Respiratory Review of 2018: Asthma

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Clinical Study in 2017

2017. 3- 2018. 2

- N Engl J Med : 3
- Lancet &
  Lancet Respir Med: 12
- JAMA: 4
- BMJ: 0
- Ann Intern Med: 0

- Am J Respir Crit Care Med: 42
- Thorax: 6
- Chest: 13
- Eur Respir J: 62

- J Allergy Clin Immunol: 85

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1 Risk Factors

Traffic-related air pollution exposure is associated with allergic sensitization, asthma, and poor lung function in middle age.

Bowatte G, et al. J Allergy Clin Immunol 2017;139:122-9

2 Pharmacologuc Management

3 Treatment of Severe Asthma

4 Asthma in Special Populations

Environmental Risk Factors

Traffic-related air pollution exposure is associated with allergic sensitization, asthma, and poor lung function in middle age

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Melbourne, Sydney, Brisbane, Perth, and Hobart, Australia

- Tasmanian Longitudinal Health Study (TAHS) in 1968
  - 8,583 children aged 7 years
  - 1,405 attended laboratory study
- To quantify the association between TRAP exposure and allergic sensitization, asthma, and lung function
- To determine whether these associations are modified by variants in Glutathione S-Transferase genes (GSTs).

Bowatte G, et al. J Allergy Clin Immunol 2017;139:122-9

Annual NO_2 Exposure and Proximity to Major Roads

Annual NO_2 exposure

Type of allergen/respiratory outcomes	Unadjusted				Adjusted*			
	OR	95% CI	*P* value	n/N	OR	95% CI	*P* value	n/N
Atopy	1.17	1.06-1.29	<.01	759/1361	1.14	1.02-1.28	.02	748/1348
Cat allergen sensitization	1.35	1.21-1.51	<.01	227/1360	1.31	1.15-1.49	<.01	221/1347
HDM sensitization	1.21	1.10-1.34	<.01	568/1361	1.20	1.08-1.34	<.01	559/1348
Any mold sensitization	1.15	1.01-1.30	.03	173/1361	1.11	0.96-1.28	.16	169/1348
Mix grass and rye sensitization	1.14	1.03-1.25	.01	473/1361	1.05	0.94-1.17	.37	463/1348
Current wheeze	1.04	0.94-1.15	.40	390/1367	1.14	1.02-1.28	.02	387/1349
Current asthma	1.09	0.99-1.21	.09	323/1367	1.10	0.97-1.24	.13	320/1349
Current nonatopic asthma†	0.95	0.77-1.16	.61	94/1367	0.96	0.76-1.22	.75	93/1349
Current atopic asthma†	1.14	1.02-1.28	.02	229/1367	1.14	1.00-1.30	.05	227/1349

Living <200 m from a major road

Type of allergen/respiratory outcomes	Unadjusted				Adjusted			
	OR	95% CI	*P* value	n/N	OR	95% CI	*P* value	n/N
Atopy	1.23	0.96-1.56	.10	759/1361	1.26	0.99-1.62	.06	748/1348
Cat allergen sensitization	1.23	0.90-1.68	.19	227/1360	1.28	0.93-1.76	.13	221/1347
HDM sensitization	1.31	1.03-1.66	.03	568/1361	1.33	1.04-1.70	.02	559/1348
Any mold sensitization	0.93	0.64-1.33	.68	173/1361	0.93	0.64-1.34	.68	169/1348
Mix grass and rye sensitization	1.10	0.86-1.41	.47	473/1361	1.12	0.87-1.45	.38	463/1348
Current wheeze	1.38	1.07-1.78	.01	390/1367	1.38	1.06-1.80	.02	387/1349
Current asthma	1.24	0.94-1.62	.13	323/1367	1.21	0.91-1.59	.19	320/1349
Current nonatopic asthma†	1.19	0.75-1.88	.47	94/1367	1.21	0.76-1.94	.42	93/1349
Current atopic asthma†	1.26	0.92-1.72	.15	229/1367	1.21	0.88-1.66	.25	227/1349

GSTT1 Interactions for Outcomes

Outcomes	*GSTT1* variant	n/N	NO_2 OR	NO_2 95% CI	NO_2 *P* value	NO_2 P_{int}	<200 m OR	<200 m 95% CI	<200 m *P* value	<200 m P_{int}
Atopy	Non-null	535/965	1.10	0.97-1.25	.13	.08	1.18	0.88-1.58	.27	.04
	Null	102/188	1.51	1.04-2.20	.03		2.66	1.30-5.43	.01	
Cat allergen sensitization	Non-null	156/965	1.25	1.08-1.45	<.01	.06	—	—	—	—
	Null	28/187	1.95	1.27-2.99	<.01		—	—	—	
HDM sensitization	Non-null	413/965	1.14	1.01-1.29	<.01	.10	1.22	0.92-1.63	.17	.04
	Null	73/188	1.58	1.12-2.24	<.01		2.59	1.32-5.05	.01	
Current wheeze	Non-null	273/963	—	—	—	—	1.18	0.85-1.62	.32	.02
	Null	56/190	—	—	—		3.00	1.48-6.10	<.01	
Current asthma	Non-null	219/963	—	—	—	—	1.05	0.75-1.48	.77	.01
	Null	47/190	—	—	—		2.92	1.43-5.95	<.01	
Current atopic asthma	Non-null	156/963	—	—	—	—	1.11	0.76-1.64	.60	.01
	Null	33/190	—	—	—		3.53	1.56-7.98	<.01	

- TRAP exposure is associated with increased risk of allergic sensitization, asthma, and lower levels of lung function.
- Carriers of GSTT1 null may be at a greater risk for these outcomes.

1 Risk Factors

2 **Pharmacologic Management**

- ICS in Early Asthma
- LAMA as add-on therapy to ICS
- SMART
- ICA/LABA in a Real World Setting

3 Treatment of Severe Asthma

4 Asthma in Special Populations

ICS in Early Mild Asthma

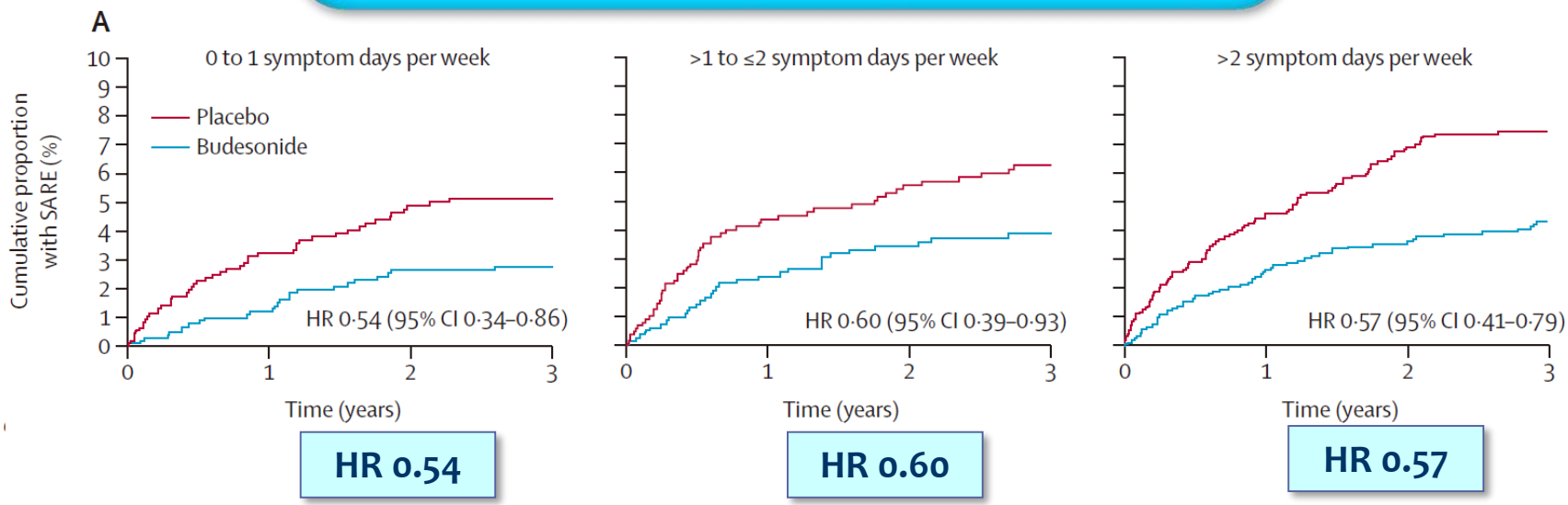
Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study

Helen K Reddel, William W Busse, Søren Pedersen, Wan C Tan, Yu-Zhi Chen, Carin Jorup, Dan Lythgoe, Paul M O'Byrne

- Conventionally, ICS treatment is recommended for patients with symptoms on more than 2 days per week.
- To assess the validity of the symptom-based cutoff for starting ICS
- Post-hoc analysis of the 3 year START study
- 7,138 patients with mild asthma diagnosed within the previous 2 years and no previous regular ICS

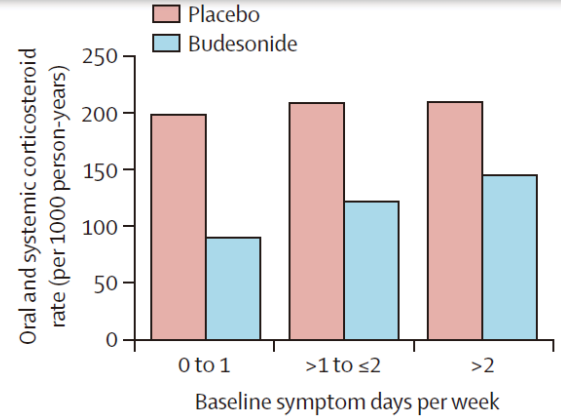
Reddel HK, et al. Lancet 2017;389:357-66

Time to first severe event (SARE)



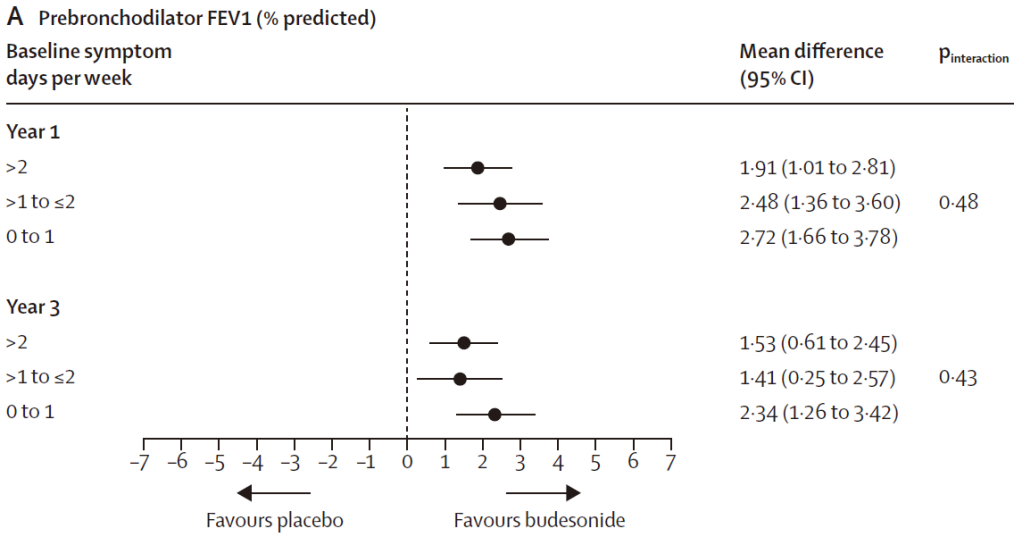
HR 0.54 **HR 0.60** **HR 0.57**

Ratio for severe exacerbations

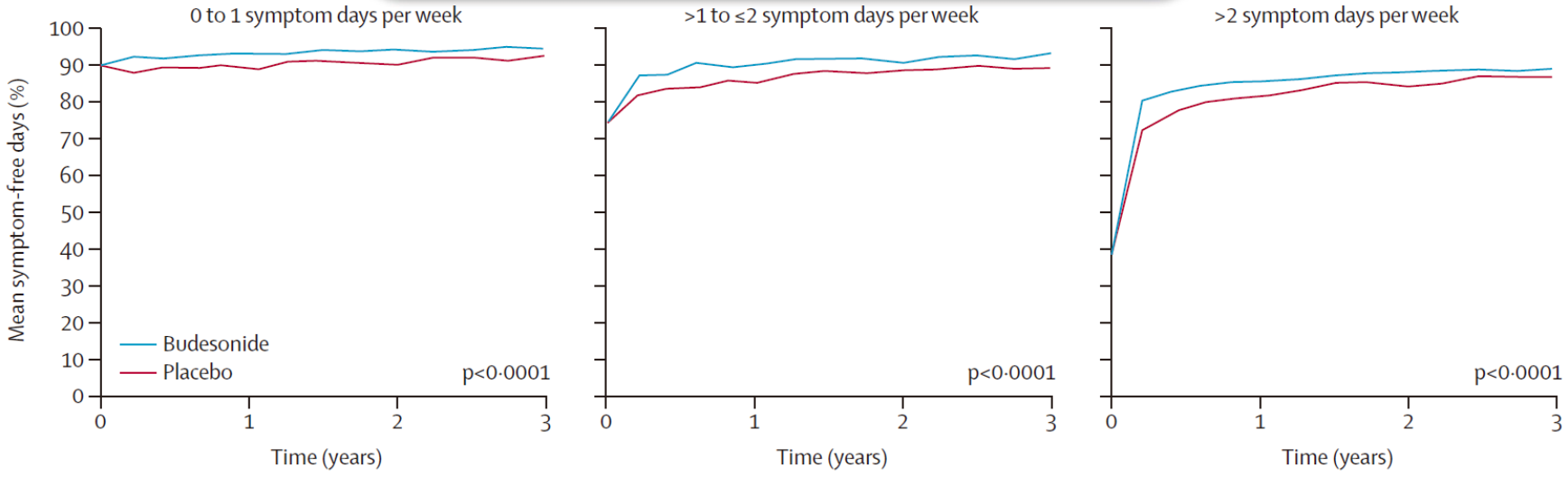


Rate ratio (95 % CI)	0·48 (0·38–0·61)	0·56 (0·44–0·71)	0·66 (0·55–0·80)

Pre-bronchodilator lung function



Symptom-free days



Conclusion

Box 3-4. Recommended options for initial controller treatment in adults and adolescents

Presenting symptoms	Preferred initial controller
Asthma symptoms or need for SABA less than twice a month; no waking due to asthma in last month; and no risk factors for exacerbations (Box 2-2B, p17), including no exacerbations in the last year	No controller (Evidence D)*
Infrequent asthma symptoms, but the patient has one or more risk factors for exacerbations (Box 2-2B); e.g. low lung function, or exacerbation requiring OCS in the last year, or has ever been in intensive care for asthma	Low dose ICS** (Evidence D)*
Asthma symptoms or need for SABA between twice a month and twice a week, or patient wakes due to asthma once or more a month	Low dose ICS** (Evidence B)
Asthma symptoms or need for SABA more than twice a week	Low dose ICS** (Evidence A) Other less effective options are LTRA or theophylline

GINA 2018

- In mild asthma, ICS reduces serious asthma-related events, even in patients with infrequent symptoms.
- Further studies
  - RCTs comparing the effect of ICS and as-needed SABA alone
  - Alternative strategy: as-needed ICS intake driven by concomitant β2-agonist

LAMA as Add-on Therapy to ICS

JAMA | Original Investigation

Association of Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists With Asthma Control in Patients With Uncontrolled, Persistent Asthma

A Systematic Review and Meta-analysis

Diana M. Sobieraj, PharmD; William L. Baker, PharmD; Elaine Nguyen, PharmD, MPH; Erin R. Weeda, PharmD; Craig I. Coleman, PharmD; C. Michael White, PharmD; Stephen C. Lazarus, MD; Kathryn V. Blake, PharmD; Jason E. Lang, MD, MPH

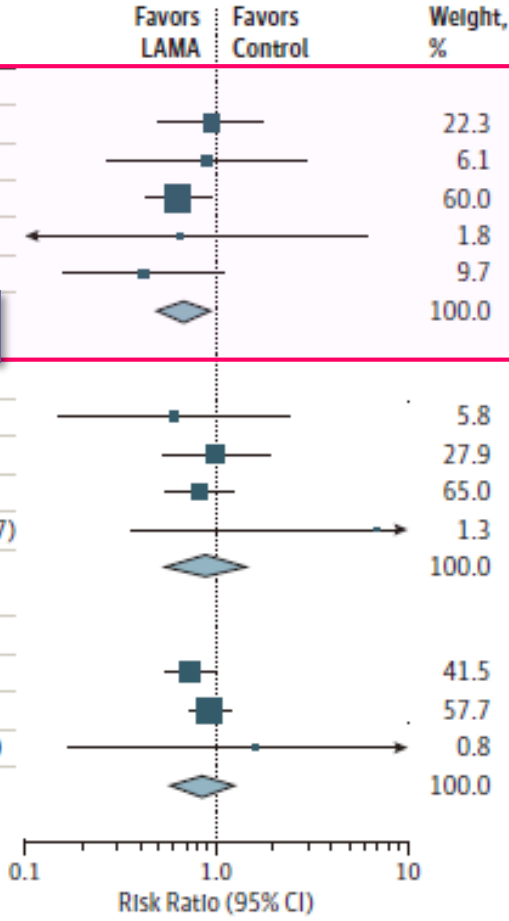
- 58 citations included 15 unique RCTs and 7,122 participants
- Earliest data through November 28, 2017
  - LAMA+ICS vs placebo+ICS
  - LAMA+ICS vs LABA+ICS
  - LAMA+ICS/LABA vs ICS/LABA

Sobieraj DM, et al. JAMA 2018, in press

Exacerbations Requiring Systemic Steroid

A Exacerbations requiring systemic corticosteroid

Source	LAMA Add-on Therapy: Total No. of Participants	LAMA Add-on Therapy: No. With Events	Control: Total No. of Participants	Control: No. With Events	Absolute Risk Difference, % (95% CI)	Risk Ratio (95% CI)	Weight, %
ICS + LAMA vs ICS + placebo (control)							
Bateman et al,[17] 2011	16	128	17	126	-1.0 (-9.3 to 7.3)	0.93 (0.49 to 1.75)	22.3
Paggiaro et al,[21] 2016	7	309	4	155	-0.3 (-3.3 to 2.7)	0.88 (0.26 to 2.95)	6.1
Kerstjens Trial 1 and 2,[18] 2015	53	1036	43	523	-3.1 (-5.8 to -0.4)	0.62 (0.42 to 0.92)	60.0
Lee et al,[19] 2015	3	298	1	64	-0.6 (-3.8 to 2.7)	0.64 (0.07 to 6.09)	1.8
Hamelmann et al,[22] 2016	7	259	9	138	-3.8 (-8.4 to 0.7)	0.41 (0.16 to 1.09)	9.7
Overall (random-effects model) Heterogeneity: $I^2=0\%$; $\tau^2=0$; $P=.69$	86	2030	74	1006	-1.7 (-3.7 to 0.3)	**0.67** (0.48-0.92)	100.0
ICS + LAMA vs ICS + LABA (control)							
Peters et al,[29] 2010	3	71	5	71	-2.8 (-10.4 to 4.8)	0.60 (0.15 to 2.42)	5.8
Bateman et al,[17] 2011	16	128	17	134	-0.2 (-8.2 to 7.8)	0.99 (0.52 to 1.87)	27.9
Kerstjens Trial 1 and 2,[18] 2015	53	1036	341	541	-1.2 (-3.6 to 1.3)	0.81 (0.54 to 1.24)	65.0
Lee et al,[19] 2015	3	298	0	295	1.0 (-0.3 to 2.3)	6.93 (0.36 to 133.57)	1.3
Overall (random-effects model) Heterogeneity: $I^2=0\%$; $\tau^2=0$; $P=.49$	75	1533	56	1041	0.1 (-2.1 to 2.3)	0.87 (0.53 to 1.42)	100.0
ICS and LABA + LAMA vs ICS and LABA (control)							
Kerstjens Trial 1,[26] 2012	53	237	68	222	-8.3 (-16.3 to -0.2)	0.73 (0.54 to 0.99)	41.5
Kerstjens Trial 2,[26] 2012	69	216	81	232	-3.0 (-11.7 to 5.8)	0.91 (0.70 to 1.19)	57.7
Hamelmann et al,[28] 2017	3	257	1	135	0.4 (-1.5 to 2.4)	1.58 (0.17 to 15.00)	0.8
Overall (random-effects model) Heterogeneity: $I^2=0\%$; $\tau^2=0$; $P=.47$	125	710	150	589	-0.5 (-8.1 to 7.0)	0.84 (0.57 to 1.22)	100.0



Single Maintenance and Reliever Therapy

JAMA | Original Investigation

Association of Inhaled Corticosteroids and Long-Acting β-Agonists as Controller and Quick Relief Therapy With Exacerbations and Symptom Control in Persistent Asthma
A Systematic Review and Meta-analysis

Diana M. Sobieraj, PharmD; Erin R. Weeda, PharmD; Elaine Nguyen, PharmD, MPH; Craig I. Coleman, PharmD; C. Michael White, PharmD; Stephen C. Lazarus, MD; Kathryn V. Blake, PharmD; Jason E. Lang, MD, MPH; William L. Baker, PharmD

- 42 citations included 16 unique RCTs and 22,748 participants
- Single maintenance and reliever therapy (SMART) vs
  ICS with or without a LABA used as controller therapy and
  SABA as reliever therapy

Sobieraj DM, et al. JAMA 2018, in press

Exacerbations Requiring Steroid, Hospitalization, or ER visits

Figure 2. Association of SMART With Exacerbations Requiring Systemic Corticosteroids, Hospitalization, or ED Visits Among Patients Aged 12 Years or Older vs the Same Dose of Inhaled Corticosteroids and LABA Controller Therapy

Source	SMART Group		Control Group		Absolute Risk Difference (95% CI), %	Risk Ratio (95% CI)	Weight, %
	Total No. of Participants	No. With Event	Total No. of Participants	No. With Event			
Vogelmeier et al,[23] 2012	1067	132	1076	167	-3.1 (-6.1 to -0.2)	0.80 (0.64 to 0.99)	21.6
Rabe et al,[25] 2006	1107	143	1138	245	-8.6 (-11.7 to -5.5)	0.60 (0.50 to 0.72)	25.2
Atienza et al,[24] 2013	1049	170	1042	229	-5.8 (-9.1 to -2.4)	0.74 (0.62 to 0.88)	27.0
Papi et al,[26] 2013	852	99	849	152	-6.3 (-9.6 to -2.9)	0.65 (0.51 to 0.82)	18.7
Patel et al,[27] 2013	151	28	152	50	-14.4 (-24.1 to -4.6)	0.56 (0.38 to 0.84)	7.6
Overall (random-effects model)	4226	572	4257	843	-6.4 (-10.2 to -2.6)	**0.68** (0.58-0.80)	100.0

Heterogeneity: $I^2 = 29\%$, $P = .23$
Test for overall effect: $t_4 = -6.44$, $P < .001$

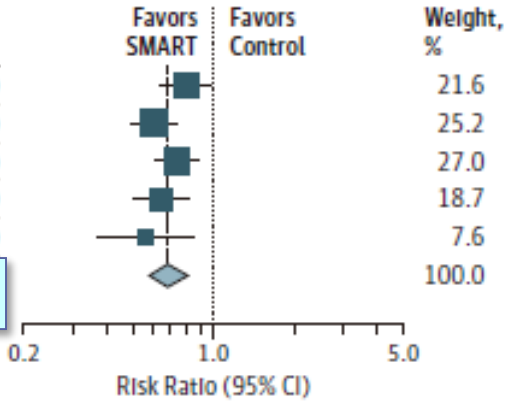
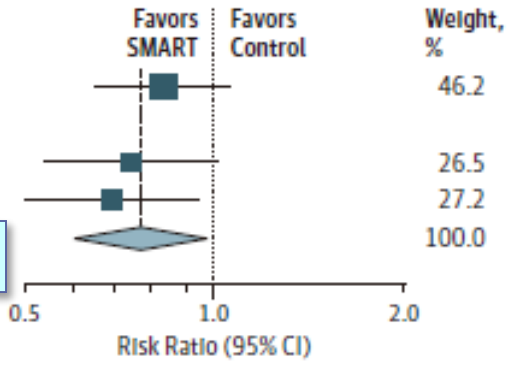


Figure 3. Association of SMART With Exacerbations Requiring Systemic Corticosteroids, Hospitalization, or ED Visits Among Patients Aged 12 Years or Older vs a Higher Dose of Inhaled Corticosteroids and LABA Controller Therapy

Source	SMART Group		Control Group		Absolute Risk Difference (95% CI), %	Risk Ratio (95% CI)	Weight, %
	Total No. of Participants	No. With Event	Total No. of Participants	No. With Event			
Bousquet et al,[32] 2007	1151	108	1153	130	-2.7 (-5.2 to 0.6)	0.83 (0.65 to 1.06)	46.2
Kuna et al,[33] 2007							
Comparison 1	552	47	1099	126	-2.9 (-5.9 to 0.1)	0.74 (0.54 to 1.02)	26.5
Comparison 2	552	47	1119	138	-3.8 (-6.8 to -0.8)	0.69 (0.50 to 0.95)	27.2
Overall (random-effects model)	2254	202	3371	394	-2.7 (-5.2 to -0.3)	**0.77** (0.60-0.98)	100.0

Heterogeneity: $I^2 = 0\%$, $P = .64$
Test for overall effect: $t_2 = -4.71$, $P = .04$



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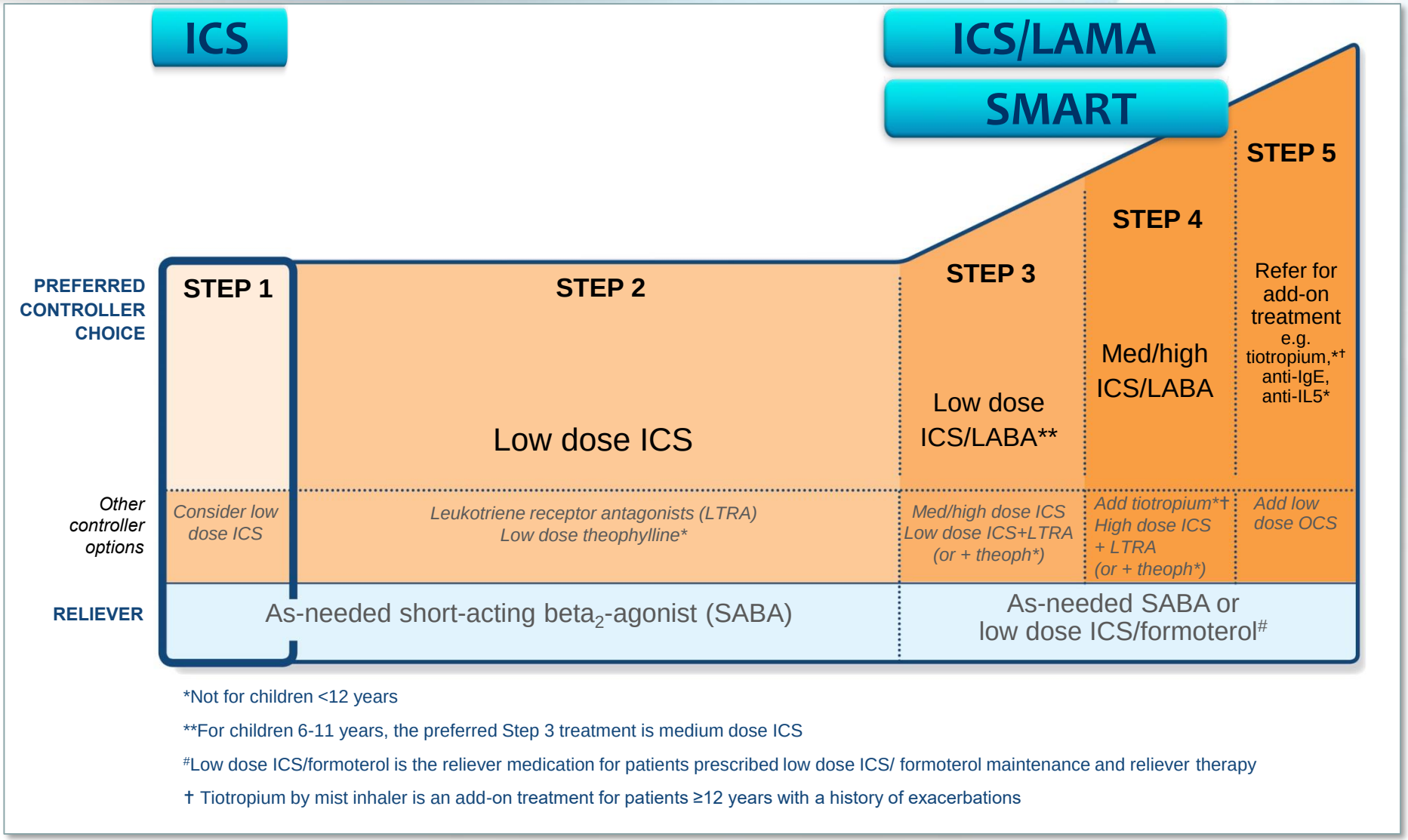


*Not for children <12 years

**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS

#Low dose ICS/formoterol is the reliever medication for patients prescribed low dose ICS/ formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

ICS/LABA in a Real World Setting

Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open-label, parallel group, randomised controlled trial

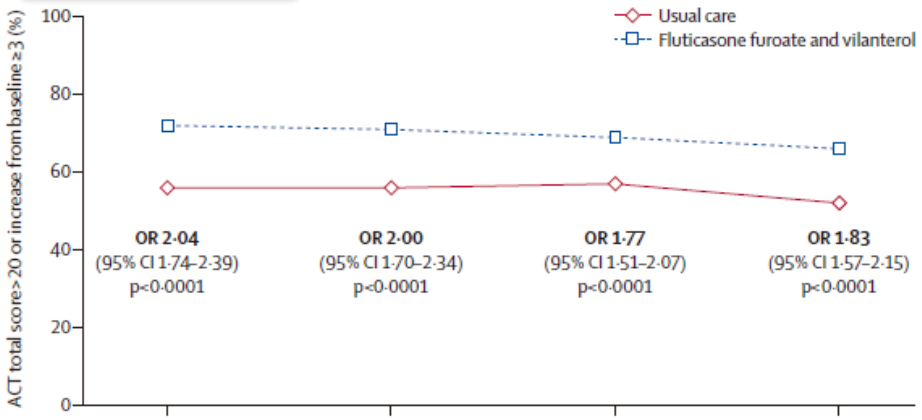
Ashley Woodcock, Jørgen Vestbo*, Nawar Diar Bakerly, John New, J Martin Gibson, Sheila McCorkindale, Rupert Jones, Susan Collier, James Lay-Flurrie, Lucy Frith, Loretta Jacques, Joanne L Fletcher, Catherine Harvey, Henrik Svedsater, David Leather, on behalf of the Salford Lung Study Investigators†*

- Open-label, randomized, controlled trial at general practice clinics
- Two arm effectiveness trial (4,233 patients)
  - Once-daily combination of fluticasone furoate with vilanterol
  - Optimised usual care
- Primary endpoint
  - the percentage of patients who achieved an ACT score of 20 or greater or an increase in ACT score from baseline of 3 or greater at 24 weeks (termed responders)

Woodcock A, et al. Lancet 2017;390:2247-55

Primary Outcome: ACT Responders

All patients

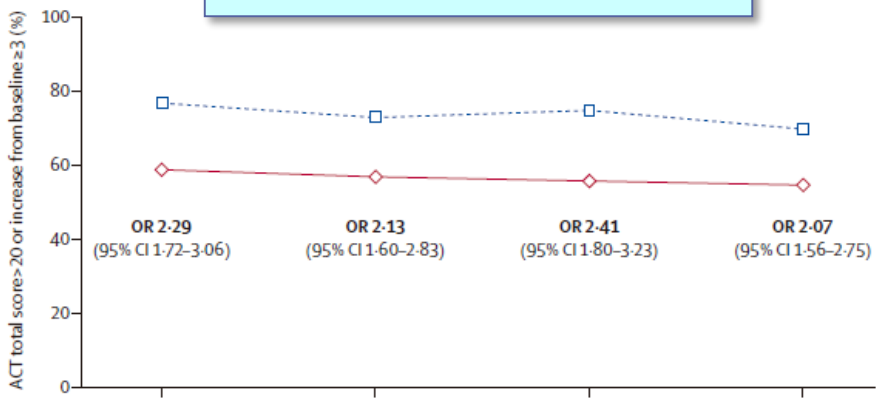


At week 24

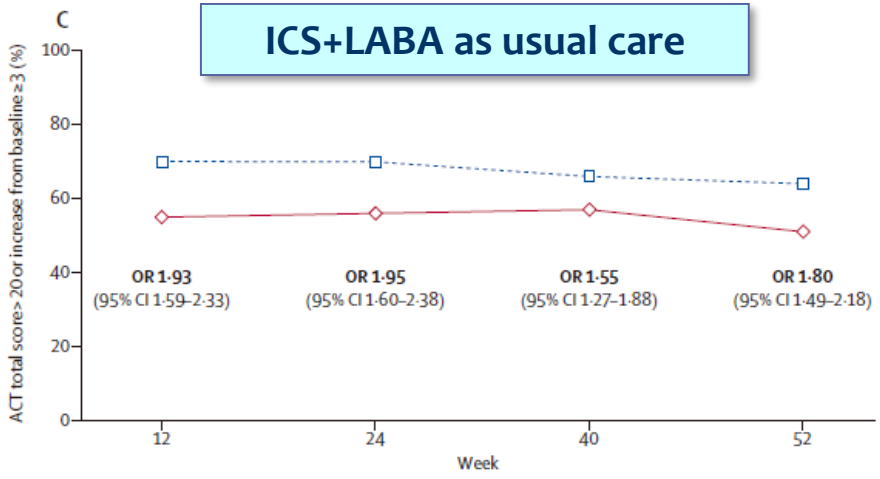
- FF/Vilanterol: 71%
- Usual care : 56%

OR: 2.00 (95% CI 1.70-2.34; p<0.001)

ICS as usual care

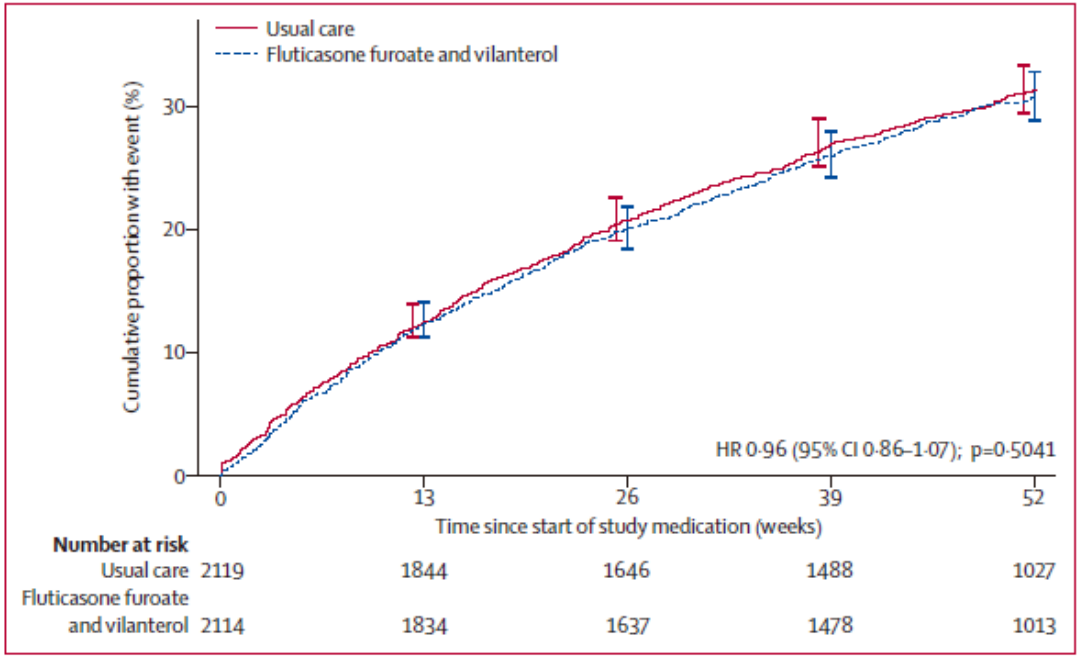


ICS+LABA as usual care



Other Outcomes

Time to first exacerbation



	Usual care	Fluticasone furoate and vilanterol
Cardiovascular disease	69 (29·6)	42 (23·3)
Asthma and bronchospasm	40 (17·2)	24 (13·3)
Pneumonia	21 (8·4)	21 (10·7)
Lower respiratory tract infection (excluding pneumonia)	8 (3·4)	7 (3·9)
Decreased bone mineral density and associated fractures	52 (22·3)	35 (19·4)
Effects on glucose	22 (9·4)	18 (10·0)
Hypersensitivity	5 (2·1)	7 (3·9)
Effects on potassium	1 (0·4)	4 (2·2)
Corticosteroid-associated eye disease	7 (3·0)	9 (5·0)
Adrenal suppression	1 (0·4)	0
Local steroid effects	0	1 (0·6)
Tremors	0	0

Data shown for 4751 patients in the total population (according to actual treatment received at the time of event reporting), given as numbers of events with rates per 1000 patient-years in parentheses, including patients in the fluticasone furoate and vilanterol group who had modified their treatment and were receiving usual care at the time of the event.

Table 2: **On-treatment serious adverse events of special interest**

1 Risk Factors

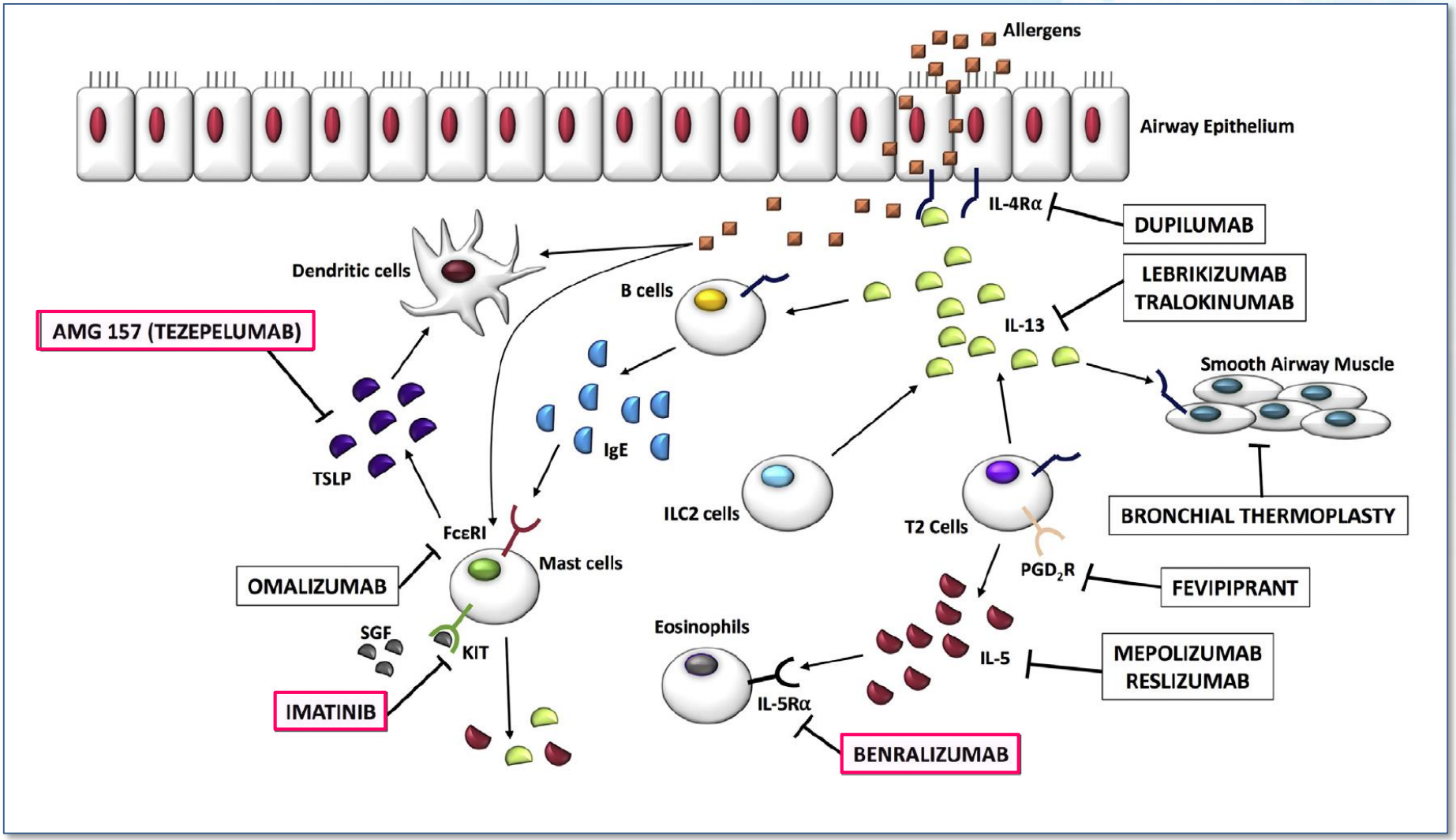
2 Pharmacologic Management

3 **Treatment of Severe Asthma**

- Biologic Therapies
- Macrolide Treatment

4 Asthma in Special Populations

Biologic Therapies for Severe Asthma



Peters SP, et al. J Allergy Clin Immunol Pract 2017;5:S15-24

Glucocorticoid Sparing of Benralizumab

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*

- Mepolizumab & reslizumab
  - Monoclonal Ab against IL-5
  - add-on therapies to treat asthma exacerbations and control symptoms in severe asthma
- Mepolizumab: glucocorticoid-sparing effect

Bel EH, et al. N Engl J Med 2014;371:1189-97

- Benralizumab
  - a monoclonal Ab specific for the alpha subunit of the IL-5 receptor

Nair P, et al. N Engl J Med 2017;376:2448-58

Benralizumab in Severe Asthma

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**

Bleecker ER, et al. Lancet 2016;388:2115-27

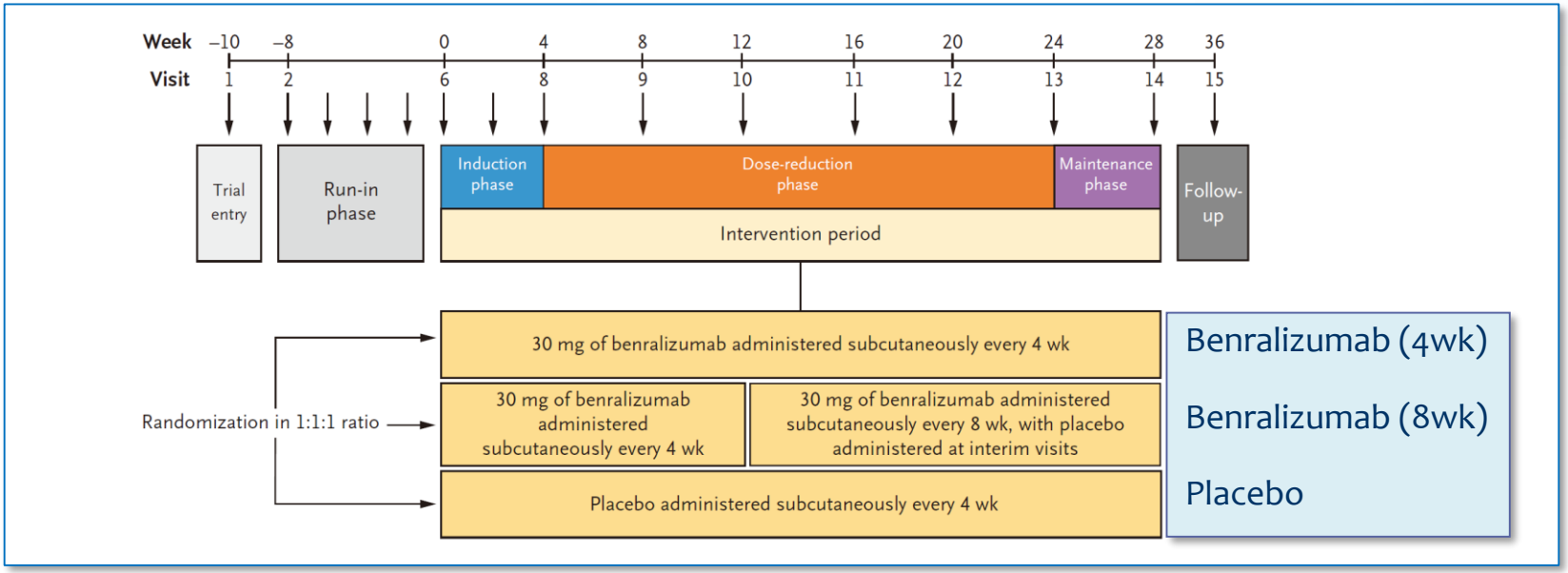
Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial

*J Mark FitzGerald, Eugene R Bleecker, Parameswaran Nair, Stephanie Korn, Ken Ohta, Marek Lommatzsch, Gary T Ferguson, William W Busse, Peter Barker, Stephanie Sproule, Geoffrey Gilmartin, Viktoria Werkström, Magnus Aurivillius, Mitchell Goldman, on behalf of the CALIMA study investigators**

FitzGerald JM, et al. Lancet 2016;388:2128-41

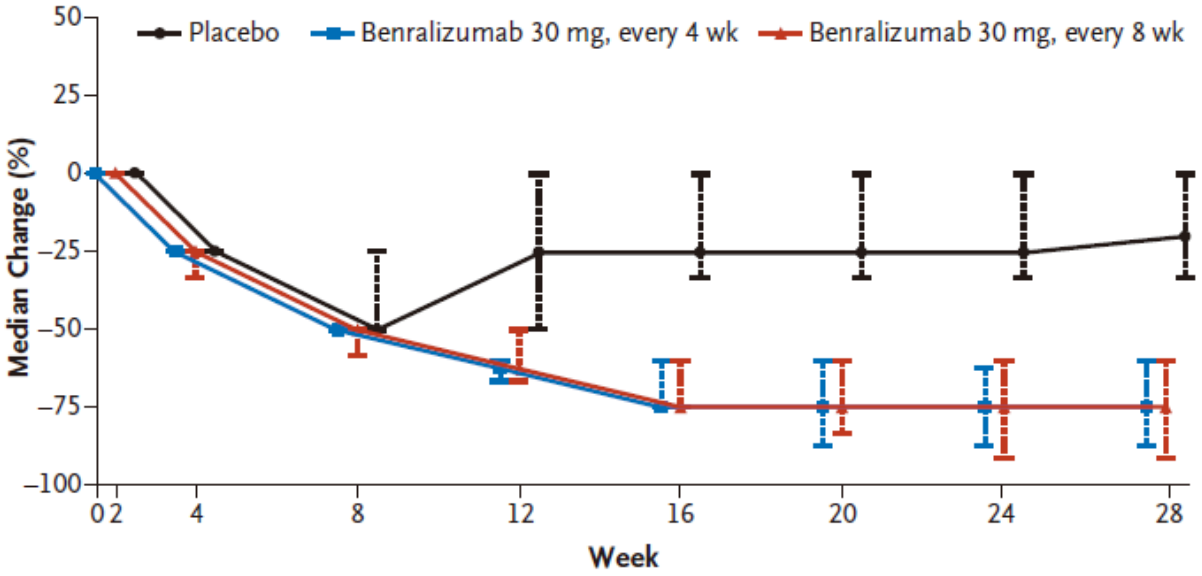
ZONDA Clinical Trial

- ZONDA trial
  - A randomized, double-blind, parallel-group, placebo-controlled trial
  - 369 patients :receiving oral glucocorticoid (OGC) therapy for at least 6 continuous months
  - Primary end point: the percentage change in the oral glucocorticoid dose from baseline to week 28



Change in OGC Dose

A Change from Baseline in Oral Glucocorticoid Dose

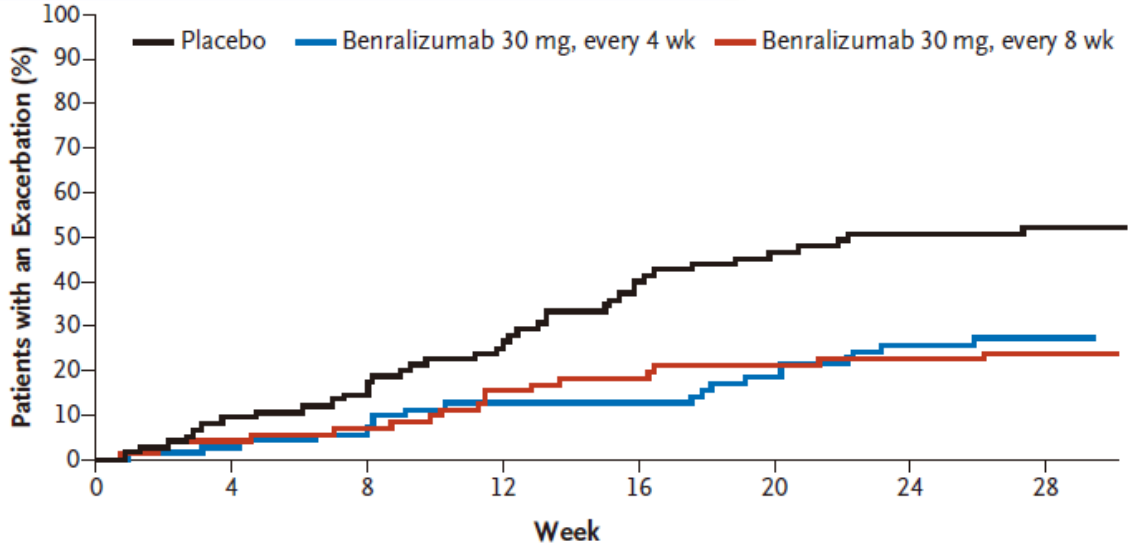


No. at Risk								
Benralizumab 30 mg, every 4 wk	72	70	70	69	69	68	66	68
Benralizumab 30 mg, every 8 wk	70	72	67	69	69	66	69	68
Placebo	74	75	73	74	74	73	73	72

- The Odds of percentage reduction in the OCG dose
  - 4.09 (every 4 wk) & 4.12 (every 8 wk)

Time to First Exacerbation

Time to first exacerbation



Hazard ratio

0.39 (4 wk)

0.32 (8 wk)

Annual asthma exacerbation

	Benralizumab every 4 wk	Benralizumab every 8 wk
Marginal rate	0.83 vs 1.83	0.54 vs 1.83
Rate ratio	0.45 (P=0.003)	0.30 (P<0.001)

Predictors of Benralizumab Response

Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies

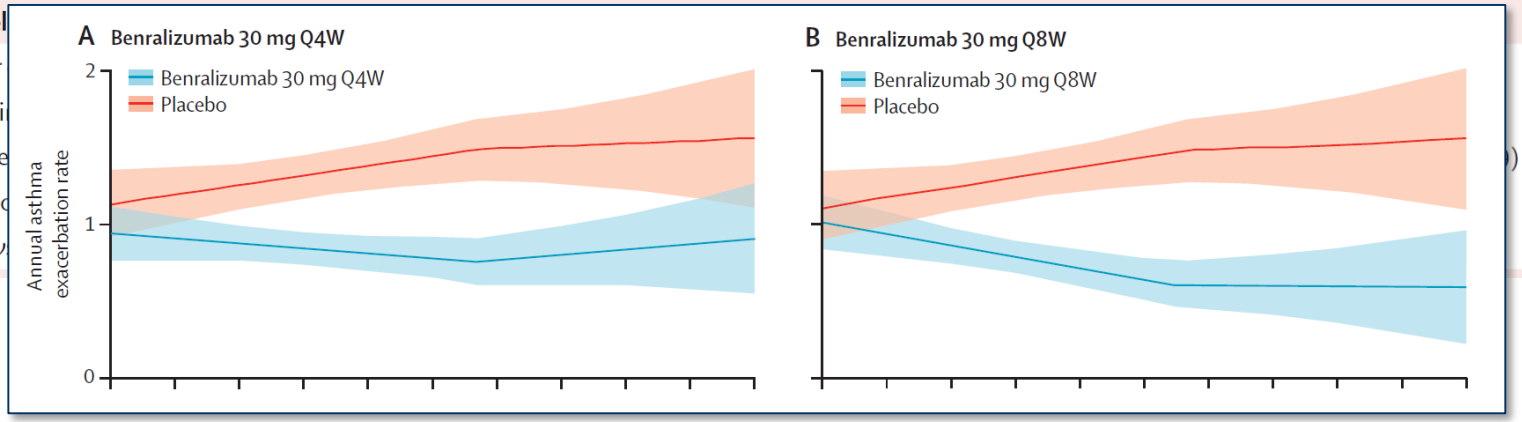
J Mark FitzGerald, Eugene R Bleecker, Andrew Menzies-Gow, James G Zangrilli, Ian Hirsch, Paul Metcalfe, Paul Newbold, Mitchell Goldman

- 2,295 patients with severe, uncontrolled asthma
- Primary endpoint: annual exacerbation rate

	Two exacerbations in previous year			Three or more exacerbations in previous year		
	Placebo	Benralizumab Q4W	Benralizumab Q8W	Placebo	Benralizumab Q4W	Benralizumab Q8W
Annual exacerbation rate						
Number of patients analysed	300	322	308	215	194	198
Rate estimate (95% CI)	0·80 (0·67 to 0·96)	0·52 (0·42 to 0·63)	0·58 (0·48 to 0·71)	1·79 (1·51 to 2·14)	0·98 (0·80 to 1·21)	0·82 (0·65 to 1·02)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·28 (−0·46 to −0·10)	−0·22 (−0·40 to −0·03)	..	−0·81 (−1·18 to −0·44)	−0·98 (−1·34 to −0·62)
Rate ratio *vs* placebo (95% CI)	..	0·65 (0·49 to 0·85)	0·73 (0·55 to 0·95)	..	0·55 (0·42 to 0·72)	0·45 (0·34 to 0·60)
p value *vs* placebo	..	0·0016	0·0194	..	<0·0001	<0·0001

FitzGerald JM, et al. Lancet Respir Med 2018;6:51-64

	Placebo (n=777)	Benralizumab Q4W (n=756)	Benralizumab Q8W (n=762)
≥0 cells per µL			
Number of patients analysed	770	748	751
Rate estimate (95% CI)	1·16 (1·05 to 1·28)	0·73 (0·65 to 0·82)	0·75 (0·66 to 0·84)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·43 (−0·57 to −0·28)	−0·41 (−0·56 to −0·27)
Rate ratio *vs* placebo (95% CI)	..	0·63 (0·54 to 0·74)	0·64 (0·55 to 0·75)
p value *vs* placebo	..	<0·0001	<0·0001
≥150 cells per µL			
Number of patients analysed	648	647	646
Rate estimate (95% CI)	1·14 (1·02 to 1·28)	0·69 (0·61 to 0·79)	0·72 (0·63 to 0·82)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·45 (−0·60 to −0·29)	−0·42 (−0·58 to −0·27)
Rate ratio *vs* placebo (95% CI)	..	0·61 (0·51 to 0·72)	0·63 (0·53 to 0·74)
p value *vs* placebo	..	<0·0001	<0·0001
≥300 cells per µL			
Number of patients analysed	511	511	499
Rate estimate (95% CI)	1·14 (1·00 to 1·29)	0·68 (0·59 to 0·78)	0·65 (0·56 to 0·75)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·46 (−0·64 to −0·29)	−0·49 (−0·67 to −0·32)
Rate ratio *vs* placebo (95% CI)	..	0·59 (0·49 to 0·72)	0·57 (0·47 to 0·69)
p value *vs* placebo	..	<0·0001	<0·0001
≥450 cel			
Number			
Rate esti			
Absolute			)
Rate ratio			
p value *v*			



Tezepelumab in Uncontrolled Asthma

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.

- Tezepelumab (AMG 157)
  - a human monoclonal Ab specific for TSLP
  - A proof-of-concept study in mild atopic asthma (31 patients, 12 wks)
    : reduction of allergen-induced bronchoconstriction and type 2 inflammation

Gauvreau GM, et al. N Engl J Med 2014;370:2102-10

- Phase 2, randomized, double-blind, placebo-controlled trial
  - Uncontrolled asthma treated with LABA+ICS
  - Subcutaneous tezepelumab over a 52-weeks treatment period
  - Primary endpoint: annualized rate of asthma exacerbations

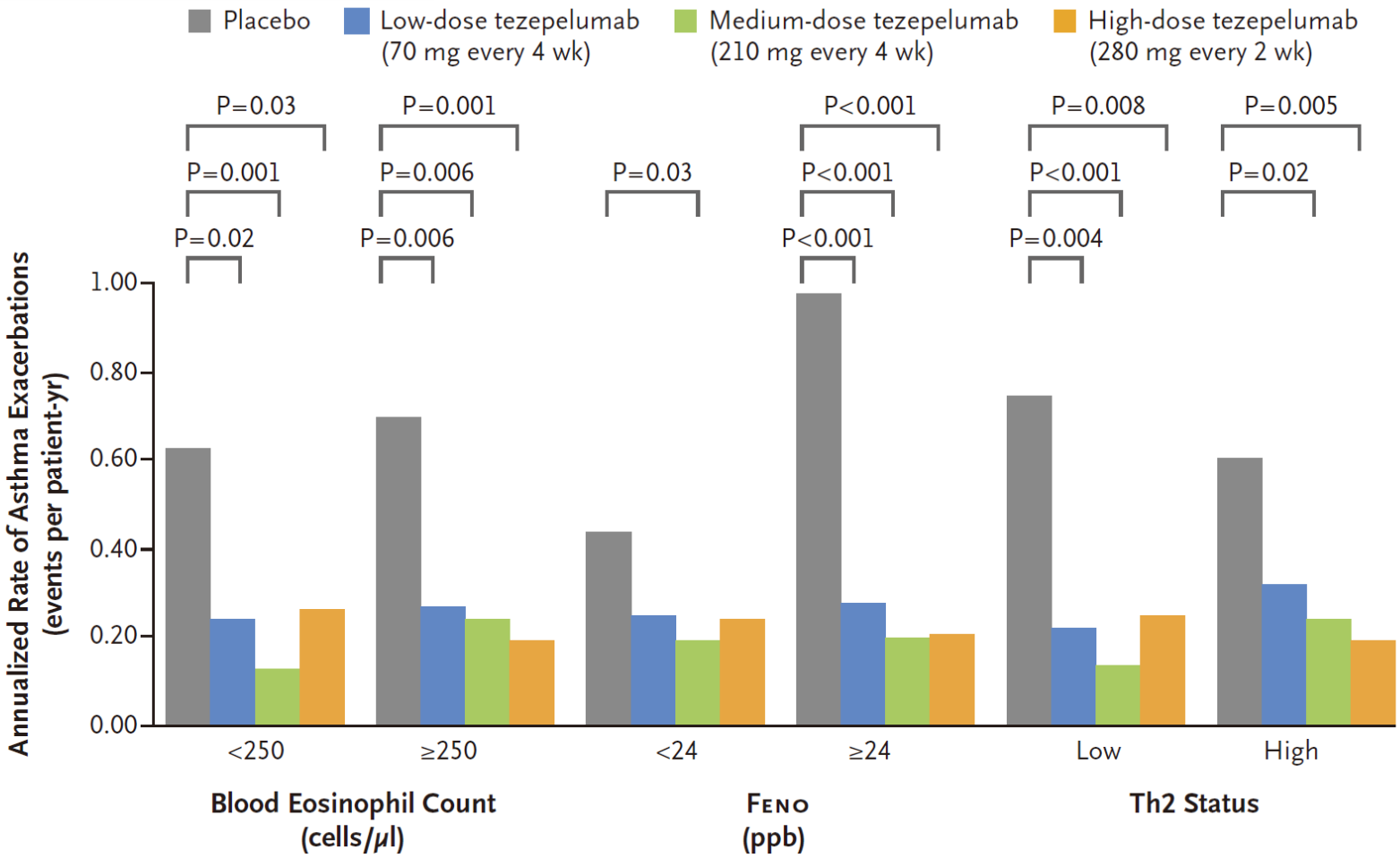
Corren J, et al. N Engl J Med 2017;377:936-46

Rate of Asthma Exacerbations and FEV_1 Change

Variable	Placebo (N = 148)	Low-Dose Tezepelumab (N = 145)	Medium-Dose Tezepelumab (N = 145)	High-Dose Tezepelumab (N = 146)
Annualized rate of asthma exacerbations through wk 52 — events per patient-yr (90% CI)	0.67 (0.57 to 0.80)	0.26 (0.19 to 0.34)	0.19 (0.13 to 0.27)	0.22 (0.16 to 0.30)
Relative reduction vs. placebo — % (90% CI)	—	61 (39 to 75)	71 (53 to 82)	66 (47 to 79)
P value	—	<0.001	<0.001	<0.001
FEV_1 before bronchodilation				
No. of patients evaluated	141	137	128	125
Least-squares mean change from baseline at wk 52 — % of predicted value	−0.99	7.11	7.27	9.37
Difference vs. placebo (95% CI)	—	8.11 (2.39 to 13.82)	8.26 (2.50 to 14.03)	10.36 (4.60 to 16.13)
P value*	—	0.006	0.005	<0.001
Least-squares mean change from baseline at wk 52 — liters	−0.05	0.07	0.06	0.11
Difference vs. placebo (95% CI)	—	0.12 (0.02 to 0.21)	0.11 (0.02 to 0.20)	0.15 (0.06 to 0.25)
P value*	—	0.01	0.02	0.002

Rate of Asthma Exacerbations

Subpopulation analysis

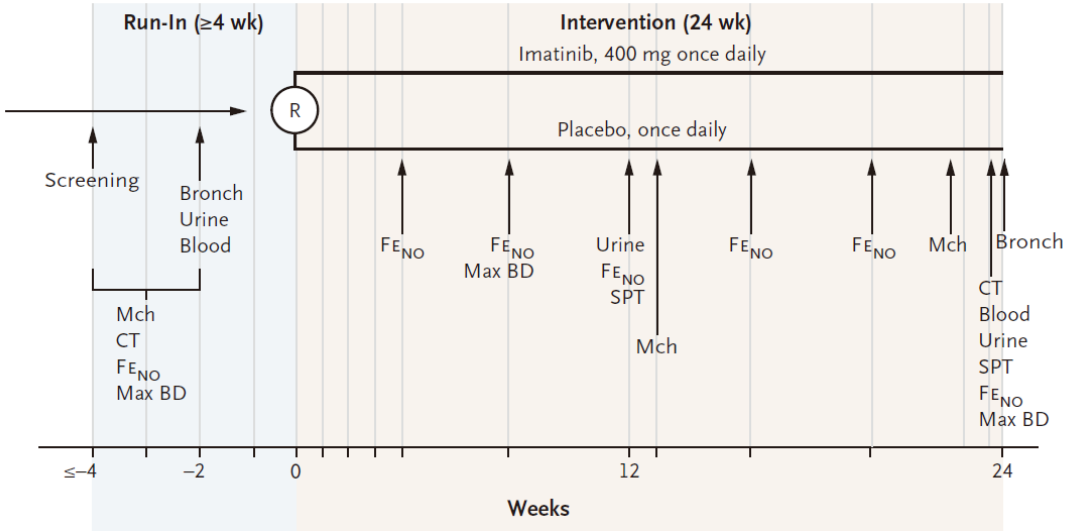


KIT Inhibition in Severe Asthma

KIT Inhibition by Imatinib in Patients with Severe Refractory Asthma

Katherine N. Cahill, M.D., Howard R. Katz, Ph.D., Jing Cui, M.D., Ph.D., Juying Lai, M.D., Shamsah Kazani, M.D., Allison Crosby-Thompson, M.S., Denise Garofalo, B.A., Mario Castro, M.D., Nizar Jarjour, M.D., Emily DiMango, M.D., Serpil Erzurum, M.D., Jennifer L. Trevor, M.D., Kartik Shenoy, M.D., Vernon M. Chinchilli, Ph.D., Michael E. Wechsler, M.D., Tanya M. Laidlaw, M.D., Joshua A. Boyce, M.D., and Elliot Israel, M.D.

- Imatinib
  - Inhibits the tyrosin kinase activity of KIT
  - reduces BM mast cell numbers and serum tryptase levels
- Randomized, double-blind, placebo-controlled, 24-week trial

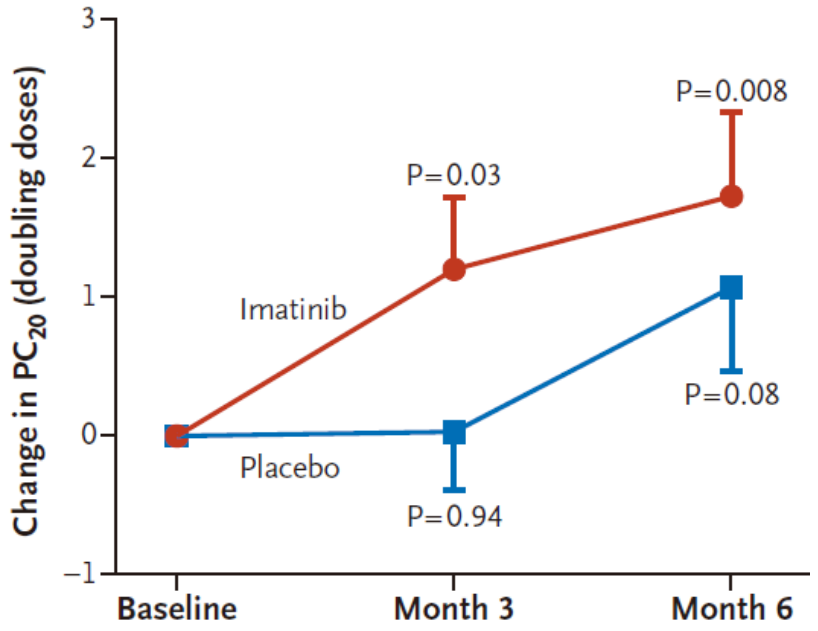


62 patients with poorly controlled severe asthma

Nair P, et al. N Engl J Med 2017;376:2448-58

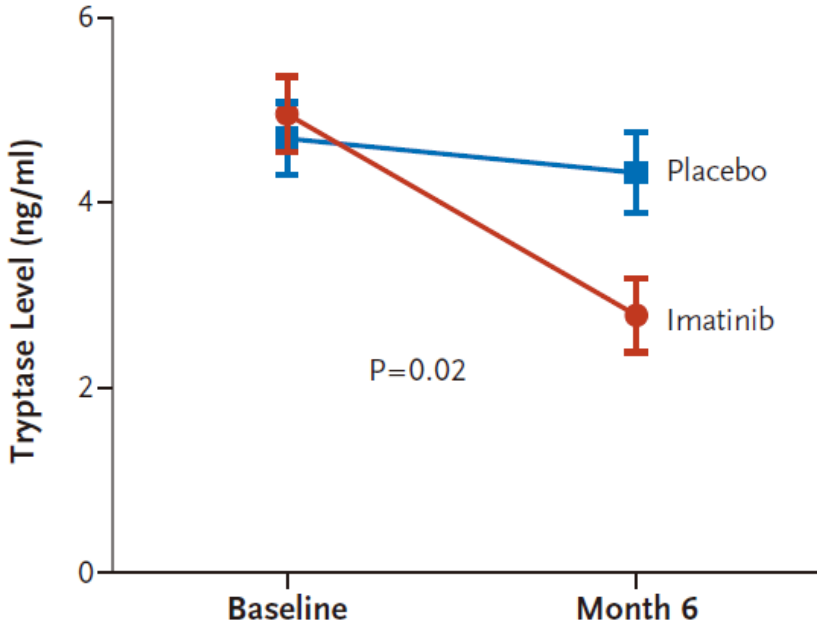
Change in Airway Hyperresponsiveness

Methacholine reactivity



Im: 1.73±0.60
Pl : 1.07±0.60
(p=0.048)

Tryptase in serum



Im: 0.56±1.39
Pl : 2.02±2.32
(p=0.02)

Table 2. Change from Baseline to 6 Months in Clinical and Inflammatory Measures with Imatinib and Placebo.*

Measure	Change from Baseline		P Value
	Imatinib	Placebo	
PEF (liters/min)			
Morning	7.3±46.1	−6.4±39.3	0.38
Evening	8.3±53.6	−8.2±37.2	0.31
FE_{NO} (ppb)	7.89±33.0	−5.92±33.2	0.11
Maximum post-bronchodilation FEV_1 (liters)	0.01±0.2	−0.08±0.26	0.10
ACQ-6 score	−0.62±0.96	−0.49±0.89	0.31
AQLQ score	0.55±1.0	0.25±0.80	0.11
ASUI score	0.07±0.20	0.05±0.18	0.62
Airway-wall thickness (%)†	−0.0040± 0.03	−0.0027±0.02	0.13
Airway-wall area (%)†	0.0002±0.02	0.0002±0.02	0.25
Peripheral-blood eosinophil count per cubic millimeter	−10.22±50.6	−2.59±25.6	0.94
BAL eosinophils (%)	2.55±8.8	−2.63±10.4	0.15
Tryptase-positive mast-cell count per square millimeter			
Total airway	−54.2±96.5	−32.3±79.8	0.11
Airway smooth muscle	−102.7±167.9	−79.2±157.3	0.07

Azithromycin in Uncontrolled Asthma

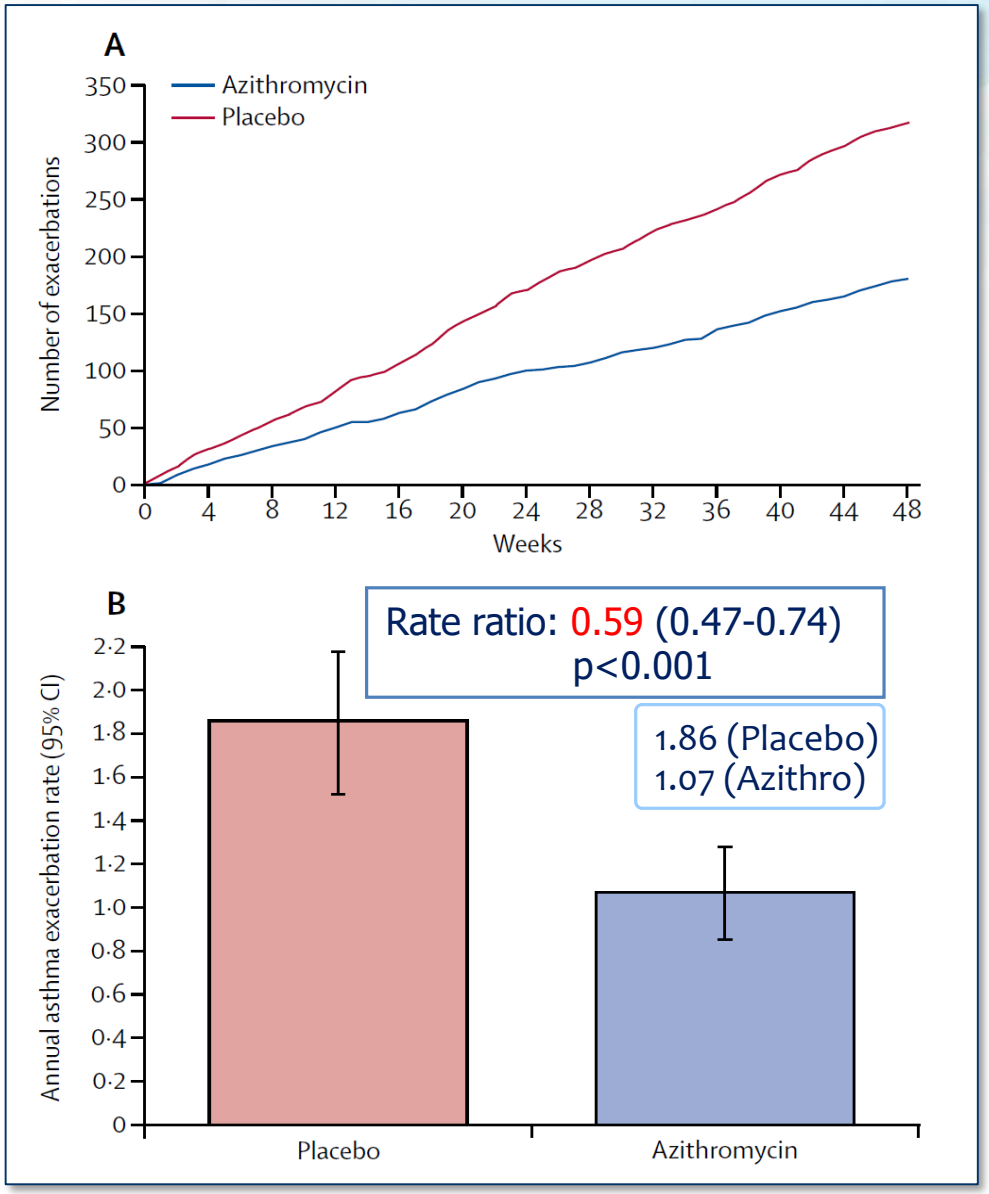
Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial

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

- A randomized, double-blind, placebo controlled paralleled group trial
- 420 patients with symptomatic asthma despite current use of ICS and LABA
- Azithromycin 500 mg three times per week for 48 weeks
- Primary endpoint
  - rate of total asthma exacerbations over 48 weeks
  - asthma quality of life

Gibson PG, et al. Lancet 2017;390:659-68

Asthma Exacerbations During 48 Weeks of Treatment



At least one exacerbation

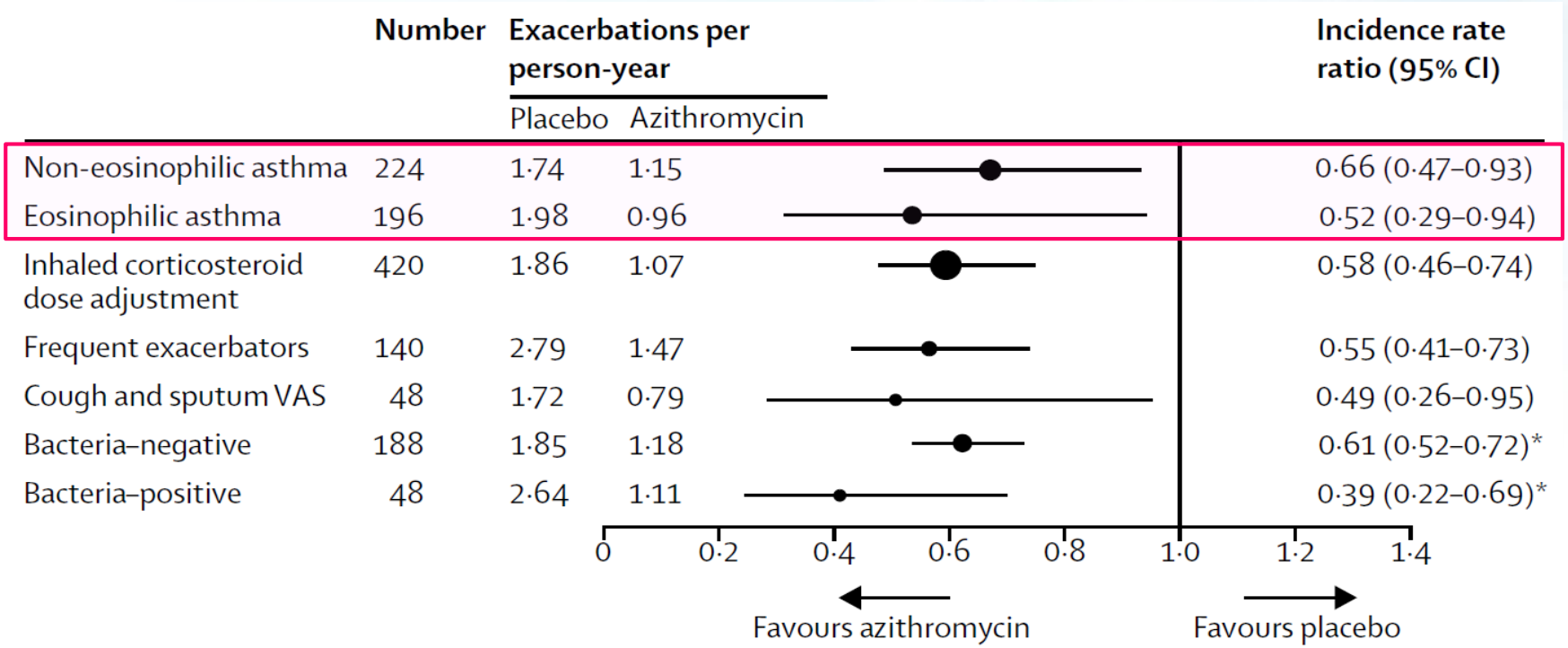
- Placebo: 61%
- Azithromycin: 44%
  (p<0.001)

Time to exacerbation

- Hazard ratio (95% CI)
  =0.65 (0.50-0.85)
  (p=0.001)

Subgroup Analysis

Effect of add-on azithromycin treatment on asthma exacerbations



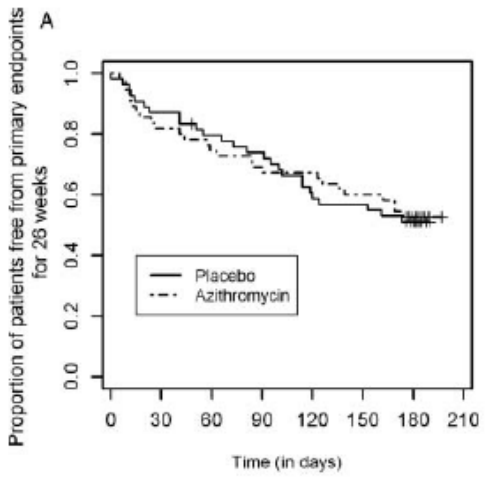
Effect of Treatment on Outcomes

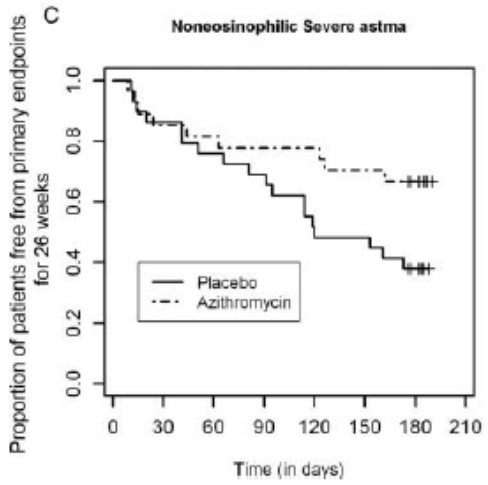
	Placebo	Azithromycin
Primary endpoints		
Asthma exacerbation rate		
Number of patients analysed	207	213
Rate estimate (95% CI)	1·86 (1·54 to 2·18)	1·07 (0·85 to 1·29)
Absolute difference estimate (95% CI)	..	−0·46 (−0·79 to −0·14)
Incidence rate ratio *vs* placebo (95% CI)*	..	0·59 (0·47 to 0·74), p<0·0001
Quality of life		
Number of patients analysed	204	209
AQLQ mean score end of treatment (mean, 95% CI)	5·55 (5·40 to 5·70)	5·73 (5·58 to 5·88)
AQLQ mean score end of treatment difference *vs* placebo (adjusted mean, 95% CI)†	..	0·36 (0·21 to 0·52), p=0·001‡
Secondary endpoints		
Symptoms		
Number of patients analysed	207	213
ACQ6 score end of treatment (mean, 95% CI)	1·31 (1·18 to 1·44)	1·21 (1·07 to 1·35)
ACQ6 score end of treatment difference vs placebo (adjusted mean, 95% CI)†	..	−0·20 (−0·34 to −0·05)

Azithromycin might be a useful add-on therapy in asthma.

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

Guy G Brusselle,[1] Christine VanderStichele,[1] Paul Jordens,[2] René Deman,[3] Hans Slabbynck,[4] Veerle Ringoet,[5] Geert Verleden,[6] Ingel K Demedts,[7] Katia Verhamme,[8] Anja Delporte,[1] Bénédicte Demeyere,[1] Geert Claeys,[9] Jerina Boelens,[9] Elizaveta Padalko,[9] Johny Verschakelen,[10] Georges Van Maele,[11] Ellen Deschepper,[11] Guy F P Joos[1]





	AZISAST Thorax 2013;68:322-29	AMAZES Lancet 2017;390:659-68
Patient (N)	109	420
Duration	26 weeks	48 weeks
Azithromycin	250mg three times a week	500mg three times a week

1 Risk Factors

2 Pharmacologic Management

3 Treatment of Severe Asthma

4 Asthma in Special Populations

Excess gestational weight gain in first trimester is a risk factor for exacerbation of asthma during pregnancy: A prospective study of 1283 pregnancies

Ali Z, et al. J Allergy Clin Immunol 2018;141:761-7

Exacerbation During Pregnancy

Excessive gestational weight gain in first trimester is a risk factor for exacerbation of asthma during pregnancy: A prospective study of 1283 pregnancies

Zarqa Ali, MD,[a] Lisbeth Nilas, DMSc,[b,c] and Charlotte Suppli Ulrik, DMSc[a,c] *Hvidovre and Copenhagen, Denmark*

- Since 2007, all pregnant women referred to give birth at Hvidovre Hospital, Denmark, have been offered participation in the prospective Management of Asthma during Pregnancy (MAP) program.
- Over an 8-year period, a total of 1283 pregnancies in 1208 women

- To identify pregnancy-related risk factors for acute exacerbations of asthma during pregnancy

Ali Z, et al. J Allergy Clin Immunol 2018;141:761-7

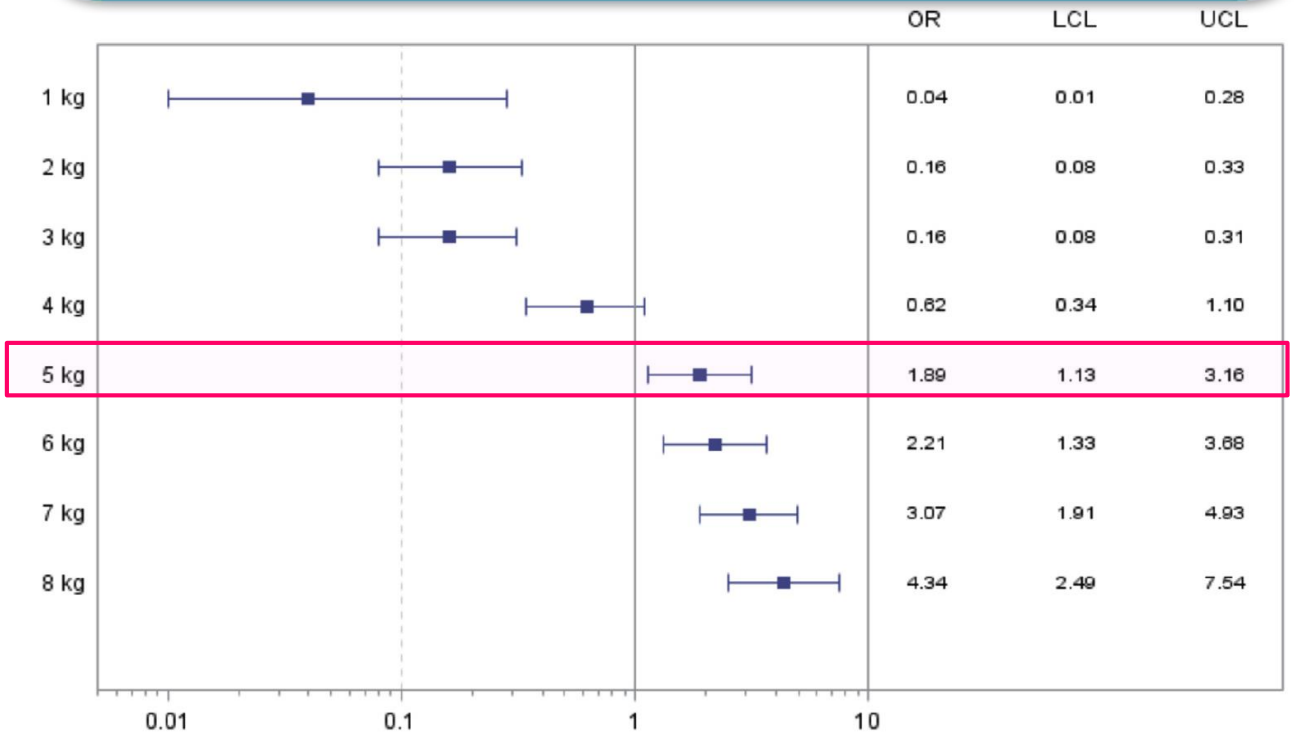
Risk Factor for Exacerbation

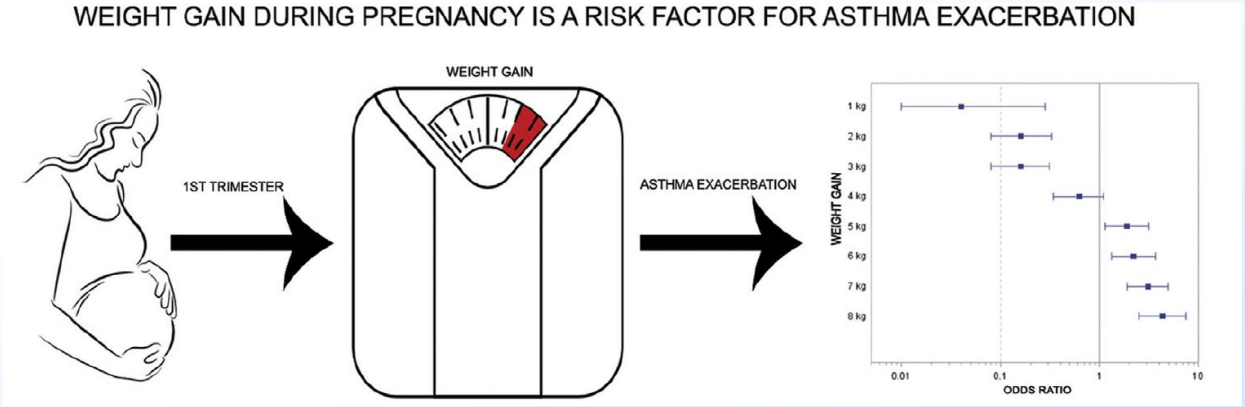
TABLE II. Comparison of characteristics between pregnancies complicated by exacerbation vs no exacerbation (upper panel) and severe exacerbation vs no severe exacerbation (lower panel) in 1283 pregnancies enrolled in the MAP program

Characteristic	Exacerbation (n = 252)	No exacerbation (n = 1031)	OR_{crude} (95% CI)	OR_{adj} (95% CI)	*P* value
Maternal age (y)	31.8 (4.7)	30.9 (4.8)	1.04 (1.01-1.07)	1.05 (1.02-1.08)	.003
Sex (male)	130 (51.6)	512 (49.7)	0.87 (0.65-1.16)	1.09 (0.80-1.48)	.57
Sex (female)	110 (43.7)	495 (48.0)			
Nulliparous	138 (54.8)	734 (71.2)	0.49 (0.37-0.65)	0.59 (0.44-0.81)	<.001
Multiparous	114 (45.2)	297 (28.8)			
Singleton	240 (95.2)	1007 (97.7)	2.10 (1.03-4.25)	1.50 (0.70-3.20)	.29
Gemelli	12 (4.8)	24 (2.3)			
Pre-pregnancy BMI (kg/m^2)	23.7 (4.2)	24.3 (4.5)	0.97 (0.94-1.00)	0.96 (0.93-0.99)	.04
GWG in the first trimester (kg)	7.3 (3.5)	4.1 (3.4)	1.27 (1.22-1.32)	1.22 (1.17-1.28)	<.001
Total GWG (kg)	14.8 (4.6)	11.6 (5.7)	1.13 (1.09-1.17)	1.13 (1.09-1.17)	<.001

Characteristic	Severe exacerbation (n = 99)	No severe exacerbation (n = 1184)	OR_{crude} (95% CI)	OR_{adj} (95% CI)	*P* value
Maternal age (y)	32.1 (5.2)	31.0 (4.7)	1.05 (1.00-1.09)	1.05 (1.00-1.10)	.02
Sex (male)	54 (54.5)	588 (49.7)	0.76 (0.49-1.17)	1.25 (0.79-1.99)	.33
Sex (female)	40 (40.4)	565 (47.7)			
Nulliparous	48 (48.5)	824 (69.6)	0.41 (0.27-0.62)	0.51 (0.33-0.78)	.002
Multiparous	51 (51.5)	360 (30.4)			
Singleton	95 (96.0)	1152 (97.3)	1.52 (0.53-4.38)	0.94 (0.31-2.87)	.91
Gemelli	4 (4.0)	32 (2.7)			
Pre-pregnancy BMI (kg/m^2)	24.1 (4.6)	24.2 (4.5)	0.99 (0.95-1.04)	0.99 (0.94-1.04)	.67
GWG in the first trimester (kg)	8.0 (3.6)	4.4 (3.5)	1.25 (1.19-1.32)	1.20 (1.13-1.27)	<.001
Total GWG (kg)	15.3 (4.7)	12.0 (5.7)	1.13 (1.08-1.18)	1.11 (1.06-1.17)	<.001

Cutoff of GWG in the 1st trimester of pregnancy





SUMMARY

- Traffic-related air pollution exposures confer an increased risk of allergic sensitization, asthma, and lower levels of lung function.
- In mild asthma, ICS reduces serious asthma-related events, even in patients with infrequent symptoms.
- LAMA as add-on therapy to ICS is associated with a lower risk of asthma exacerbations.
- The use of SMART is associated with a lower risk of asthma exacerbations.

- Benralizumab reduces the oral glucocorticoid dose.
- Tezepelumab (anti-TSLP) results in a lower rate of exacerbations.
- Imatinib decreases AHR and tryptase release.
- Azithromycin as add-on therapy decreases the exacerbation frequency.

- Excessive GWG in the first trimester is a risk factor for asthma exacerbation during pregnancy.

Thank You for Your Attention