Asthme sévère
Options thérapeutiques

Module 4 Pneumologie

Lyon (visio), le 13 03 2025

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& VIRPATH

What's new in GINA 2021 (adults and adolescents)?

STARTING TREATMENT

in adults and adolescents with diagnosis of asthma

Track 1 is preferred if the patient is likely to be poorly adherent with daily controller ICS-containing therapy is recommended even if the symptoms are infrequent, as it reduces the risk of severe exacerbations and need for OCS

FIRST ASSESS:

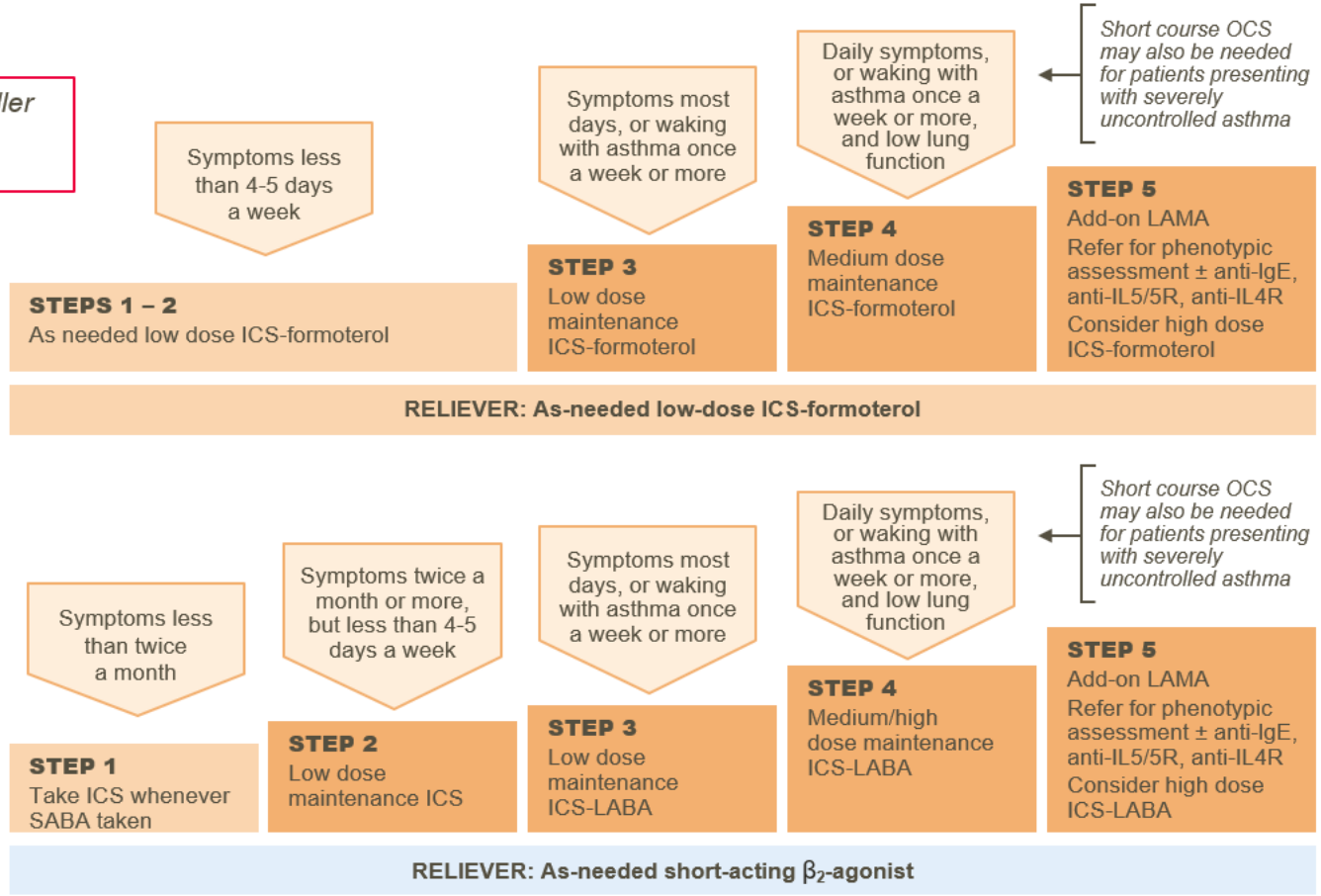
- Confirm diagnosis
- Symptom control and modifiable risk factors, including lung function
- Comorbidities
- Inhaler technique and adherence
- Patient preferences and goals

START HERE IF

CONTROLLER and **PREFERRED RELIEVER** (Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

START HERE IF

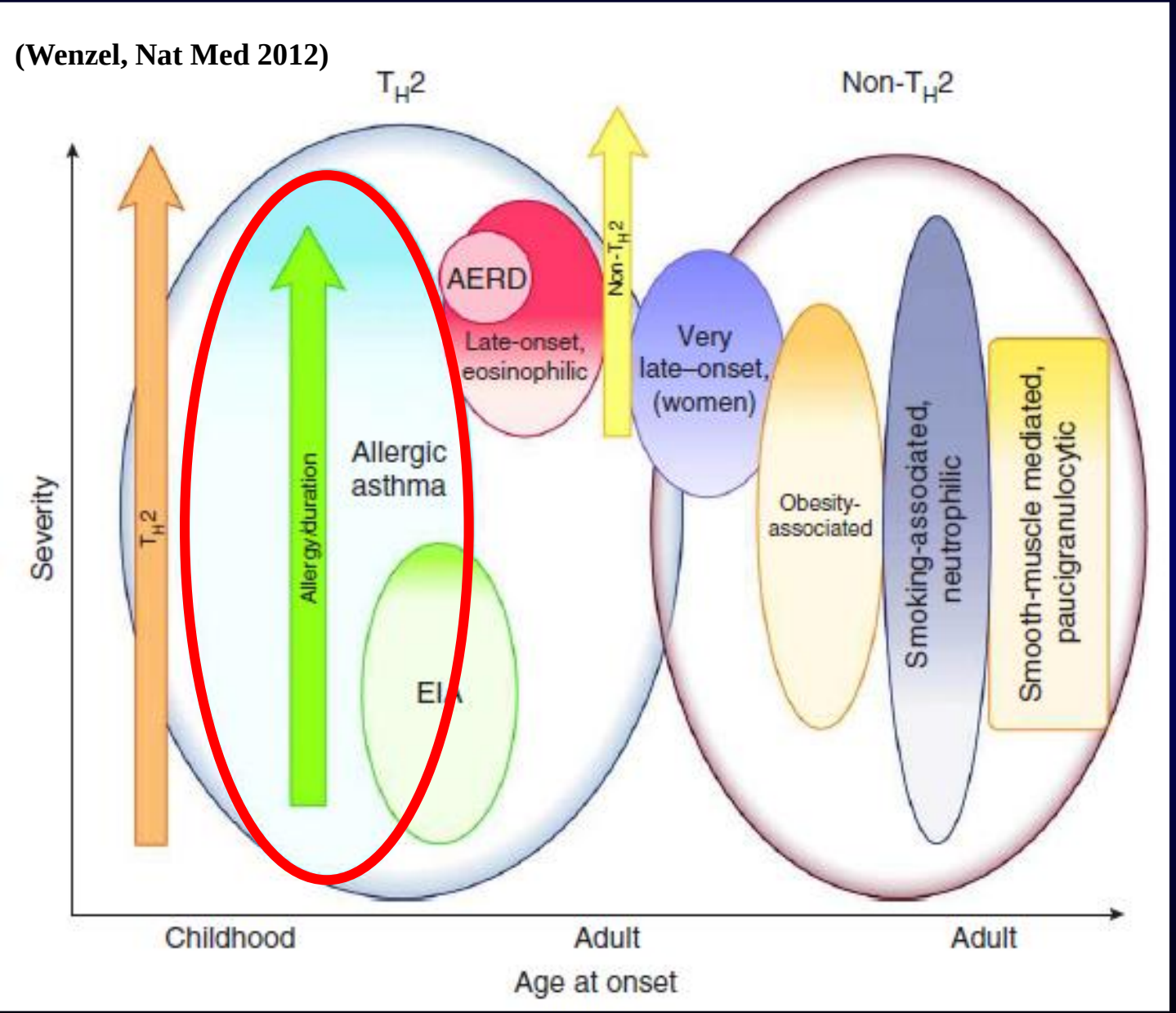
CONTROLLER and **ALTERNATIVE RELIEVER** (Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller therapy



1. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention 2021. Available at: http://www.ginasthma.org/

Du phénotype au choix thérapeutique

(Wenzel, Nat Med 2012)

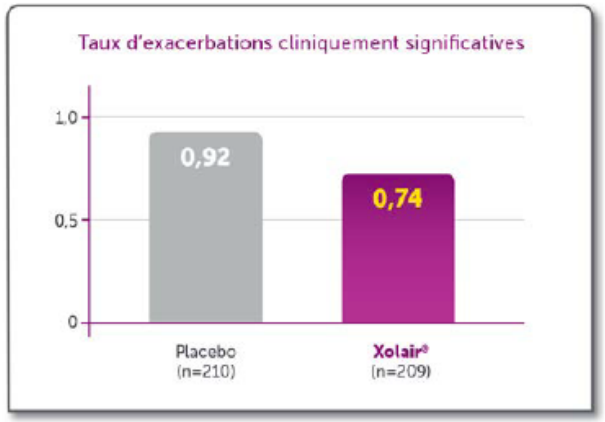


Réduction des exacerbations

Critère principal [16,19,24]

Étude INNOVATE

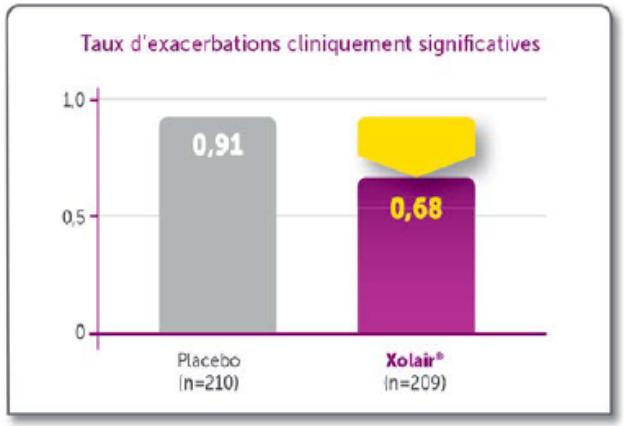
Réduction des exacerbations cliniquement significatives au cours des 28 semaines de traitement



-19,4%

p=0,153 (NS)

Analyse principale sans ajustement sur les exacerbations à l'entrée de l'étude



-26%

p=0,042
Rapport des taux : 0,738
IC 95 % : [0,552-0,998]

Analyse principale avec ajustement sur les exacerbations à l'entrée de l'étude

Taux d'exacerbations cliniquement significatives :

Nombre d'exacerbations cliniquement significatives (aggravation de l'asthme nécessitant le recours à une corticothérapie systémique) rapporté au nombre de patients inclus.

Ajustement sur le taux d'exacerbations cliniquement significatives :

En raison de la différence constatée, a posteriori, de gravité entre les groupes omalizumab et placebo (fréquence d'exacerbations plus importante dans le groupe Xolair® à l'inclusion), une analyse (modèle de régression de Poisson) avec ajustement sur le taux d'exacerbations au cours des 14 mois précédant l'inclusion a été effectuée pour l'analyse du critère principal.[19]

16. Résumé des Caractéristiques du Produit Xolair®.
19. Avis de la Commission de la Transparence de Xolair®. HAS 4 janvier 2006.
24. Humbert M. *et al.* Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy 2005;60:309-316. Etude retenue lors de l'évaluation de l'AMM et du dossier de transparence.

Xolair omalizumab Solution injectable en seringue préremplie 75 mg / 150 mg

Pas d'essai contrôlé randomisé omalizumab vs placebo, pour démontrer une capacité de l'anti-IgE à permettre une épargne en corticoïdes oraux

CHEST Original Research
ASTHMA

Does Omalizumab Make a Difference to the Real-life Treatment of Asthma Exacerbations?

Results From a Large Cohort of Patient With Severe Uncontrolled Asthma

CHEST 2013; 143(2):398–405

Lamiae Grimaldi-Bensouda, PharmD, PhD; Mahmoud Zureik, MD, PhD; Michel Aubier, MD, PhD; Marc Humbert, MD, PhD; Jean Levy, MD; Jacques Benichou, MD, PhD; Mathieu Molimard, MD, PhD; and Lucien Abenhaim, MD, PhD; for the Pharmacoepidemiology of Asthma and Xolair (PAX) Study Group

PAX

Table 1—*Characteristics of Cohort Participants*

Variable	Lost to Follow-up (n = 61)	Followed Up (n = 767)	*P* Value
Female sex	40 (66)	485 (63)	.72
Age, y	51.0 ± 15.8	54.4 ± 15.6	.10
18-40	19 (31)	143 (19)	.04
41-60	28 (46)	366 (48)	…
>60	14 (23)	258 (34)	…
Nonsmoker	41 (67)	509 (66)	.89
BMI ≥ 30 kg/m²	16 (26)	181 (24)	.11
Specific allergy	44 (72)	486 (68)	.30
Total circulating IgE, IU/mL			.19
0-30	1 (2)	59 (8)	
30-700	28 (47)	403 (53)	
700-1,000	2 (3)	30 (4)	
≥ 1,000	5 (8)	62 (8)	
Not reported	23 (39)	203 (27)	
Comorbid conditions			
Allergic rhinitis	41 (67)	426 (56)	.09
Angioedema	6 (10)	71 (9)	.89
Urticaria	7 (11)	119 (16)	.40
Allergy to drugs	9 (9)	184 (24)	.09
Gastroesophageal reflux	22 (36)	287 (38)	.83
Severe exacerbations	3 (4.9)	74 (9.7)	.29
Duration of asthma, y	25.6 ± 16.0	27.3 ± 17.1	.44
Medication at start			
ICS	60 (98)	751 (98)	.81
LABA mimetic	59 (97)	746 (97)	.80
Oral corticosteroid	23 (37.7)	309 (40.3)	.69
Omalizumab	14 (23)	284 (37)	.03
LTRA	33 (54.1)	365 (47.6)	.33
Other	18 (30)	265 (35)	.42

Data are presented as No. (%) or mean ± SD. ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LTRA = leukotriene receptor antagonist.

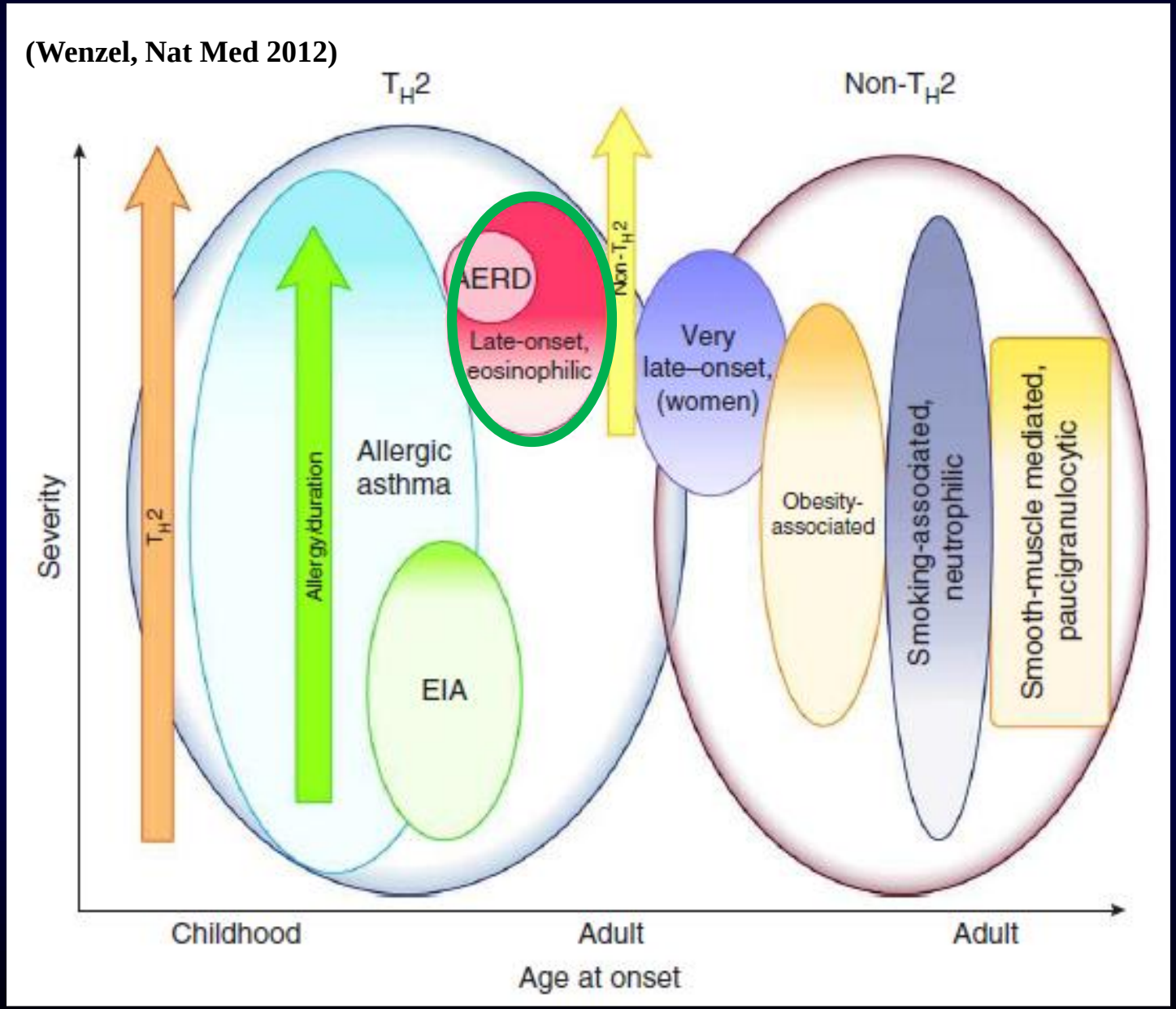
Table 4—*Rates and AHRs of Severe Exacerbations Following Exposure or Not to Omalizumab*

Variable	Rate per 100 Person-y: Total	Absence of Omalizumab	During Omalizumab Use	UHR[a]	AHR[b] (95% CI)
Hospitalization and ED visit					
Entire cohort (n = 767, 1,208 person-y)	30.6	33.4	20.8	0.56	0.57 (0.43-0.78)
In users of omalizumab at least once (n = 374, 564.9 person-y) during omalizumab use (298.9 person-y) and in the absence of omalizumab use (265.9 person-y)	26.2	32.3	20.8	0.53	0.40 (0.28-0.58)
Allergic patients only (n = 486, 750 person-y)	28.0	31.9	20.2	0.50	0.53 (0.39-0.75)
Use of oral corticosteroids (entire cohort)	…	73.8	49.2	*P* < .001	…

AHR = adjusted hazard ratio; UHR = unadjusted hazard ratio. See Table 1 legend for expansion of other abbreviation.
[a]Cox proportional hazard model.
[b]Andersen-Gill extension of the Cox proportional hazard model for correlated data, adjusted with a propensity score for age, sex, smoking history, BMI, gastroesophageal reflux, allergic status, allergic rhinitis, use of oral corticosteroids or LTRAs, and recent severe exacerbations.

Du phénotype au choix thérapeutique

(Wenzel, Nat Med 2012)



Response to anti-IL5 and "true eosinophil phenotype"

Study	Intervention	Sputum eos at entry	Success
Flood-Page (AJRCCM, 2007)	mepolizumab	5% patients had >3% eos	X
Kips (AJRCCM, 2003)	reslizumab	~30% patients had >3% eos	X
Haldar (NEJM, 2009)	mepolizumab	all had >3% on one occasion in 2 yrs	√
Castro, Nair (AJRCCM, 2011)	reslizumab	all had >3% at randomization	√√
Nair (NEJM, 2009)	mepolizumab	All had >3% on ≥3 occasions	√√√

Hargreave FE, Nair P. Chest 2011; 139: 1270-3.

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

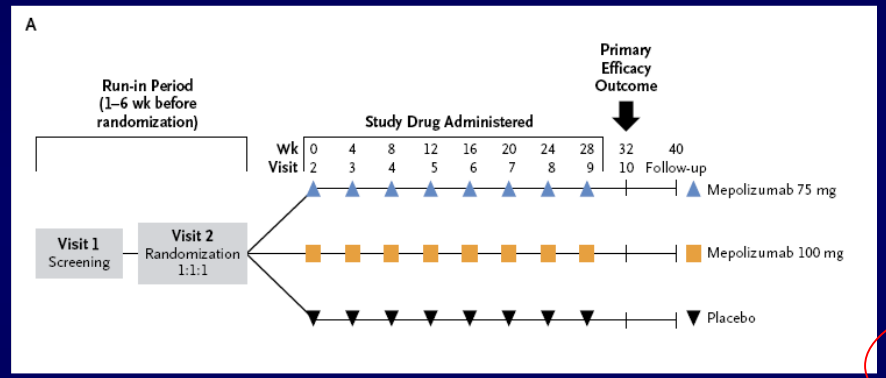
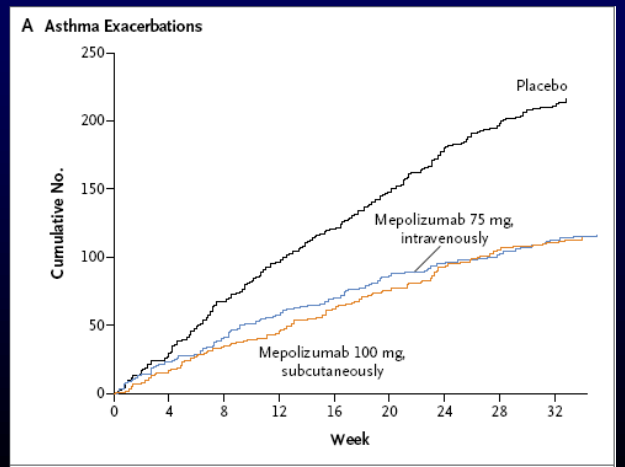
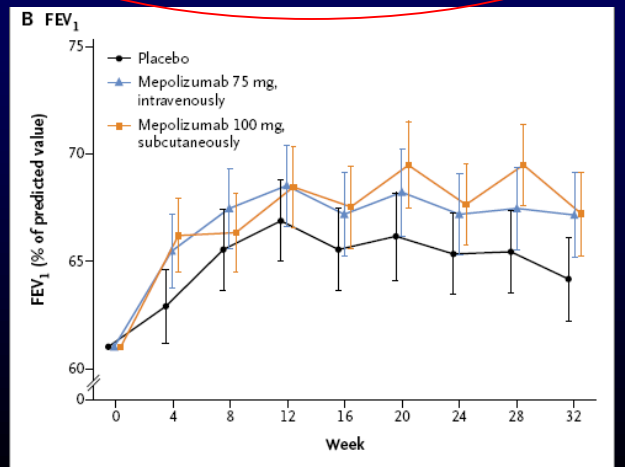


Table 1. Characteristics of the Patients at Baseline in the Intention-to-Treat Population.*

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)





The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 25, 2014 VOL. 371 NO. 13

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

Elisabeth H. Bel, M.D., Ph.D., Sally E. Wenzel, M.D., Philip J. Thompson, M.D., Charlene M. Prazma, Ph.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., Hector G. Ortega, M.D., Sc.D., and Ian D. Pavord, D.M., for the SIRIUS Investigators*

135 asthmatiques éosinophiliques sévères

SIRIUS

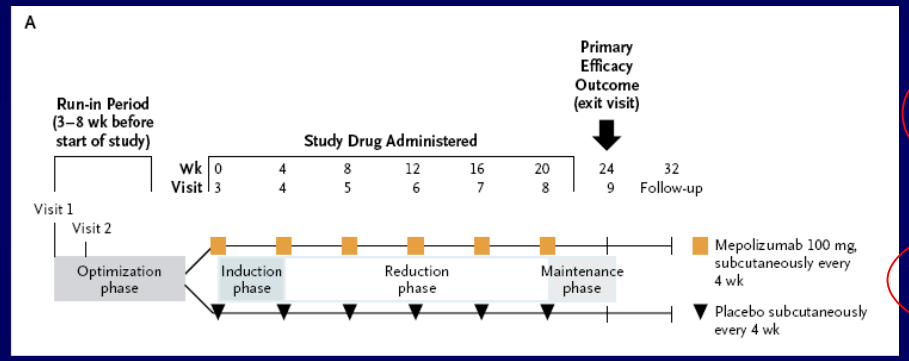
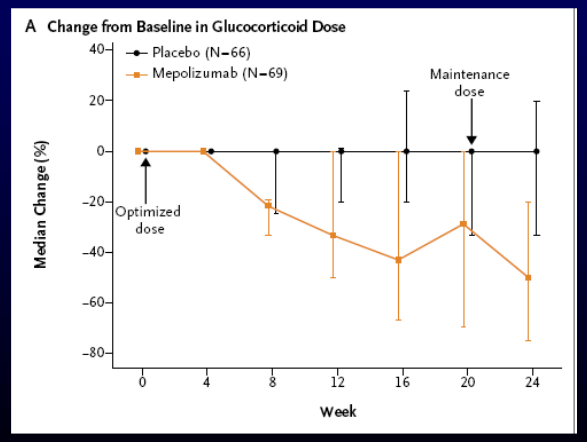
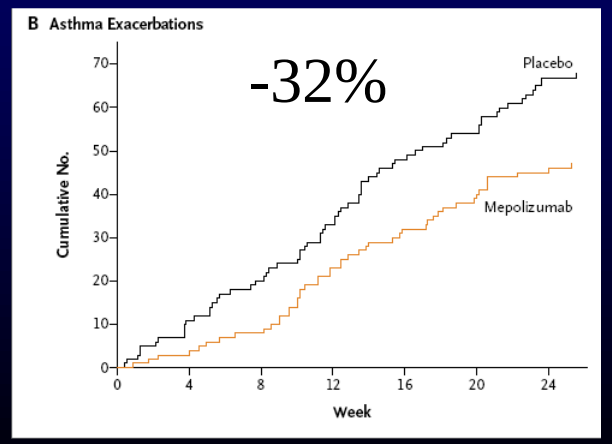
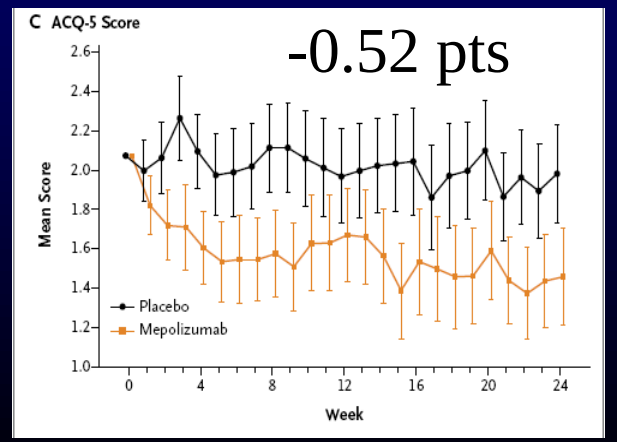


Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Placebo (N=66)	Mepolizumab (N=69)
Mean age (range) — yr	50 (28–70)	50 (16–74)
Female sex — no. (%)	30 (45)	44 (64)
Body-mass index†	29.5±6.0	27.8±5.9
Former smoker — no. (%)	25 (38)	28 (41)
Duration of asthma — yr	20.1±14.4	17.4±11.8
Median daily oral glucocorticoid dose — mg‡		
At screening	15.0	12.5
During optimization phase	12.5	10.0
Duration of oral glucocorticoid use ≥5 yr — no. (%)	31 (47)	34 (49)
FEV_1 before bronchodilation		
Mean — liters	2.00±0.82	1.90±0.66
Percent of predicted value	57.8±18.5	59.6±17.0
FEV_1:FVC ratio before bronchodilation — %§	61±11.7	63±12.4
Percent reversibility of FEV_1	24.8±18.1	27.3±17.4
ACQ-5 score¶	2.0±1.2	2.2±1.3
SGRQ score‖	45±18	50±18
Geometric mean IgE on $\log_e$ scale — U/ml	114±1	117±1
Geometric mean blood eosinophil count on $\log_e$ scale — cells/μl**	230±1001	250±1245
Severe exacerbations in previous year — no./patient	2.9±2.8	3.3±3.4
Exacerbations in the previous year requiring hospitalization — no. (%)	9 (14)	14 (20)
History of asthma-related intubation — no. (%)	3 (5)	2 (3)







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

	All patients (n=1204)			High-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per µL (n=809)			High-dosage ICS plus LABA with baseline blood eosinophils <300 cells per µL (n=395)		
	Placebo (n=407)	Benralizumab 30 mg Q4W (n=399)	Benralizumab 30 mg Q8W (n=398)	Placebo (n=267)	Benralizumab 30 mg Q4W (n=275)	Benralizumab 30 mg Q8W (n=267)	Placebo (n=140)	Benralizumab 30 mg Q4W (n=124)	Benralizumab 30 mg Q8W (n=131)
Age (years)	48·7 (14·9)	50·1 (13·4)	47·6 (14·5)	48·6 (14·7)	49·2 (13·1)	47·6 (14·6)	49·0 (15·3)	52·0 (13·9)	47·8 (14·3)
Age group (years)									
≥12 to <18	23 (6%)	11 (3%)	19 (5%)	12 (4%)	8 (3%)	10 (4%)	11 (8%)	3 (2%)	9 (7%)
≥18 to 75	384 (94%)	388 (97%)	379 (95%)	255 (96%)	267 (97%)	257 (96%)	129 (92%)	121 (98%)	122 (93%)
Sex									
Male	138 (34%)	124 (31%)	146 (37%)	87 (33%)	102 (37%)	93 (35%)	51 (36%)	22 (18%)	53 (40%)
Female	269 (66%)	275 (69%)	252 (63%)	180 (67%)	173 (63%)	174 (65%)	89 (64%)	102 (82%)	78 (60%)
Race									
White	302 (74%)	285 (71%)	287 (72%)	191 (72%)	191 (69%)	192 (72%)	111 (79%)	94 (76%)	95 (73%)
Black or African American	16 (4%)	15 (4%)	15 (4%)	10 (4%)	11 (4%)	10 (4%)	6 (4%)	4 (3%)	5 (4%)
Asian	50 (12%)	54 (14%)	50 (13%)	36 (13%)	39 (14%)	35 (13%)	14 (10%)	15 (12%)	15 (11%)
Other*	39 (10%)	45 (11%)	46 (12%)	30 (11%)	34 (12%)	30 (11%)	9 (6%)	11 (9%)	16 (12%)
Ethnic group									
Hispanic or Latino	77 (19%)	73 (18%)	80 (20%)	57 (21%)	52 (19%)	52 (19%)	20 (14%)	21 (17%)	28 (21%)
Not Hispanic or Latino	330 (81%)	326 (82%)	318 (80%)	210 (79%)	223 (81%)	215 (81%)	120 (86%)	103 (83%)	103 (79%)
Body-mass index (kg/m²)	28·9 (7·1)	29·2 (7·1)	28·2 (6·2)	28·7 (7·0)	28·9 (6·9)	27·7 (6·1)	29·3 (7·1)	29·9 (7·3)	29·3 (6·2)
Missing data	0	2	0	0	2	0	0	0	0
Eosinophil count (cells per µL)	370 (0–2690)	390 (0–3440)	360 (0–3100)	500 (300–2690)	500 (300–3440)	500 (300–3100)	130 (0–290)	160 (0–297)	180 (0–290)
Missing data	4	4	6	3	1	4	1	3	2
Central eosinophil count (cells per µL)	350 (0–3580)	360 (0–3170)	325 (0–3110)	480 (70–2220)	470 (40–3170)	460 (10–3110)	130 (0–3580)	160 (0–760)	150 (0–460)
Missing data	12	12	16	9	6	10	3	6	6
Prebronchodilator FEV$_1$ (L)	1·660 (0·584)	1·655 (0·553)	1·680 (0·582)	1·654 (0·580)	1·673 (0·577)	1·660 (0·574)	1·672 (0·594)	1·615 (0·493)	1·721 (0·597)
Predicted normal (%)	56·6% (15·0)	57·4% (14·1)	56·1% (14·6)	56·4% (14·6)	56·5% (14·4)	55·5% (14·6)	57·0% (15·7)	59·4% (13·2)	57·3% (14·7)
Missing data	7	6	1	5	2	1	2	4	0
Prebronchodilator FEV$_1$/FVC	61 (13)	62 (12)	61 (13)	61 (13)	62 (12)	60 (13)	62 (13)	63 (12)	62 (14)
Missing data	7	6	1	5	2	1	2	4	0
Reversibility (%)	20% (−26 to 154)	18% (−7 to 136)	22% (−12 to 157)	20% (−26 to 154)	18% (−7 to 136)	21% (−10 to 157)	20% (−7 to 138)	17% (−2 to 96)	22% (−12 to 134)
Missing data	26	24	23	16	13	14	10	11	9
ACQ-6 score†	2·87 (0·94)	2·77 (0·96)	2·80 (0·88)	2·90 (0·95)	2·77 (0·95)	2·81 (0·89)	2·82 (0·93)	2·78 (1·00)	2·78 (0·85)

(Table 1 coninues on next page)

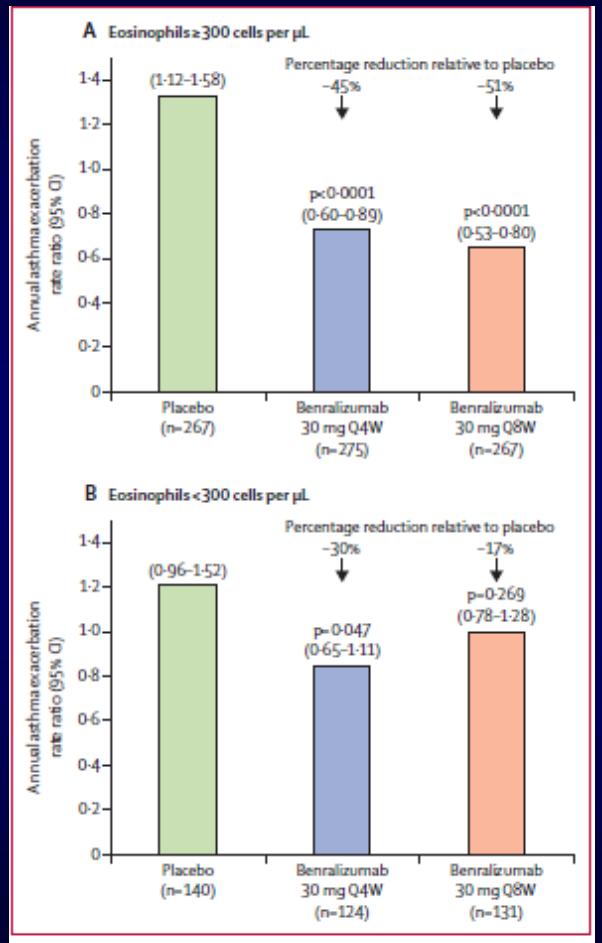


Figure 2: **Annual asthma exacerbation rate estimates at 48 weeks according to baseline blood eosinophil concentrations**
Data for patients with baseline blood eosinophils (A) ≥300 cells per µL and (B) <300 cells per µL in the full analysis set are shown. Estimates were calculated using a negative binomial 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).

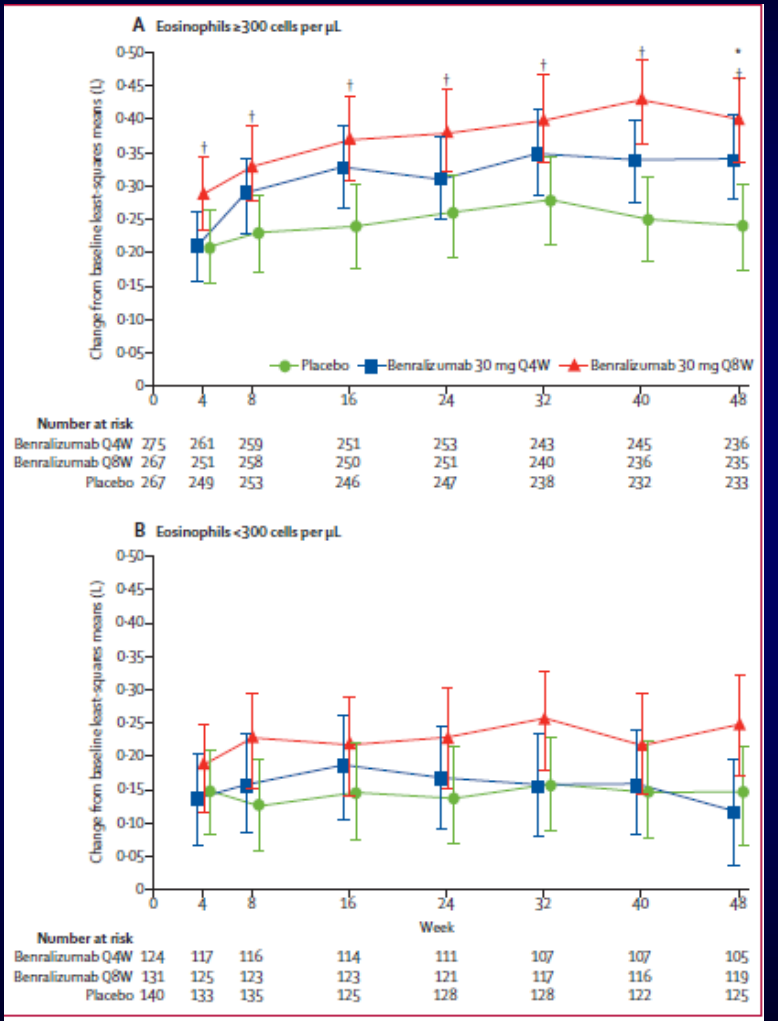


Figure 3: **Change from baseline in prebronchodilator forced expiratory volume in 1 s according to baseline blood eosinophil concentrations**
Data for patients with baseline blood eosinophils (A) ≥300 cells per µL and (B) <300 cells per µL in the full analysis set are shown. Q4W=every 4 weeks. Q8W=every 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.

ZONDA

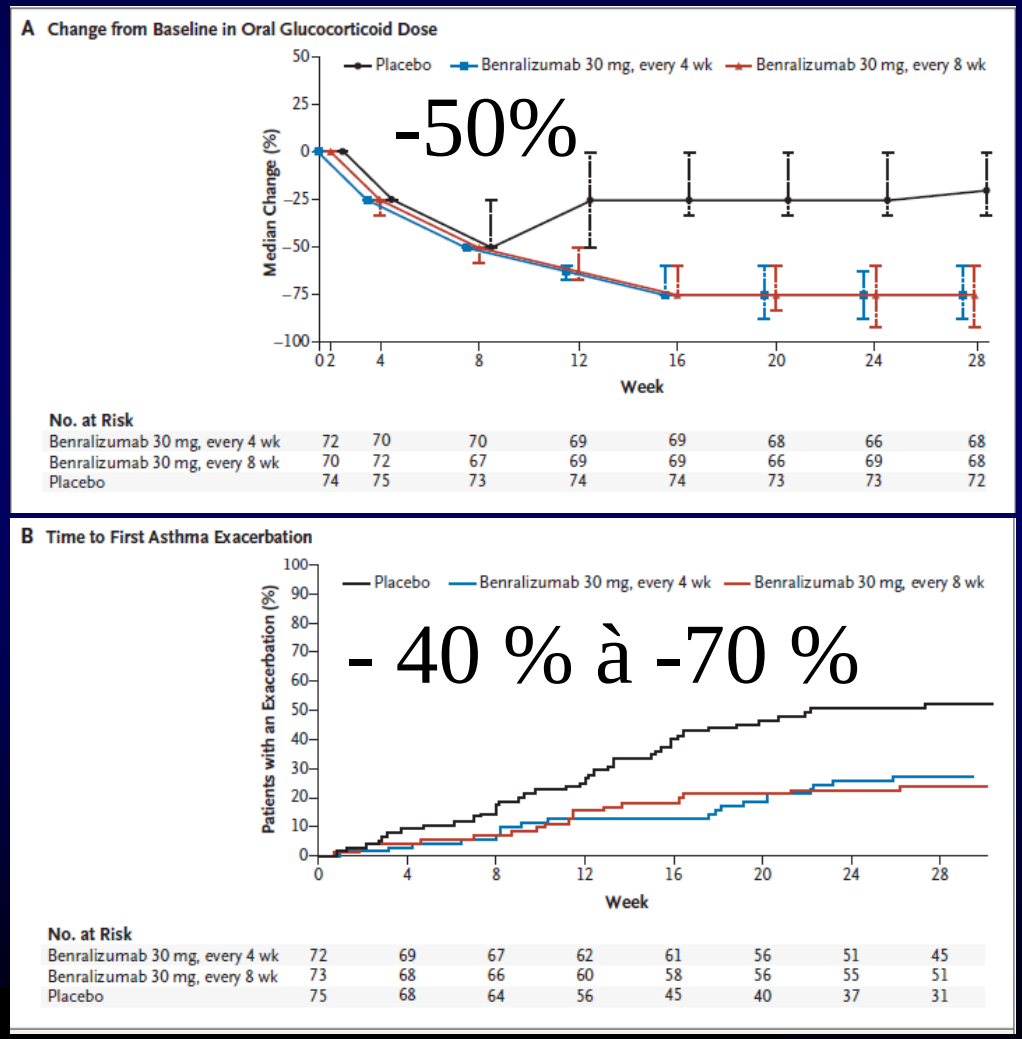
Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma

Parameswaran Nair, M.D., Ph.D., Sally Wenzel, M.D., Klaus F. Rabe, M.D., Ph.D., Arnaud Bourdin, M.D., Ph.D., Njira L. Lugogo, M.D., Piotr Kuna, M.D., Ph.D., Peter Barker, Ph.D., Stephanie Sproule, M.Math., Sandhia Ponnarambil, M.D., and Mitchell Goldman, M.D., for the ZONDA Trial Investigators*

NEJM 2017

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

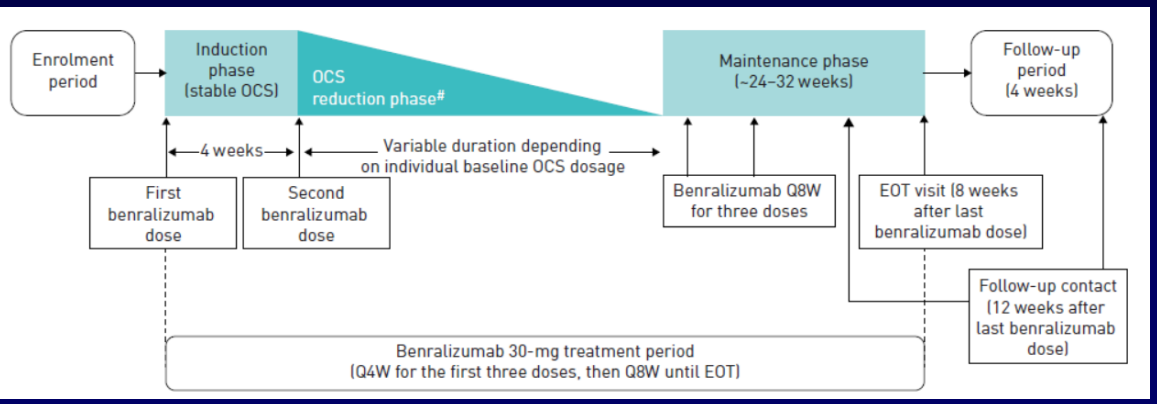
Characteristic	Placebo (N=75)	Benralizumab, Every 4 Wk (N=72)	Benralizumab, Every 8 Wk (N=73)
Age — yr	49.9±11.7	50.2±12.0	52.9±10.1
Female sex — no. (%)	48 (64)	40 (56)	47 (64)
Body-mass index†	28.7±5.2	29.8±6.8	30.2±6.5
Median smoking history (range) — pack-yr	6.0 (1 to 9)	5.5 (2 to 9)	5.0 (1 to 8)
Median time since asthma diagnosis (range) — yr	10.5 (1.1 to 54.5)	13.3 (1.2 to 52.3)	16.3 (1.3 to 53.0)
Median oral glucocorticoid dose (range) — mg/day			
At trial entry‡	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)
At end of run-in phase	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)
Mean inhaled glucocorticoid dose (range) — μg/day	1232 (250 to 5000)	1033 (250 to 3750)	1192 (100 to 3250)
Leukotriene-receptor antagonist — no. (%)	25 (33)	28 (39)	29 (40)
No. of exacerbations in previous 12 mo	2.5±1.8	2.8±2.0	3.1±2.8
FEV_1 before bronchodilation			
Value — liters	1.931±0.662	1.850±0.741	1.754±0.635
Percent of predicted normal value	62.0±16.5	57.4±18.0	59.0±17.9
FEV_1:FVC ratio before bronchodilation — %	62±13	59±13	59±12
Median percent reversibility of FEV_1 (range)§	16.4 (−5.4 to 93.4)	18.2 (−3.0 to 126.0)	22.6 (−3.4 to 88.0)
Total asthma symptom score¶	2.4±1.0	2.5±1.0	2.3±1.1
ACQ-6 score‖	2.7±1.0	2.6±1.1	2.4±1.2
AQLQ(S)+12 score**	4.1±1.1	4.2±1.1	4.4±1.2
Blood eosinophil count			
Median count (range) — cells/mm^3††	535 (160 to 4550)	462 (160 to 1740)	437 (154 to 2140)
Distribution — no. (%)			
≥150 to <300 cells/mm^3	11 (15)	10 (14)	12 (16)
≥300 cells/mm^3	64 (85)	62 (86)	61 (84)



Corticosteroid tapering with benralizumab treatment for eosinophilic asthma: PONENTE Trial

ERJ Open Res 2019

Andrew Menzies-Gow[1], Jonathan Corren[2,3], Elisabeth H. Bel[4], Jorge Maspero[5], Liam G. Heaney[6], Mark Gurnell[7], Peter Wessman[8], Ubaldo J. Martin[9], Shahid Siddiqui[9] and Esther Garcia Gil[10]



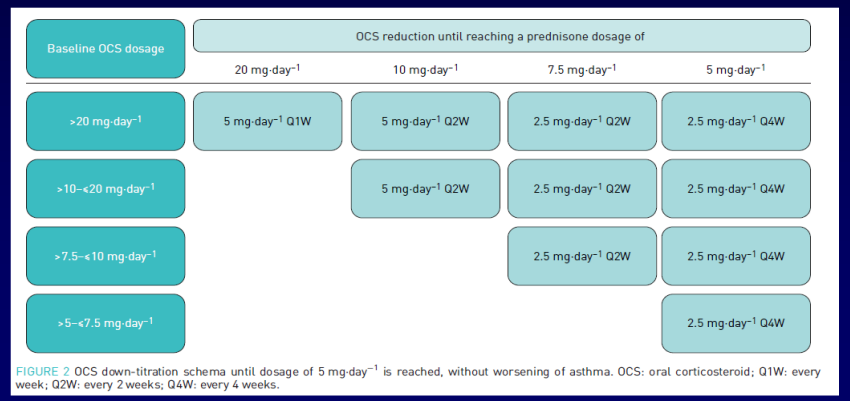


FIGURE 2 OCS down-titration schema until dosage of 5 mg·day^{-1} is reached, without worsening of asthma. OCS: oral corticosteroid; Q1W: every week; Q2W: every 2 weeks; Q4W: every 4 weeks.

Evaluation axe surrénalien à 4 semaines

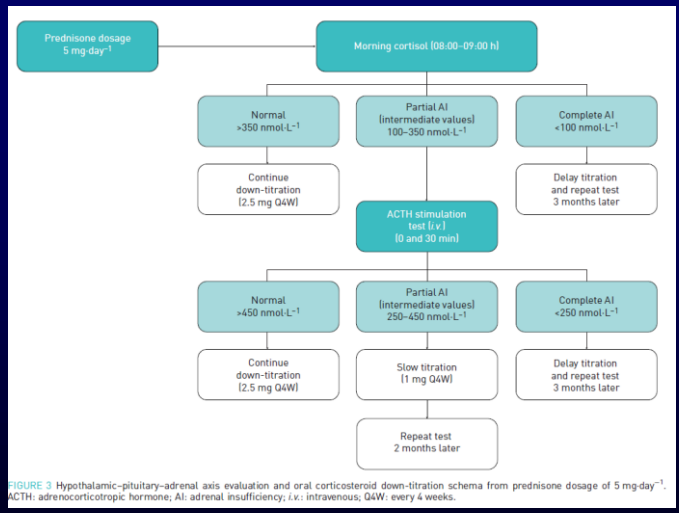


FIGURE 3 Hypothalamic–pituitary–adrenal axis evaluation and oral corticosteroid down-titration schema from prednisone dosage of 5 mg·day^{-1}. ACTH: adrenocorticotropic hormone; AI: adrenal insufficiency; i.v.: intravenous; Q4W: every 4 weeks.

Proportion de patients parvenant, sans perte de contrôle de l'asthme, pendant au moins 4 semaines, à :

1.une diminution de 100 % de la dose quotidienne de CSO → **62%**

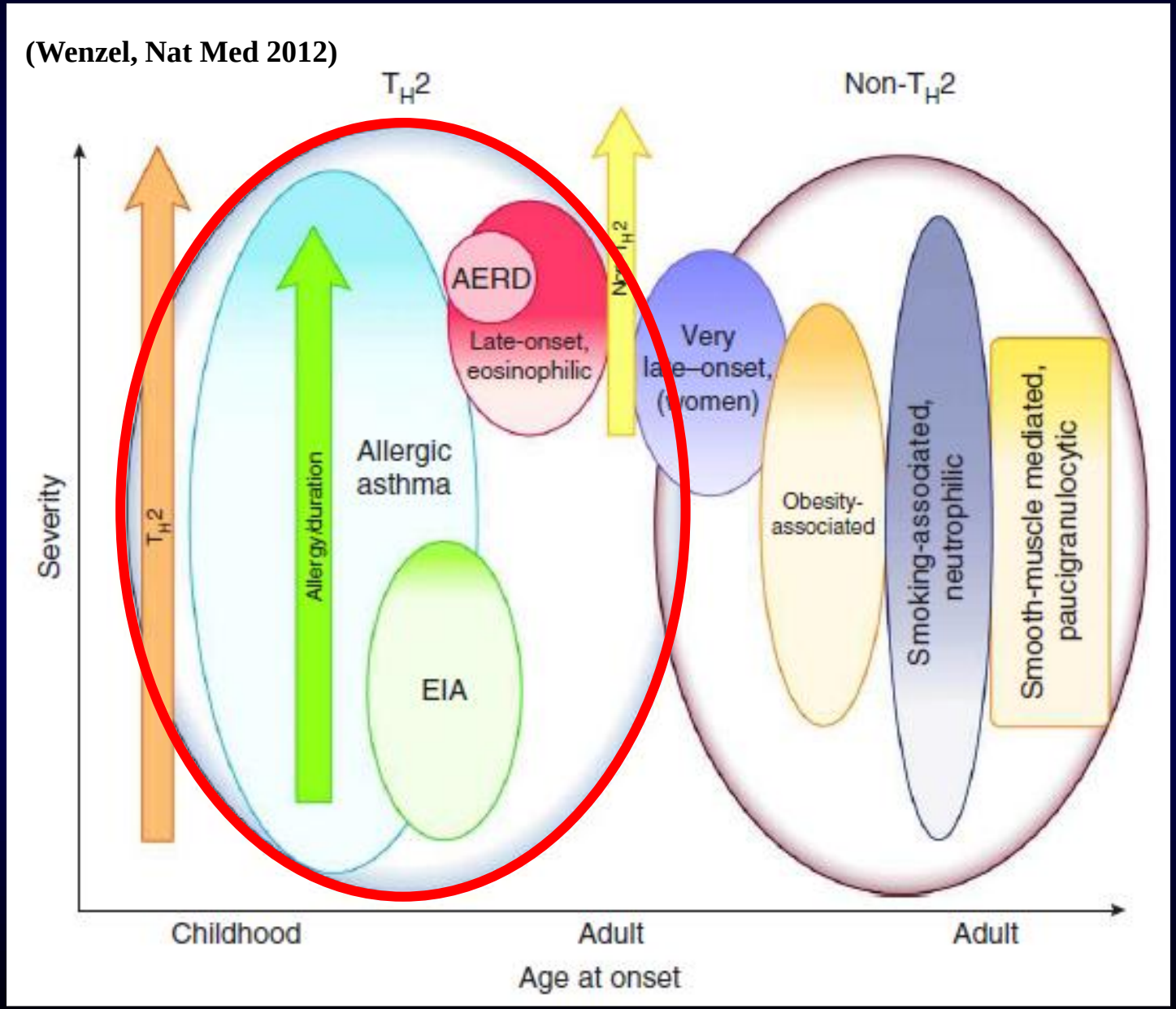
2. une diminution de 100 % ou à une dose quotidienne ≤ 5 mg, si les CSO n'ont pas pu être diminués davantage en raison d'une insuffisance surrénalienne → **81%**

vs réduction de plus de **50%** des CSO chez 2/3 des patients et **50%** de patients sevrés des CSO (ZONDA)

Menzies Gow et al. *Corticosteroid tapering with benralizumab treatment for eosinophilic asthma: PONENTE Trial. ERJ Open Res 2019; 5: 00009-2019*

Du phénotype au choix thérapeutique

(Wenzel, Nat Med 2012)



ORIGINAL ARTICLE

Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma

M. Castro, J. Corren, I.D. Pavord, J. Maspero, S. Wenzel, K.F. Rabe, W.W. Busse, L. Ford, L. Sher, J.M. FitzGerald, C. Katelaris, Y. Tohda, B. Zhang, H. Staudinger, G. Pirozzi, N. Amin, M. Ruddy, B. Akinlade, A. Khan, J. Chao, R. Martincova, N.M.H. Graham, J.D. Hamilton, B.N. Swanson, N. Stahl, G.D. Yancopoulos, and A. Teper

QUEST

Table 1. Selected Baseline Demographic and Clinical Characteristics of the Patients (Intention-to-Treat Population).*

Characteristic	Placebo, 1.14 ml (N=317)	Dupilumab, 200 mg (N=631)	Placebo, 2.00 ml (N=321)	Dupilumab, 300 mg (N=633)	Overall Population (N=1902)
Age — yr	48.2±15.6	47.9±15.3	48.2±14.7	47.7±15.6	47.9±15.3
Female sex — no. (%)	198 (62.5)	387 (61.3)	218 (67.9)	394 (62.2)	1197 (62.9)
Prebronchodilator FEV_1 — liters	1.76±0.61	1.78±0.62	1.75±0.57	1.78±0.60	1.78±0.60
Percent of predicted normal value	58.43±13.22	58.38±13.52	58.35±13.87	58.51±13.52	58.43±13.52
FEV_1 reversibility — %	25.06±18.76	27.39±22.79	26.45±17.65	25.73±23.79	26.29±21.73
No. of exacerbations in past year	2.07±1.58	2.07±2.66	2.31±2.07	2.02±1.86	2.09±2.15
Use of high-dose inhaled glucocorticoid — no. (%)	172 (54.3)	317 (50.2)	167 (52.0)	323 (51.0)	979 (51.5)
ACQ-5 score†	2.71±0.73	2.76±0.80	2.77±0.77	2.77±0.76	2.76±0.77
Ongoing atopic or allergic condition — no. (%)	266 (83.9)	509 (80.7)	266 (82.9)	524 (82.8)	1565 (82.3)
Nasal polyposis or chronic rhinosinusitis — no. (%)	73 (23.0)	141 (22.3)	80 (24.9)	145 (22.9)	439 (23.1)
Former smoker — no. (%)	59 (18.6)	126 (20.0)	67 (20.9)	116 (18.3)	368 (19.3)
No. of pack-yr	3.96±2.81	3.89±2.69	4.07±3.12	4.15±3.04	4.02±2.89
Biomarker levels					
Blood eosinophil count — cells/mm^3					
Mean	370±338	349±345	391±419	351±369	360±366
Median (range)	270 (0–2200)	250 (0–3610)	265 (0–3580)	250 (0–4330)	255 (0–4330)
FE_{NO} — ppb	34.47±28.54	34.45±34.91	38.39±38.00	34.01±29.74	34.97±32.85
Total IgE — IU/ml	394±625	461±818	448±797	415±701	432±747

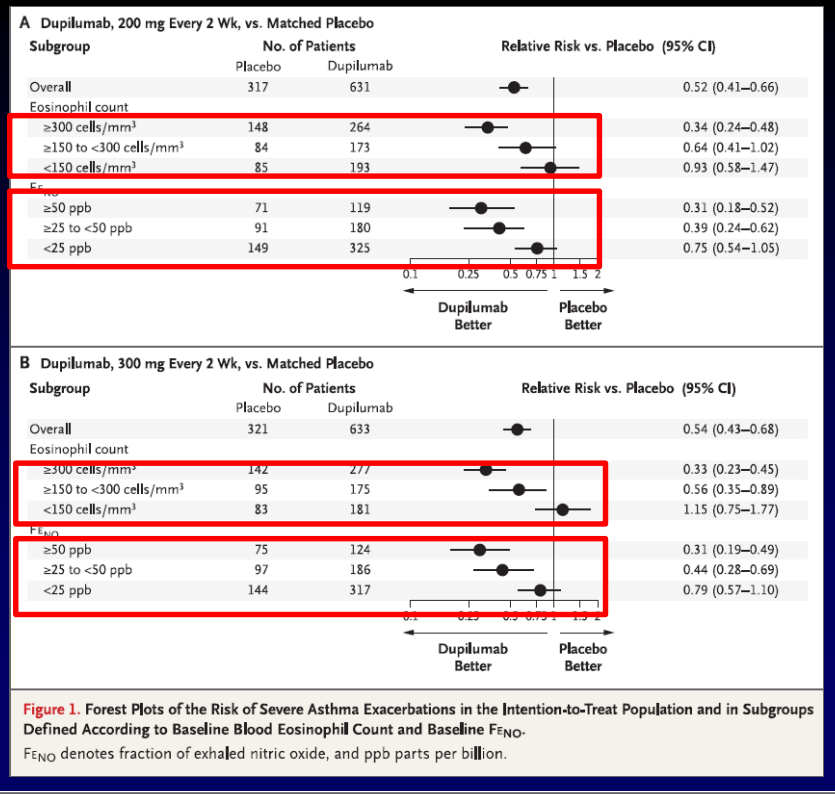
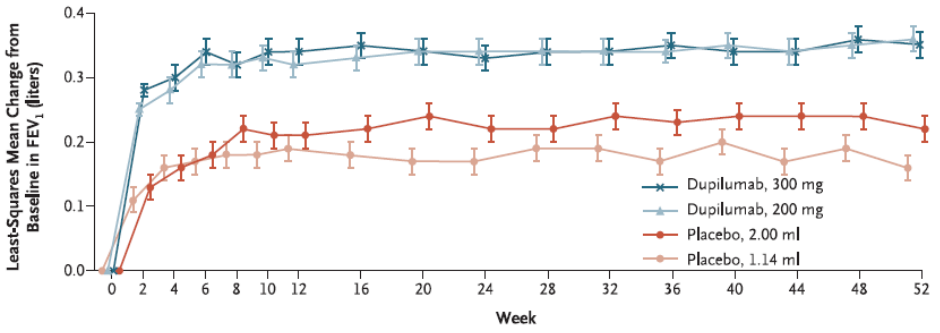


Figure 1. Forest Plots of the Risk of Severe Asthma Exacerbations in the Intention-to-Treat Population and in Subgroups Defined According to Baseline Blood Eosinophil Count and Baseline FE_{NO}.

FE_{NO} denotes fraction of exhaled nitric oxide, and ppb parts per billion.



No. at Risk

Dupilumab, 300 mg	633	625	614	612	609	598	610	611	593	596	586	579	584	584	570	562	488
Dupilumab, 200 mg	631	610	613	615	604	607	611	605	601	599	589	585	590	577	581	570	477
Placebo, 2.00 ml	321	313	311	313	311	309	313	310	304	296	304	301	301	297	292	290	250
Placebo, 1.14 ml	317	315	307	301	305	301	307	300	303	300	290	286	289	287	288	281	240

Figure 2. Change in the Prebronchodilator FEV_1 from Baseline over the 52-Week Intervention Period in the Intention-to-Treat Population.

Patients received dupilumab at a dose of 200 or 300 mg every 2 weeks or a matched-volume placebo. For the lower dose of dupilumab, the matched placebo had a volume of 1.14 ml. For the higher dose of dupilumab, the matched placebo had a volume of 2.00 ml. P<0.001 for the comparisons of each dupilumab dose with matched placebo at week 12. I bars represent the standard error. FEV_1 denotes forced expiratory volume in 1 second.

ORIGINAL ARTICLE

Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma

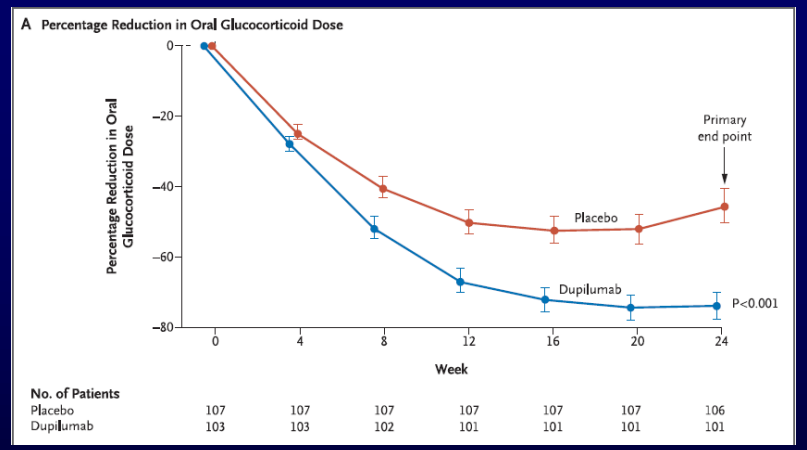
Klaus F. Rabe, M.D., Ph.D., Parameswaran Nair, M.D., Ph.D., Guy Brusselle, M.D., Ph.D., Jorge F. Maspero, M.D., Mario Castro, M.D., Lawrence Sher, M.D., Hongjie Zhu, Ph.D., Jennifer D. Hamilton, Ph.D., Brian N. Swanson, Ph.D., Asif Khan, M.B., B.S., M.P.H., Jingdong Chao, Ph.D., Heribert Staudinger, M.D., Ph.D., Gianluca Pirozzi, M.D., Ph.D., Christian Antoni, M.D., Ph.D., Nikhil Amin, M.D., Marcella Ruddy, M.D., Bolanle Akinlade, M.D., Neil M.H. Graham, M.B., B.S., M.D., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., and Ariel Teper, M.D.

N ENGL J MED 378;26 NEJM.ORG JUNE 28, 2018

VENTURE

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Placebo Group (N = 107)	Dupilumab Group (N = 103)	Total (N = 210)
Age — yr	50.7±12.8	51.9±12.5	51.3±12.6
Male sex — no. (%)	42 (39)	41 (40)	83 (40)
No. of severe asthma exacerbations in previous year	2.17±2.24	2.01±2.08	2.09±2.16
Time since first oral glucocorticoid prescription — yr	1.64±3.54	1.77±3.52	1.70±3.52
Daily oral glucocorticoid dose — mg/day			
Dose before adjustment phase	11.83±6.02	11.79±6.40	11.81±6.20
Adjusted dose	11.75±6.31	10.75±5.90	11.26±6.12
Prebronchodilator FEV_1 — liters	1.63±0.61	1.53±0.53	1.58±0.57
Prebronchodilator FEV_1 — % of predicted value	52.69±15.14	51.64±15.28	52.18±15.18
FEV_1 reversibility — liters†	0.28±0.32	0.29±0.31	0.28±0.31
Any relevant medical history — no. (%)‡	86 (80)	76 (74)	162 (77)
Nasal polyposis	38 (36)	33 (32)	71 (34)
Food allergy	10 (9)	10 (10)	20 (10)
Former smoker — no. (%)	17 (16)	24 (23)	41 (20)
Time since cessation of smoking — yr	16.98±11.01	13.99±10.96	15.23±10.94
ACQ-5 score§	2.58±1.09	2.42±1.24	2.50±1.16
Blood eosinophil count — cells/mm^3	325±298	370±316	347±307
FE_{NO} — ppb	39.62±34.12	35.55±28.34	37.61±31.38



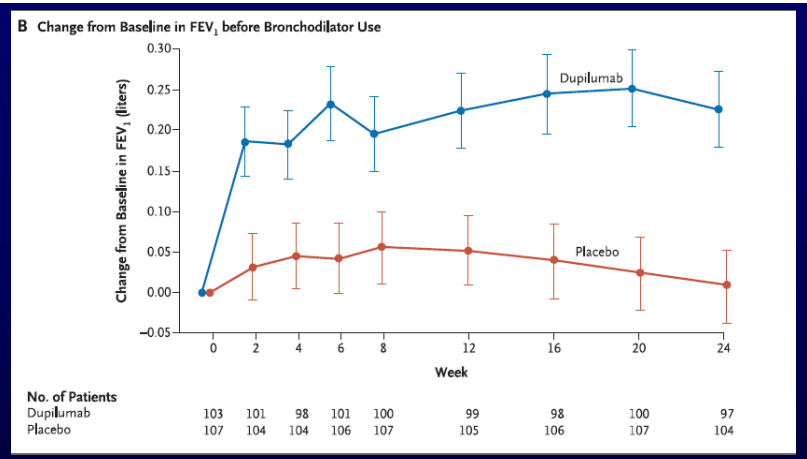
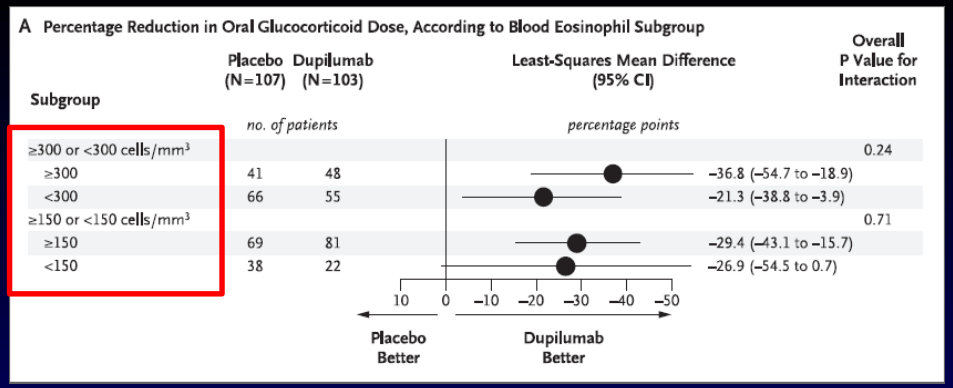


Figure 1. Primary End Point at Week 24 and Change in Prebronchodilator FEV_1 during the 24-Week Intervention Period (Intention-to-Treat Population).

The primary end point was the percentage reduction in the oral glucocorticoid dose at week 24. Values are least-squares means, and I bars represent the standard error. Values are slightly offset from each other at each time point for clarity. The dashed line in each panel indicates baseline. The intention-to-treat population included all the patients who underwent randomization; data were analyzed according to the assigned trial group, regardless of the trial regimen received. FEV_1 denotes forced expiratory volume in 1 second.



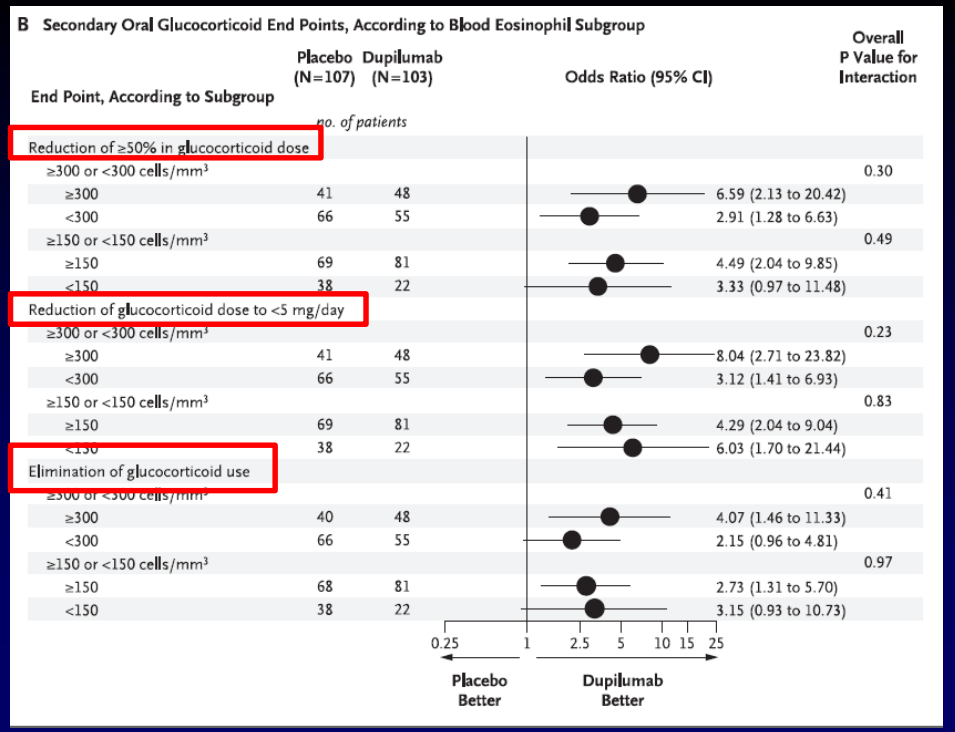


Figure 2. Primary End Point and Secondary Oral Glucocorticoid End Points at Week 24, According to Baseline Blood Eosinophil Subgroup.

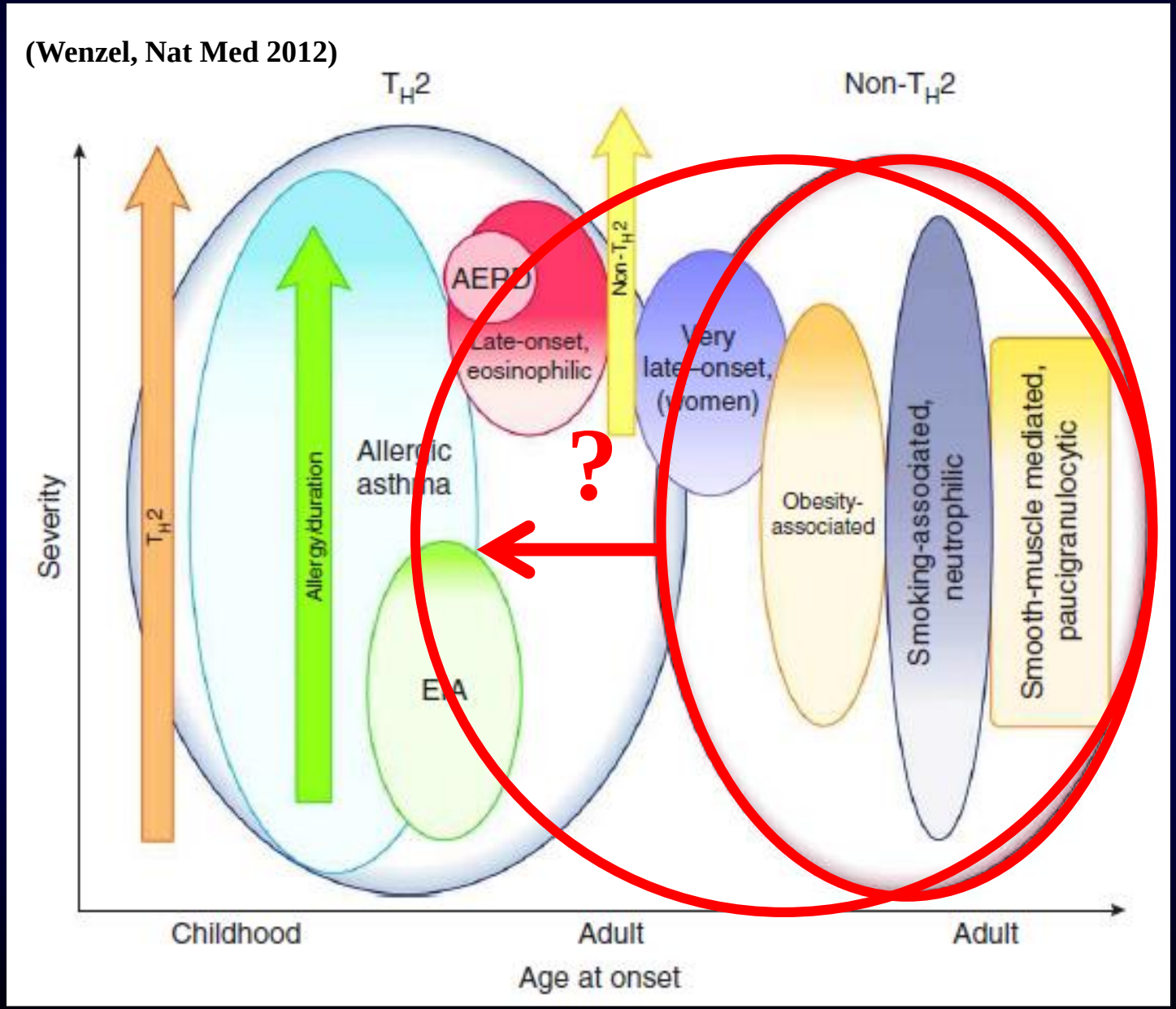
These data have not been controlled for multiple comparisons. Only the patients whose glucocorticoid dose was 30 mg per day or less at baseline were included in the analysis of the end point regarding the elimination of glucocorticoid use.

Table 2. Overview of Adverse Events during 24-Week Intervention Period and Injection-Site Reactions (Safety Population).*

Event	Placebo Group (N = 107)	Dupilumab Group (N = 103)
	number (percent)	
Any adverse event	69 (64)	64 (62)
Any serious adverse event	6 (6)	9 (9)
Any adverse event leading to death	0	0
Any adverse event leading to permanent discontinuation of trial regimen	4 (4)	1 (1)
Adverse event occurring in ≥5% of patients in either group†		
Viral upper respiratory tract infection	19 (18)	9 (9)
Bronchitis	6 (6)	7 (7)
Sinusitis	4 (4)	7 (7)
Influenza	6 (6)	3 (3)
Eosinophilia‡	1 (1)	14 (14)
Injection-site reaction§	4 (4)	9 (9)
≥1 measurement of blood eosinophil count >3000 cells/mm³	1 (1)	13 (13)

Du phénotype au choix thérapeutique

(Wenzel, Nat Med 2012)

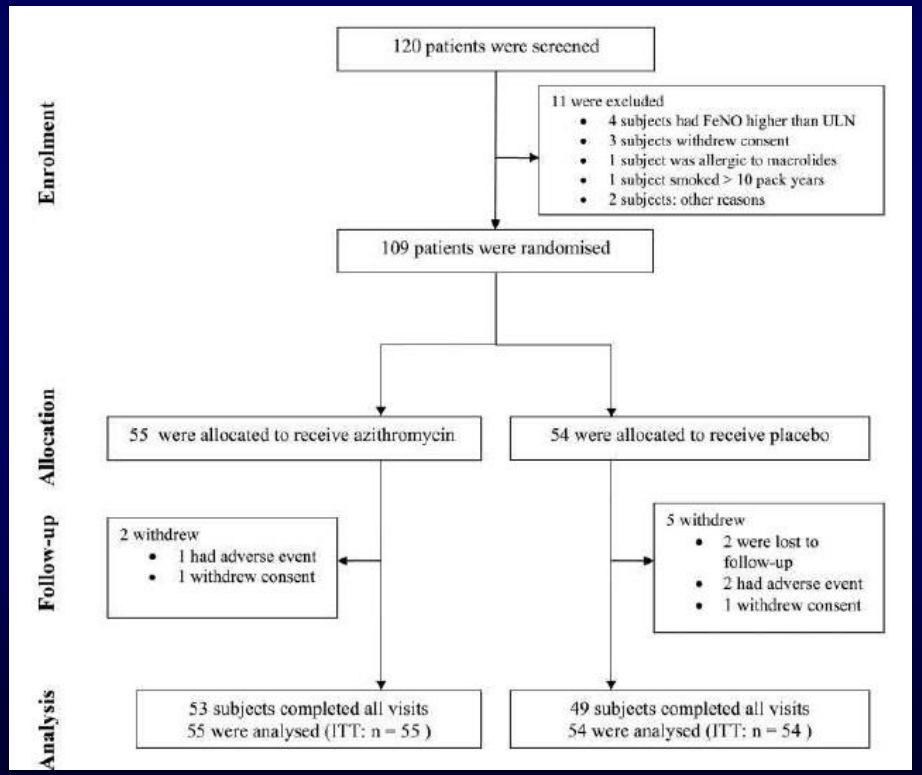


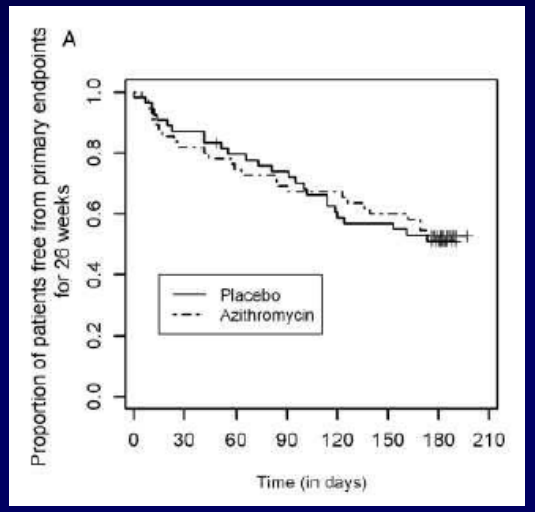
THORAX

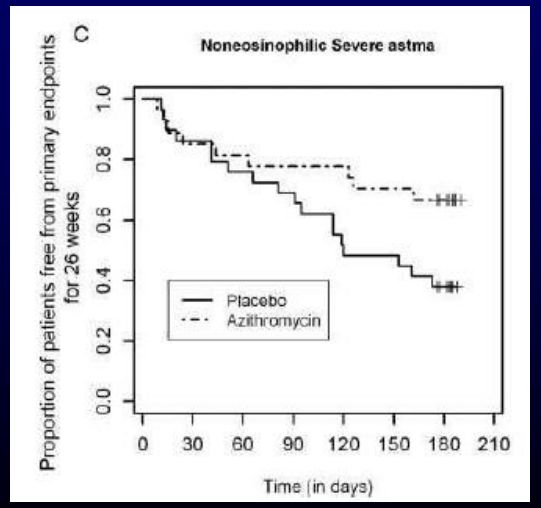
Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial

Thorax 2013

Guy G Brusselle, Christine VanderStichele, Paul Jordens, et al.







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

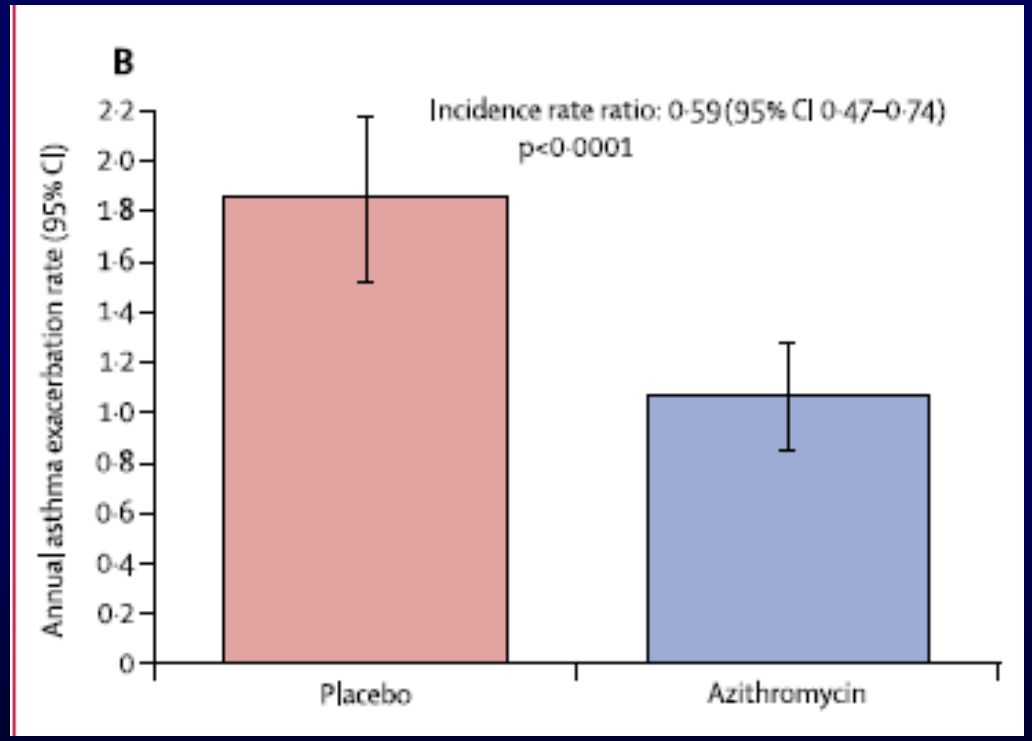
Peter G Gibson, Ian A Yang, John W Upham, Paul N Reynolds, Sandra Hodge, Alan L James, Christine Jenkins, Matthew J Peters, Guy B Marks, Melissa Baraket, Heather Powell, Steven L Taylor, Lex E X Leong, Geraint B Rogers, Jodie L Simpson

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)

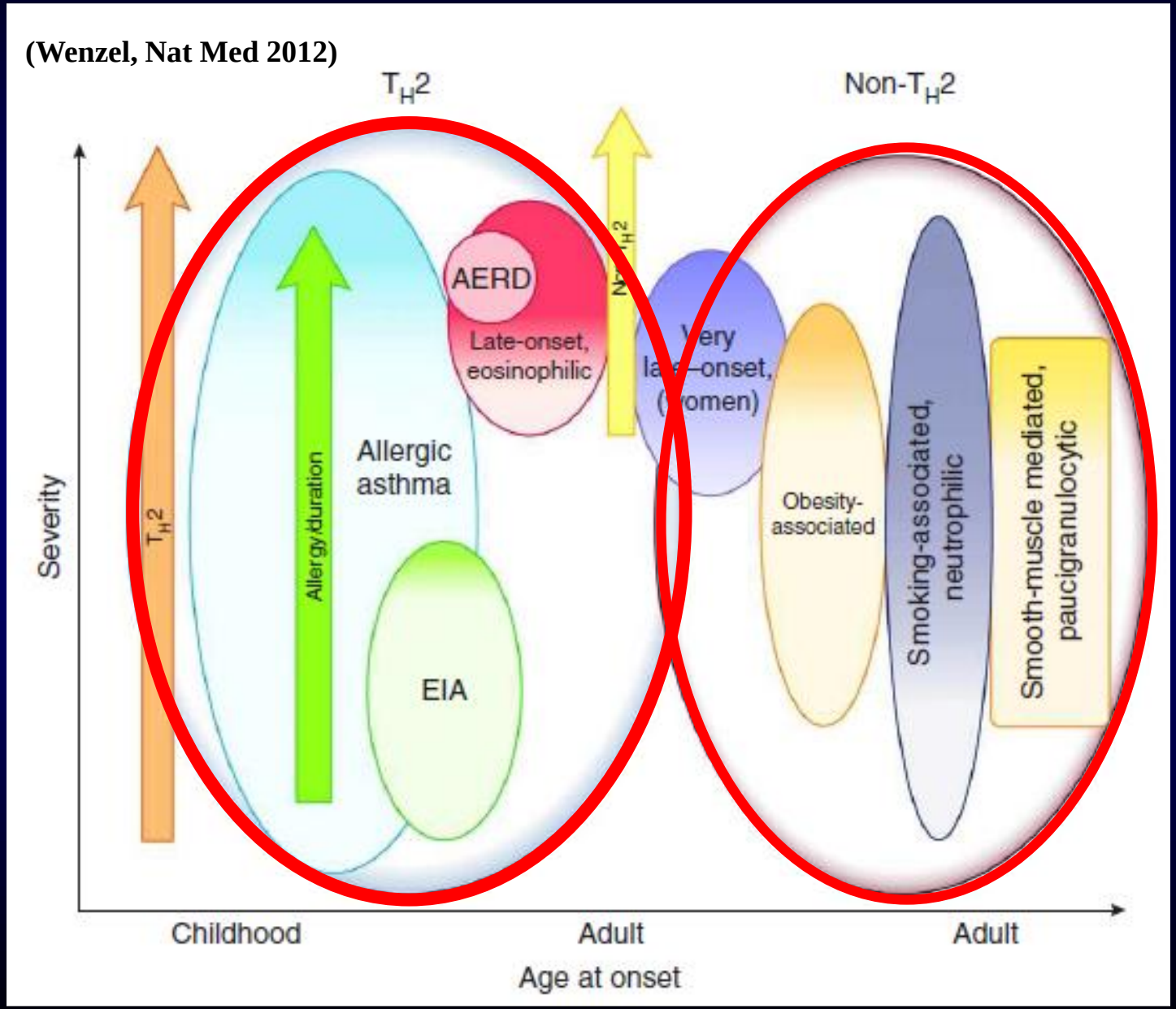
Data are median (IQR), mean (SD), or n (%). AQLQ=Asthma Quality of Life Questionnaire. ACQ6=Asthma Control Questionnaire. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity.

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

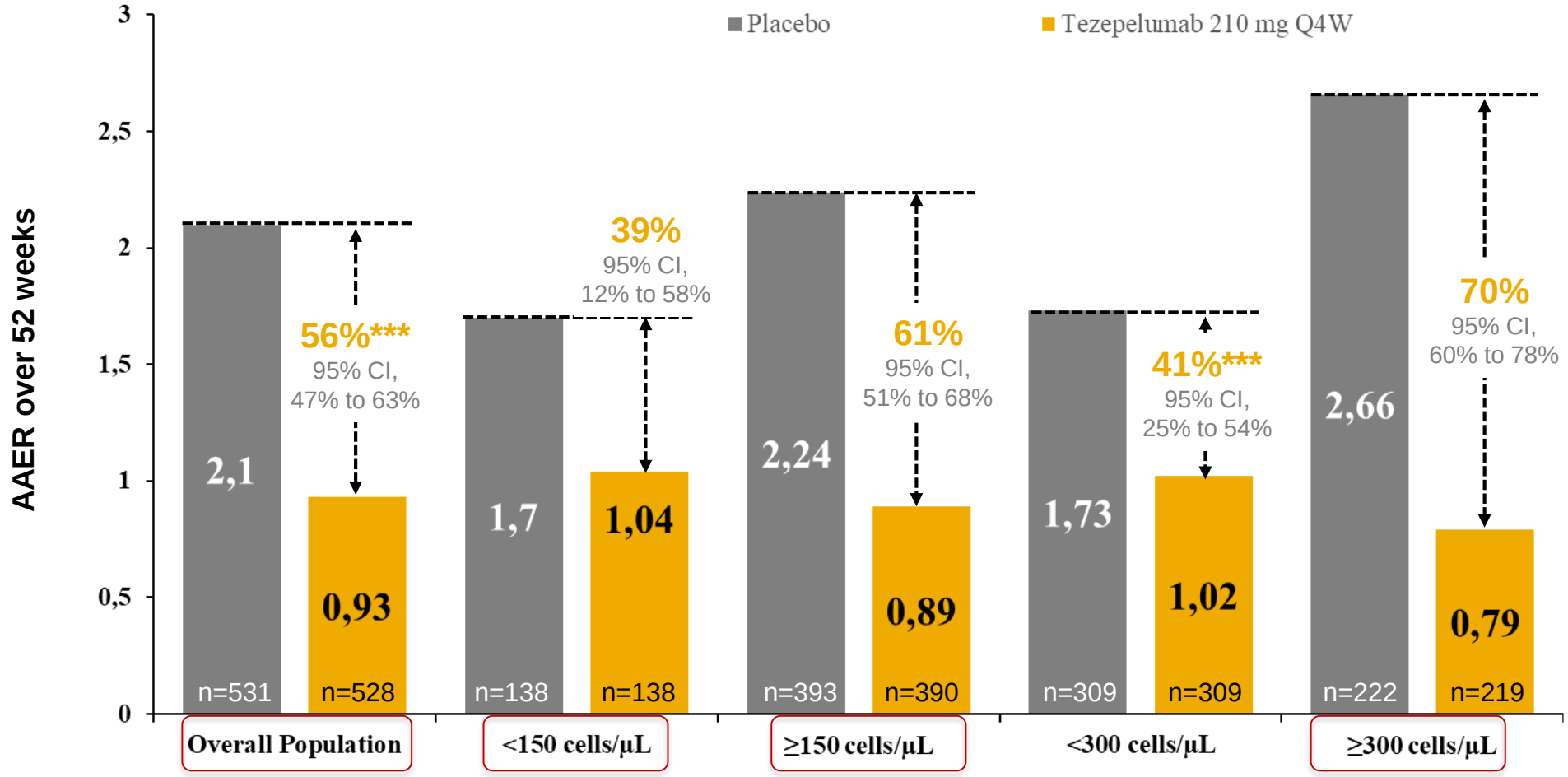


Du phénotype au choix thérapeutique

(Wenzel, Nat Med 2012)



NAVIGATOR:
Effect on Asthma Exacerbations By Eosinophil Count

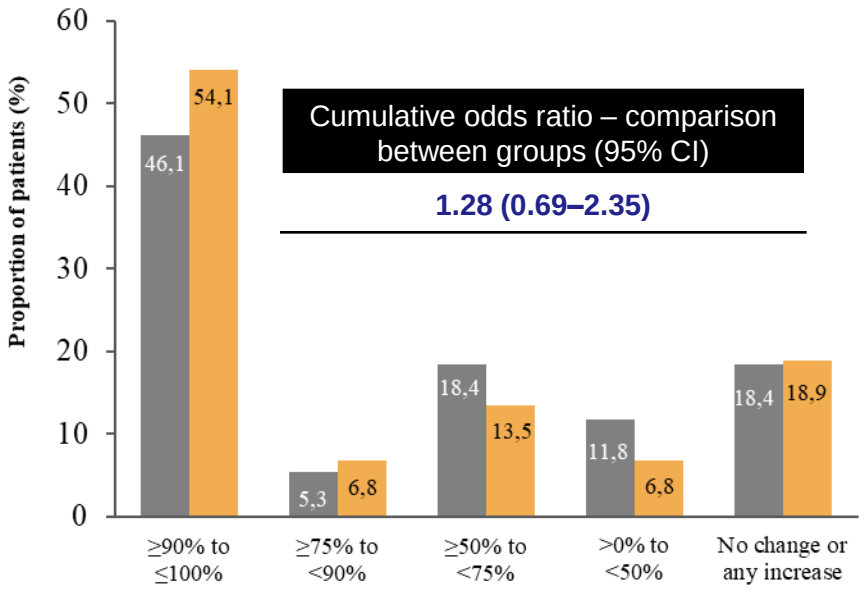


Tezepelumab significantly reduced the AAER relative to placebo in the overall population and in patients with a low blood eosinophil count

Menzies-Gow et al, *N Engl J Med*. 2021

Tézépélumab
Critères de jugement principal de l'essai de phase 3 Source [1]

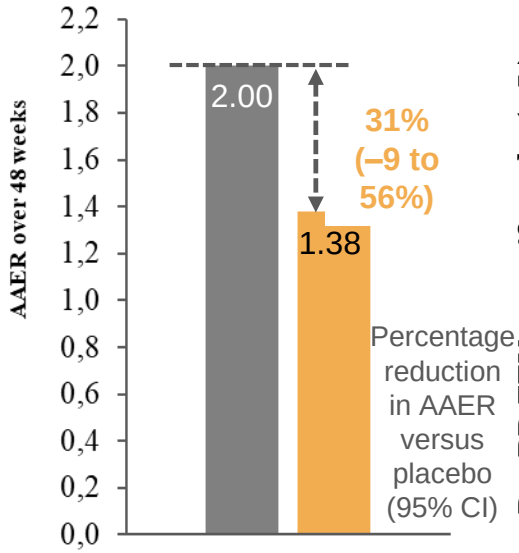
Primary endpoint: OCS reduction[1]



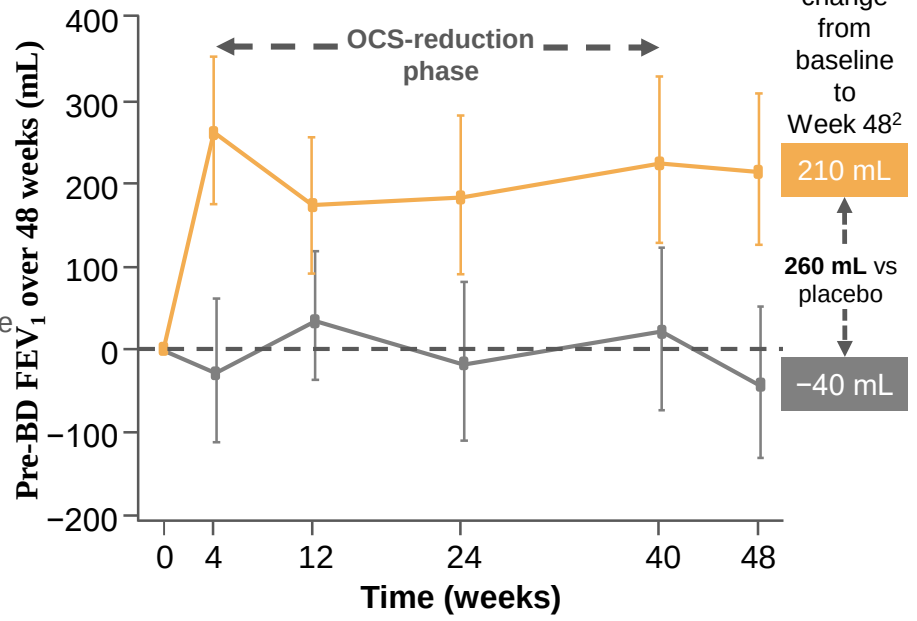
Reduction from baseline in final daily OCS dose

Secondary endpoints:

AAER[1]



Pre-BD FEV_1[1]



- At Week 48, the primary endpoint was not met. The odds of achieving a category of greater percentage reduction in daily maintenance OCS dose, while not losing asthma control, were not significantly higher with tezepelumab than with placebo (OR, 1.28; 95% CI, 0.69–2.35; p=0.43)[1]
- Tezepelumab showed nominal improvements compared with placebo in AAER, pre-BD FEV_1, ACQ-6 score, and AQLQ(S)+12 score[1]

Placebo (n=76) Tezepelumab 210 mg Q4W (n=74)

AAER = Annualized Asthma Exacerbation Rate; ACQ-6 = Asthma Control Questionnaire-6; AQLQ(S)+12 = Standardized Asthma Quality of Life Questionnaire for 12 Years and Older; BD = Bronchodilator; CI = Confidence Interval; FEV_1 = Forced Expiratory Volume in 1 Second; LS = Least Squares; OCS = Oral Corticosteroids; OR = Odds Ratio; Q4W = Every 4 Weeks

1. Wechsler M et al. Online ahead of print. *Lancet Respir Med*. 2022; doi:10.1016/S2213-2600(21)00537-3

AS: Thérapies ciblées: Conclusions

1) Proposer des alternatives thérapeutiques aux AS (paliers IV/V GINA)

2) Nombreux phénotypes AS

3) Caractérisation des mécanismes (endotype)
→ Thérapeutiques ciblées

4) Omalizumab, Mepolizumab, Benralizumab, Dupilumab, Tézépélumab disponibles

5) Quelques candidats sérieux en développement actuel

anti-TSP inhalé, anti-IL-33…

6) Place respective des uns par rapport aux autres ? Stratégie future ?

7) Autres biothérapies candidates

Nombreuses, dont beaucoup peu ou pas évaluées

Anti-IL-17…

8) Autres alternatives: Azithromycine ?

Autres molécules (anti-CRTH2, TKI …) ?, TB ?…