase 2 study in HDM allergic asthma

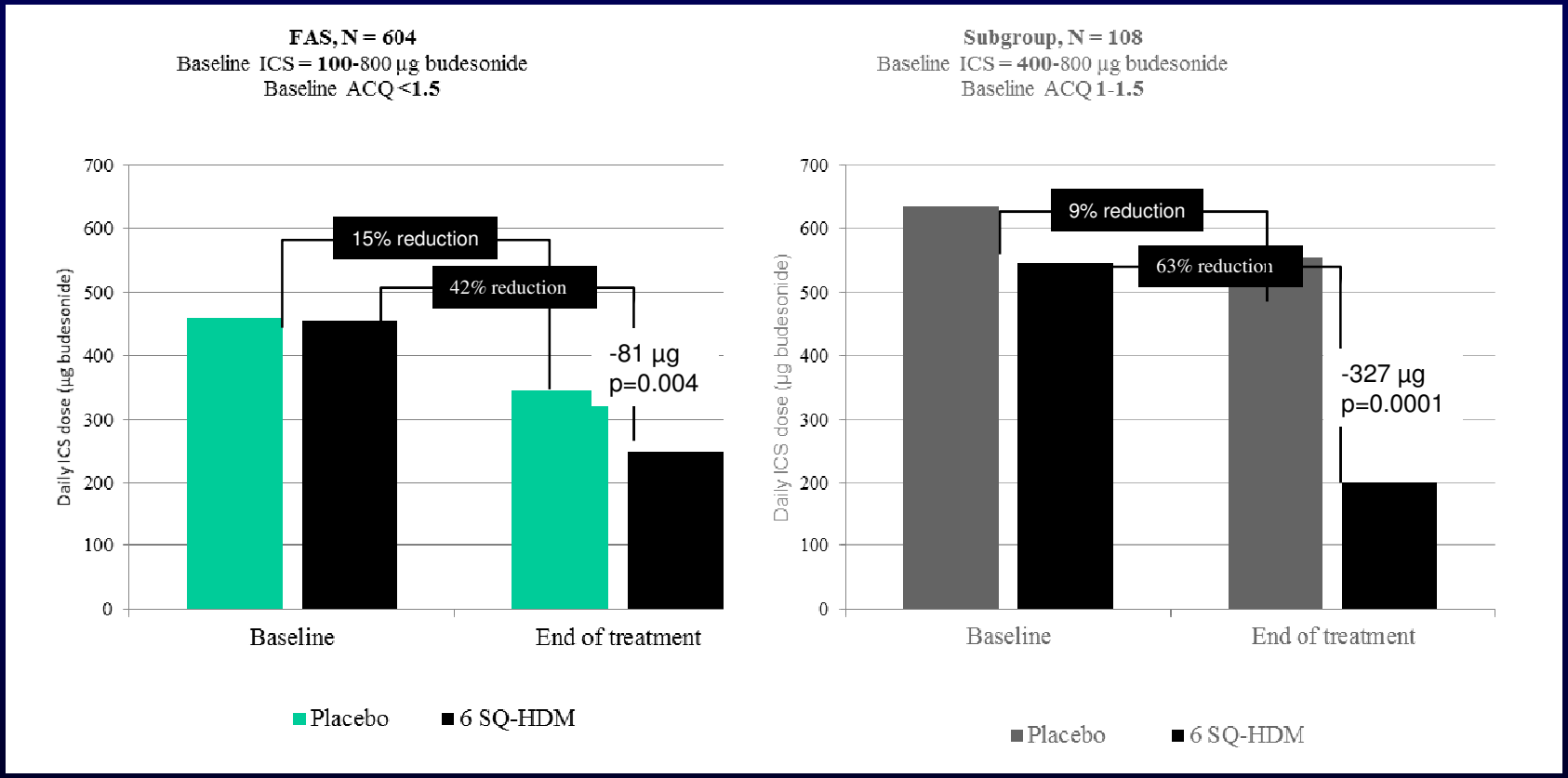


EudraCT Number: 2006-001795-20

The study was a ICS sparing trial- and ICS use was standardised to budesonide and adjusted to the lowest possible dose to maintain adequate asthma control. This ICS adjustment was done both before and during maintenance treatment with HDM tablet.

The trial included a 4-week baseline assessment period after the first ICS adjustment period and a 4-week efficacy assessment period after a second ICS adjustment period lasting approximately 8 weeks.

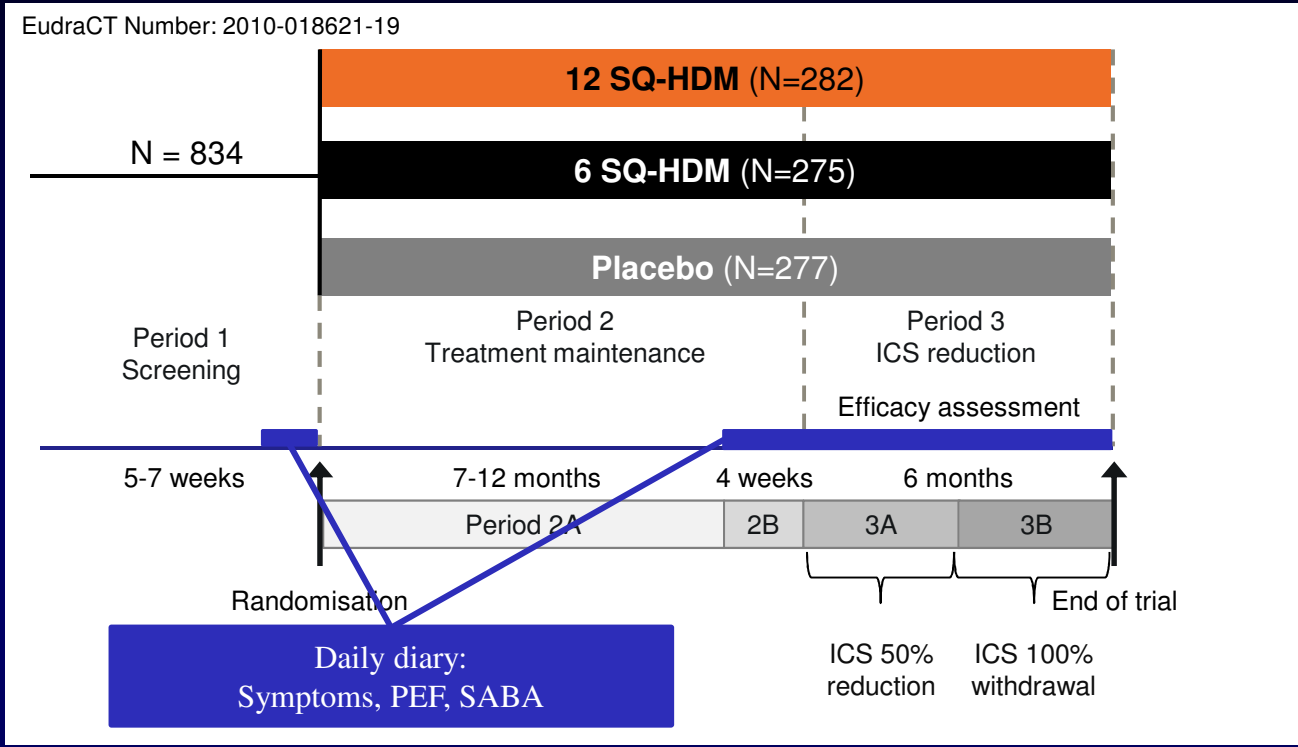
MT-02 Increased reduction of ICS in partly controlled asthmatic patients



FAS= Full Analysis Set

[Mosbech H et al. J Allergy Clin Immunol 2014; in-press]

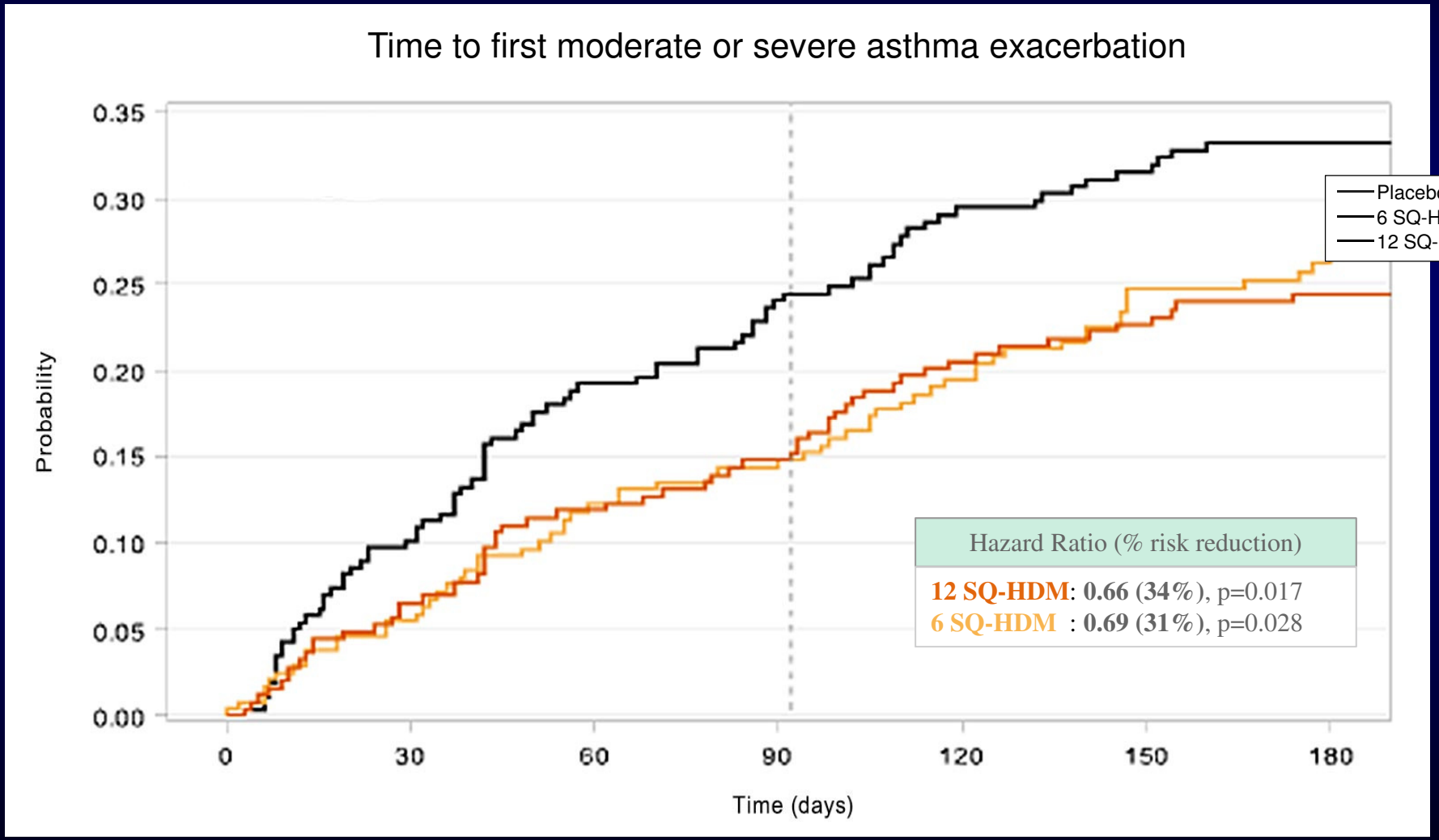
MITRA – Trial design



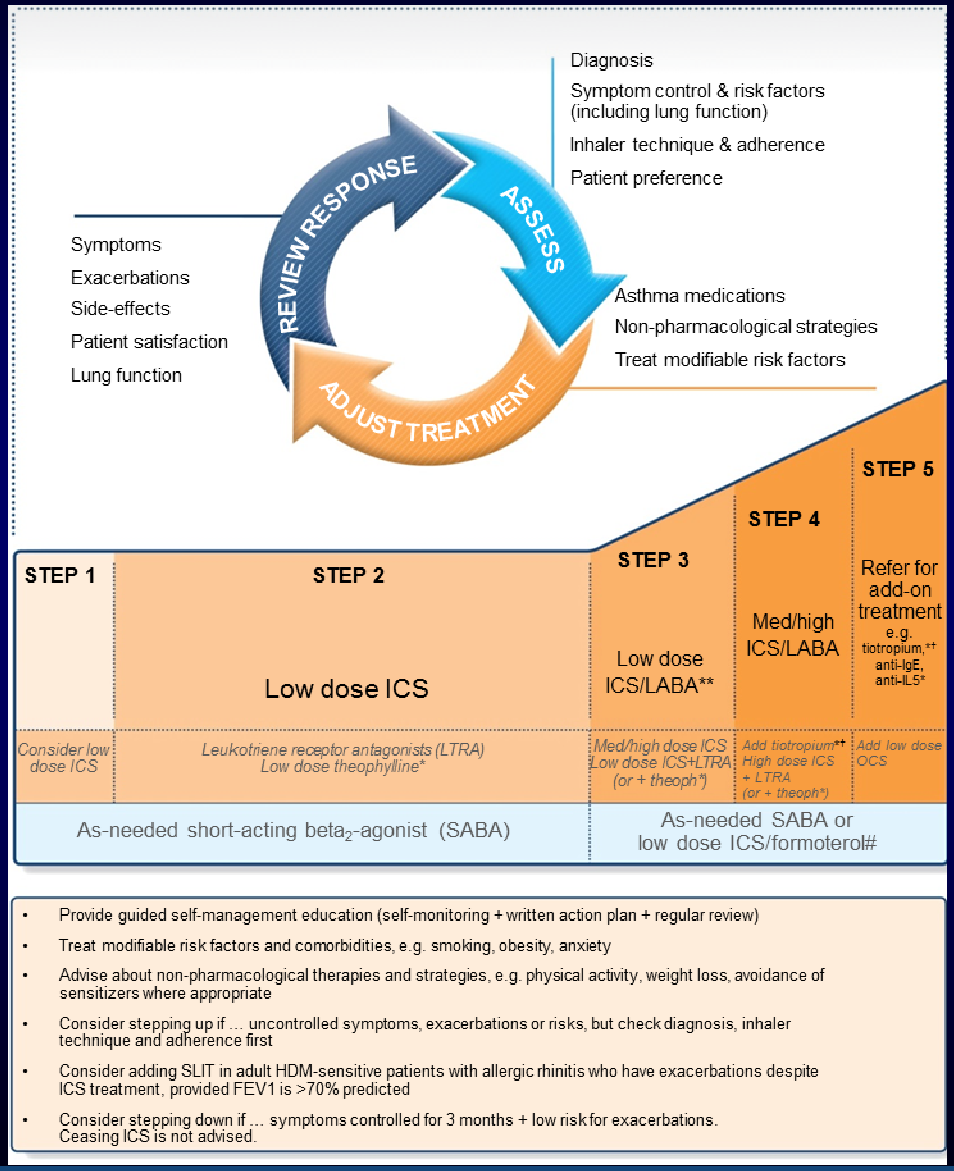
Besides the HDM tablet, subjects received concomitant ICS during the treatment maintenance period which is called period 2 on the slide. Approximately 4 weeks before the end of this period, subjects restarted daily diary recordings. This continued throughout the rest of the trial.

Period 3 was the ICS reduction and withdrawal period. The period started around the 1st of October. All subjects had their ICS use reduced by 50% for 3 months after which ICS was completely withdrawn for additional 3 months. Treatment with the HDM tablet or placebo was continued until the end of this reduction-withdrawal period.

Primary endpoint met for both doses



Stepwise approach to control asthma symptoms and reduce risk



REMEMBER TO....

- Provide guided self-management education (self-monitoring + written action plan + regular review)
- Treat modifiable risk factors and comorbidities, e.g. smoking, obesity, anxiety
- Advise about non-pharmacological therapies and strategies, e.g. physical activity, weight loss, avoidance of sensitizers where appropriate
- Consider stepping up if ... uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique and adherence first
- Consider adding SLIT in adult HDM-sensitive patients with allergic rhinitis who have exacerbations despite ICS treatment, provided FEV1 is >70% predicted
- Consider stepping down if ... symptoms controlled for 3 months + low risk for exacerbations. Ceasing ICS is not advised.

SLIT added as an option

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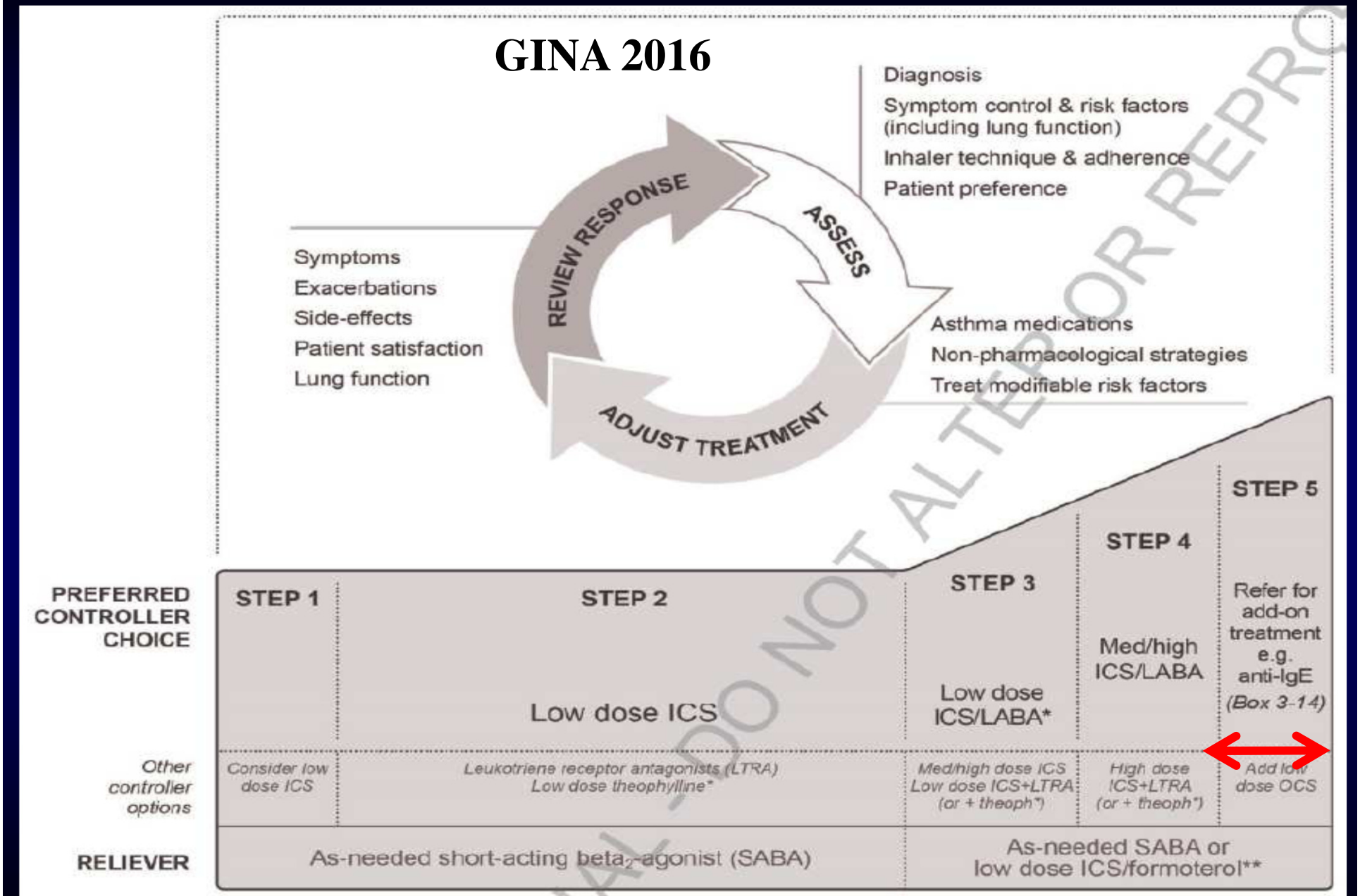
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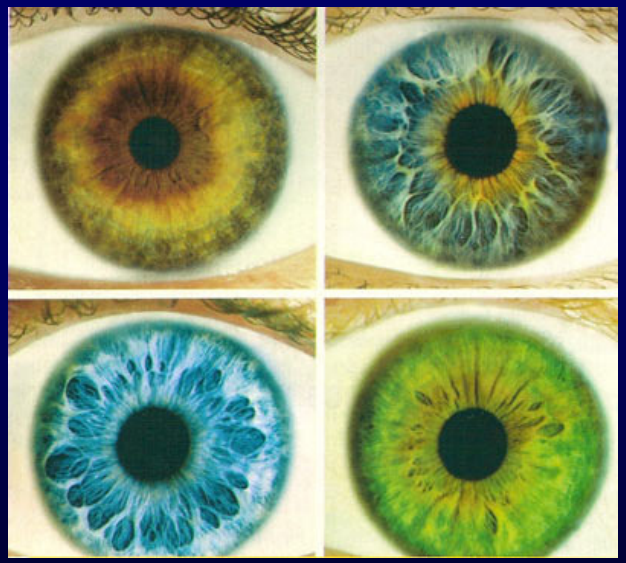
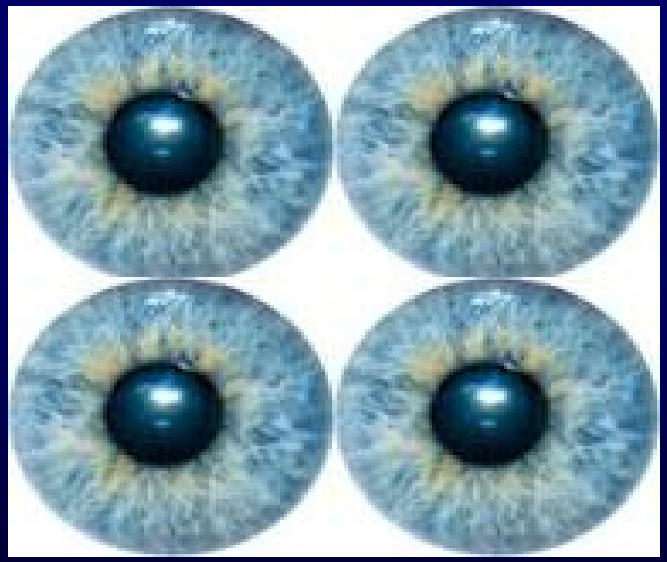
As-needed SABA or low dose ICS/formoterol**

AS: phenotypage

Caractéristiques observables d'un individu

Elles résultent de l'intéraction de son génotype avec l'environnement

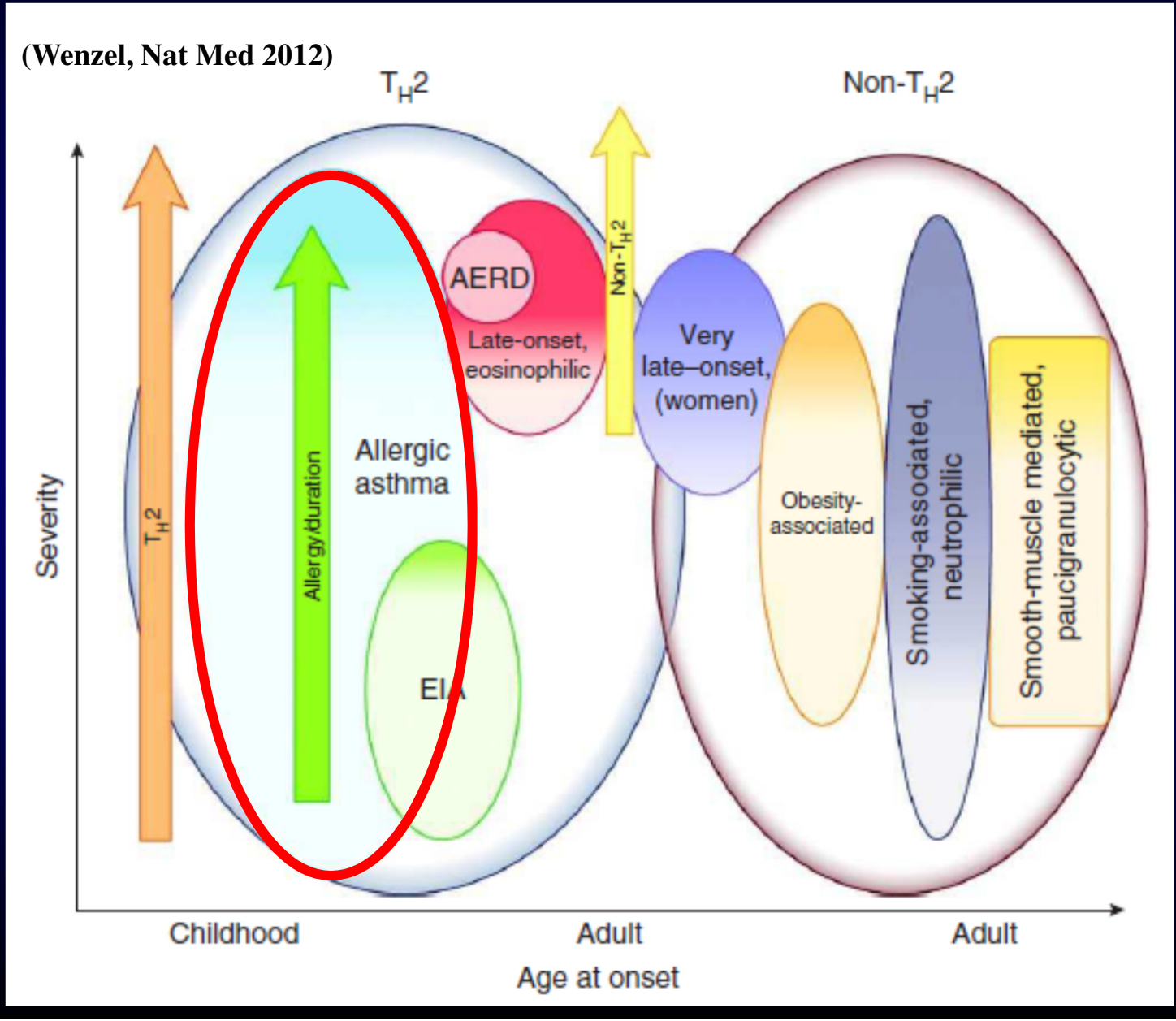




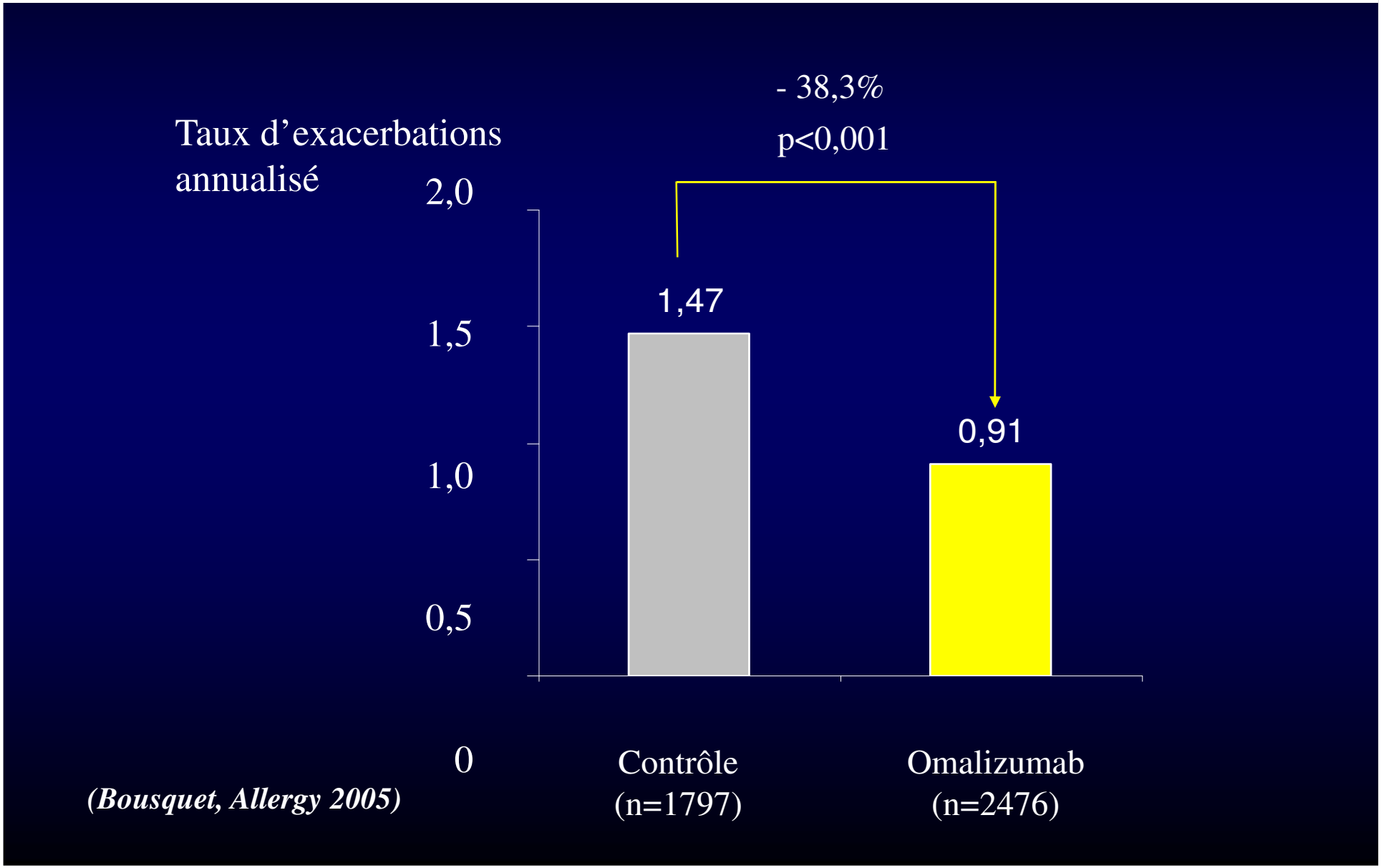
Identification biomarqueur

Propositions de phénotypes « théoriques » Th2/nonTH2 et de l'âge de survenue

(Wenzel, Nat Med 2012)



Omalizumab réduit le taux d'exacerbations (Analyse groupée)



(Bousquet, Allergy 2005)

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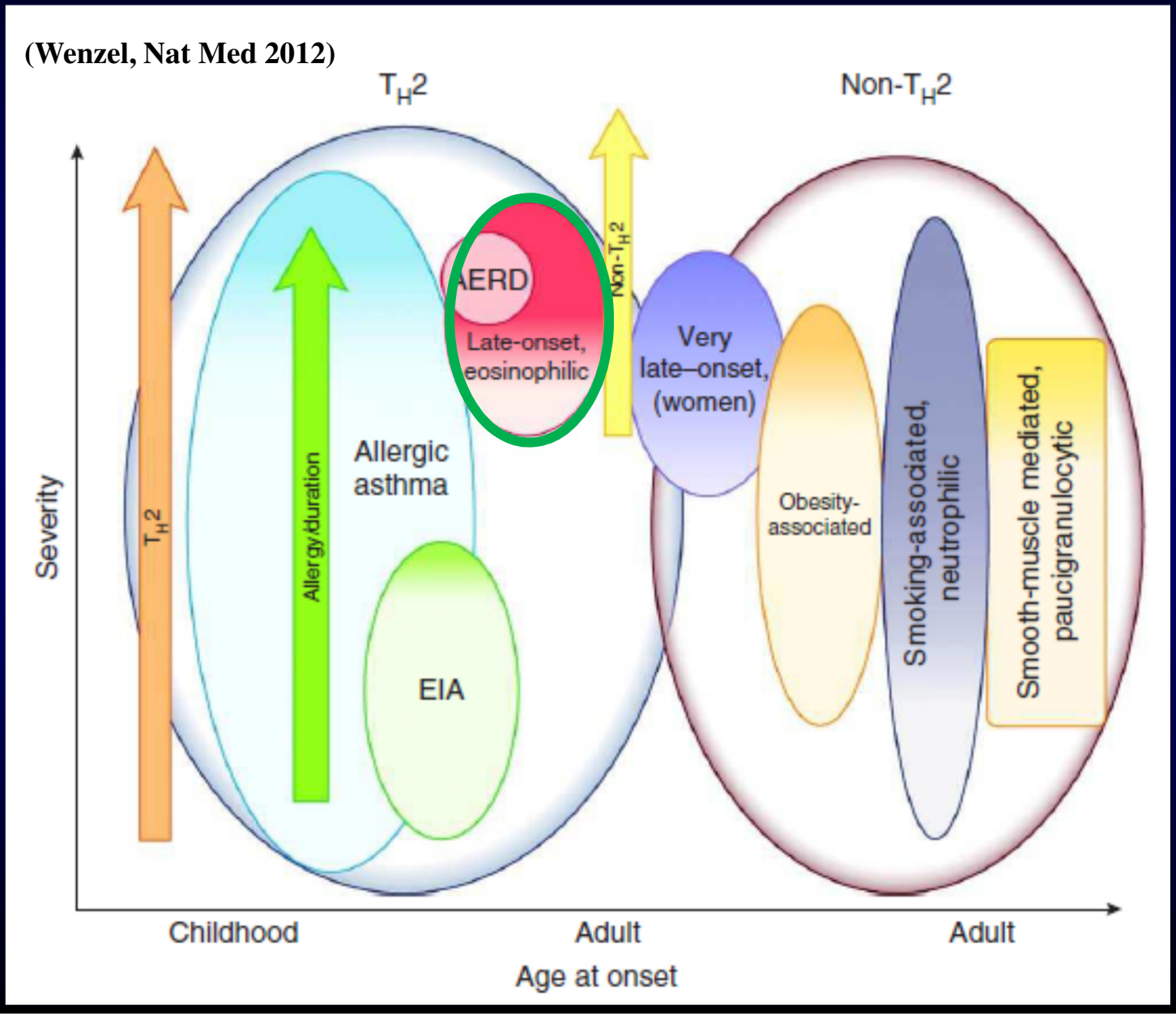


ORIGINAL ARTICLE

Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma

Hector G. Ortega, M.D., Sc.D., Mark C. Liu, M.D., Ian D. Pavord, D.M., Guy G. Brusselle, M.D., J. Mark FitzGerald, M.D., Alfredo Chetta, M.D., Marc Humbert, M.D., Ph.D., Lynn E. Katz, Pharm.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., and Pascal Chanez M.D., Ph.D., for the MENSA Investigators*

N Engl J Med 2014;371:1198-207.

MENSA

576 asthmatiques éosinophiliques exacerbateurs

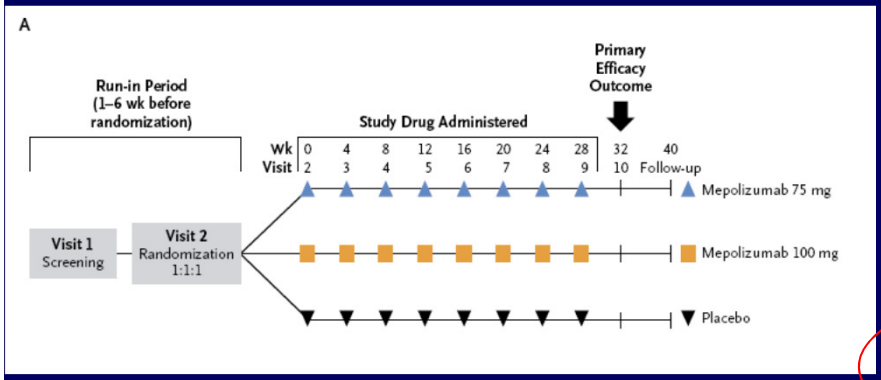
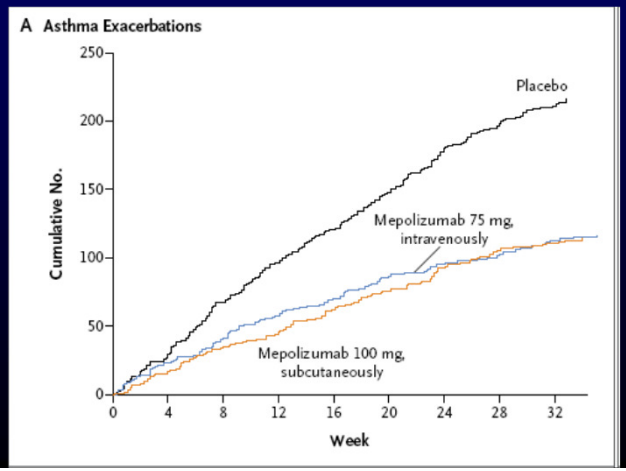
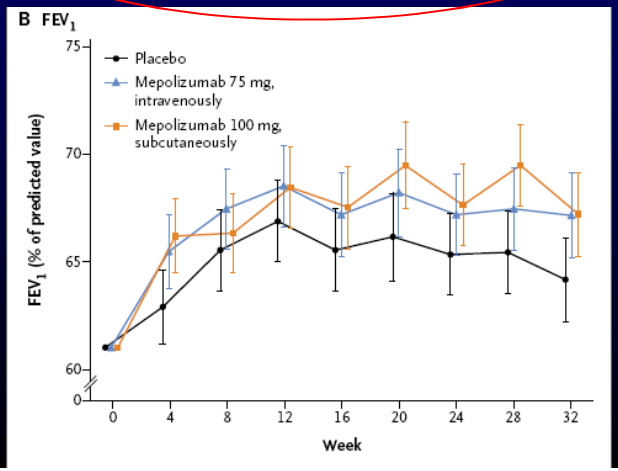


Table 1. Characteristics of the Patients at Baseline in the Intention-to-Treat Population.*

Characteristic	Placebo (N=191)	Mepolizumab	
		Intravenous (N=191)	Subcutaneous (N=194)
Mean age (range) — yr	49 (12–76)	50 (13–82)	51 (12–81)
Female sex — no. (%)	107 (56)	106 (55)	116 (60)
Body-mass index†	28.0±5.6	27.7±5.7	27.6±6.2
Former smoker — no. (%)	57 (30)	52 (27)	50 (26)
Duration of asthma — yr	19.5±14.6	19.8±14.0	20.5±12.9
Use of oral glucocorticoids			
Maintenance use — no. (%)	44 (23)	48 (25)	52 (27)
Mean daily dose (range) — mg‡	15.1 (5–80)	12.0 (1–40)	12.6 (2–50)
Allergic rhinitis — no. (%)	95 (50)	91 (48)	95 (49)
FEV_1			
Before bronchodilation — liters§	1.86±0.63	1.86±0.70	1.73±0.66
Percent of predicted value before bronchodilation¶	62.4±18.1	61.4±18.3	59.3±17.5
Reversibility — %	27.4±20.8	25.4±19.6	27.9±24.0
FEV_1:FVC ratio — %‖	64±13	64±13	63±13
Morning peak expiratory flow — liters/min	277±106	269±112	255±108
Score on Asthma Control Questionnaire**	2.28±1.19	2.12±1.13	2.26±1.27
Score on St. George's Respiratory Questionnaire††	46.9±19.8	44.4±19.4	47.9±19.4
Geometric mean IgE on $\log_e$ scale — U/ml	150±1.5	180±1.5	150±1.5
Geometric mean blood eosinophil count on $\log_e$ scale — cells/μl‡‡	320±938	280±987	290±1050
Asthma exacerbations			
Severe episodes in previous year — no./patient	3.6±2.8	3.5±2.2	3.8±2.7
Necessitating hospitalization in previous year — no. (%)	35 (18)	41 (21)	33 (17)
History of asthma-related intubation — no. (%)	3 (2)	10 (5)	8 (4)





SIROCCO

Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial

*Eugene R Bleecker, J Mark FitzGerald, Pascal Chanez, Alberto Papi, Steven F Weinstein, Peter Barker, Stephanie Sproule, Geoffrey Gilmartin, Magnus Aurivillius, Viktoria Werkström, Mitchell Goldman, on behalf of the SIROCCO study investigators**

Lancet 2016

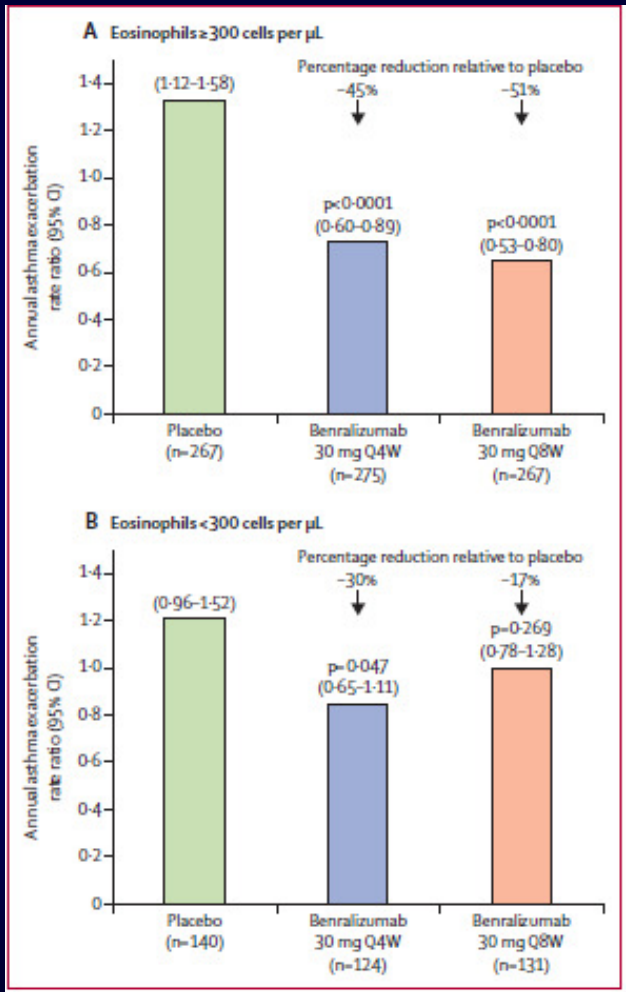


Figure 2: **Annual asthma exacerbation rate estimates at 48 weeks according to baseline blood eosinophil concentrations**

Data for patients with baseline blood eosinophils (A) ≥300 cells per µL and (B) <300 cells per µL in the full analysis set are shown. Estimates were calculated using a negative binomial model, with adjustment for treatment, region, oral corticosteroid use at time of randomisation, and previous exacerbations. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W).

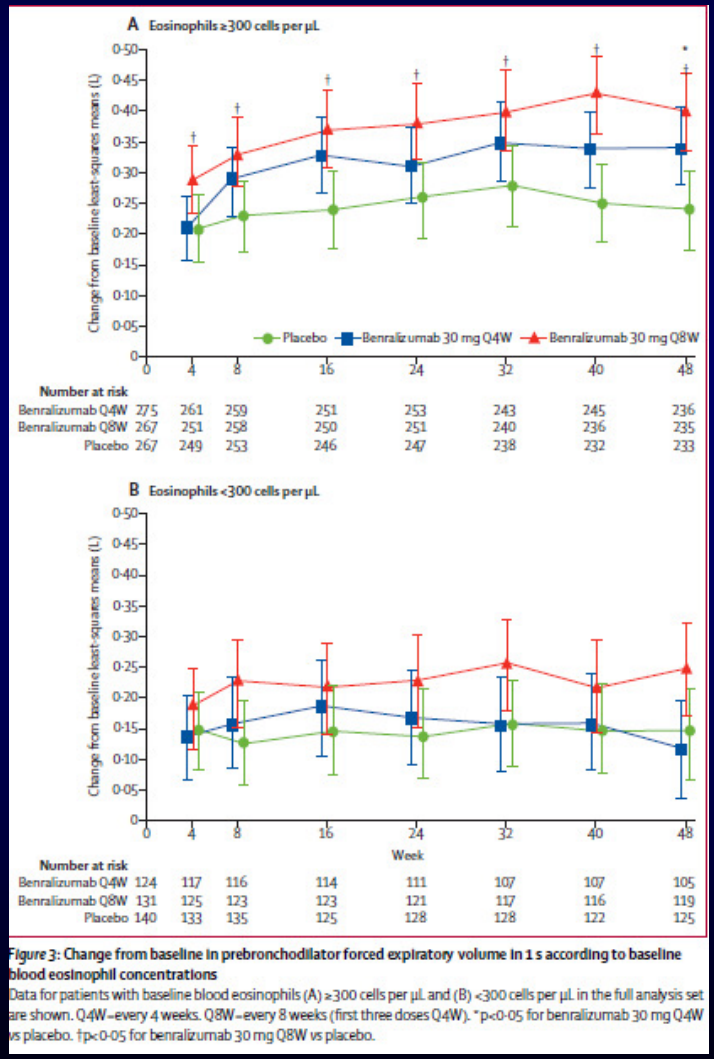


Figure 3: **Change from baseline in prebronchodilator forced expiratory volume in 1 s according to baseline blood eosinophil concentrations**

Data for patients with baseline blood eosinophils (A) ≥300 cells per µL and (B) <300 cells per µL in the full analysis set are shown. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). *p<0·05 for benralizumab 30 mg Q4W vs placebo. †p<0·05 for benralizumab 30 mg Q8W vs placebo.

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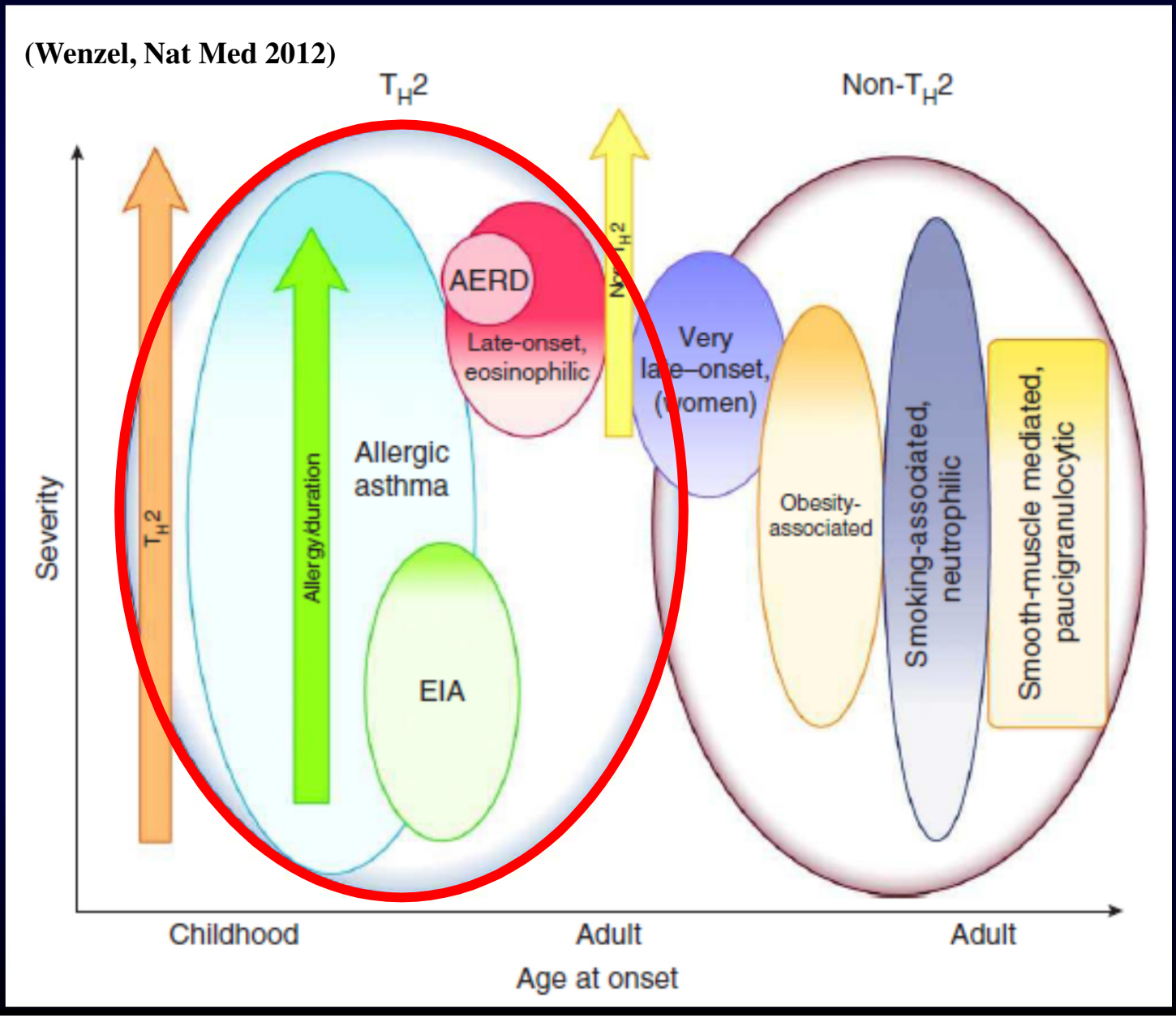
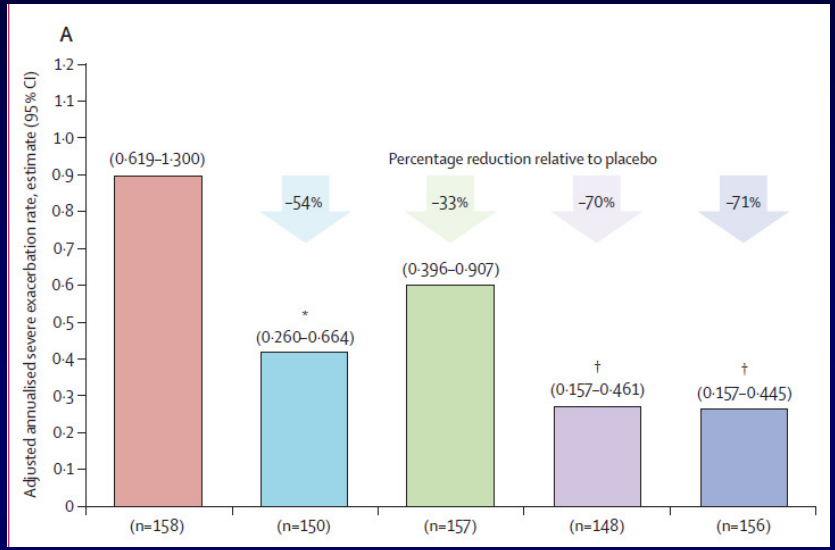


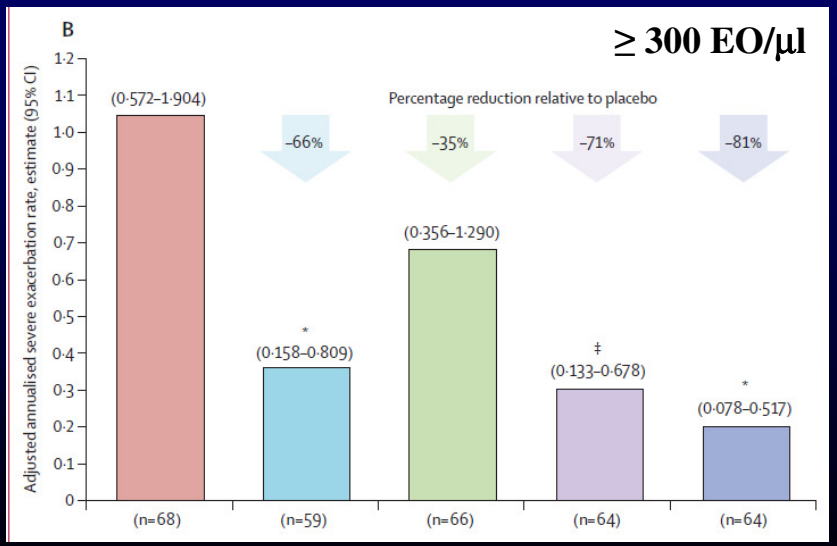
Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial

Sally Wenzel, Mario Castro, Jonathan Corren, Jorge Maspero, Lin Wang, Bingzhi Zhang, Gianluca Pirozzi, E Rand Sutherland, Robert R Evans, Vijay N Joish, Laurent Eckert, Neil M H Graham, Neil Stahl, George D Yancopoulos, Mariana Louis-Tisserand, Ariel Teper

(S Wenzel, Lancet 2016)



≥ 300 EO/µl



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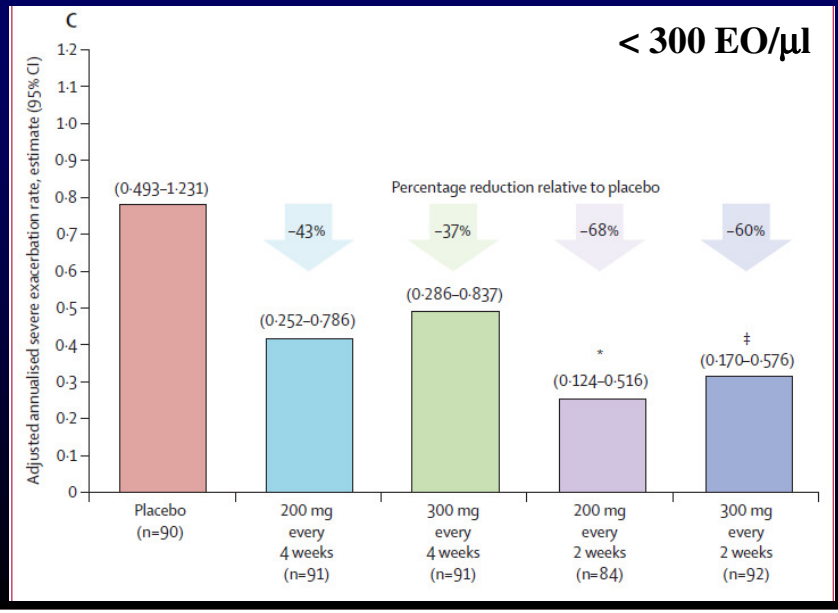
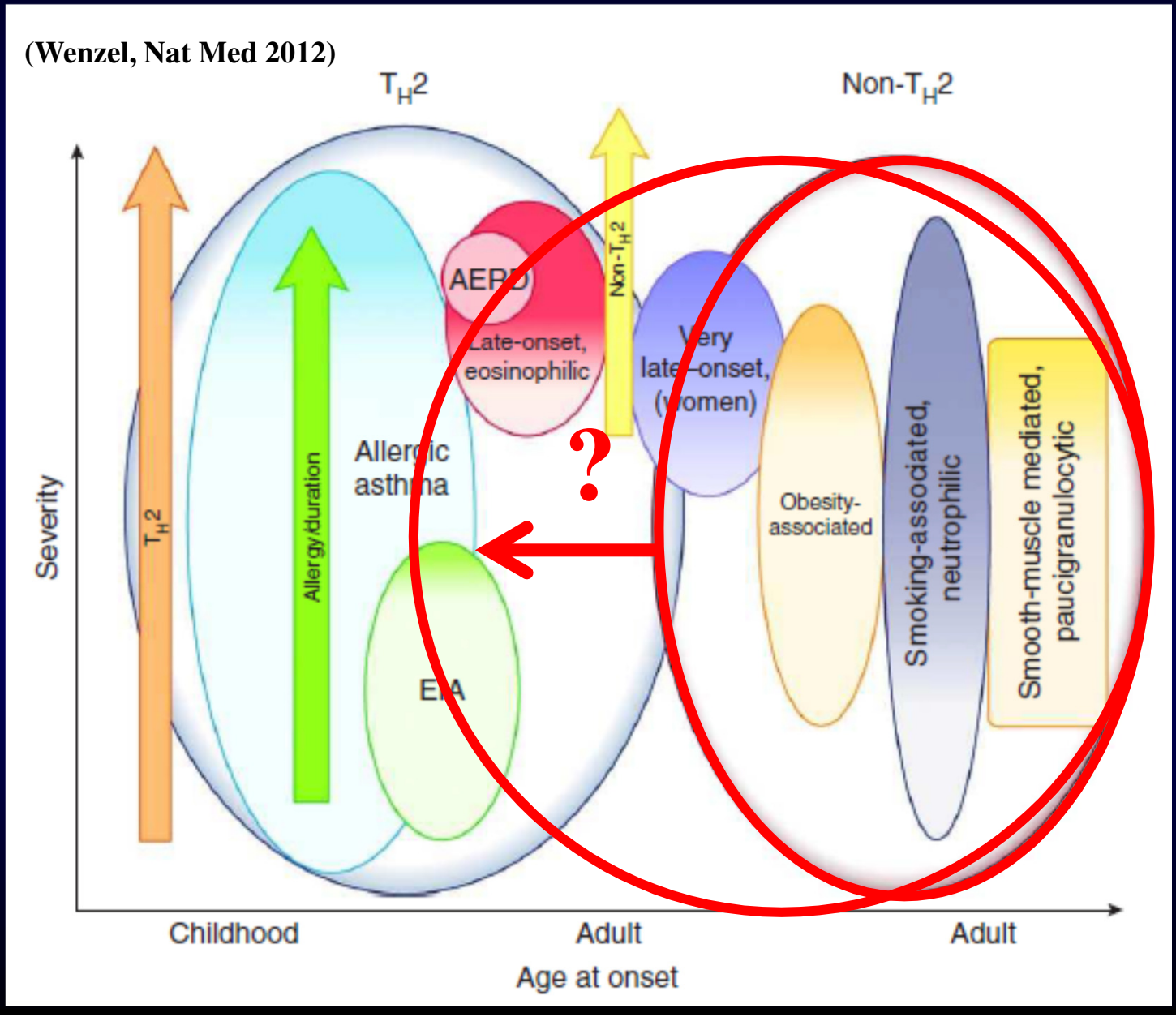


Propositions de phénotypes « théoriques » Th2/nonTH2 et de l'âge de survenue

(Wenzel, Nat Med 2012)



Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial

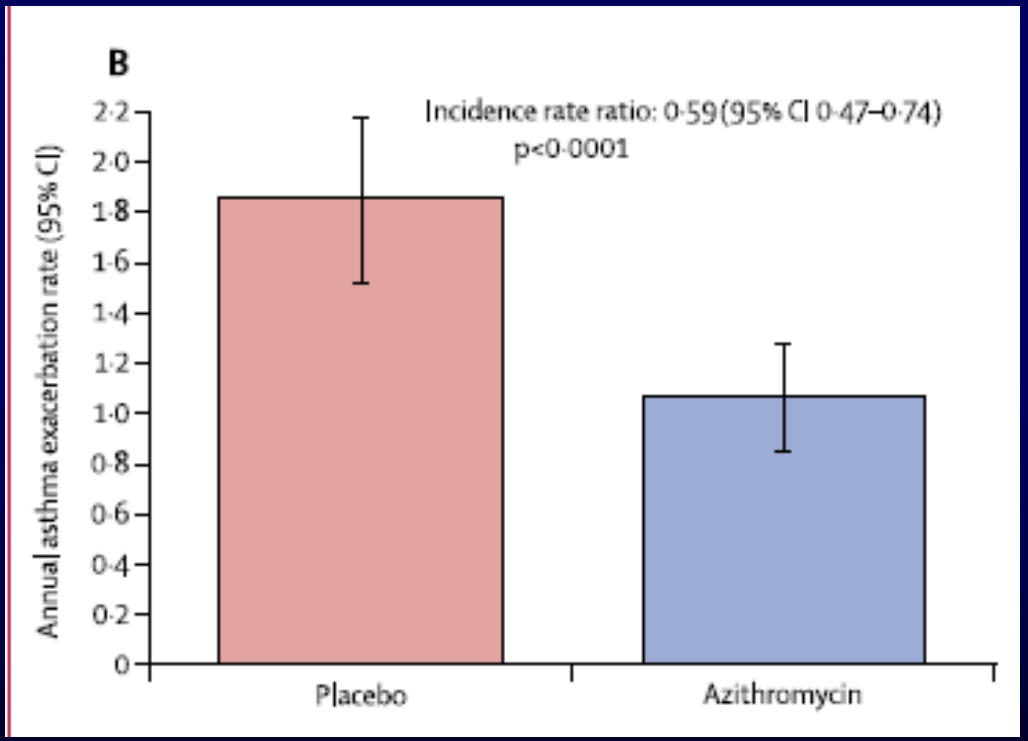
Peter G Gibson, Ian A Yang, John W Upham, Paul N Reynolds, Sandra Hodge, Alan L James, Christine Jenkins, Matthew J Peters, Guy B Marks, Melissa Baraket, Heather Powell, Steven L Taylor, Lex E X Leong, Geraint B Rogers, Jodie L Simpson

Lancet 2017; 390: 659–68

	Placebo (n=207)	Azithromycin (n=213)
Age (years)	60·01 (49·58–67·98)	61·02 (50·62–68·74)
Sex		
Female	121 (58%)	134 (63%)
Male	86 (42%)	79 (37%)
Atopy	163 (80%)	156 (74%)
Ex-smoker	81 (39%)	80 (38%)
Pack years	7·5 (1·5–18·0)	7·6 (1·75–26·0)
Body-mass index (kg/m²)	28·81 (25·48–33·11)	29·90 (25·81–34·86)
Asthma history		
Age asthma symptoms began	13 (4–40)	17 (5–40)
Age asthma diagnosed	20 (5–44)	21 (5–42)
ACQ6 score	1·55 (0·79)	1·56 (0·79)
AQLQ score	5·35 (0·89)	5·36 (0·93)
Asthma history past year		
Emergency room visit or hospital admission	0 (0–0)	0 (0–0)
Unscheduled doctor visits	1 (0–3)	1 (0–2)
Oral corticosteroid courses	1 (0–2)	1 (0–2)
Medications		
Inhaled corticosteroid daily dose, beclomethasone equivalent		
Low dose (<400 µg/day)	4 (2%)	5 (2%)
Moderate dose (400–<800 µg/day)	26 (13%)	23 (11%)
High dose (≥800 µg/day)	176 (85%)	185 (87%)
Long-acting beta agonist	205 (99%)	208 (98%)
Leukotriene modifier	6 (3%)	8 (4%)
Long-acting anti-muscarinic	33 (16%)	40 (19%)
Theophylline (slow-release)	6 (3%)	7 (3%)
Oral corticosteroid	6 (3%)	8 (4%)
Pre B2 spirometry	n=205	n=210
Pre B2 FEV_1%	73·58 (18·83)	72·33 (20·70)
Pre B2 FVC%	82·95 (15·14)	82·74 (16·06)
Pre B2 FEV_1/FVC%	68·26 (11·90)	67·46 (12·90)
Sputum cell counts	n=166	n=165
Total cell count (×10⁶) per mL	4·05 (2·16–8·90)	4·05 (2·34–7·29)
Neutrophils (%)	33·25 (16·25–55·0)	36·75 (17·25–56·75)
Eosinophils (%)	2·38 (0·50–10·5)	1·75 (0·50–7·50)
Sputum phenotype		
Eosinophilic	77 (46%)	67 (41%)
Neutrophilic	25 (15%)	21 (13%)
Paucigranulocytic	55 (33%)	70 (42%)
Mixed	9 (5%)	7 (4%)
Blood eosinophils (×10⁹) per L	0·28 (0·16–0·41)	0·20 (0·11–0·40)

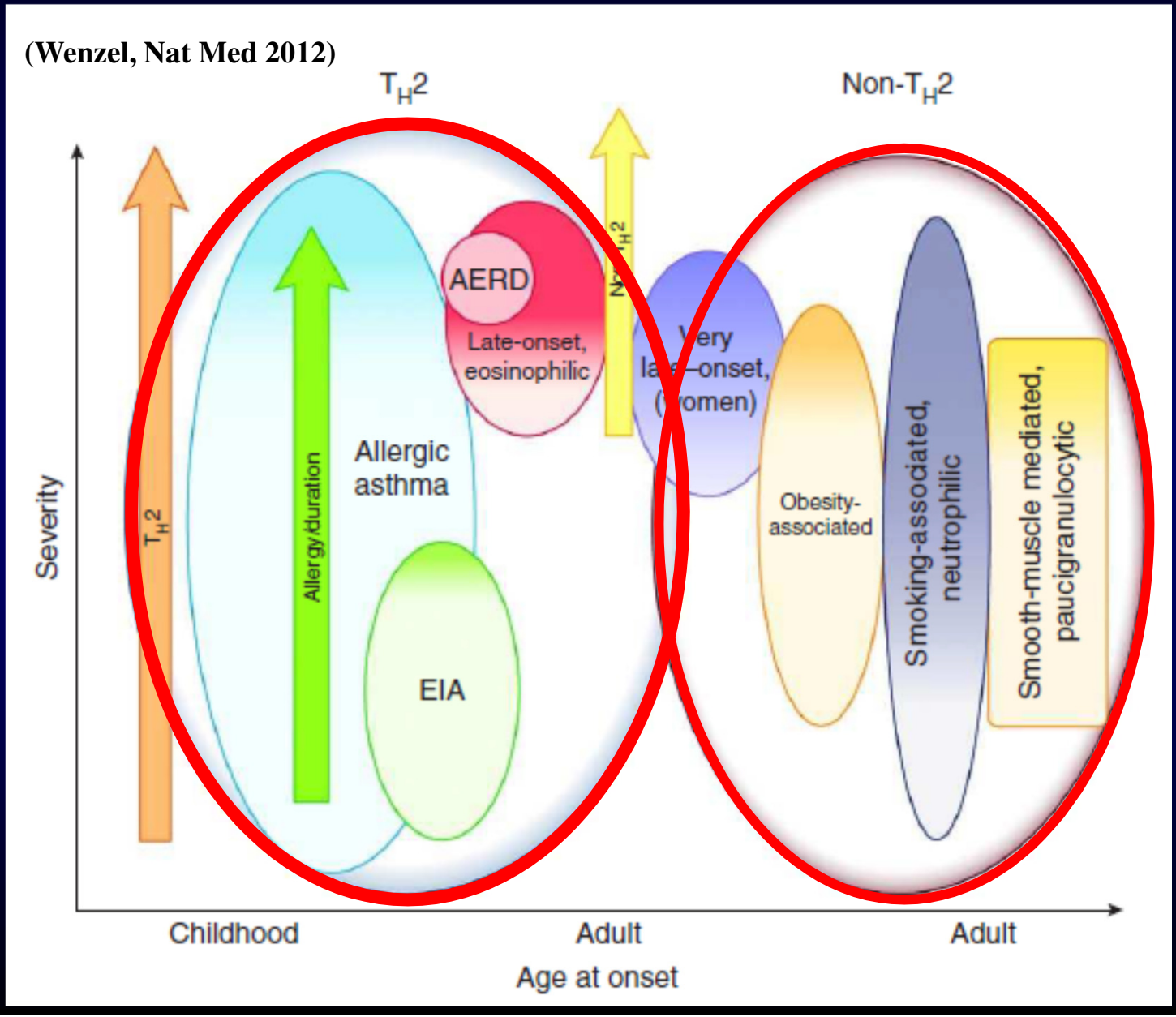
Data are median (IQR), mean (SD), or n (%). AQLQ=Asthma Quality of Life Questionnaire. ACQ6=Asthma Control Questionnaire. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity.

Table 1: **Characteristics of patients at baseline**



Propositions de phénotypes « théoriques » Th2/nonTH2 et de l'âge de survenue

(Wenzel, Nat Med 2012)



Tezepelumab in Adults with Uncontrolled Asthma

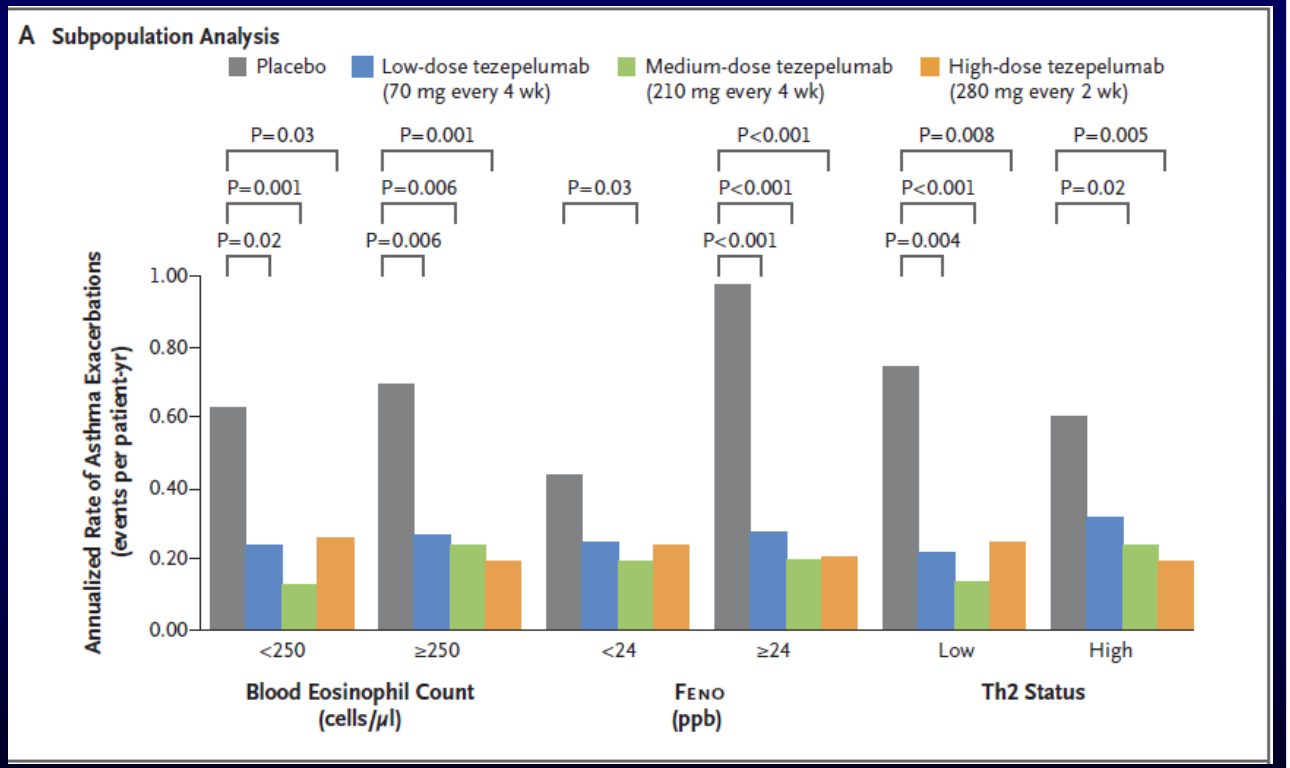
Jonathan Corren, M.D., Jane R. Parnes, M.D., Liangwei Wang, Ph.D., May Mo, M.S., Stephanie L. Roseti, A.P.N., M.S.N., Janet M. Griffiths, Ph.D., and René van der Merwe, M.B., Ch.B.

N Engl J Med 2017;377:936-46.

Thymic stromal lymphopoietin
→ Induit par Th2 (Ag)
→ Induit par non TH2 (tabac, DEP, virus)

Phase II
Tezepelumab 3 posologies vs placebo
SC , / 4 semaines
52 semaines
436/148

→ Exacerbations



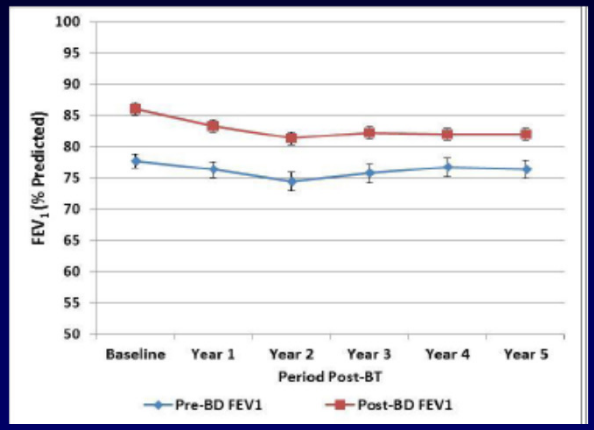
Thermoplastie bronchique: Principaux résultats cliniques

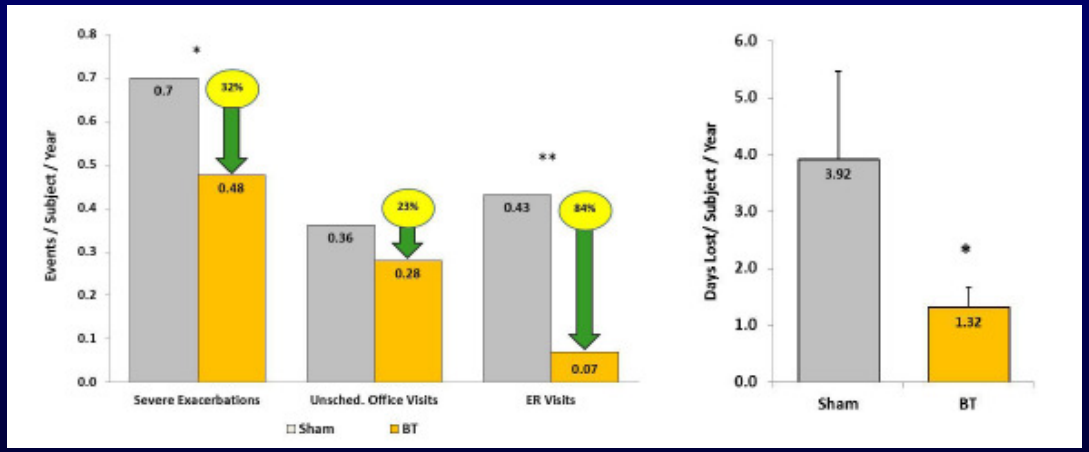
Suivi à 5 ans de 190 asthmatiques sévères traités par TB vs sham
Evaluation efficacité **et** tolérance ++

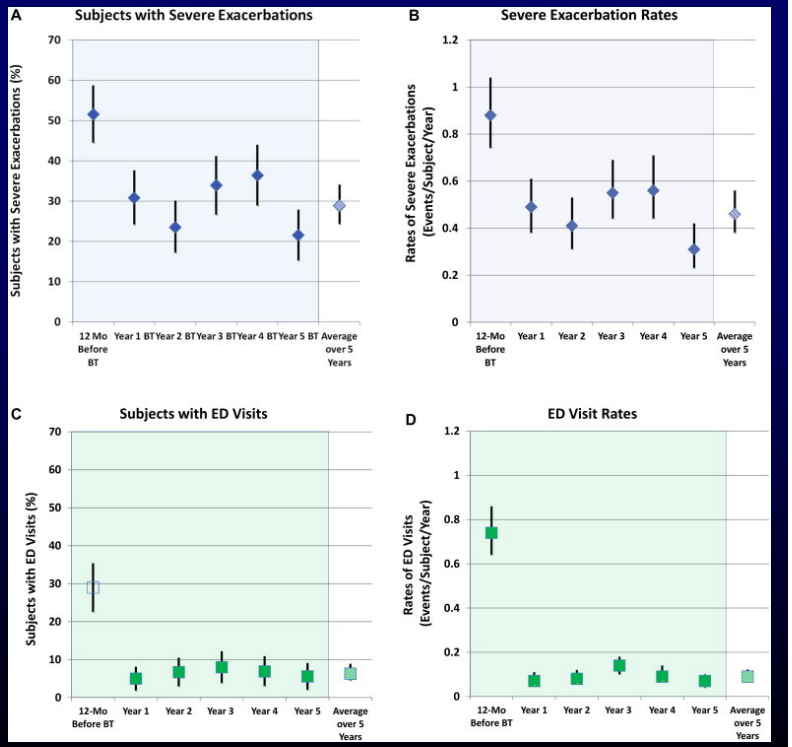
85.3 % des patients ont été suivis (162 patients)

Globalement

44% de réduction des exacerbation
78% de réduction des consultations en urgence
Réduction de18% de la CI
Evaluation TDM sans anomalies attribuables à TB



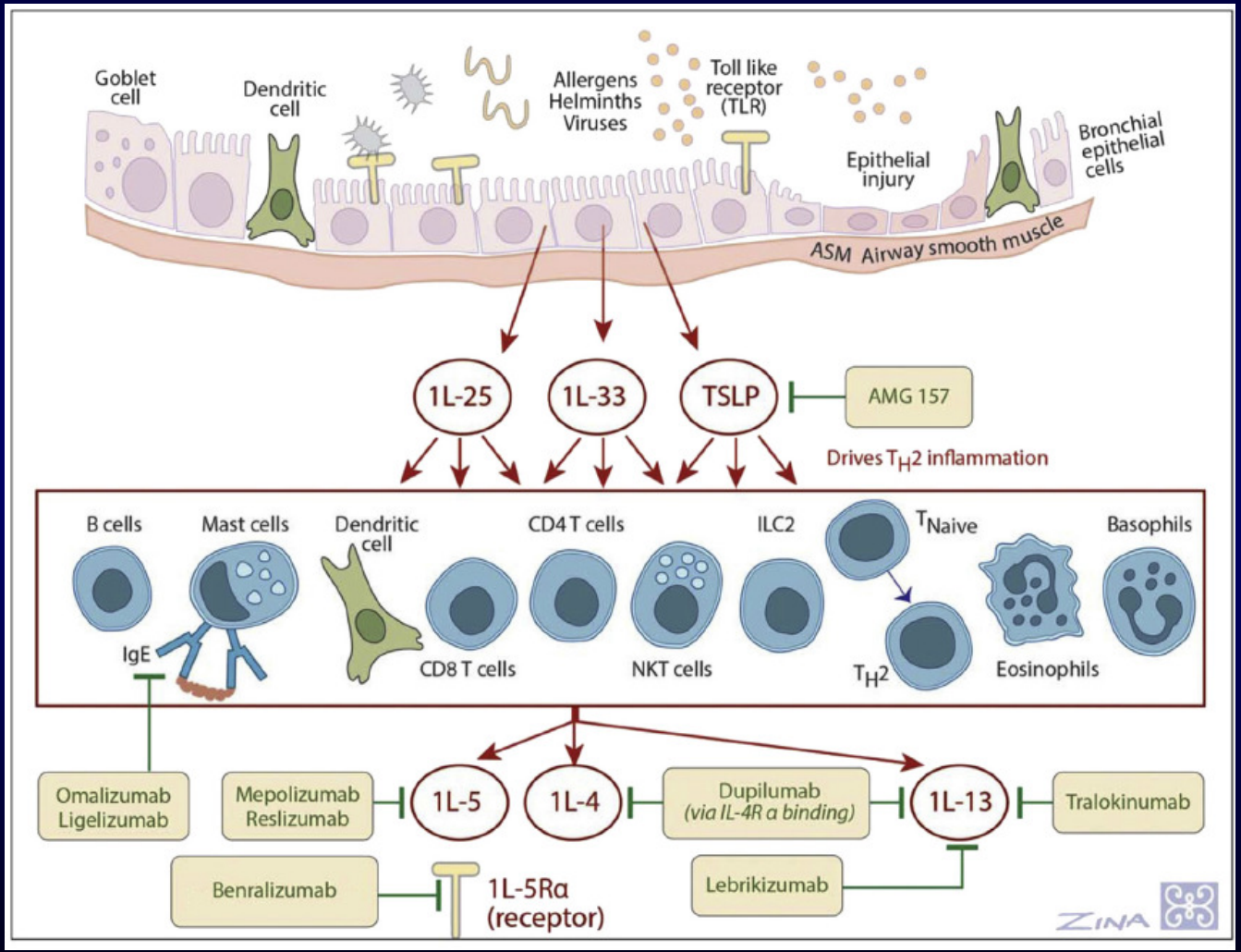




Persistance à long terme des résultats cliniques de la TB
Contrôle de l'asthme & Sécurité

(Wechsler, JACI 2013)

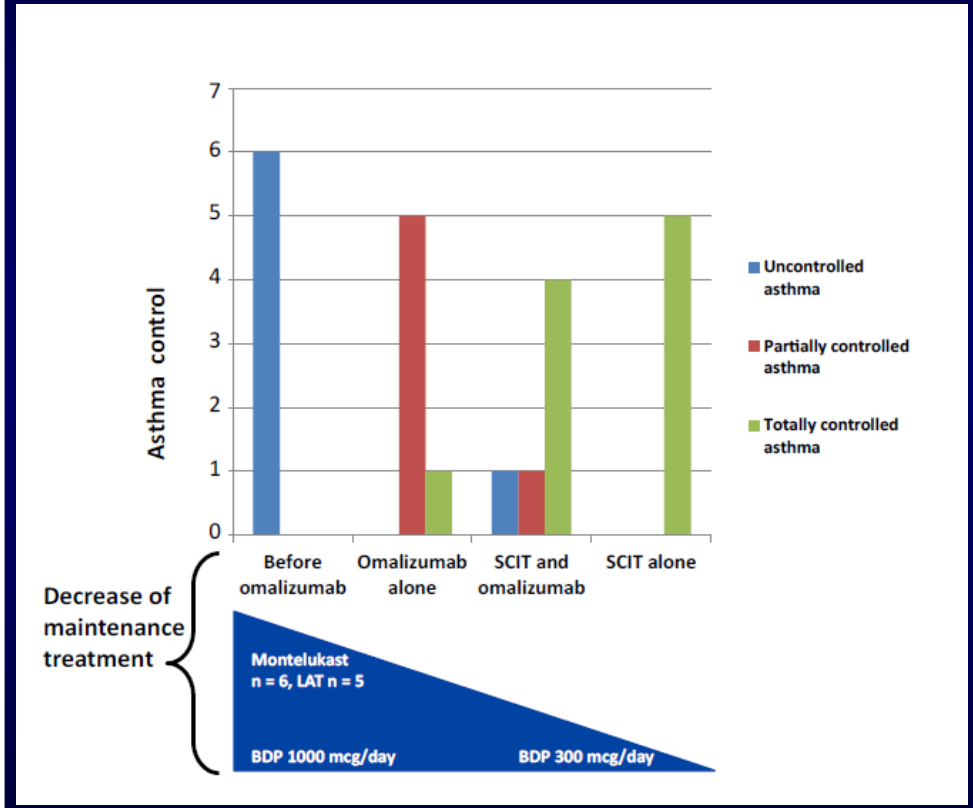
Biotherapies-Immunothérapie
Nouvelles strategies ?



ITA

Katial Jaci Pract 2017

Biothérapies-Immunothérapie: schémas mixtes ?



Lambert PAI 2014

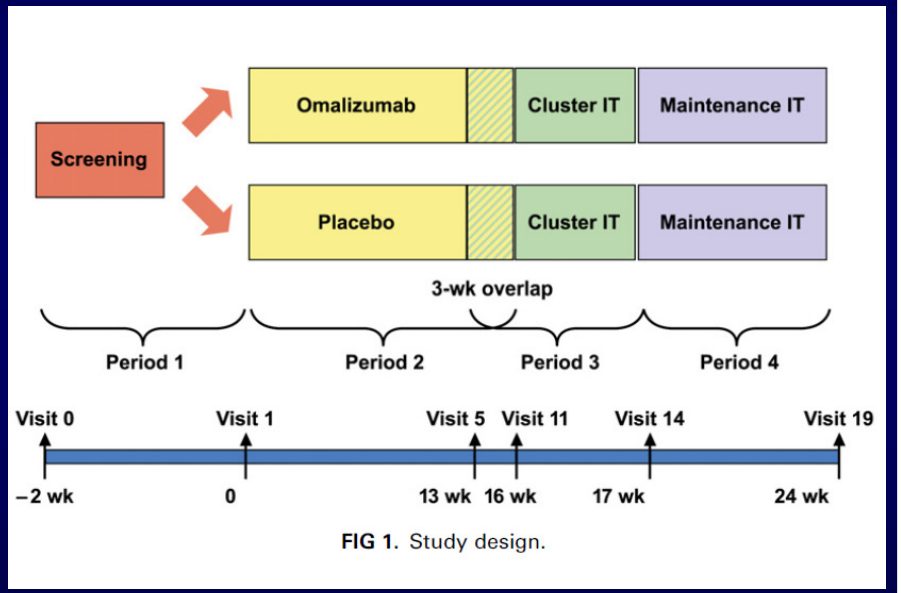


FIG 1. Study design.

Massanari Jaci 2010

Conclusions

A coté de la stratégie à « 5 paliers » du GINA: Des perspectives

Toutes ont l'objectif d'un meilleur contrôle

Utilisation CSI-LABA ALD vs paliers 1 et 2 classiques
(A évaluer mais pourquoi pas, observance faible)

Reconnaissance nationale et internationale d'une place pour ITA acarien en add-on, chez les asthmatiques partiellement contrôlés (paliers 2 et 3?)

Inclure LAMA aux LABA-CSI de palier 4
(symptômes et fonction respiratoire)

Palier 5: A côté de l'omalizumab, nouvelles biothérapies Th2, nonTH2, et globale (en attente ou en cours d'évaluation)

Echecs biothérapies ou absence d'alternative: Thermoplastie bronchique

Schémas complexes à évaluer; biothérapie-ITA, association biothérapie