TSPCCM Annual Congress AZ Satellite Symposium

Current biologic treatment for severe asthma: A target approach with benralizumab

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08/Dec/2019

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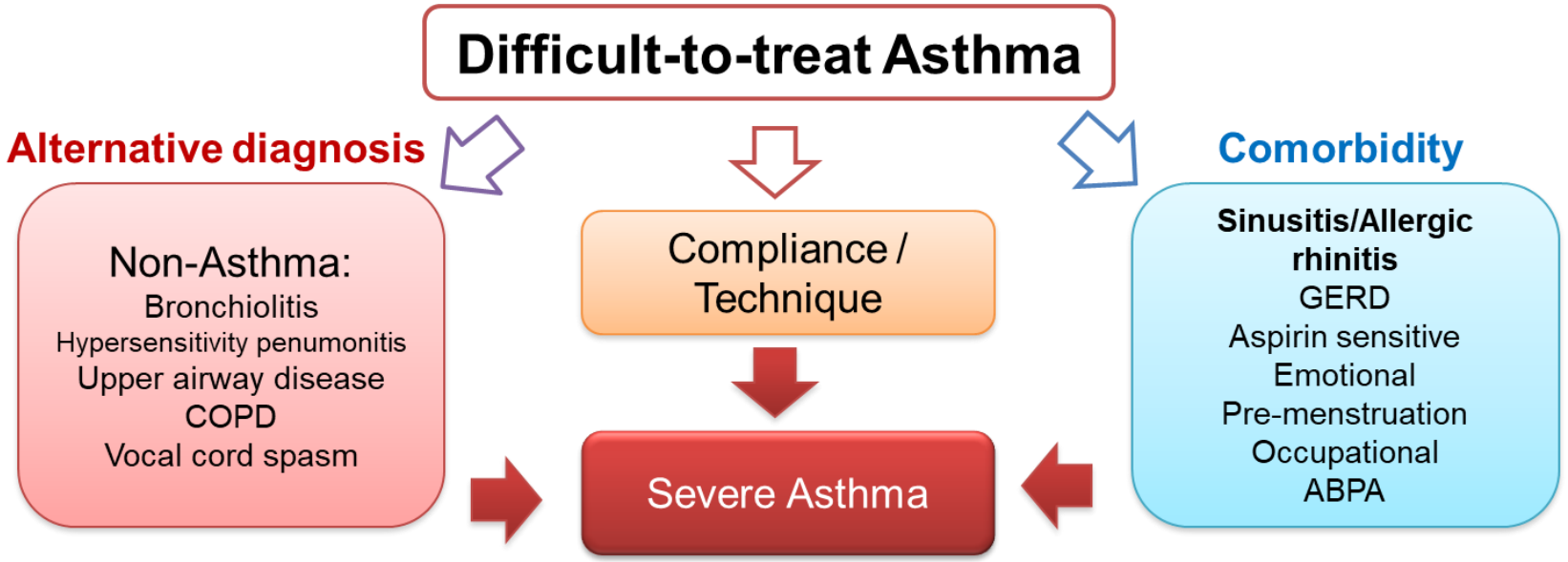
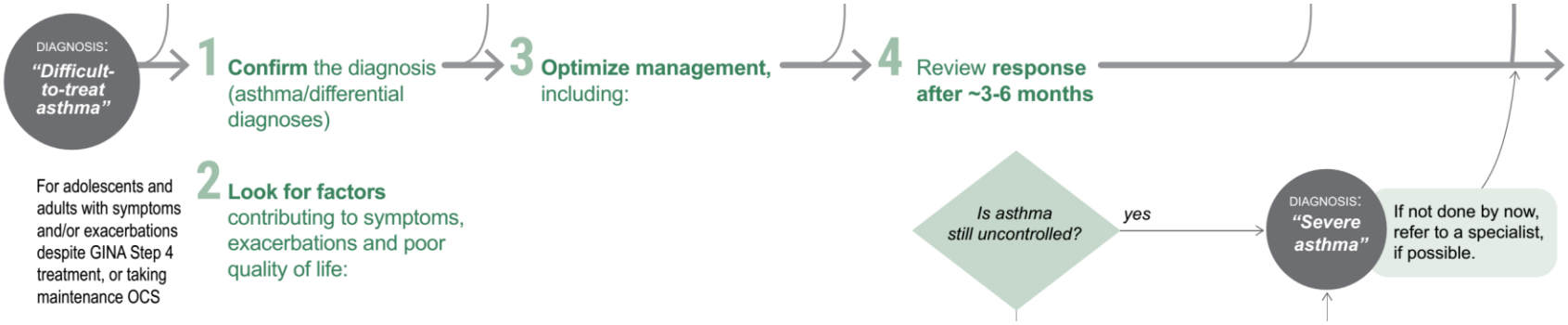
處方用藥請參考衛生福利部核准仿單說明書

Differentiation between difficult-to-treat and severe asthma



Adapted from slide of Prof. HP Kuo, 2012

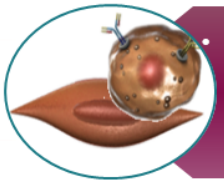


GINA DIFFICULT-TO-TREAT & SEVERE ASTHMA in adolescent and adult patients Diagnosis and Management, Apr. 2019

How do eosinophils impact airways of asthma?

Eosinophils contribute to airway obstruction and inflammation

Airway Hyperresponsiveness

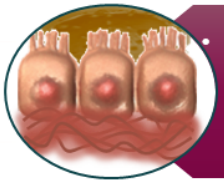


- Activated eosinophils can contribute to inflammation and AHR both directly (release of mediators) and indirectly (cellular interactions)
- Toxic mediators (eg, ECP) released by eosinophils can damage airway epithelium and increase smooth muscle reactivity

Immunomodulation

- Eosinophils synthesize, store, and secrete a variety of cytokines including Th2 cytokines (IL-4 and IL-13) and Th1 cytokines (IL-12 and IFN-γ)
- Eosinophils may stimulate lymphocyte proliferation and T cell differentiation and polarization

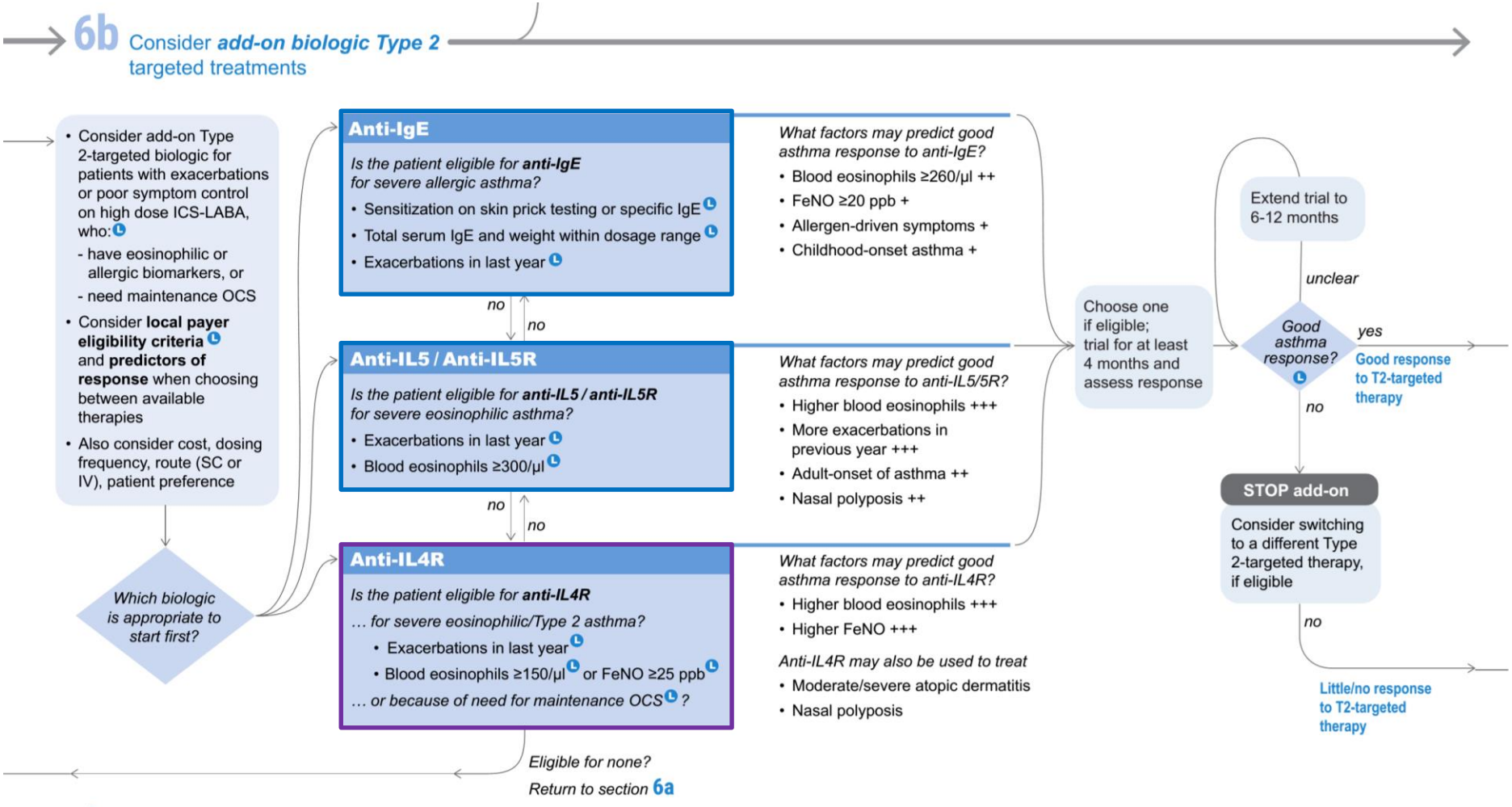
Airway Remodeling



- Eosinophils may contribute to the induction of airway remodeling through synthesis of profibrotic mediators
- Eosinophils may be an important source of TGF-β, a potent pro-fibrotic cytokine, which contributes to fibroblast proliferation and differentiation of myofibroblasts

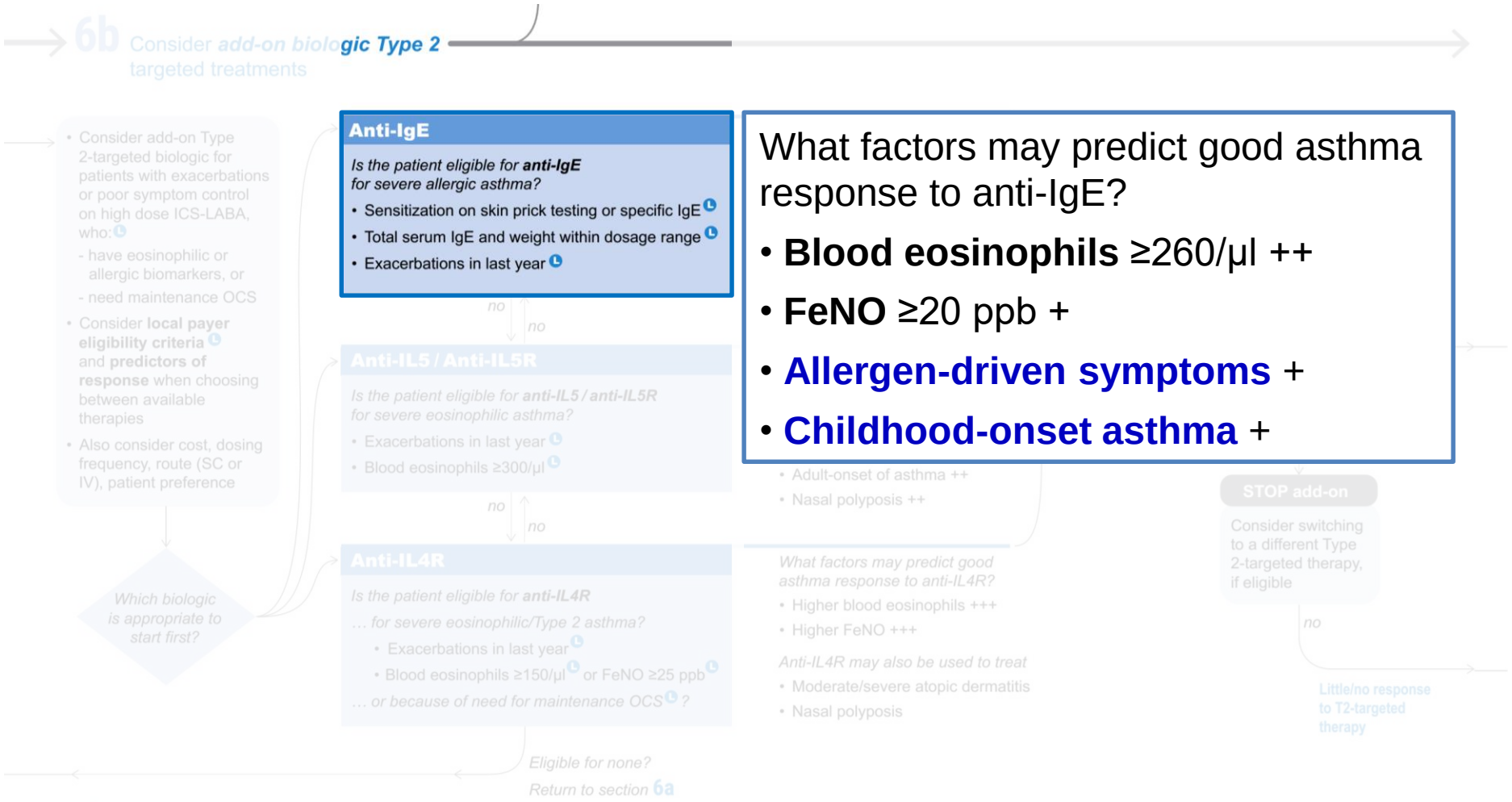
AHR = airway hyperresponsiveness; ECP = eosinophil cationic protein; IFN = interferon; IL = interleukin; TGF = transforming growth factor; Th = T helper cell.
Trivedi SG et al. *Cell Mol Life Sci*. 2007;64:1269-1289.

Add-on biologic type 2 targeted treatments



GINA DIFFICULT-TO-TREAT & SEVERE ASTHMA in adolescent and adult patients Diagnosis and Management, Apr, 2019

Add-on biologic type 2 targeted treatments



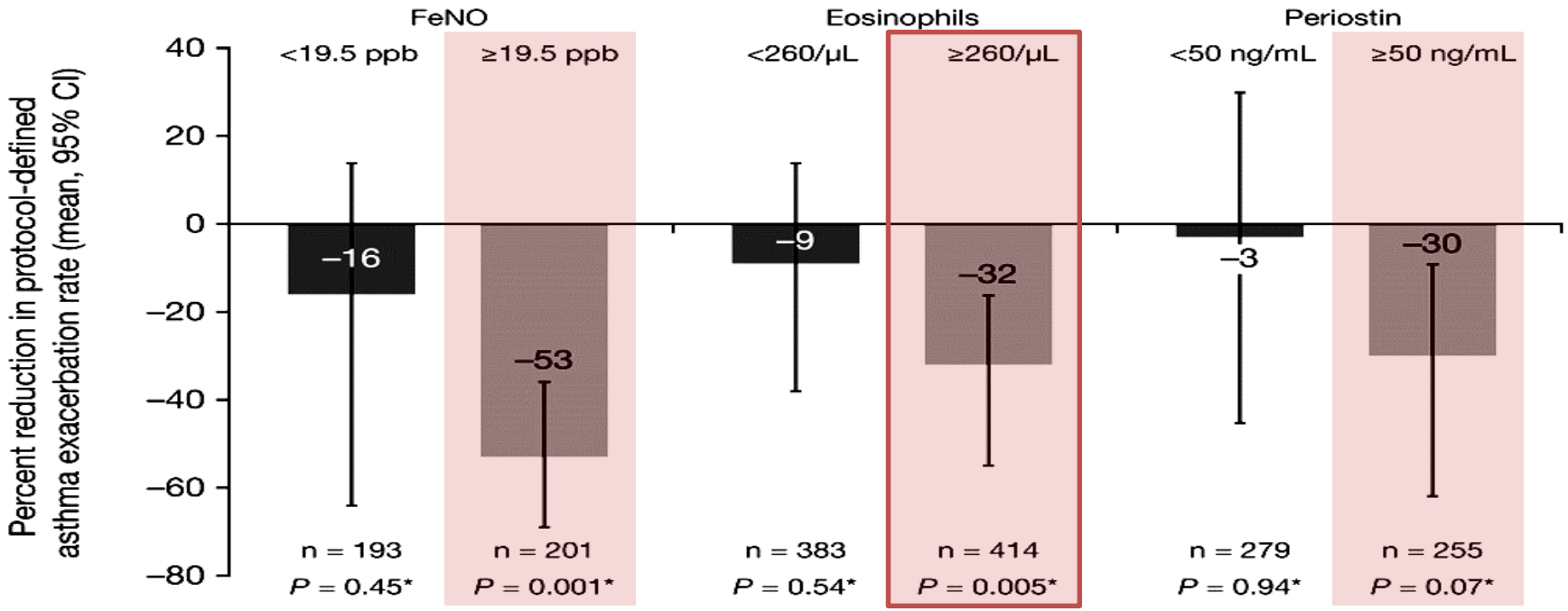
What factors may predict good asthma response to anti-IgE?

- **Blood eosinophils** ≥260/µl ++
- **FeNO** ≥20 ppb +
- **Allergen-driven symptoms** +
- **Childhood-onset asthma** +

GINA DIFFICULT-TO-TREAT & SEVERE ASTHMA in adolescent and adult patients Diagnosis and Management, Apr, 2019

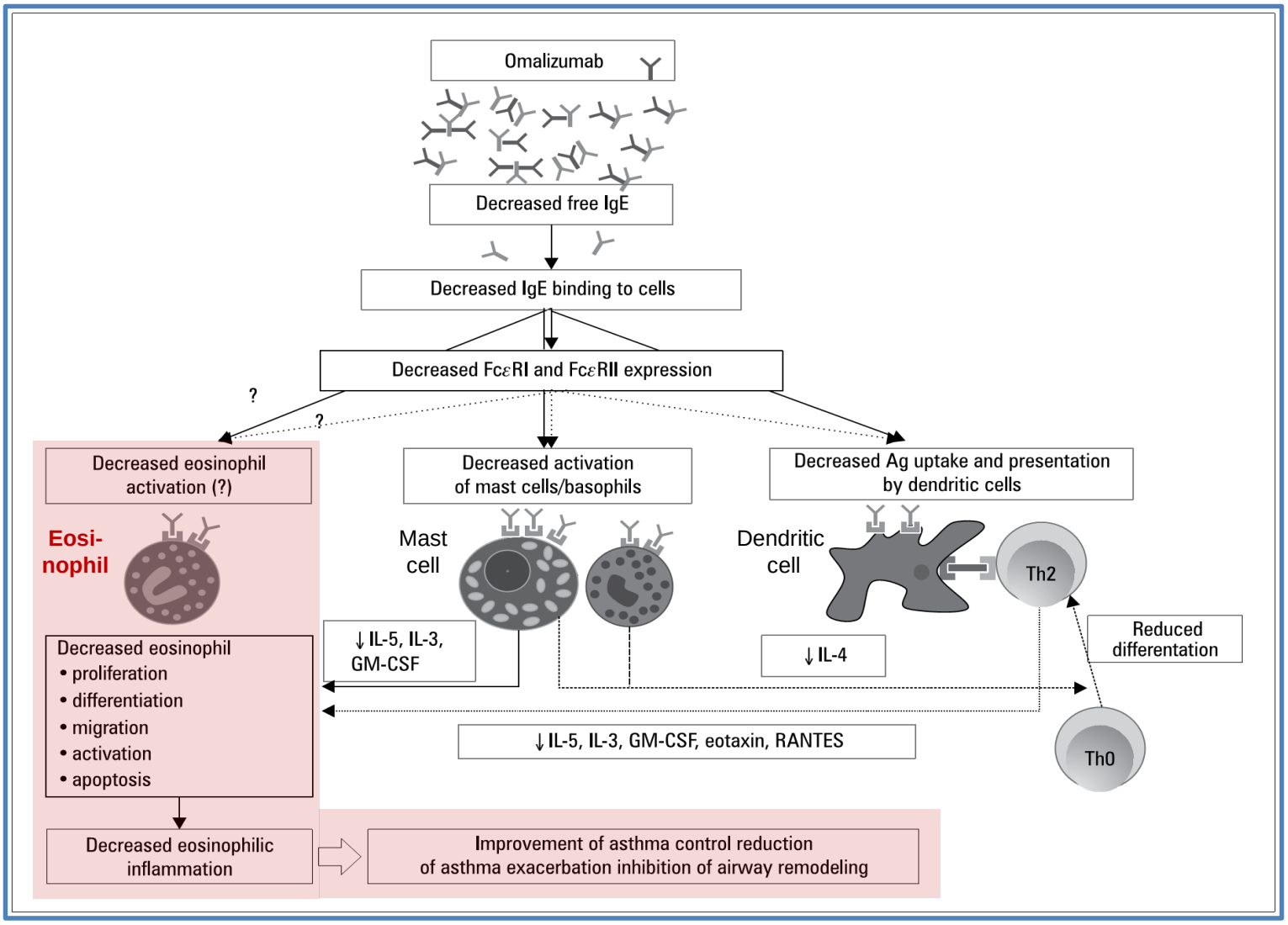
Post hoc analysis revealed omalizumab reduces exacerbation better in severe allergic asthma with eosinophilia

- Prospective, multicenter, randomized, parallel-group, double-blind, placebo-controlled study [**EXTRA**]
- 850 patients with uncontrolled severe persistent allergic asthma despite high-dose ICS plus LABA, +/- additional controllers
- 1:1 randomization to omalizumab or placebo
- 46.4% for FENO, 93.8% for blood eosinophils, and 62.8% of patients for serum periostin available



Hanania NA *et al. Am J Respir Crit Care Med*. 2013 Apr 15;187(8):804-11

Mechanism of IgE and omalizumab action: more than mast cell and allergy



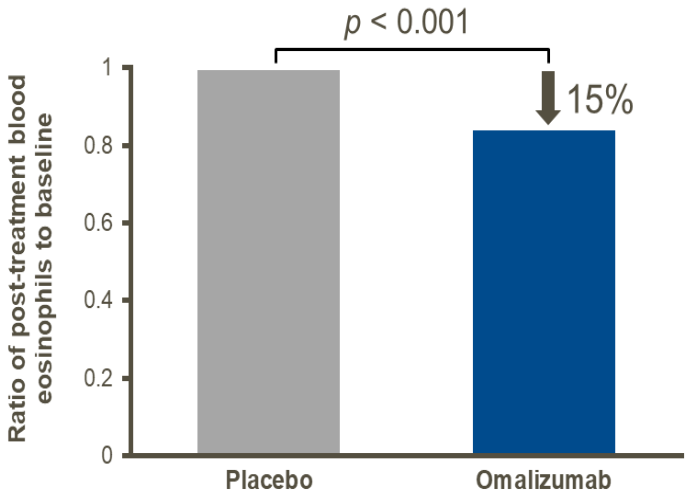
Kupryś-Lipińska I *et al. Pneumonol Alergol Pol*. 2016;84(4):232-43

Previous pool analysis revealed omalizumab reduces blood eosinophils in severe allergic asthma with eosinophilia, **BUT…**

At similar blood eosinophil level, mepolizumab reduces eosinophil count much greater than omalizumab

Pool analysis of 5 RCTs in moderate-to-severe allergic asthma (ICS~1,400 BDP eqivalent) comparing omalizumab vs placebo

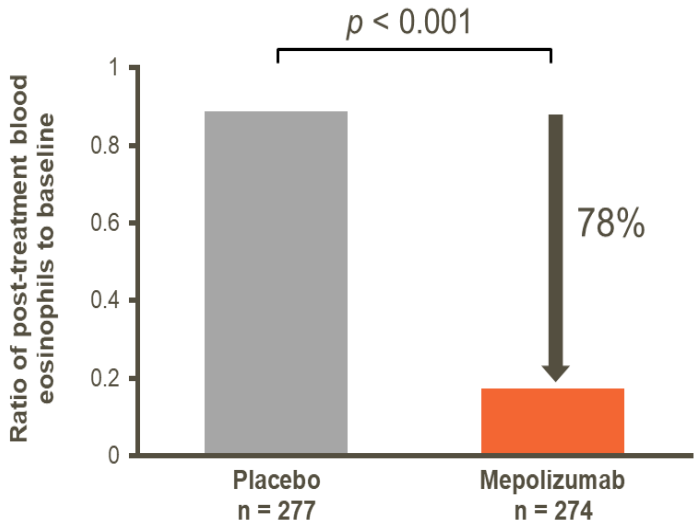
Treatment ratio 0.85 (omalizumab/placebo)[1]



Baseline mean blood eosinophil counts: 330 cells/µL (Placebo), 320 cells/µL (Omalizumab)

MUSCA

Treatment ratio 0.22 (mepolizumab/placebo)[2]



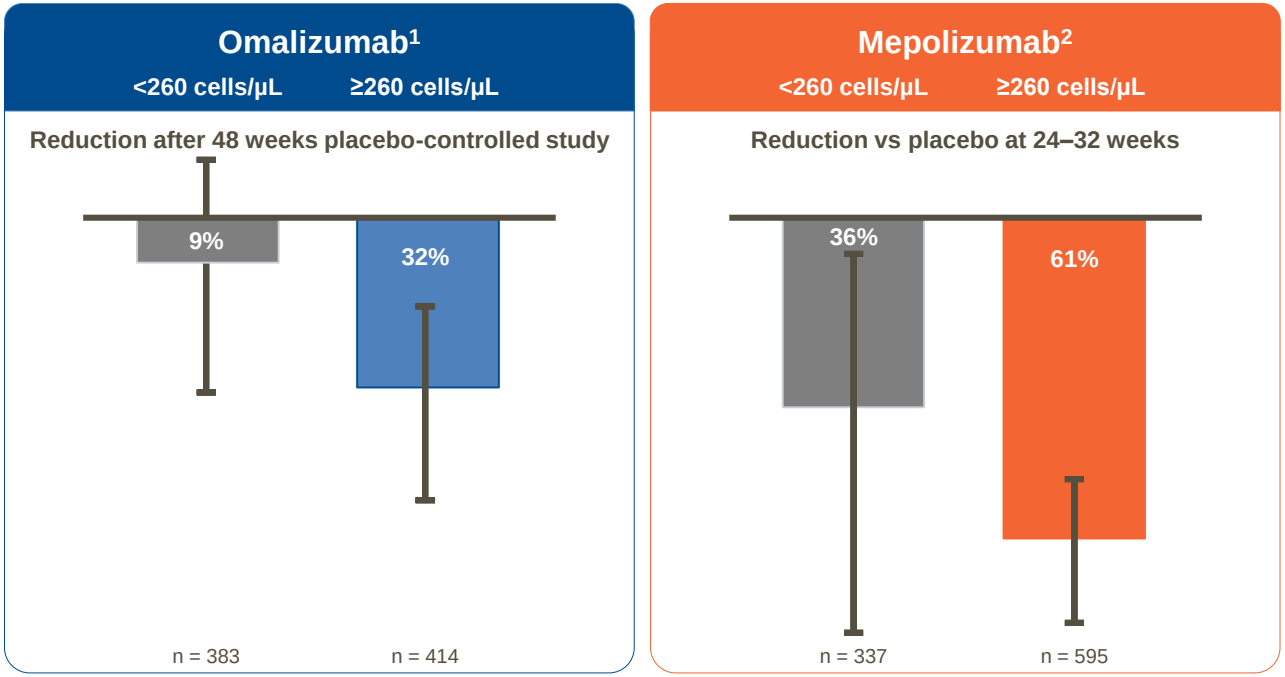
Baseline mean blood eosinophil counts[3]: 350 cells/µL (Placebo), 300 cells/µL (Mepolizumab)

Massanari M *et al. Respir Med*. 2010 Feb;104(2):188-96

Chupp GL *et al. Lancet Respir Med*. 2017 May;5(5):390-400

Previous post hoc analysis revealed omalizumab reduces exacerbation better in severe allergic asthma with eosinophilia, **BUT…**

At the same cut-off eosinophil count, mepolizumab reduces exacerbation much greater than omalizumab



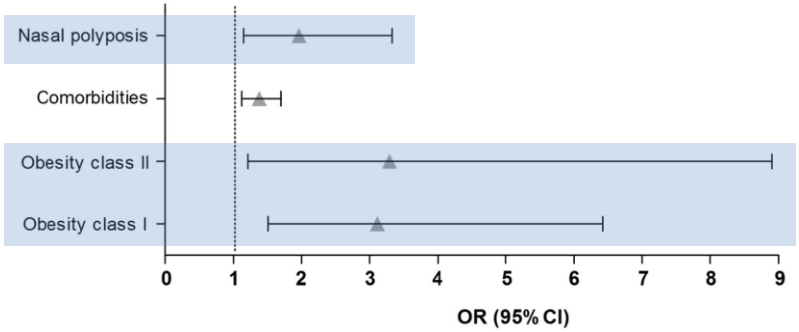
EXTRA study[1] | MENSA & MUSCA studies[2]

1. Adapted from: Hanania NA, et al. *Am J Resp Crit Care Med*. 2013;187:804–811;
2. GSK. Data on file. RF/NLA/0093/18.

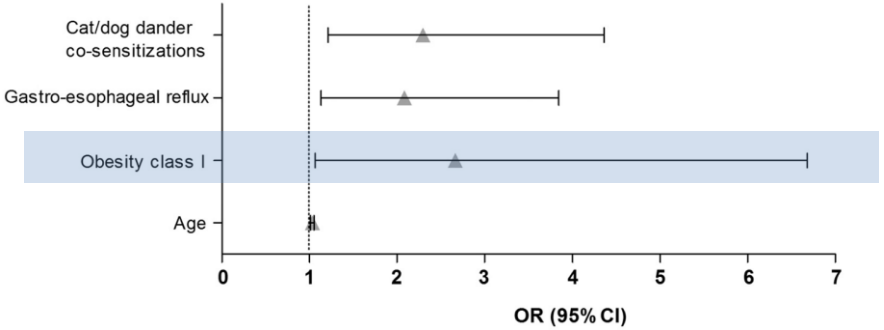
Nasal polyps and obesity associated with **poor effectiveness** in severe allergic asthma despite **omalizumab**

Retrospective study of 340 patients with **severe allergic asthma** treated with **omalizumab** (mean duration: 32 m)

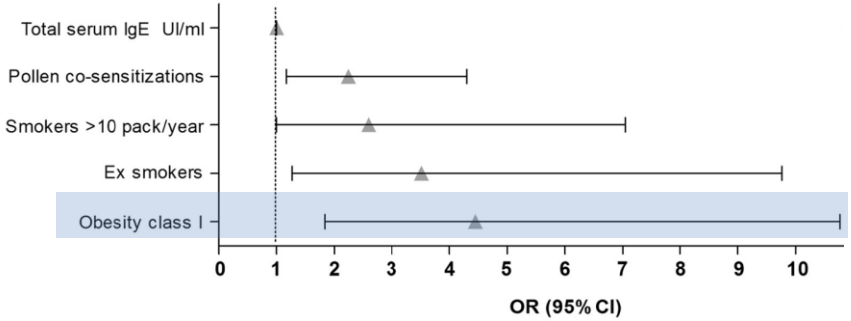
≥ 1 exacerbation



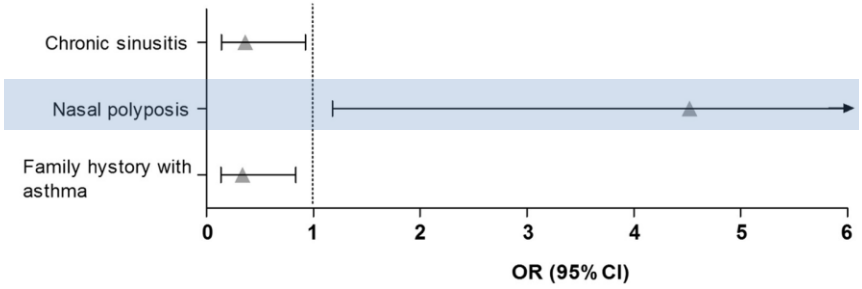
Partial/poor control



SABA use ≥ once/week



Continuing medium/high dose ICS



Sposato B *et al. Eur J Intern Med*. 2018 Jan 29. pii: S0953-6205(18)30026-8

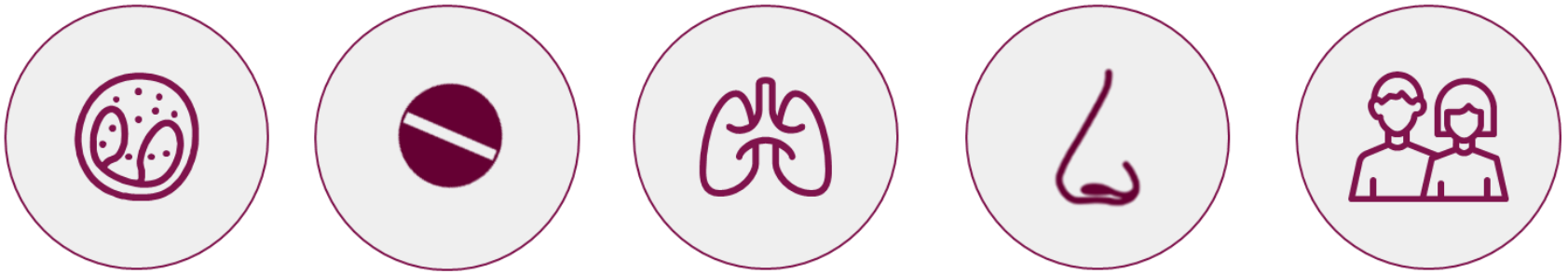
Determining phenotypes based on clinical characteristics and biomarkers

Phenotype	Characteristics
Allergic asthma	Early-onset asthma Symptoms triggered by allergies Seasonal variations in exacerbations and degree of symptoms Associated with strong family history of asthma
Eosinophilic asthma	Late-onset asthma Comorbid condition: severe sinus disease, nasal polyps, and aspirin sensitivity Frequent exacerbations requiring healthcare use May require oral corticosteroid maintenance therapy for symptom control

Opina MT *et al. Curr Allergy Asthma Rep*. 2017 Feb;17(2):10

Clinical characteristics of eosinophilic asthma

Most consistently identifiable features associated with eosinophilic asthma



AT RISK OF SEVERE EXACERBATIONS
Elevated eosinophils in peripheral blood

NEED FOR INTERMITTENT OR CONTINUOUS OCS

LOW FEV_1, OFTEN PERSISTENT AIRFLOW LIMITATION

CHRONIC RHINOSINUSITIS WITH NASAL POLYPOSIS

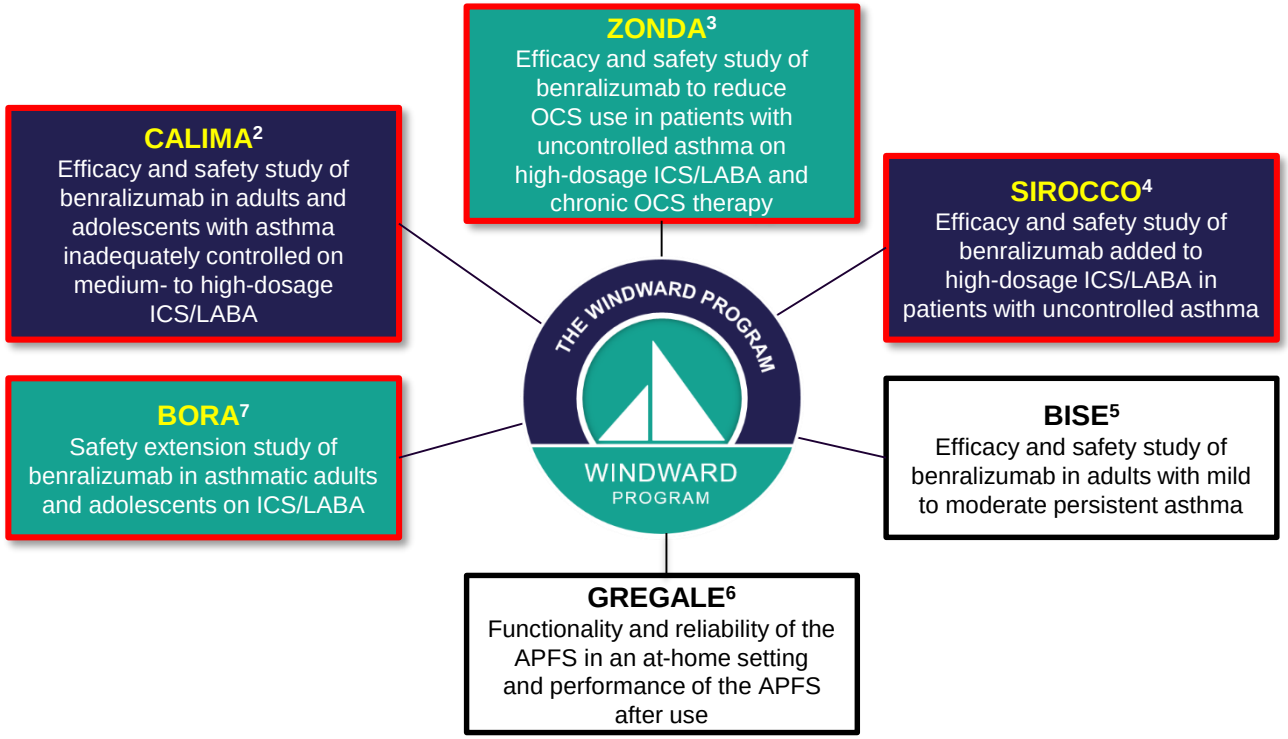
ADULT ONSET
Equal distribution between sexes

FEV_1 = forced expiratory volume in 1 second. OCS= oral corticoid steroid

1. de Groot JC et al. *ERJ Open Res.* 2015;1:00024-2015; 2. Price DB et al. *Lancet Respir Med.* 2015;3:849-858.

WINDWARD program in asthma: Benralizumab phase 3 clinical trials

- **Six Phase III trials in ~3068 patients** and at 798 sites across 26 countries[1]
- **The largest Phase III** development program for a biologic in respiratory disease[1]

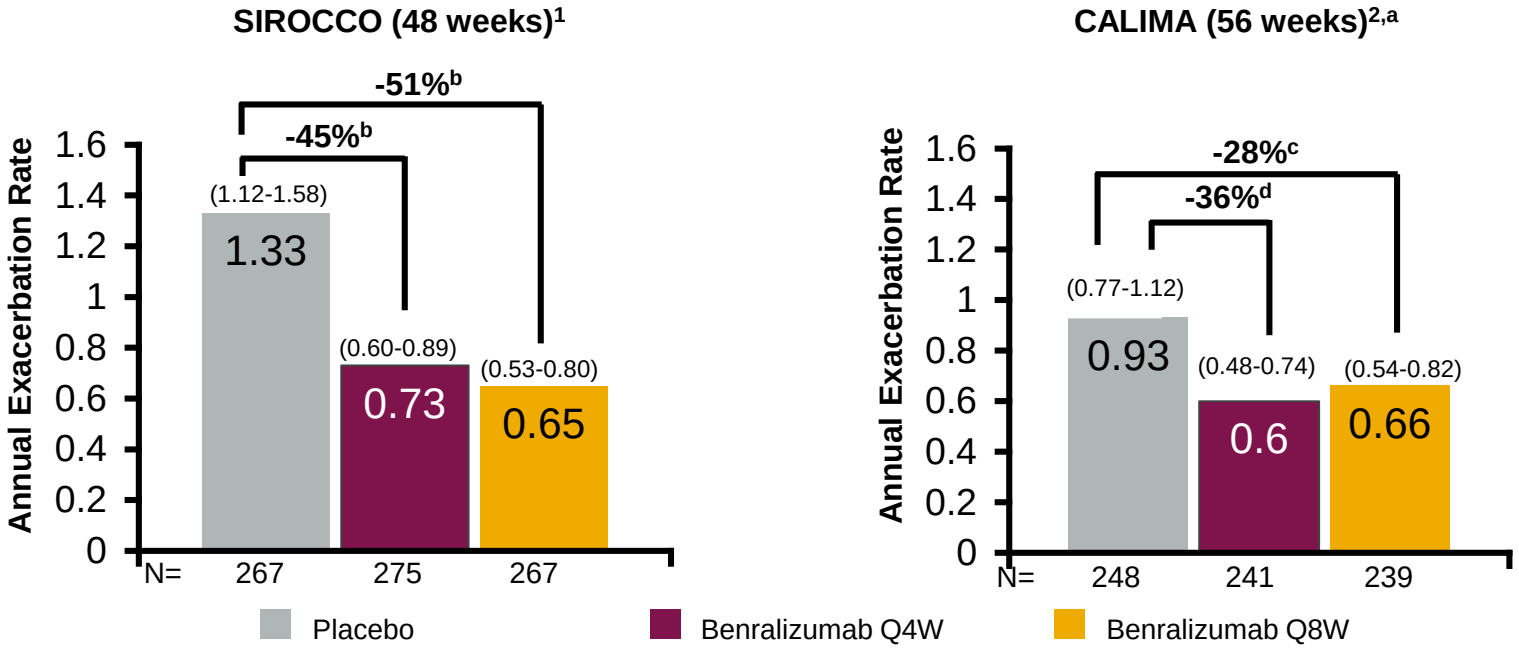


APFS = accessorized pre-filled syringe; ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; OCS = oral corticosteroid.

1. AstraZeneca Pharmaceuticals LP press release. Published May 17, 2016; 2. FitzGerald JM et al. *Lancet*. 2016;388:2128-2141; 3. Nair P et al. *N Engl J Med*. 2017;376:2448-2458; 4. Bleecker ER et al. *Lancet*. 2016;388:2115-2127; 5. Ferguson GT et al. *Lancet Respir Med.* 2017;5:568-576; 6. Ferguson GT et al. Poster presented at: ATS; May 19-24, 2017; Washington, DC. Poster P1011; 7. Study NCT02258542. ClinicalTrials.gov website.

Benralizumab reduced exacerbatioin of severe eosinophilic asthma [SIROCCO & CALIMA]

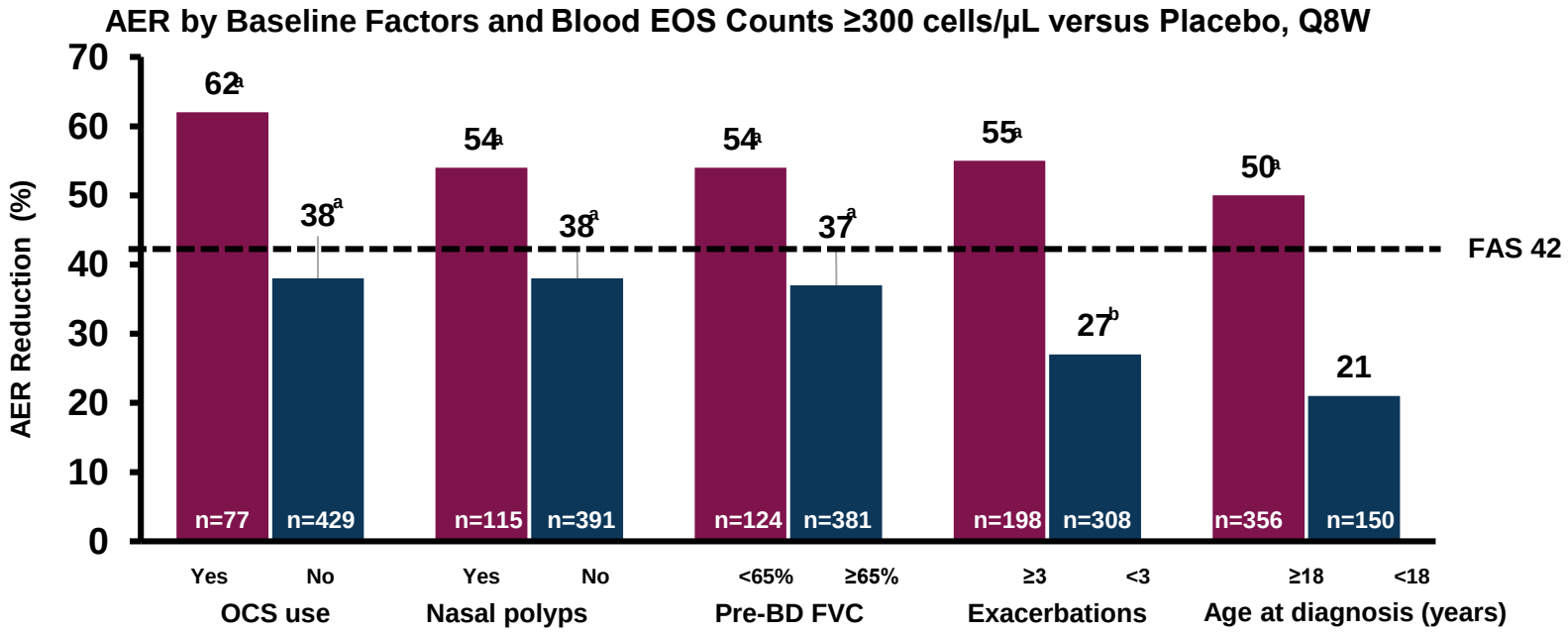
Benralizumab significantly reduced AER (Eos ≥300 cells/μL, high-dosage ICS/LABA)



1. Bleecker ER et al. *Lancet*. 2016;388:2115-2127; 2. FitzGerald JM et al. *Lancet*. 2016;388:2128-2141.

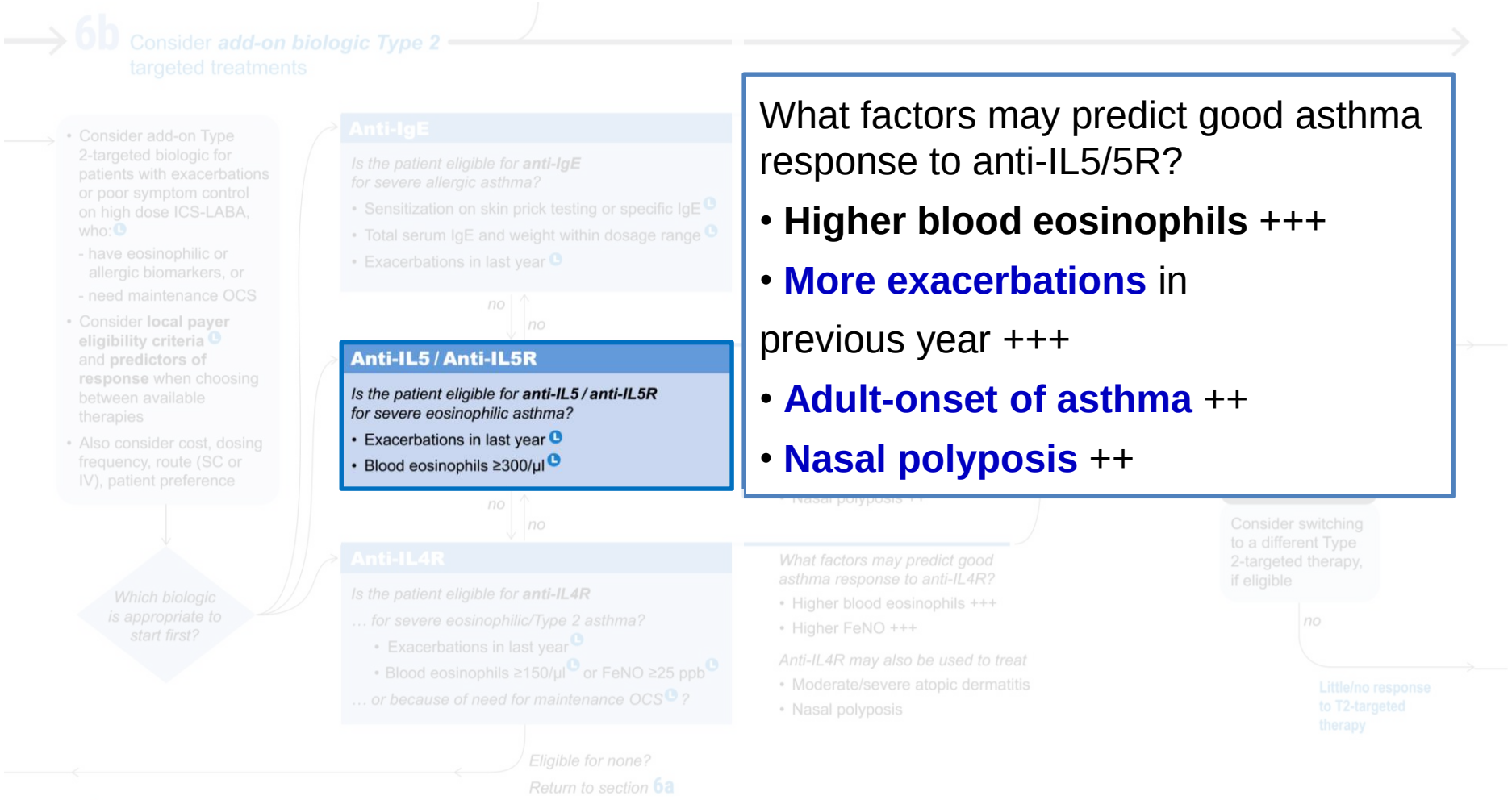
Better efficacy of benralizumab in severe eosinophilic asthma with common characteristics [SIROCCO & CALIMA]

Exacerbation rate reduction by baseline factors and blood Eos counts (Pooled SIROCCO and CALIMA; high-Dosage ICS/LABA, ≥300 Eos)



Bleecker ER et al. Poster presented at: ATS International Conference; May 18-23, 2018; San Diego, CA. Poster 16840.

Choices among biologics for severe asthma
Anti-IL5/IL5R



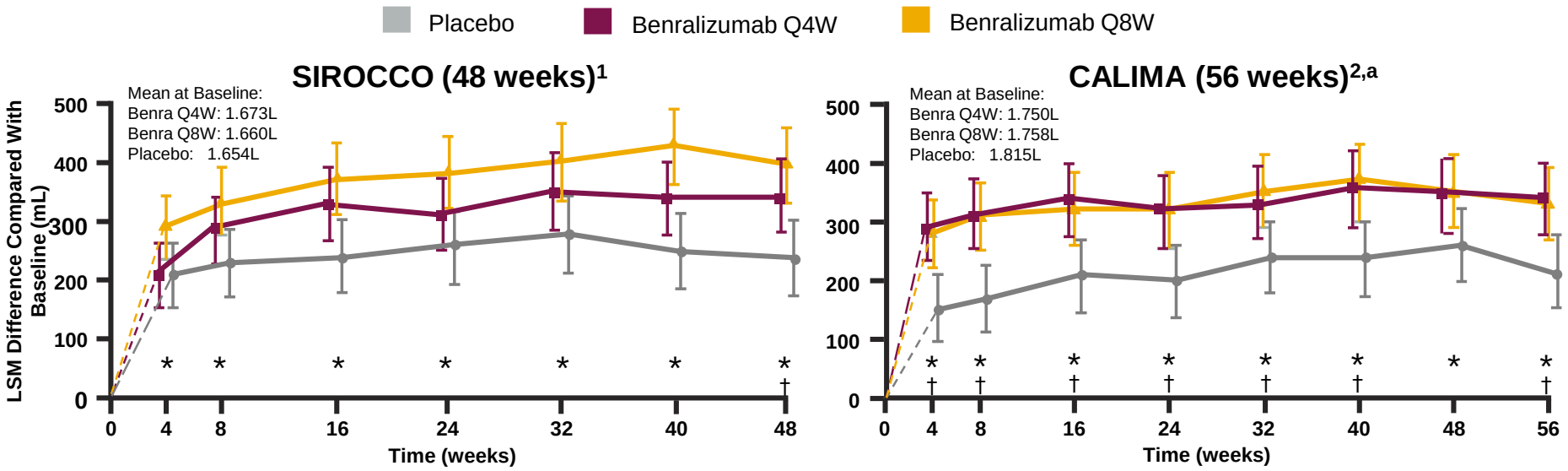
What factors may predict good asthma response to anti-IL5/5R?

- **Higher blood eosinophils** +++
- **More exacerbations** in previous year +++
- **Adult-onset of asthma** ++
- **Nasal polyposis** ++

GINA DIFFICULT-TO-TREAT & SEVERE ASTHMA in adolescent and adult patients Diagnosis and Management, Apr, 2019

Rapid improvement of FEV_1 with benralizuamab in severe eosinophilic asthma [SIROCCO & CALIMA]

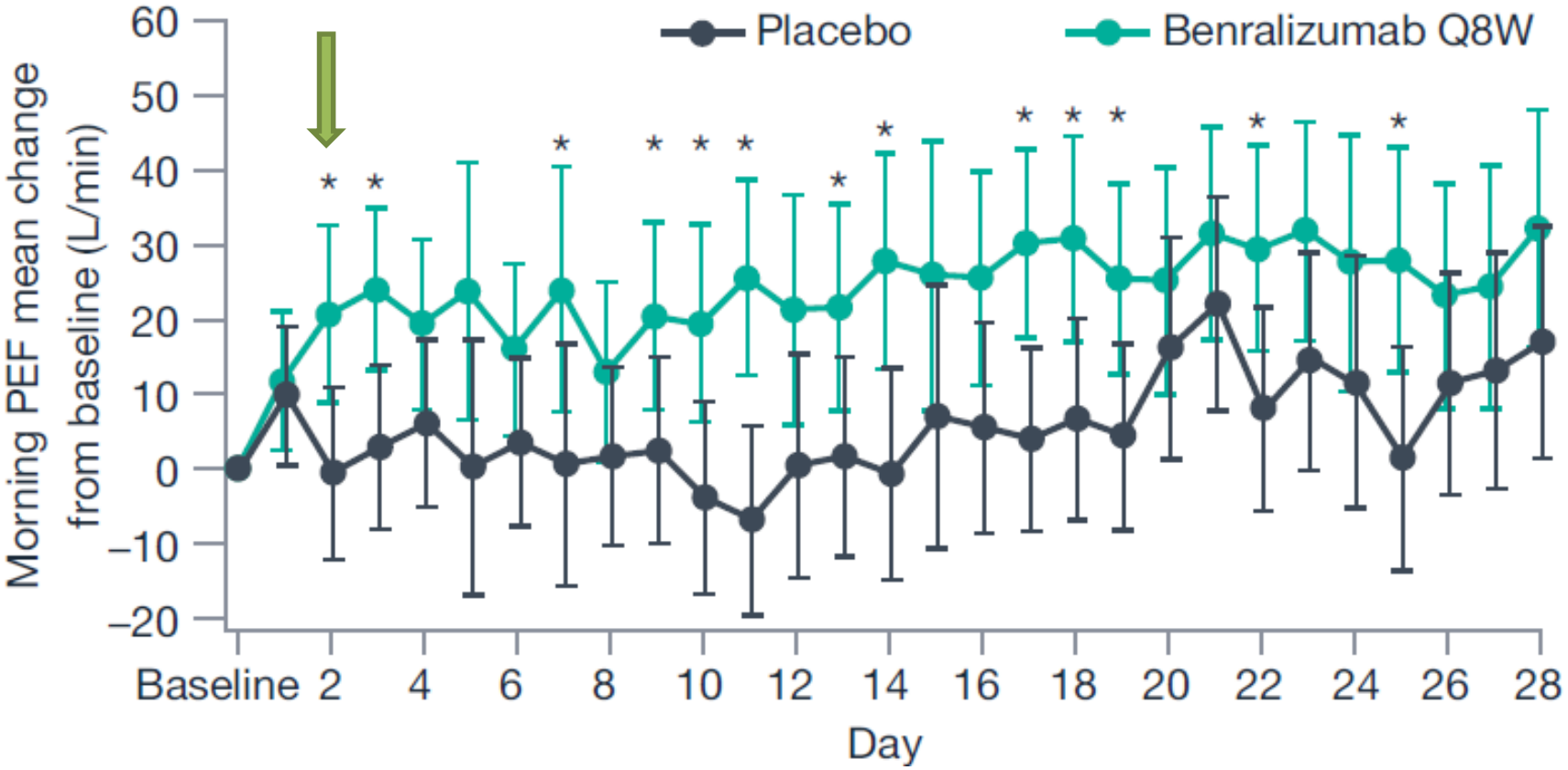
FEV_1 improvements seen after the first dose and maintained throughout treatment period (Eos ≥300 cells/µL, high-dosage ICS)



56/48 Weeks	Group LSMs	LSM Difference (95% CI)	Group LSM	Difference (95% CI)
Q4W – placebo	345 vs 239	106 (16-196); p=0.0215	340 vs 215	125 (37-213); p=0.0054
Q8W – placebo	398 vs 239	159 (68-249); p<0.001	330 vs 215	116 (28-204); p=0.0102

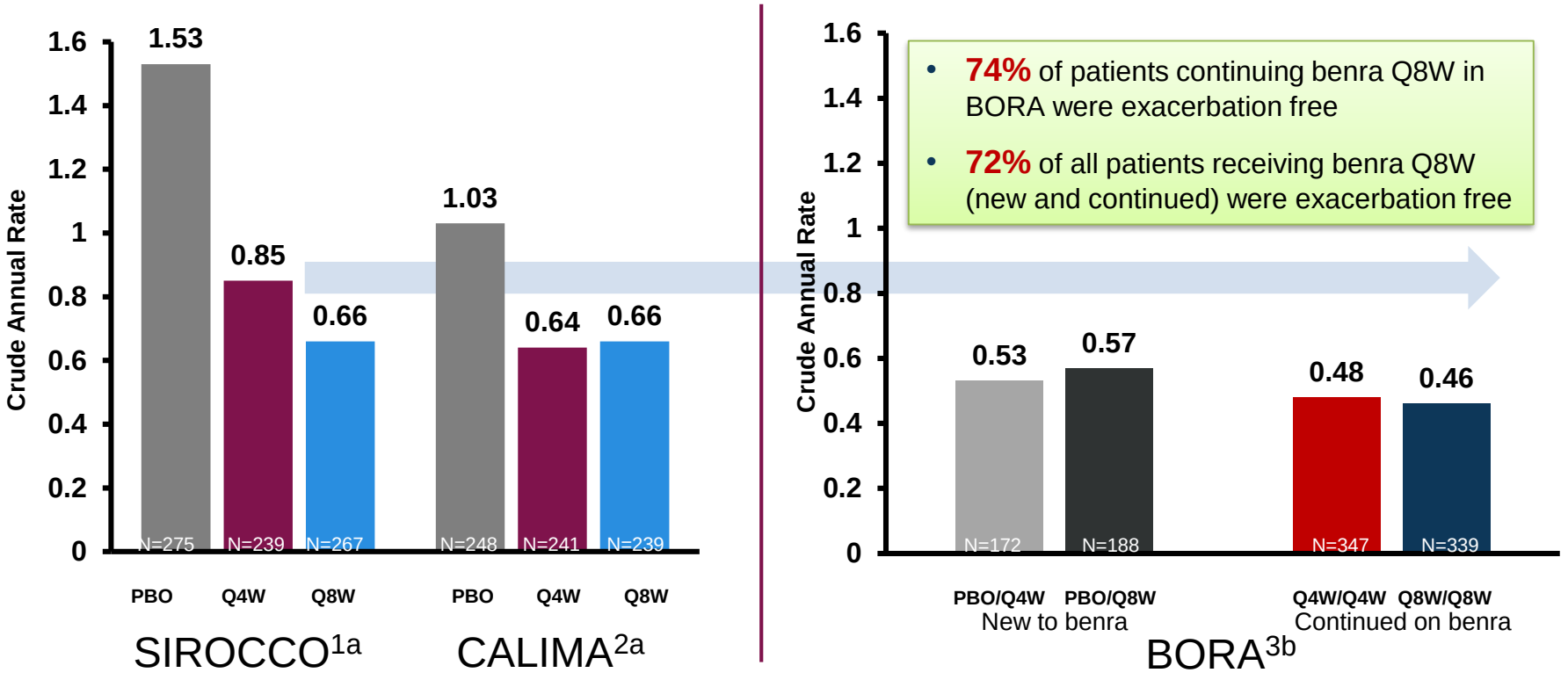
1. Bleecker ER et al. *Lancet*. 2016;388:2115-2127; 2. FitzGerald JM et al. *Lancet*. 2016;388:2128-2141.

Rapid improvement of PEF with benralizuamab in severe eosinophilic asthma [ZONDA]



Lugogo NL *et al*. Poster presentation at ATS 2018 [Poster # A101/410

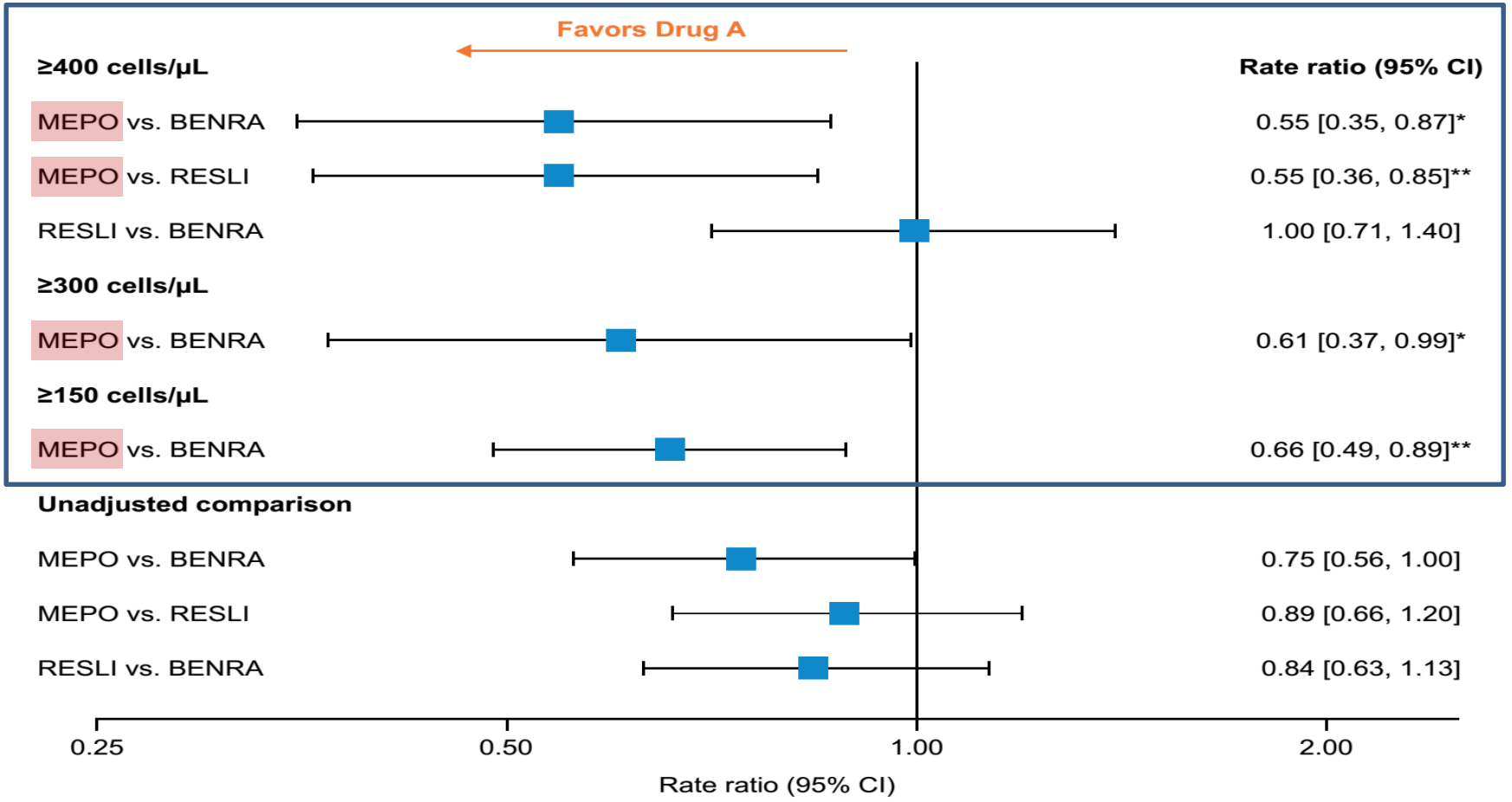
Consistent and durable effects of exacerbation reduction with benralizuamb for severe eosinophilic asthma



Please note that as head-to-head studies were not conducted between these studies it is inappropriate to make direct comparisons as the study design, demographics, and other criteria may be different.

1. Bleecker ER et al. Supplementary appendix. Lancet. 2016;388;2128-2141; 2. FitzGerald JM et al. Supplementary appendix. Lancet. 2016;388;2128-2141; 3. Busse WW et al. Presentation at: ERS International Congress; September 15-19, 2018; Paris, France.

Mepolizumab reduces exacerbation in severe eosinophilic asthma better than benralizumab and reslizumab?



Busse W *et al. J Allergy Clin Immunol*. 2019 Jan;143(1):190-200.e20

Different baseline characteristics between benralizumab and mepolizumab studies

Please note that as head-to-head studies were not conducted between these products, it is inappropriate to draw any comparisons and/or make any conclusions, as the study design, demographics, and other criteria may be different.

	Mepolizumab 100 mg Q4W MENSA[1,2]	Mepolizumab 100 mg Q4W MUSCA[3]	Benralizumab 30 mg Q8W SIROCCO[4,5,a]	Benralizumab 30 mg Q8W CALIMA[6,7,a]
Age, y	51	49.8	47.6	49
Female, %	60	54	63	62
BMI, kg/m^2	27.6	28.5	28.2	28.8
Duration of asthma, y	20.5	19.5	14.4	16.8
Exacerbations in prior 12 months, n	**3.8**	**2.9**	**2.8**	**2.7**
FEV_1 predicted, %	59.3	55.5	56.1	57.9
Proportion receiving OCS, %	**27**	**23**	**18**	**10**
Actual baseline EOS count, cells/µL	**290**	**300**	**360**	**400**
Nasal polyps, %	14	21	19	15

[a]Data presented are from the full analysis population. 1. Ortega HG *et al. N Engl J Med*. 2014;371:1198-1207; 2. Ortega HG *et al*. Supplementary appendix. *N Engl J Med*. 2014;371:1198-1207; 3. Chupp GL *et al. Lancet Respir Med* 2017; 5: 390–400; 4. Bleecker ER *et al. Lancet*. 2016;388:2115-2127; 5. Bleecker ER *et al*. Supplementary appendix. *Lancet*. 2016;388:2115-2127; 6. FitzGerald JM *et al. Lancet*. 2016;388:2128-2141; 7. FitzGerald JM *et al*. Supplementary appendix. *Lancet*. 2016;388:2128-2141;

Eur Respir J. 2018 Nov 29;52(5). pii: 1801393. doi: 10.1183/13993003.01393-2018. Print 2018 Nov.

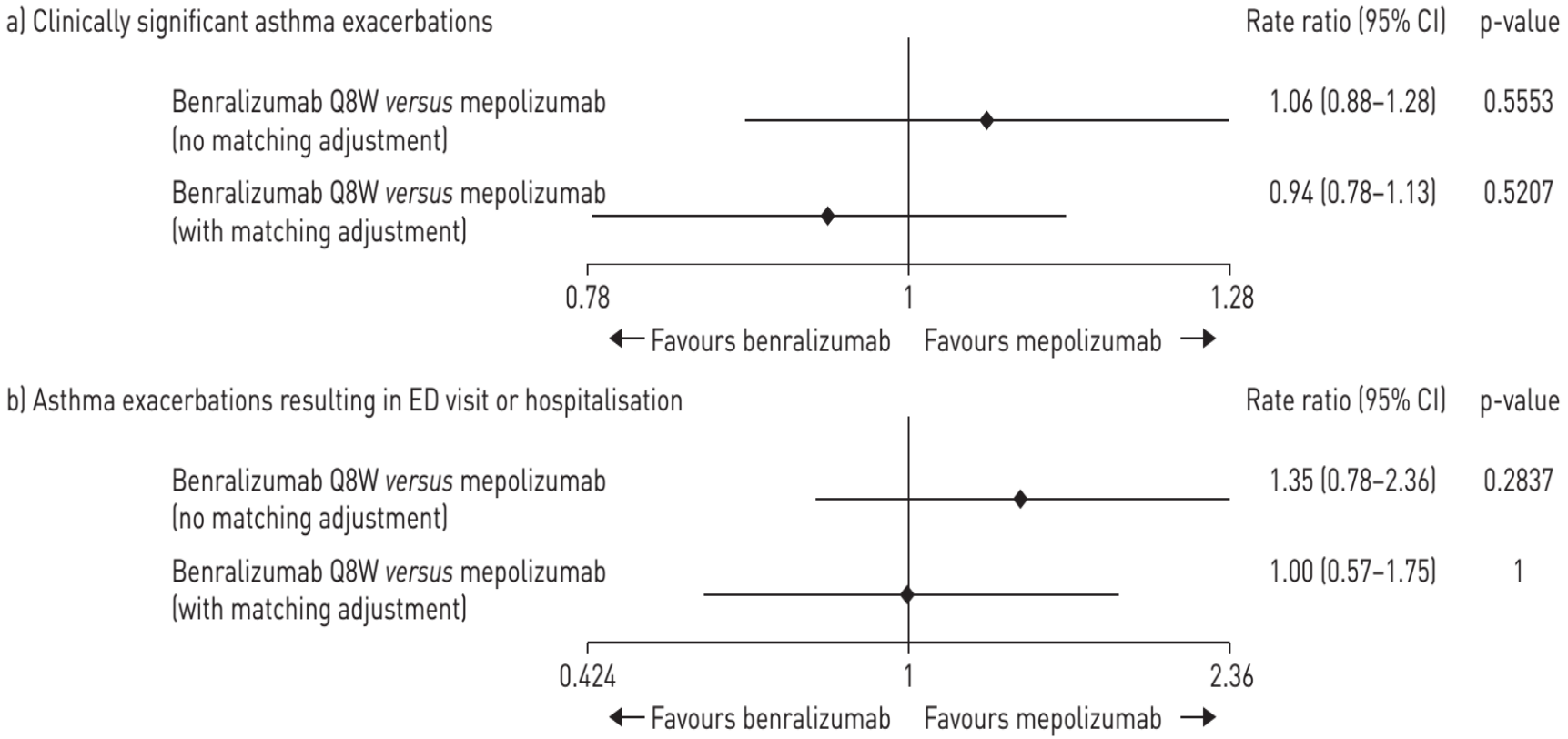
Matching-adjusted indirect comparison of benralizumab *versus* interleukin-5 inhibitors for the treatment of severe asthma: a systematic review.

Bourdin A[1,2], Husereau D[3,4], Molinari N[5], Golam S[6], Siddiqui MK[7], Lindner L[8], Xu X[9].

Baseline characteristics	SIROCCO/CALIMA[#] (before adjustment) Benralizumab Q8W, placebo	MENSA/DREAM (aggregate reported data) Mepolizumab 75 mg IV, mepolizumab 100 mg SC, placebo	SIROCCO/CALIMA (after adjustment) Benralizumab Q8W, placebo
Patients n	863	884	559[¶]
Eosinophil count			
⩾300 cells·μL^{-1}	68.02	52.45	52.43
<300 cells·μL^{-1}	31.98	47.55	47.57
Maintenance OCS use			
Yes	15.06	26.58[+]	30.24
No	84.94	73.42[+]	69.76
IgE count			
<30 IU·mL^{-1}	11.40	13.29	14.62
⩾30–⩽700 IU·mL^{-1}	71.09	70.35	70.01
>700 IU·mL^{-1}	17.51	16.35	15.37
Sex			
Male	37.43	40.05	39.08
Female	62.57	59.95	60.92
Exacerbations in previous year			
2	62.34	42.99	42.82
>2	37.66	56.79	57.18
Nasal polyps			
No	81.23	86.83	83.09
Yes	18.77	13.17	16.91
BMI mean±SD kg·m^{-2}	28.89±6.27	27.98±5.912	28.38±6.15

Similar efficacy between benralizumab and mepolizumab studies [Matching adjusted indirect comparison]

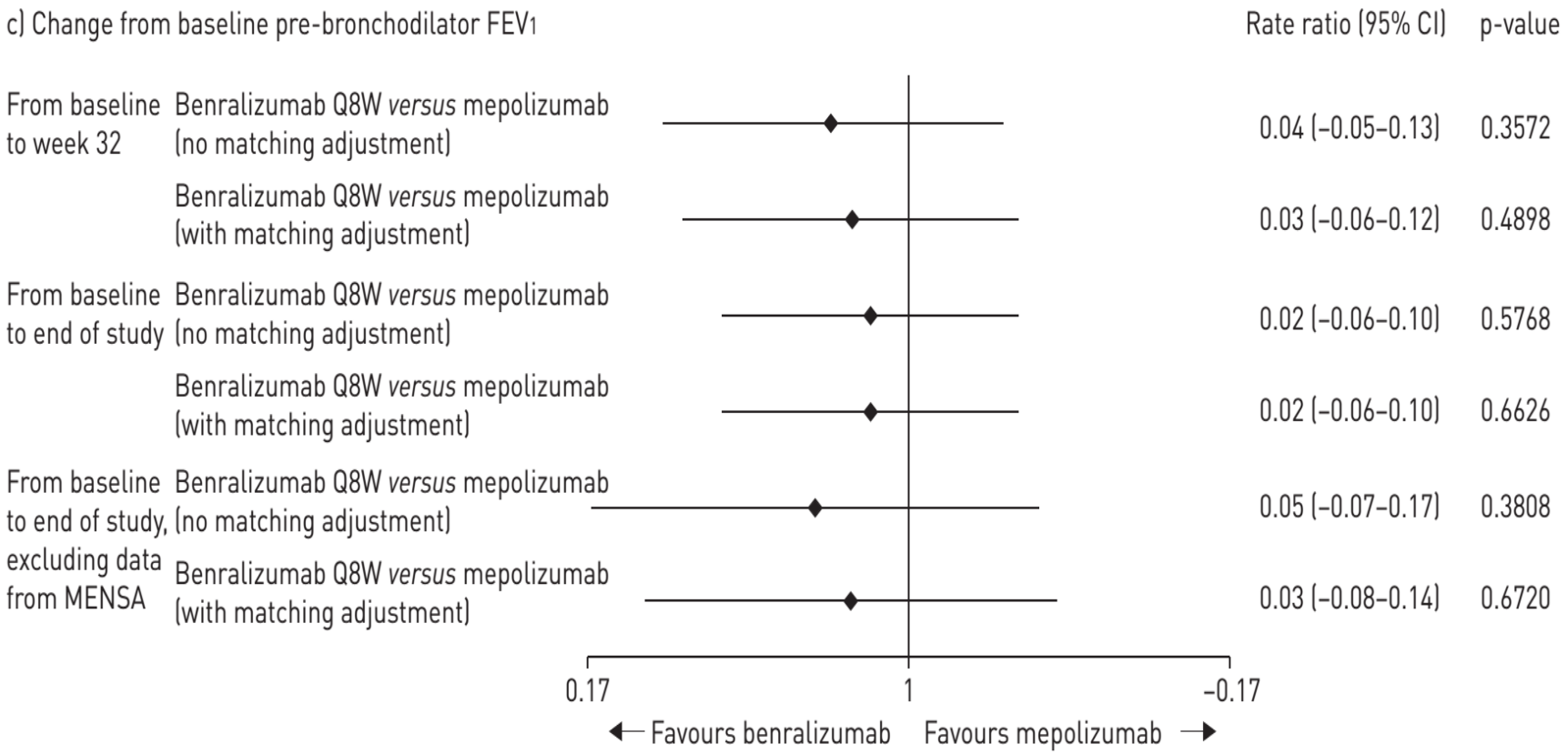
Exacerbation



Bourdin A *et al. Eur Respir J*. 2018 Nov 29;52(5). pii: 1801393

Similar efficacy between benralizumab and mepolizumab studies [Matching adjusted indirect comparison]

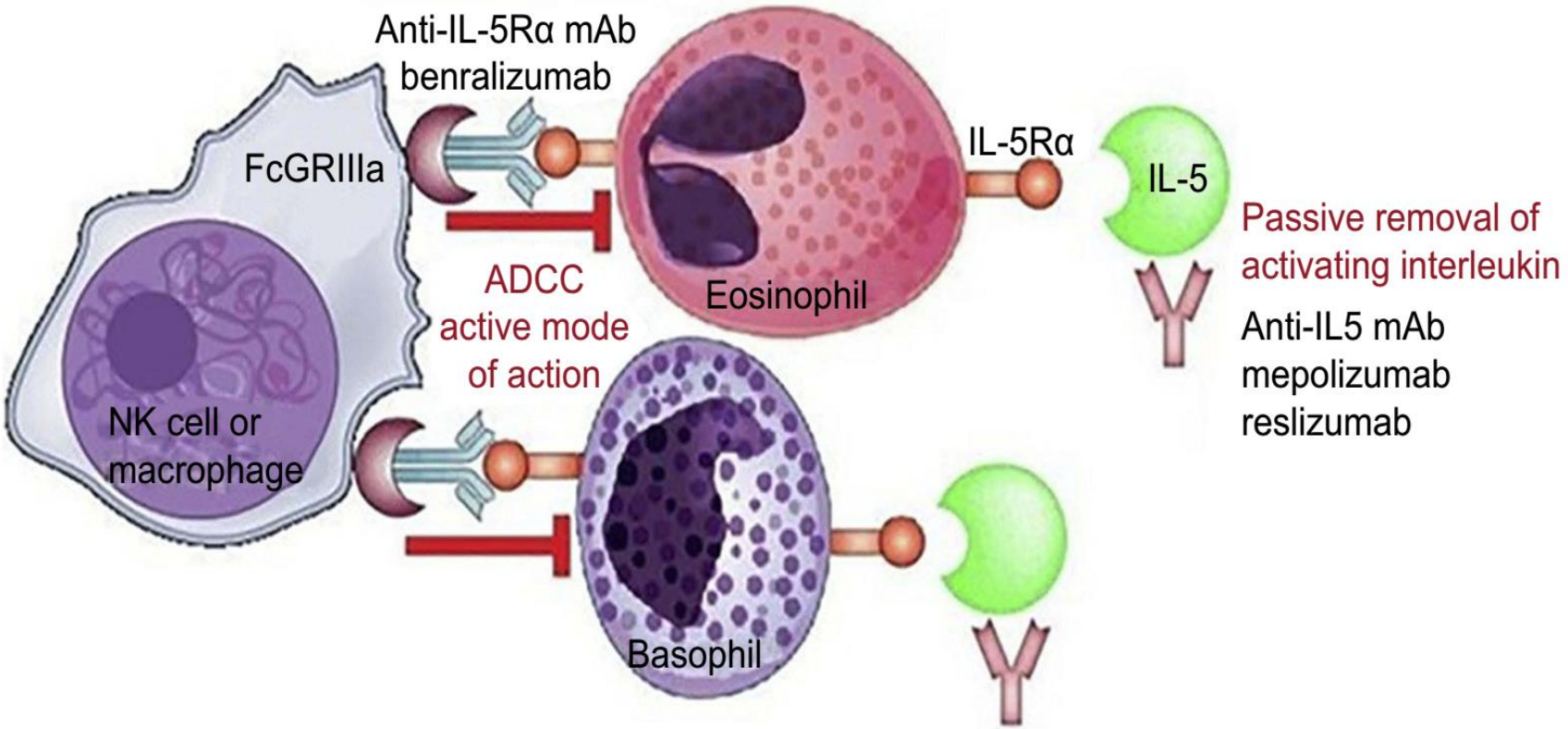
Lung function improvement



Bourdin A *et al. Eur Respir J*. 2018 Nov 29;52(5). pii: 1801393

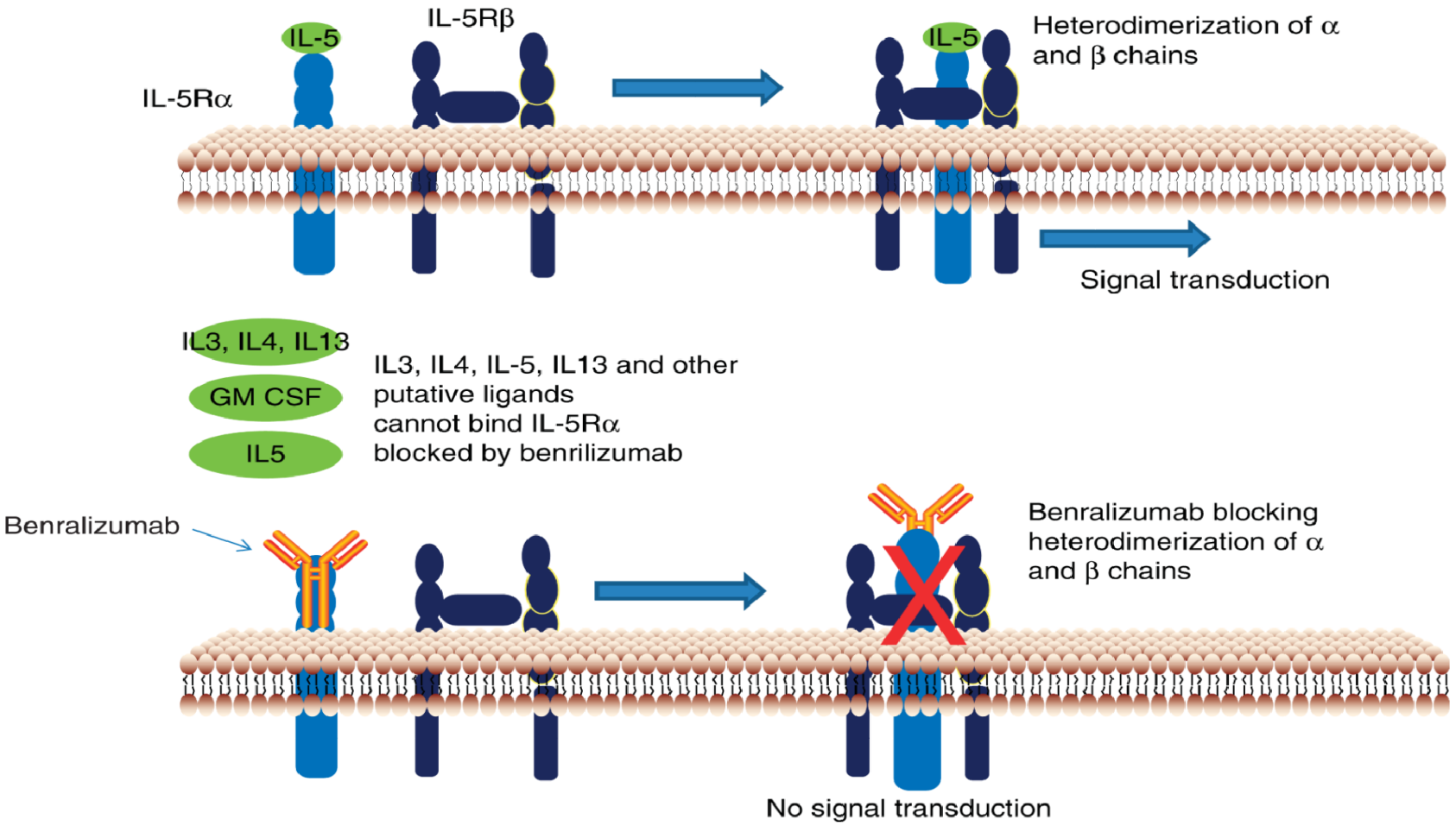
Anti-IL5 vs anti-IL5Rα monoclonal antibodies: Similar or different mechanism?

ADCC
(antibody-dependent cell-mediated cytotoxicity)



Mkorombindo T *et al. Int J Chron Obstruct Pulmon Dis*. 2019 Aug 7;14:1779-1787

Anti-IL5 vs anti-IL5Rα monoclonal antibodies: Similar or different mechanism?

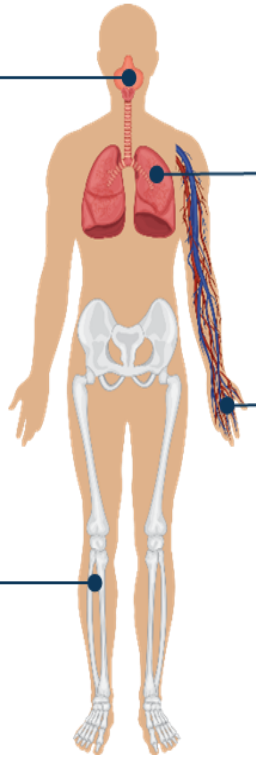


Ghazi A *et al. Expert Opin Biol Ther*. 2012 Jan;12(1):113-8

Effect of benralizumab on eosinophil depletion

Sputum
Median % change from baseline in sputum EOS counts
Benralizumab 100 + 200 mg SC (n=9) vs. placebo (n=5), Day 28, **-89.9%** vs. -66.6% (p-value not reported)

Airway
Median % change from baseline in airway mucosal/submucosal EOS
Benralizumab 100 + 200 mg SC (n=9) vs. placebo (n=5), Day 84, **-95.8%** vs. -46.7% (p=0.06)



Blood
Peripheral blood EOS counts
Benralizumab 100 + 200 mg SC (n=9) vs. placebo (n=5), Day 84, **0 x 10^3 cells/µL** vs 0.20 x 10^3 cells/µL (p-value not reported)

Bone marrow
Change from baseline in bone marrow EOS counts
Cohort 1 + 2 (benralizumab 1 mg/kg IV, n=4; benralizumab 100 mg SC, n=1) vs. placebo n=1), 28 days after last dose, **100% reduction** in EOS and EOS precursors (undetectable) with benralizumab

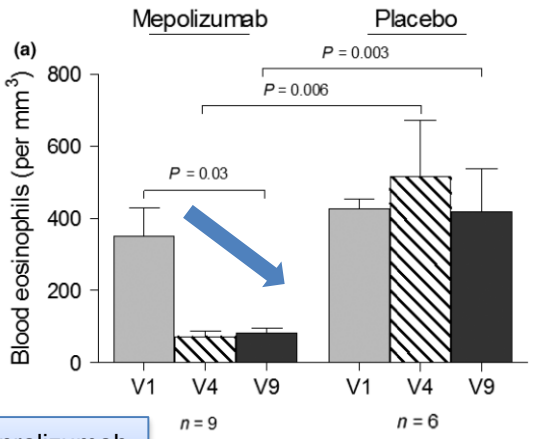
Change from baseline in peripheral blood EOS counts
Cohort 1 + 2 (post hoc analysis): benralizumab (n=14) vs. placebo (n=7), 28 days after last dose, **-100%** vs. 0% (p<0.0001)

Laviolette M *et al. J Allergy Clin Immunol*. 2013;132:1086-1096.

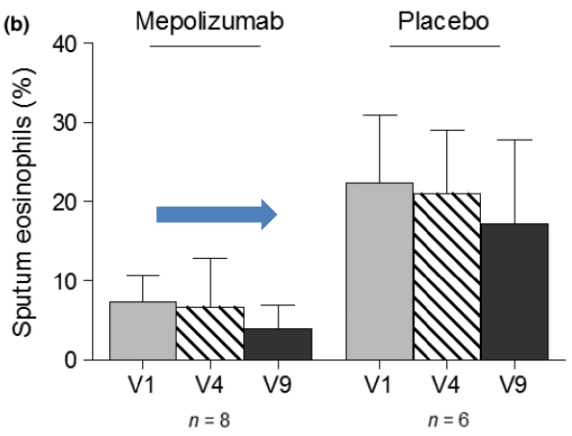
Benralizumab abrogates blood/sputum eosinophils and progenitors in OCS dependent asthma

Mepolizumab (SIRIUS)

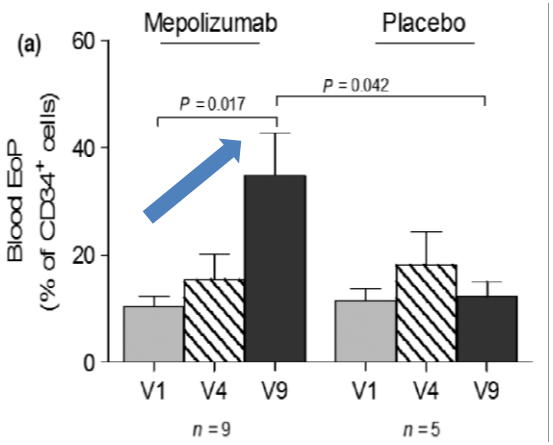
Blood eosinophils



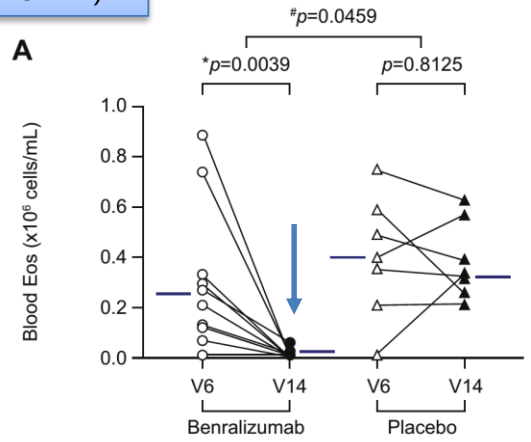
Sputum eosinophils

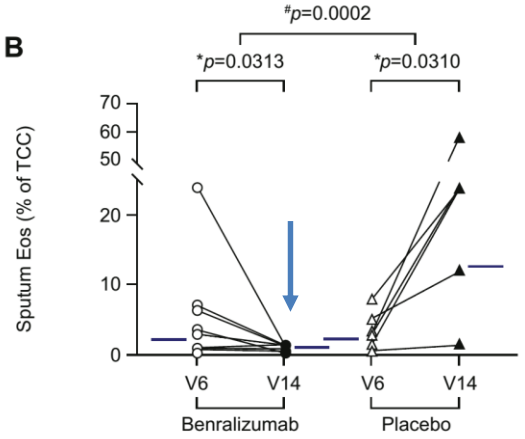


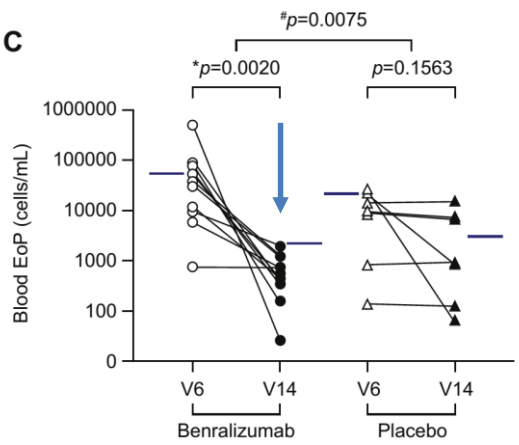
Blood eosinophil progenitors



Benralizumab (ZONDA)



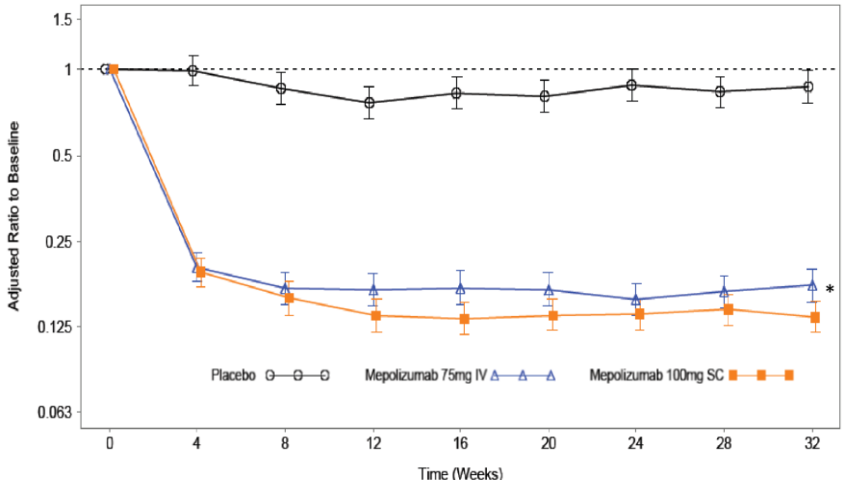




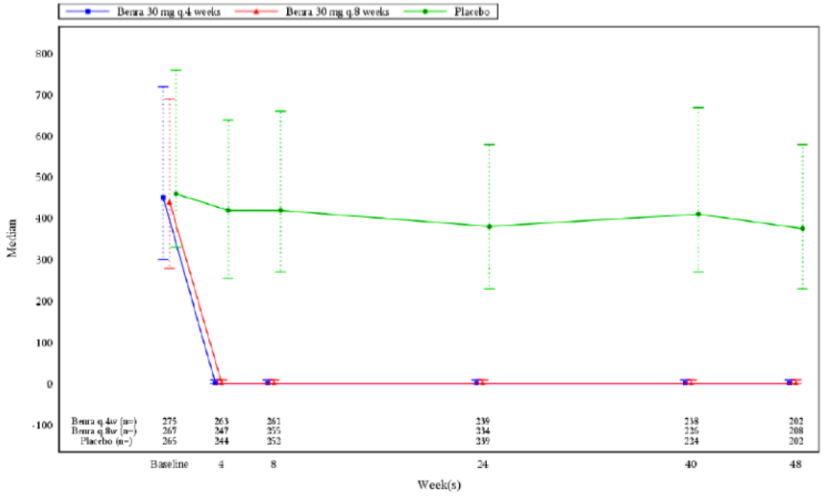
Sehmi R *et al* Clin Exp Allergy. 2016 Jun;46(6):793-802
Sehmi R *et al. J Allergy Clin Immunol*. 2018 Apr;141(4):1529-1532.e8

Benralizumab depletes blood eosinophils in severe eosinophilic asthma

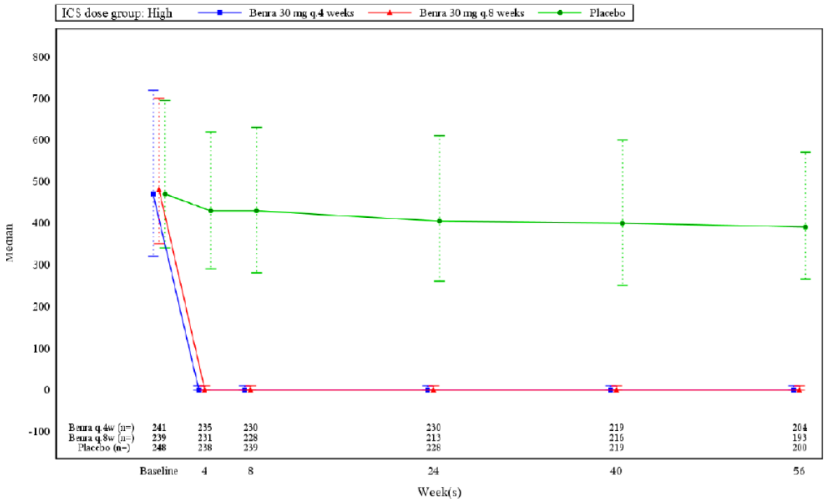
Mepolizumab [MENSA]



Benralizumab [SIROCCO]



Benralizumab [CALIMA]

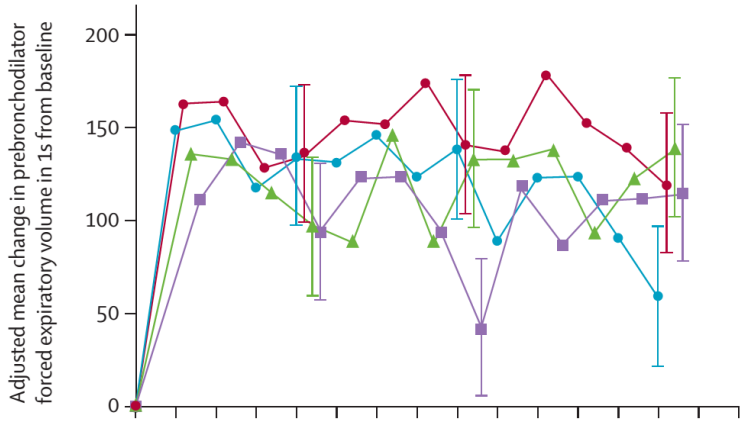


Ortega HG *et al. N Engl J Med*. 2014;371(13):1198-1207
FDA Clinical pharmacology and biopharmaceutics review(s) for Fasenra

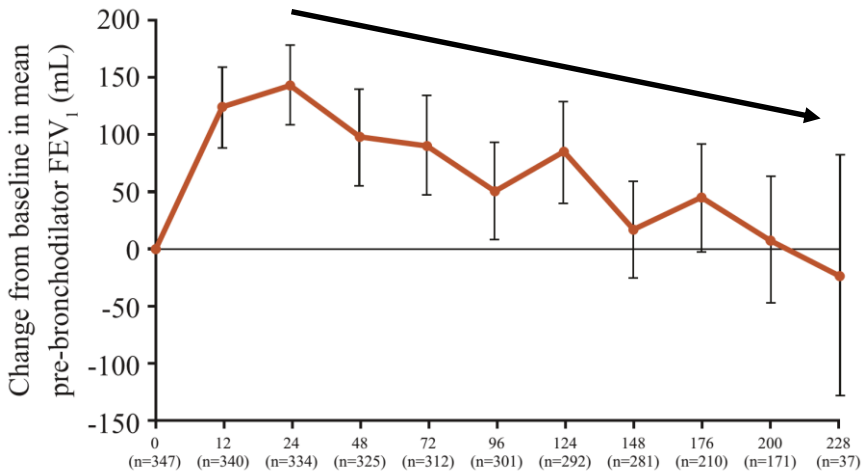
Durable lung function improvement with benralizumab for severe eosinophilic asthma

Mepolizumab
(DEAM → COLUMBA)

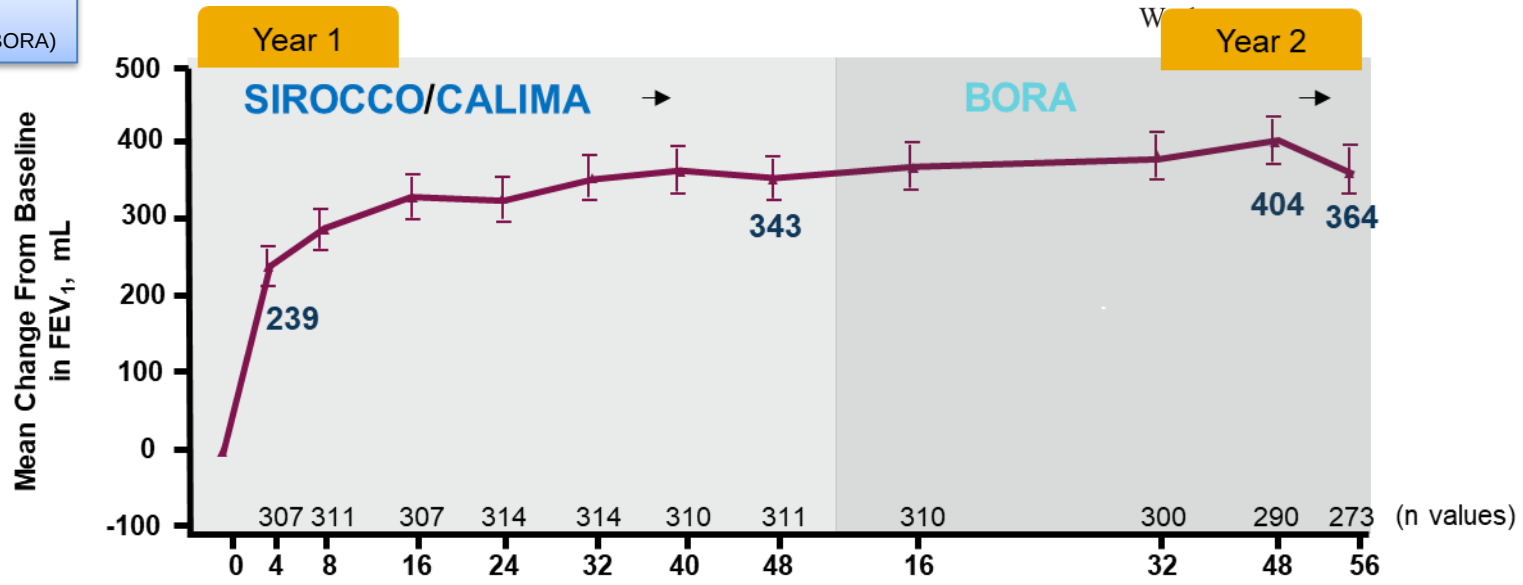
DREAM



COLUMBA



Benralizumab
(SIROCCO/CALIMA → BORA)

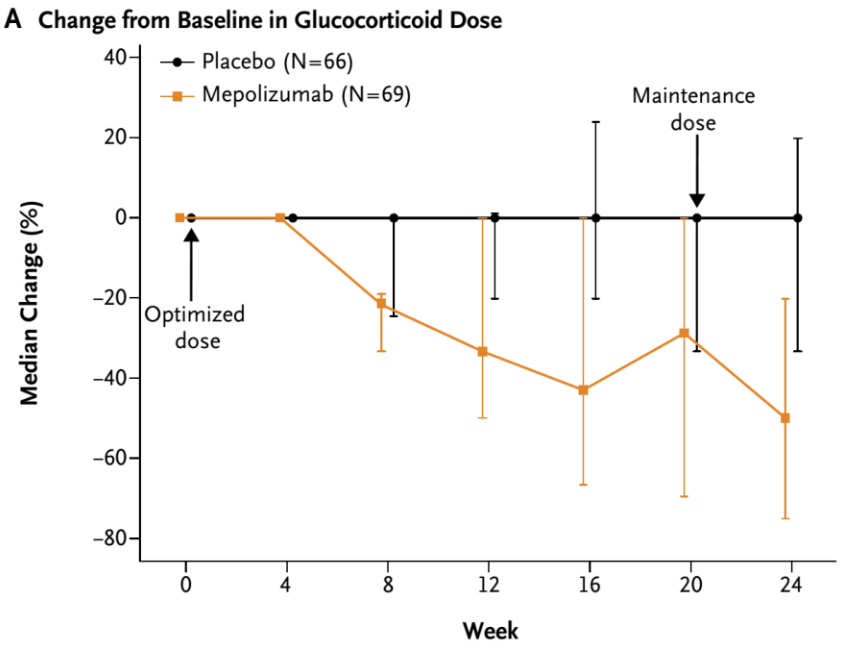


Comparison of reduced OCS dose between mepolizumab and benralizumab in OCS-dependent severe asthma

[SIRIUS vs ZONDA]

Mepolizumab [SIRIUS]

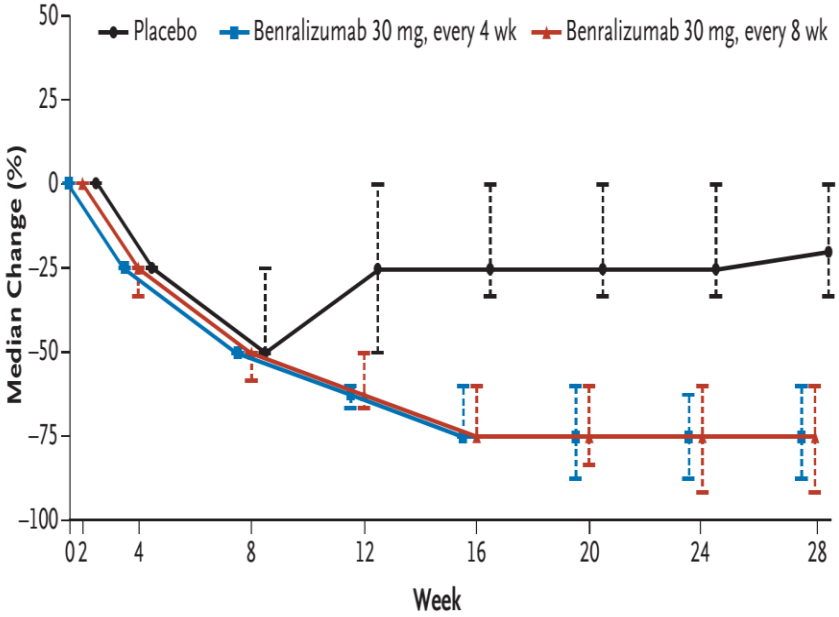
Percentage reduction from baseline in the glucocorticoid dose (**50%** vs 0; *p*=0.007)



Bel EH *et al. N Engl J Med*. 2014 Sep 25;371(13):1189-97

Benralizumab [ZONDA]

Percentage reduction from baseline in the glucocorticoid dose (**75%** vs 25%; *p<0.001*)



Nair P *et al. N Engl J Med*. 2017 Jun 22;376(25):2448-2458

Not head-to-head comparison. Please note that as head-to-head studies were not conducted between these products, it is inappropriate to draw any comparisons and/or make any conclusions as the study design, demographics and other criteria may be different.

Comparison of reduced OCS dose between mepolizumab and benralizumab in OCS-dependent severe asthma

[SIRIUS vs ZONDA]

Mepolizumab [SIRIUS]

Odds ratio for reduced OCS dose: **2.39**

Outcome	Placebo (N=66)	Mepolizumab (N=69)	Odds Ratio (95% CI)*	P Value
Reduction in oral glucocorticoid dose at 20 to 24 wk: primary outcome — no. (%)†			2.39 (1.25–4.56)	0.008
90 to 100%	7 (11)	16 (23)		
75 to <90%	5 (8)	12 (17)		
50 to <75%	10 (15)	9 (13)		
>0 to <50%	7 (11)	7 (10)		
No decrease in oral glucocorticoid dose, a lack of asthma control, or withdrawal from treatment	37 (56)	25 (36)		

Bel EH *et al. N Engl J Med*. 2014 Sep 25;371(13):1189-97

Benralizumab [ZONDA]

Odds ratio for reduced OCS dose: **4.12**

Outcome	Placebo (N=75)	Benralizumab, Every 4 Wk (N=72)	Benralizumab, Every 8 Wk (N=73)
Primary outcome			
Median oral glucocorticoid dose (range) — mg/day*			
At baseline	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)
At final visit	10.0 (0.0 to 40.0)	5.0 (0.0 to 45.0)	5.0 (0.0 to 30.0)
Median reduction from baseline (range) — % of baseline value†	25.0 (–150 to 100)	75.0 (–100 to 100)	75.0 (–50 to 100)
P value†	—	<0.001	<0.001
Reduction from baseline in final oral glucocorticoid dose — no. (%)			
≥90%	9 (12)	24 (33)	27 (37)
≥75%	15 (20)	38 (53)	37 (51)
≥50%	28 (37)	48 (67)	48 (66)
>0%	40 (53)	55 (76)	58 (79)
Any increase or no change in dose	35 (47)	17 (24)	15 (21)
Analysis of percentage reduction from baseline in oral glucocorticoid dose			
Odds ratio (95% CI)	—	4.09 (2.22 to 7.57)	4.12 (2.22 to 7.63)
P value	—	<0.001	<0.001

Nair P *et al. N Engl J Med*. 2017 Jun 22;376(25):2448-2458

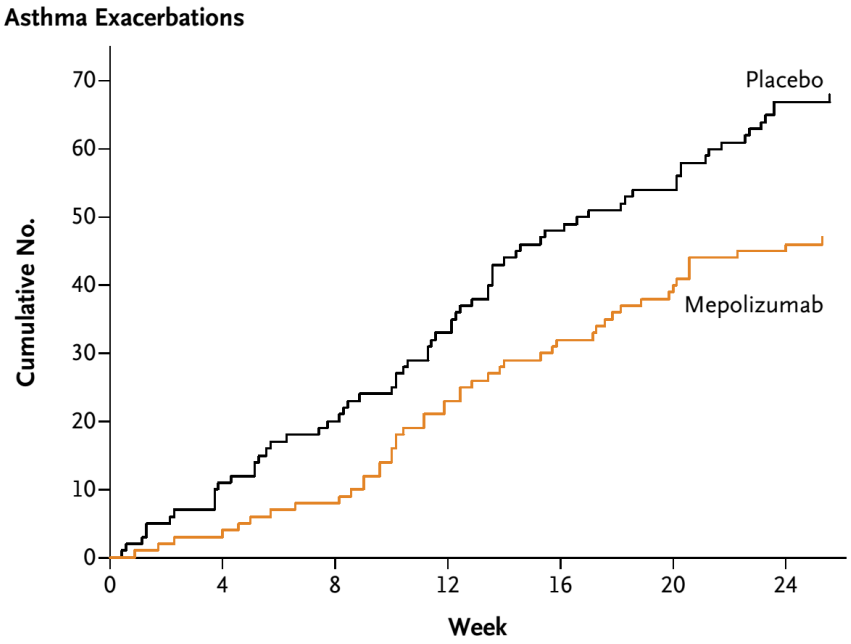
Not head-to-head comparison. Please note that as head-to-head studies were not conducted between these products, it is inappropriate to draw any comparisons and/or make any conclusions as the study design, demographics and other criteria may be different.

Comparison of reduced annualized exacerbation rate between mepolizumab and benralizumab in OCS-dependent severe asthma

[SIRIUS vs ZONDA]

Mepolizumab [SIRIUS]

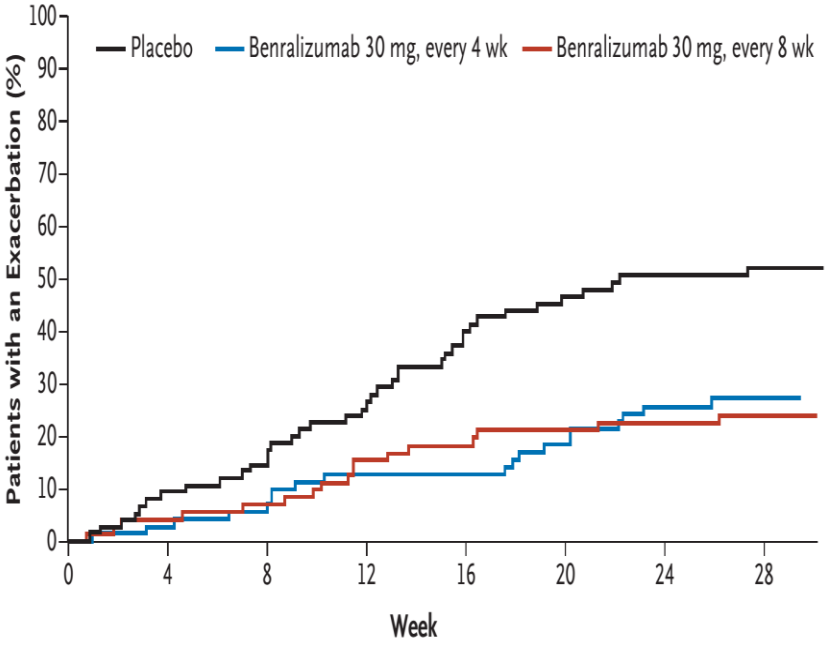
Relative reduction of **32%** in the annualized rate of exacerbations (1.44 vs. 2.12, *p*=0.04)



Bel EH *et al. N Engl J Med*. 2014 Sep 25;371(13):1189-97

Benralizumab [ZONDA]

Relative reduction of **70%** in the annualized rate of exacerbations (0.54 vs. 1.83, *p*<0.001)



Nair P *et al. N Engl J Med*. 2017 Jun 22;376(25):2448-2458

Not head-to-head comparison. Please note that as head-to-head studies were not conducted between these products, it is inappropriate to draw any comparisons and/or make any conclusions as the study design, demographics and other criteria may be different.

Safety of benralizumab in both prospective RCTs and open-label extension study

Benralizumab study in SIROCCO, CALIMA, ZONDA, BORA studies

Adverse reactions ≥5% incidence in SIROCCO[1]		
Adverse Reaction	Benralizumab Q8W (n=394)	PLACEBO (n=407)
Asthma	11%	19%
Nasopharyngitis	12%	12%
Upper respiratory tract infection	8%	9%
Headache	9%	5%
Bronchitis	5%	7%
Sinusitis	6%	7%
Influenza	5%	6%
Pharyngitis	6%	3%
Rhinitis	-	-

Adverse reactions ≥5% incidence in CALIMA[2]	
Benralizumab Q8W (n=428)	PLACEBO (n=440)
11%	15%
18%	21%
8%	9%
8%	7%
10%	12%
5%	8%
-	-
-	-
-	-

Adverse reactions ≥5% in ZONDA[3]	
Benralizumab Q8W (n=73)	PLACEBO (n=75)
-	-
15%	20%
7%	7%
8%	5%
10%	16%
5%	11%
-	-
-	-
8%	3%

Adverse reactions ≥5% incidence in BORA[4]	
Adverse Reaction	Benralizumab Q8W/Q8W (n=512)
Viral upper respiratory tractinfection	16%
Asthma	8%
Upper respiratory tract infection	6%
Bronchitis	6%
Headache	6%
Acute sinusitis	5%

Adverse event profile in the phase 3 safety extension trial (BORA)[4]

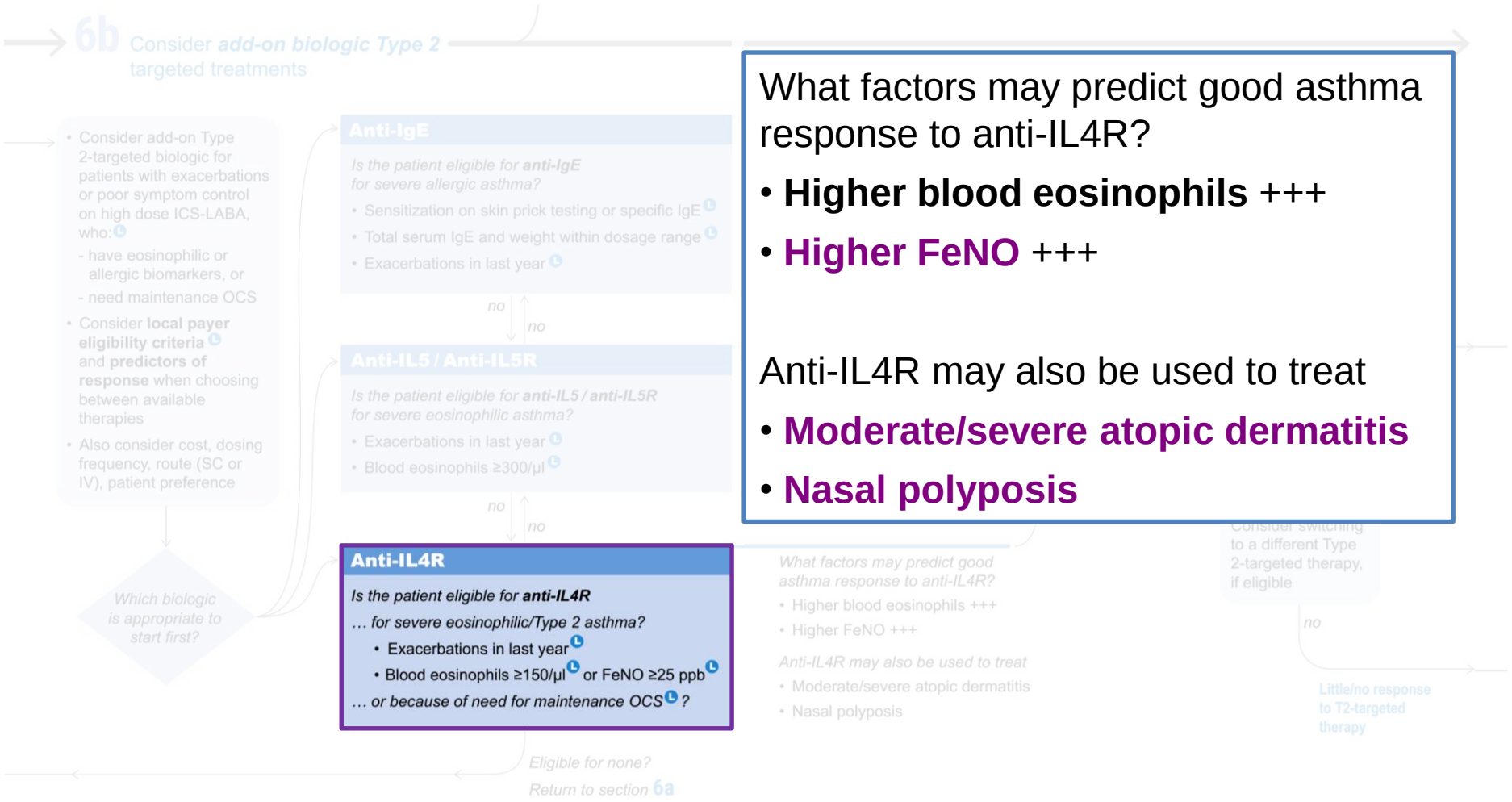
- No cases of helminth infection were reported[4]
- No safety signals that might be associated with long-term depletion of eosinophils were observed[4]

Injection site reactions

- In the pivotal trials, injection site reactions with benralizumab Q8W were similar to placebo: 2.2% vs 1.9%[5]
- In BORA, injection site reactions with benralizumab Q8W were 2%[4]

1. Bleecker ER, et al. Lancet. 2016;388:2115-2127 2. FitzGerald JM, et al. Lancet. 2016;388:2128-2141. 3. Nair P et al. N Engl J Med. 2017;376(Supple):2448-2458
4. Busse WW, et al. Long-term of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. *Lancet Respir Med*. 2019;7:46-59. 5. FASENRA [summary of product characteristics]. AstraZeneca AB, SE-151 85, Södertälje, Sweden; 2018.

Add-on biologic type 2 targeted treatments



What factors may predict good asthma response to anti-IL4R?

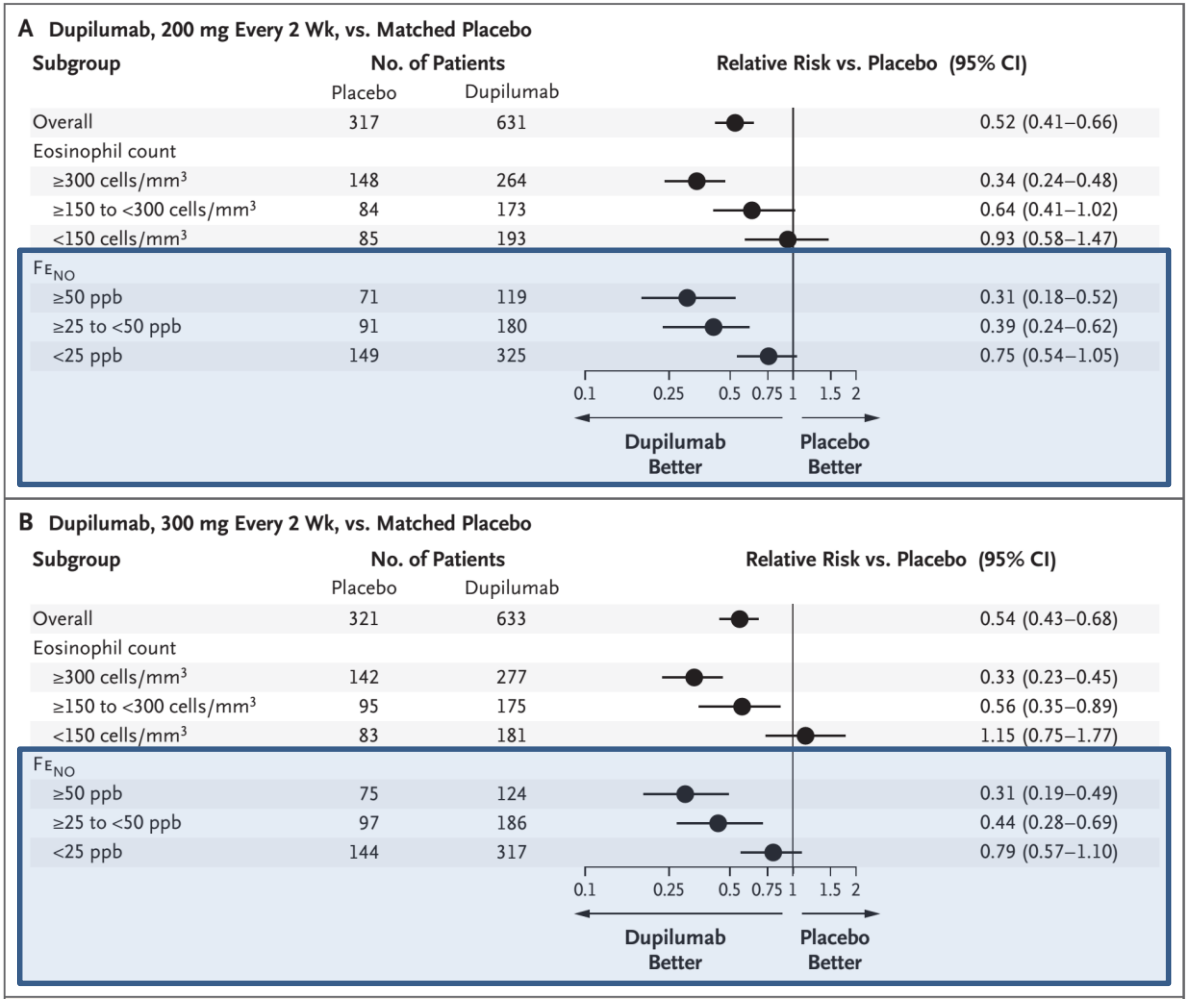
- **Higher blood eosinophils** +++
- **Higher FeNO** +++

Anti-IL4R may also be used to treat

- **Moderate/severe atopic dermatitis**
- **Nasal polyposis**

GINA DIFFICULT-TO-TREAT & SEVERE ASTHMA in adolescent and adult patients Diagnosis and Management, Apr, 2019

Better efficacy of dupilumab in uncontrolled asthma with elevated FE_{NO}



A Dupilumab, 200 mg Every 2 Wk, vs. Matched Placebo

Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	317	631	0.52 (0.41–0.66)
Eosinophil count			
≥300 cells/mm³	148	264	0.34 (0.24–0.48)
≥150 to <300 cells/mm³	84	173	0.64 (0.41–1.02)
<150 cells/mm³	85	193	0.93 (0.58–1.47)
FE_{NO}			
≥50 ppb	71	119	0.31 (0.18–0.52)
≥25 to <50 ppb	91	180	0.39 (0.24–0.62)
<25 ppb	149	325	0.75 (0.54–1.05)

B Dupilumab, 300 mg Every 2 Wk, vs. Matched Placebo

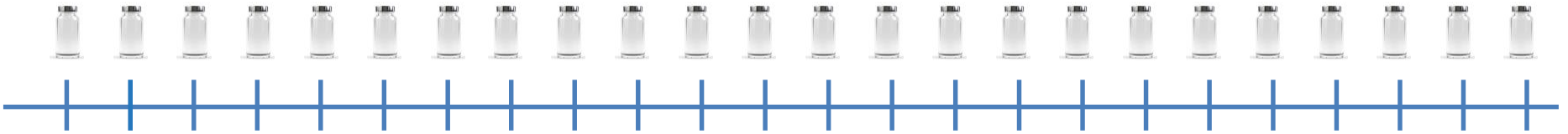
Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	321	633	0.54 (0.43–0.68)
Eosinophil count			
≥300 cells/mm³	142	277	0.33 (0.23–0.45)
≥150 to <300 cells/mm³	95	175	0.56 (0.35–0.89)
<150 cells/mm³	83	181	1.15 (0.75–1.77)
FE_{NO}			
≥50 ppb	75	124	0.31 (0.19–0.49)
≥25 to <50 ppb	97	186	0.44 (0.28–0.69)
<25 ppb	144	317	0.79 (0.57–1.10)

Castro M *et al. N Engl J Med*. 2018 Jun 28;378(26):2486-2496

For severe asthma requiring long term regular administration of biologic agents with several choices…

Which will be preferred?

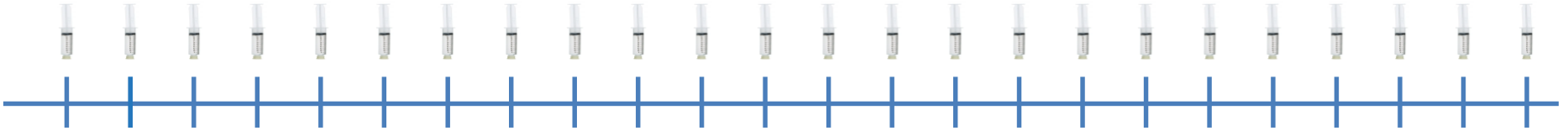
Omalizumab:1-4 vials sc q2w or q4w



Mepolizumab: 1 vial sc q4w

Benralizumab: 1 PFS sc q4w x3; then q8w

Dupilumab: 1 PFS sc q2w



Take home messages

- Clinical characteristics **[phenotype]** of eosinophilic asthma differs from allergic asthma
  - Complete evaluation in addition to biomarker check-up
- Differential effects between anti-IL5 and anti-IgE biologics in terms of reducing blood eosinophils and asthma exacerbations of severe asthma
- Benralizumab: anti-IL5R monoclonal antibodies
  - Antibody-directed cell toxicity (ADCC) of eosinophils: eosinophial deplete
  - Prevent IL-5 and other cytokines from actions on eosinophils

Take home messages

Differential clinical efficacies between benralizumab and mepolizumab in severe eosinophilic asthma?

- Matching-adjusted indirect comparison: similar efficacy
- Severe eosinophilic asthma: benralizumab might be better?
  - Durable lung function improvevement
- OCS dependent asthma: benralizumab might be better?
  - Reducing maintenance OCS dose
  - Reducing exacerbations
- User friendliness
  - Q4W*3, followed by Q8W
  - Pre-filled syringe (PFS)