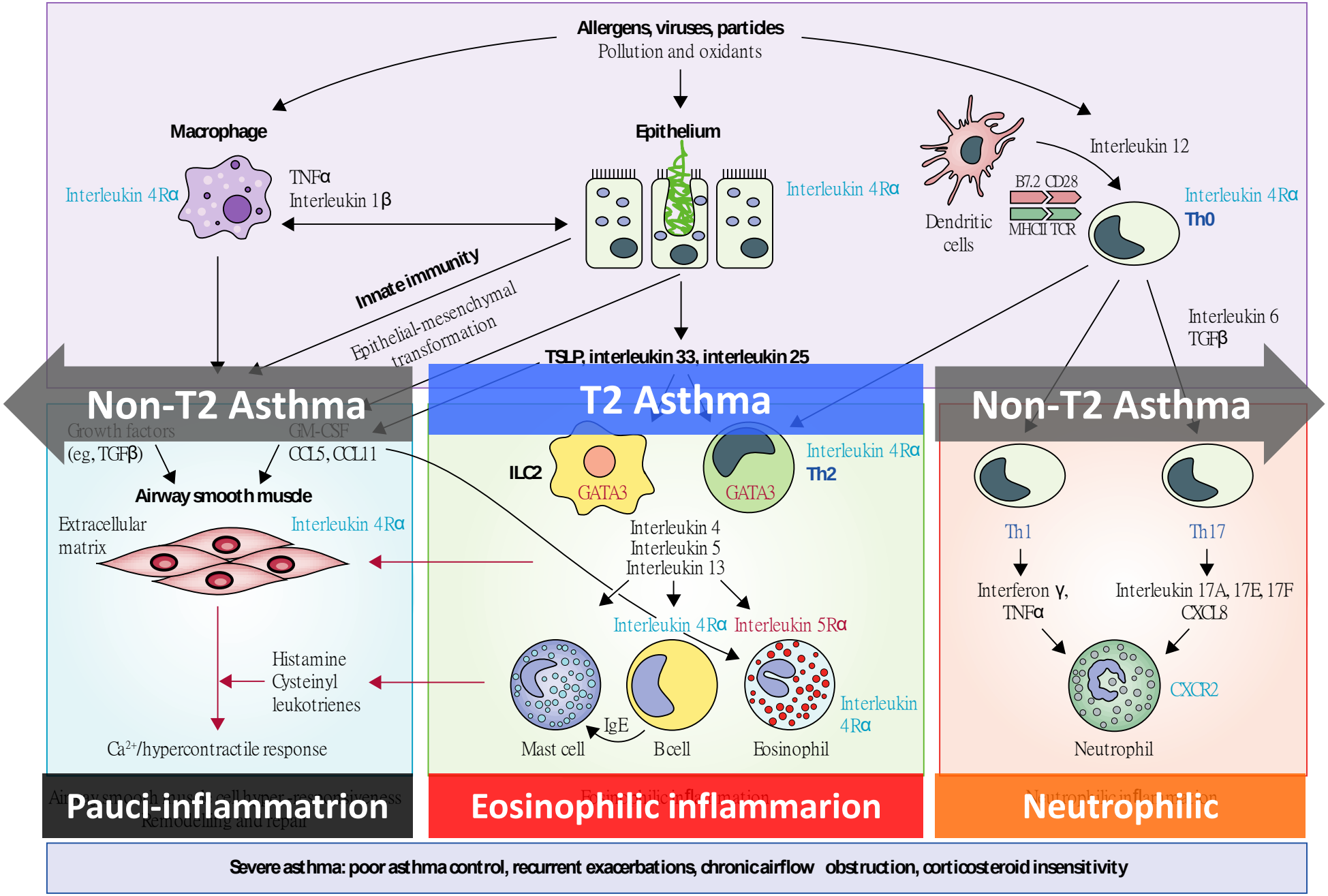
Role of eosinophils in severe asthma

What is the optimal level of eosinophils?

Kang-Yun Lee, MD PhD

Shuang Ho Hospital
Taipei Medical University

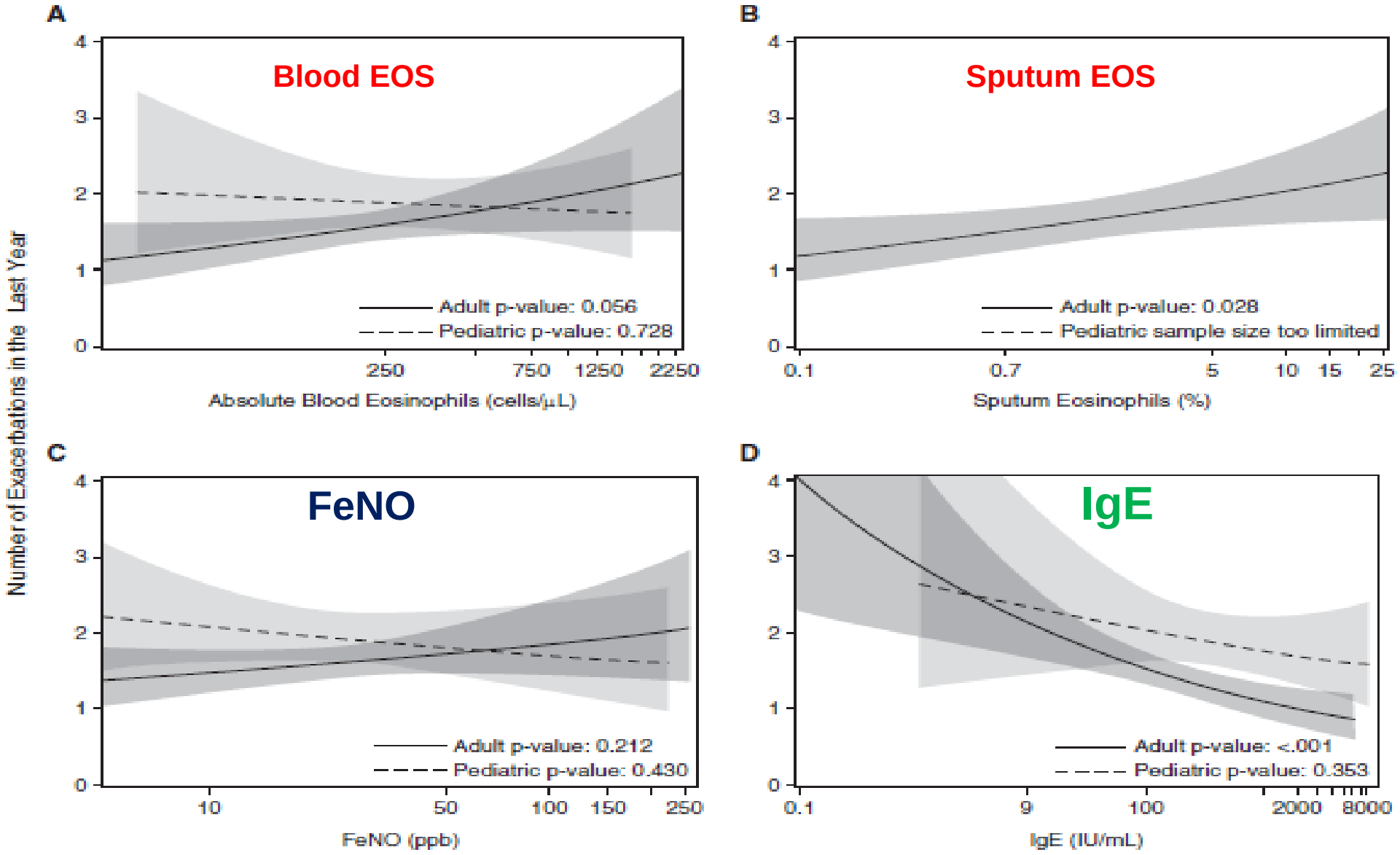
Pathophysiological Mechanisms Underlying Severe Asthma



Chung KF, Lancet 2015; 386: 1086–96

Severe asthma with frequent exacerbations

The NHLBI Severe Asthma Research Program (SARP)-3 cohort

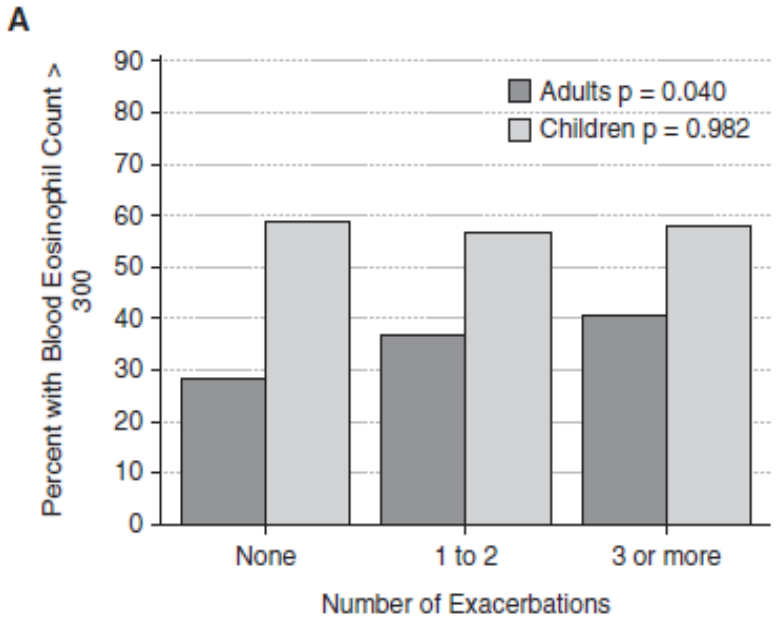


Denlinger et al. AJRCCM 195 3 302-313 2017

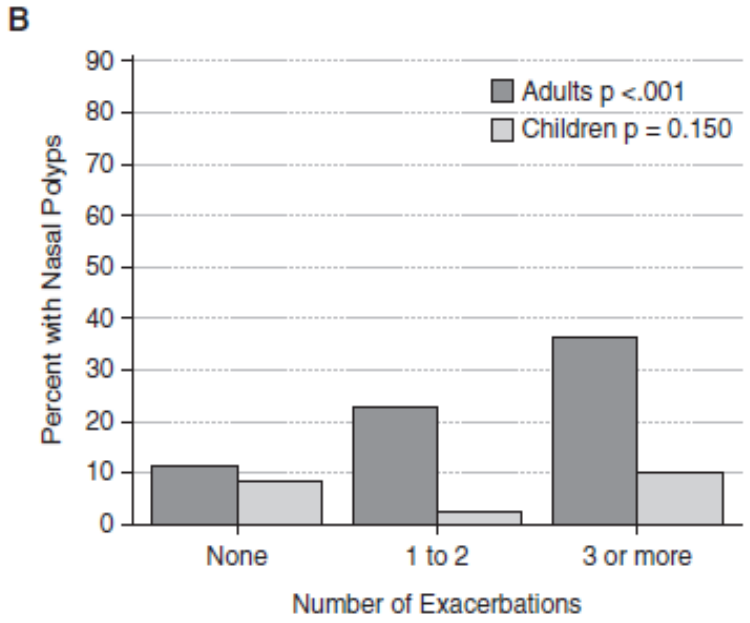
Severe asthma with frequent exacerbations

The NHLBI Severe Asthma Research Program (SARP)-3 cohort

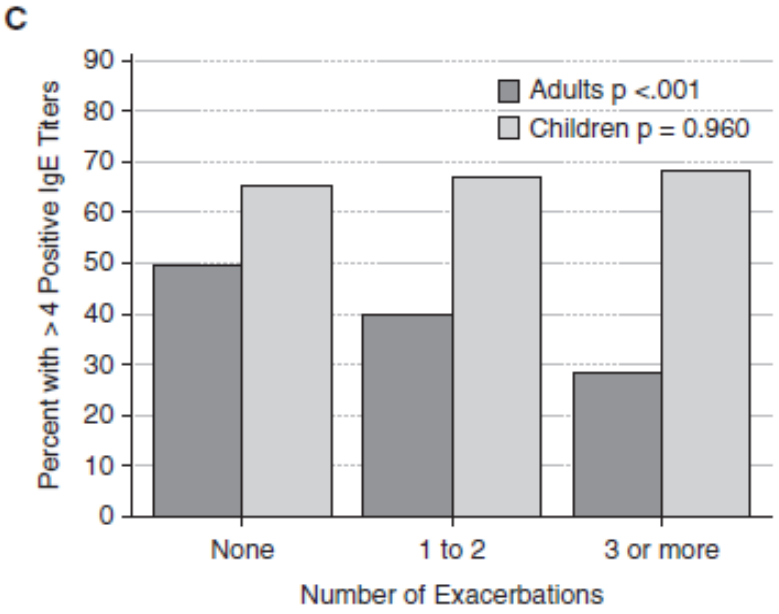
% Blood EOS>300



% Nasal polyps



% >4 positive IgE titers

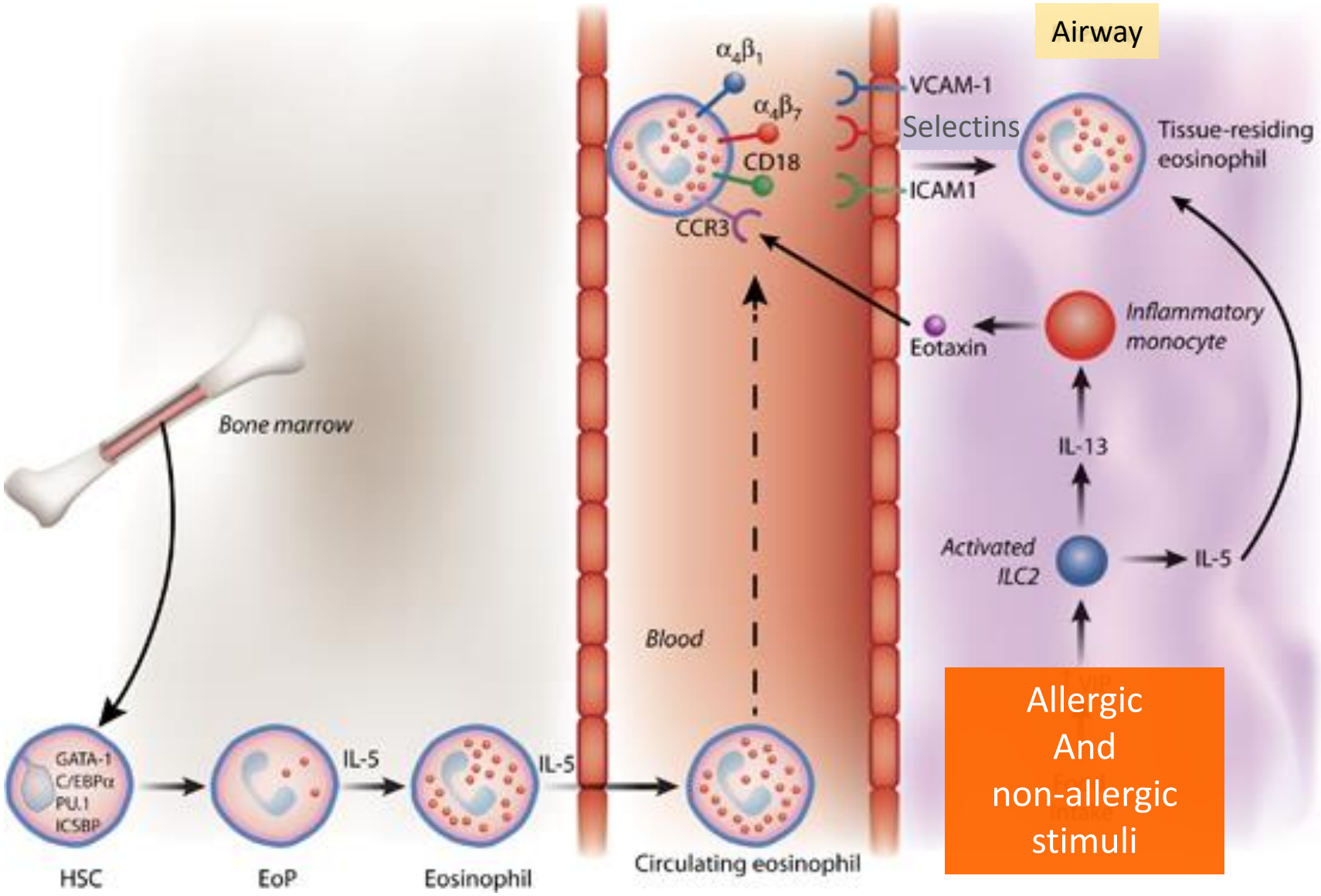


Suggest that the adult exacerbation-prone phenotype is not driven by allergic sensitization

Denlinger et al. AJRCCM 195 3 302-313 2017

Why blood EOS not sputum EOS?

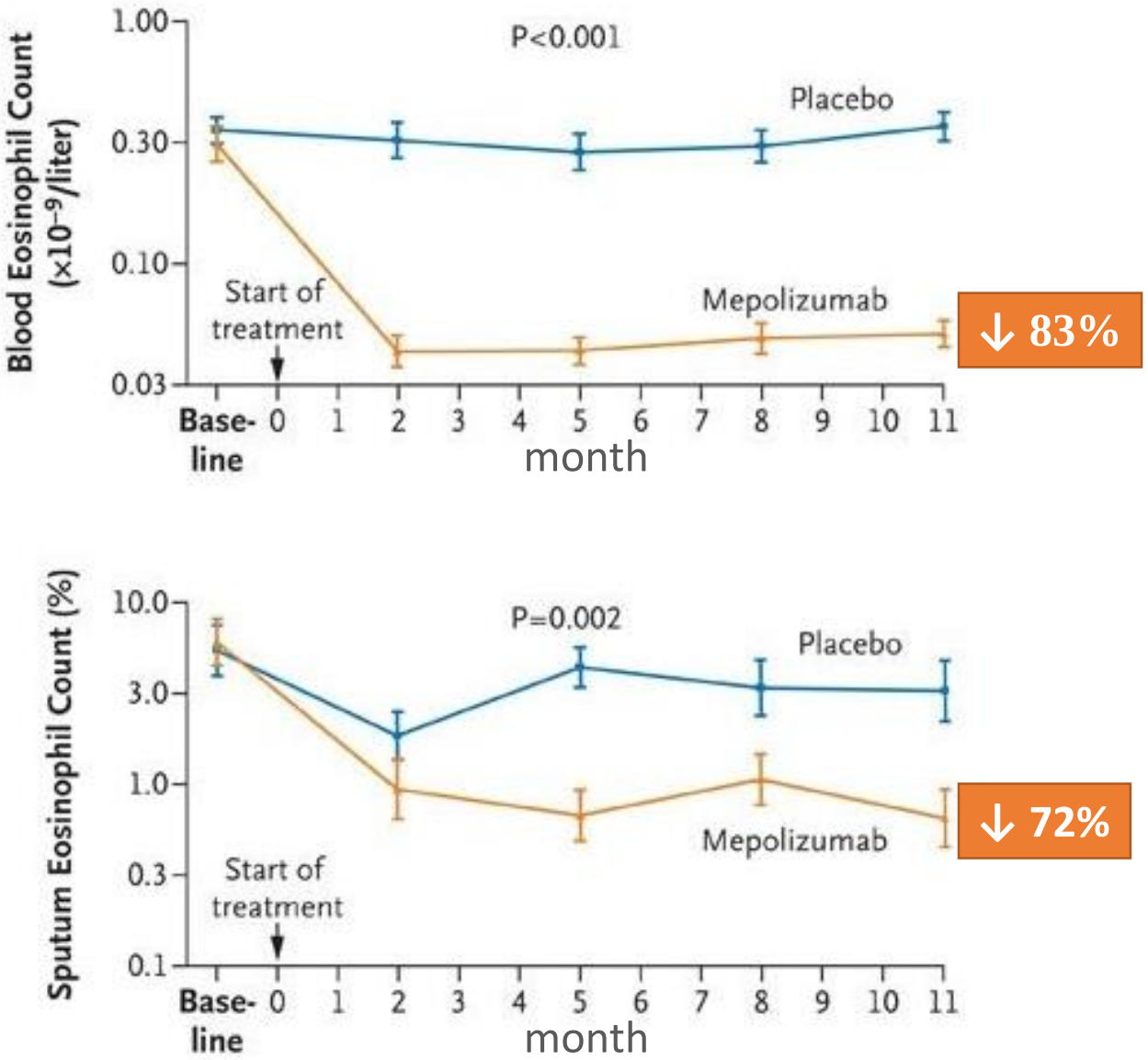
Systemic relevance of IL-5 signalling in asthma



Adapted from Travers and Rothenberg Mucosal Immunology 2015; 8: 464-475

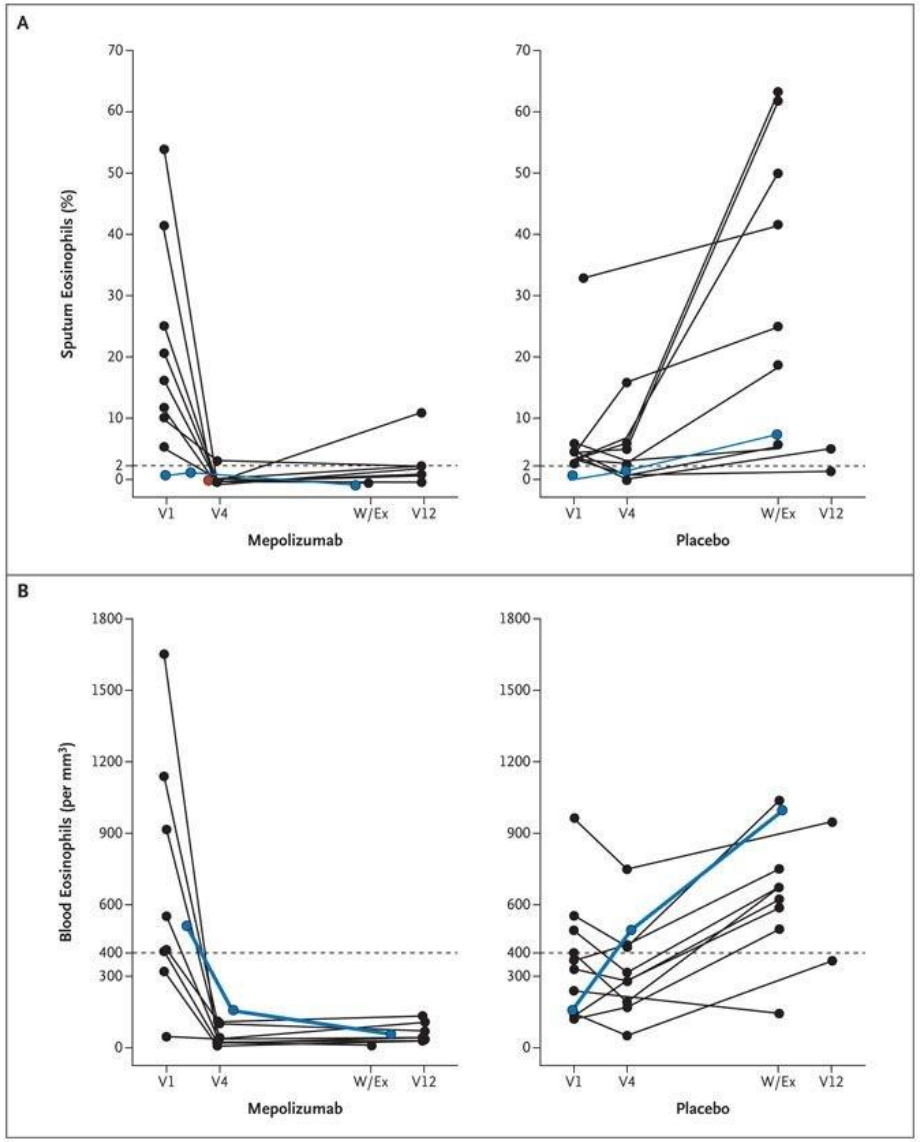
Mepolizumab significantly lowered eosinophil counts in the blood & sputum

Refractory eosinophilic asthma



Haldar et al. N Engl J Med 2009;360:973-84

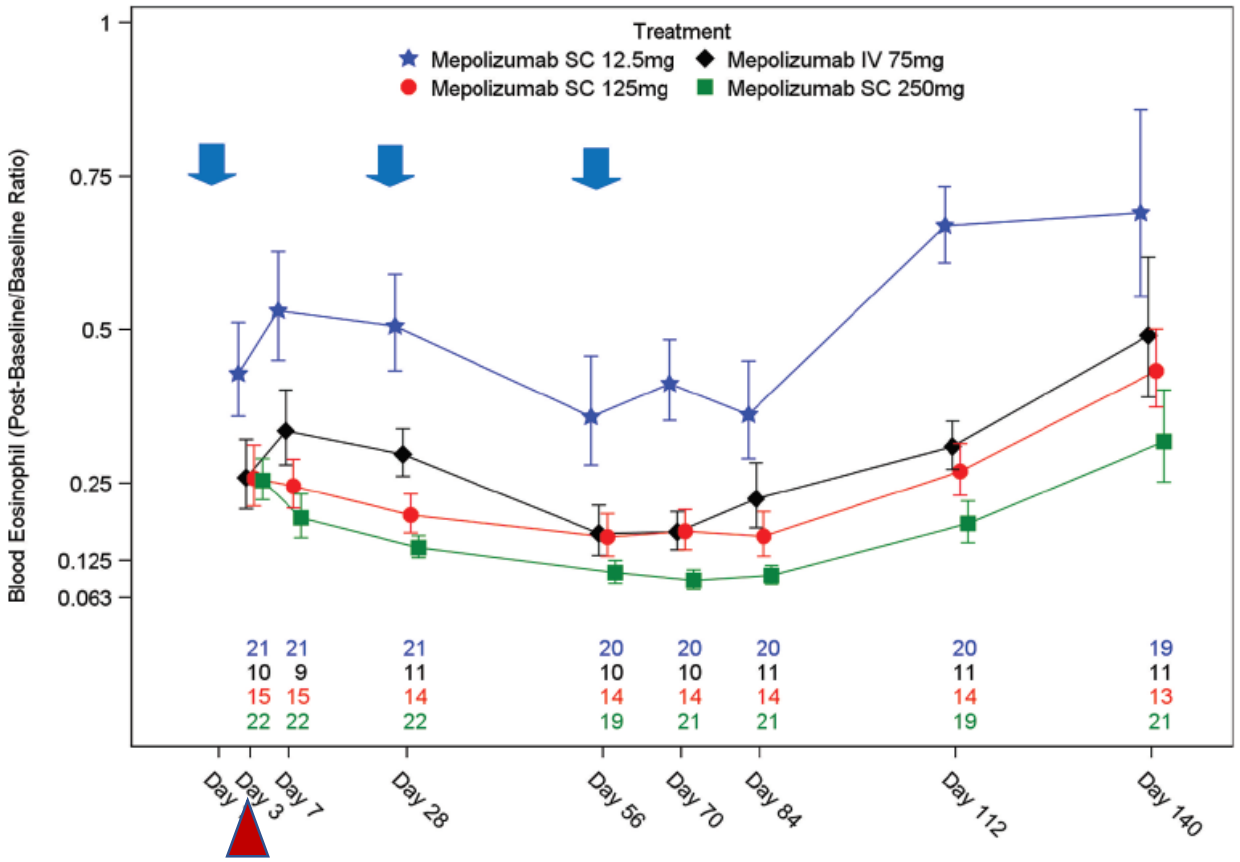
Prednisone-dependent asthma with sputum eosinophilia

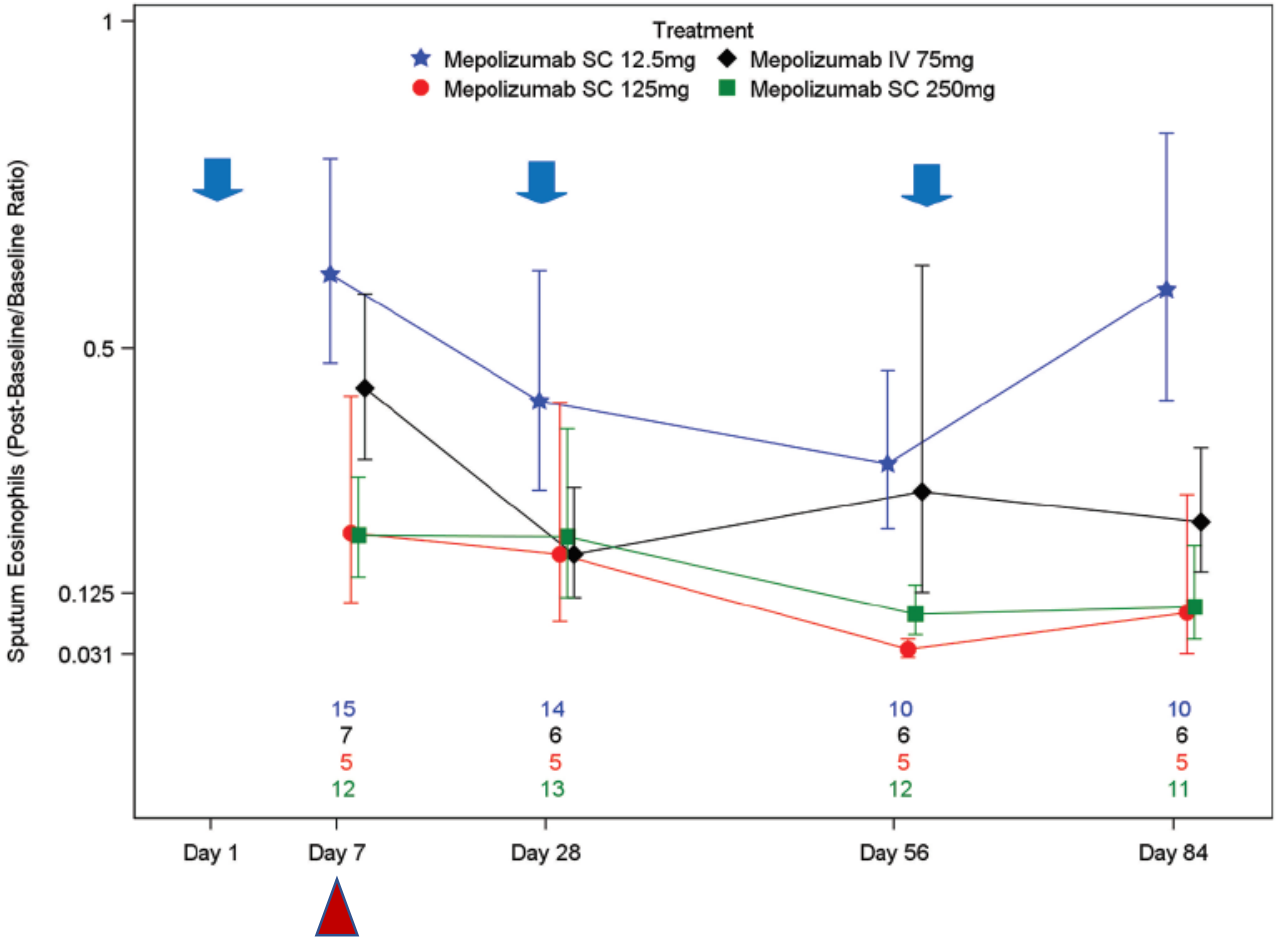


Parameswaran et al. N Engl J Med 2009;360:985-93

74% reduction in blood eosinophil levels within 48 hours

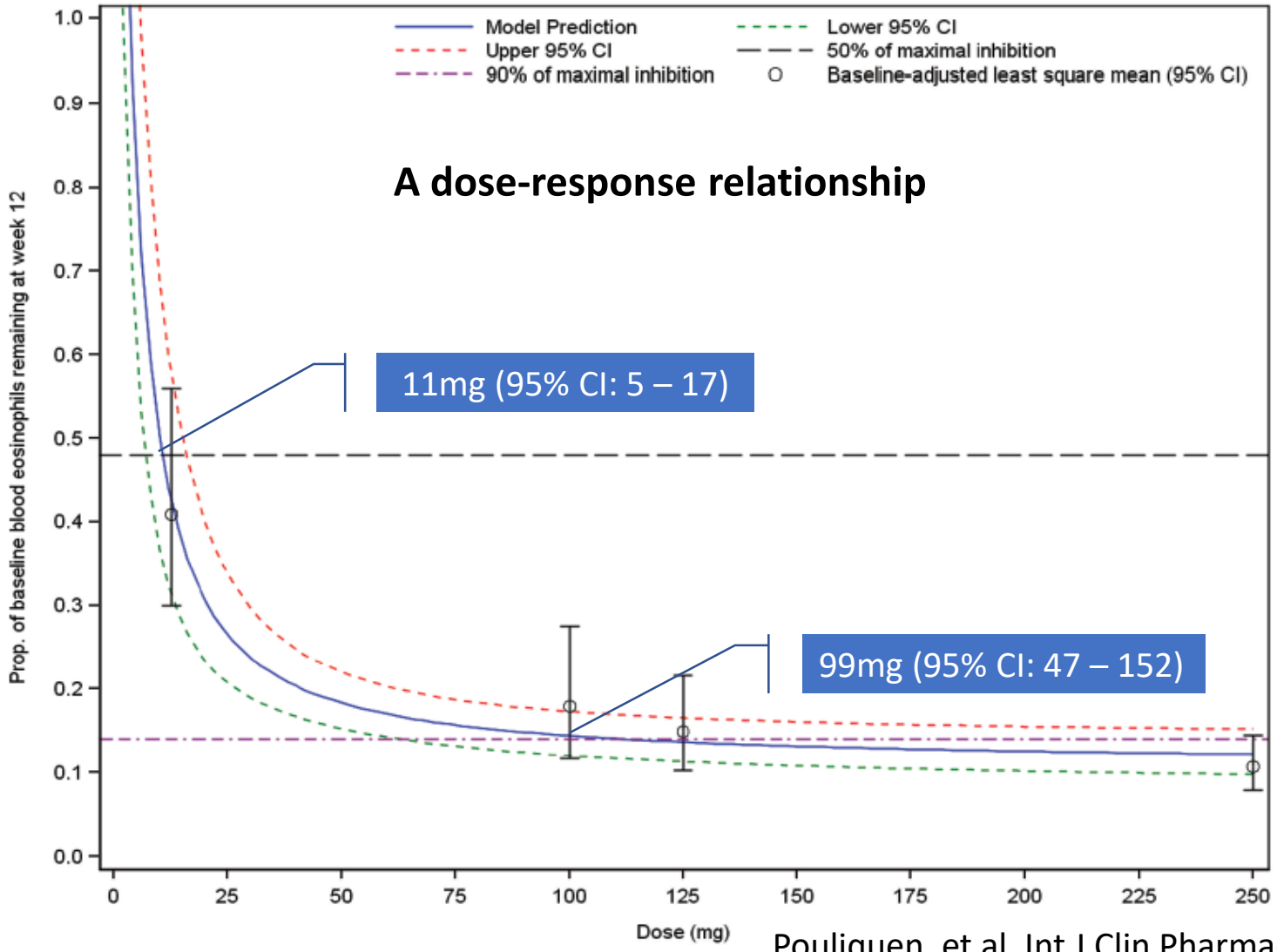
A phase IIa study in adult subjects with asthma and blood eosinophils > 300 cells/µL





Pouliquen, et al. Int J Clin Pharmacol Ther. 2015 Dec;53(12):1015-27

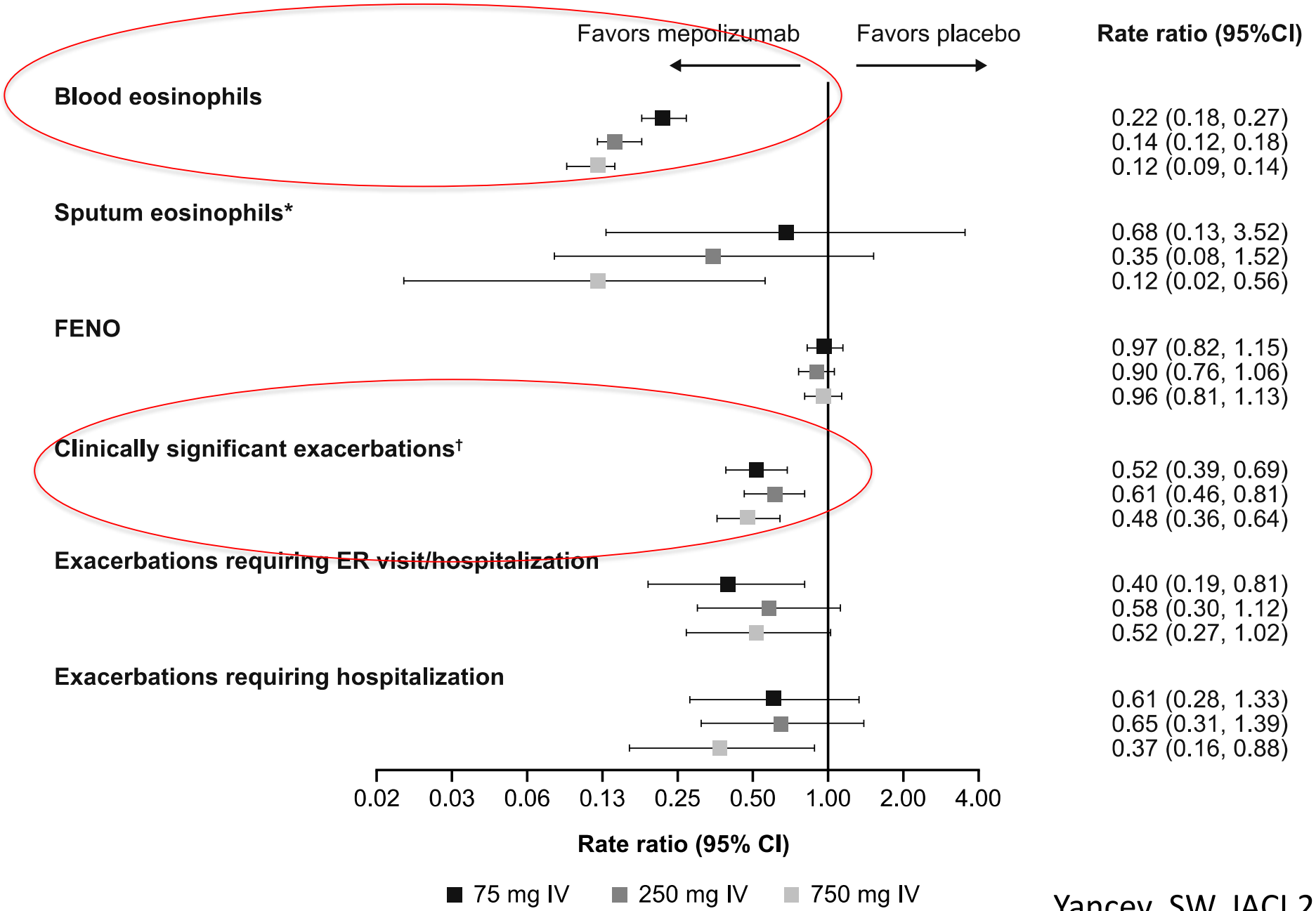
90% of maximal inhibition of blood eosinophils by Mepolizumab: 99mg sc



Pouliquen, et al. Int J Clin Pharmacol Ther. 2015 Dec;53(12):1015-27

DREAM

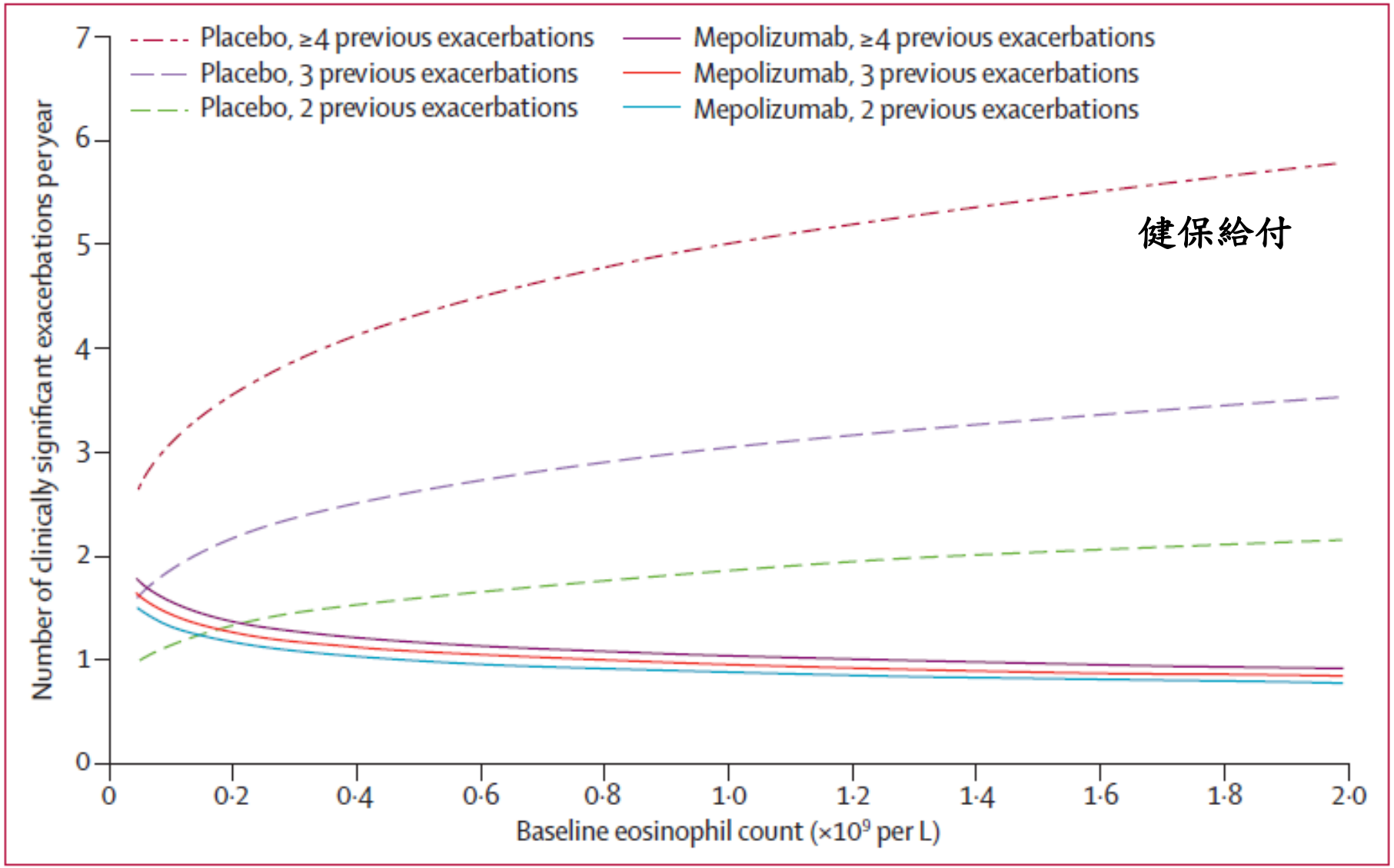
Eosinophil, FENO, & Exacerbations for Mepolizumab



Yancey SW, JACI,2017;140:1509-18.

Dose–response effect on blood eosinophil counts incorporated with exacerbation

DREAM

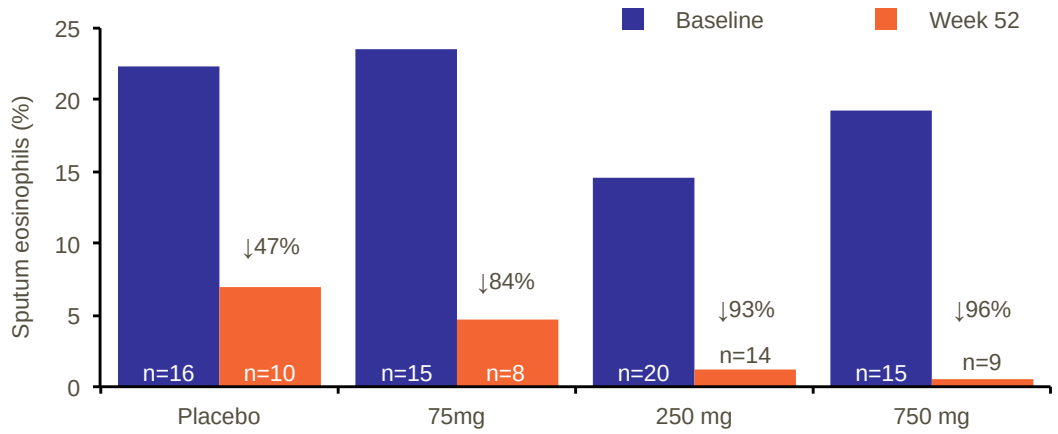


Predictive modelling of rate of exacerbations

Pavord et al. Lancet 2012; 380(9842):651-659.

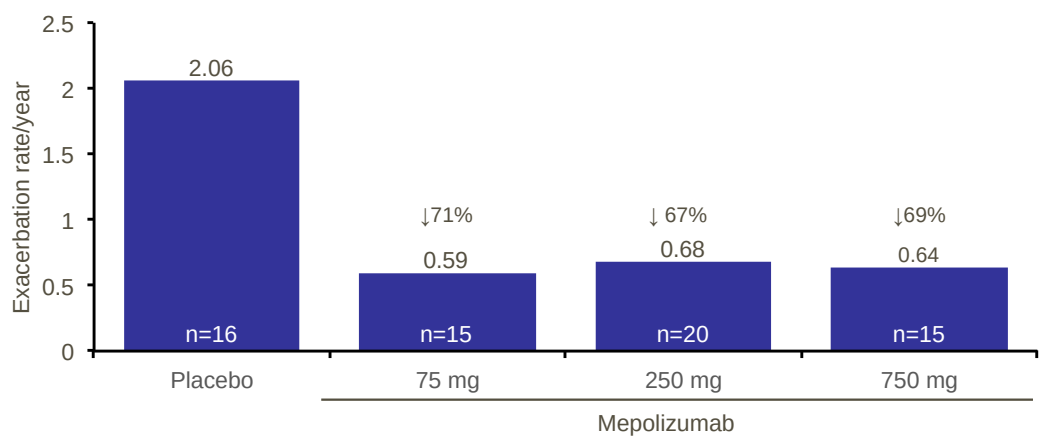
Pharmacodynamic and Clinical Efficacy Data From Patient Sputum Subgroups in DREAM Treated With Mepolizumab Across a 10-fold Dose Range

Figure 1. Pharmacodynamic effect in patients with sputum eosinophils ≥3%



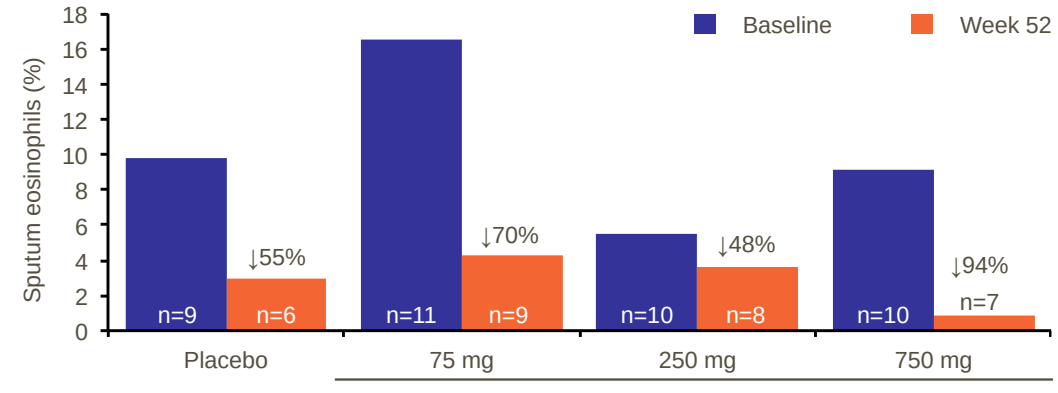
Ratio to baseline, geometric mean (SD logs): Placebo: 0.53 (2.25); 75 mg: 0.16 (2.05); 250 mg: 0.07 (2.04); 750 mg: 0.04 (2.31)

Figure 3. Exacerbation rates in patients with sputum eosinophils ≥3%



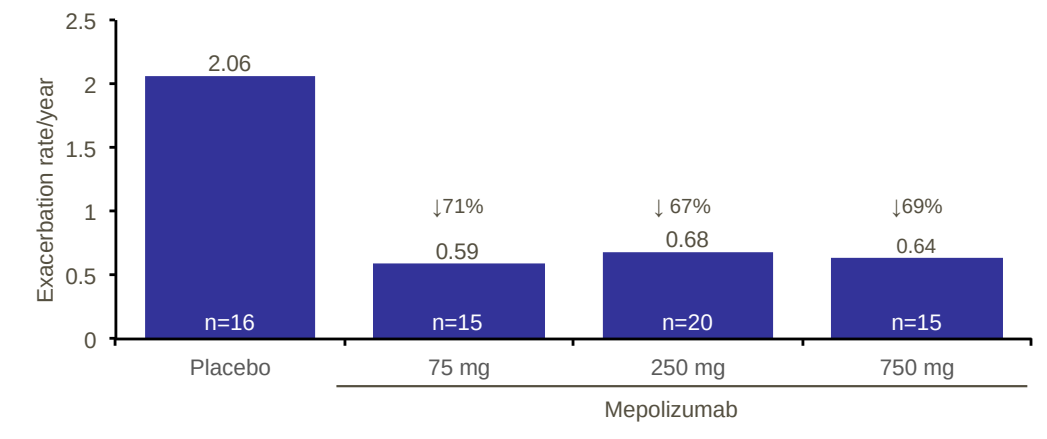
Rate ratio (95% CI): 75 mg: 0.29 (0.11, 0.72); 250 mg: 0.33 (0.15, 0.74); 750 mg: 0.31 (0.13, 0.73)

Figure 2. Pharmacodynamic effect in OCS-dependent patients



Ratio to baseline, geometric mean (SD logs): Placebo: 0.45 (2.91); 75 mg: 0.30 (2.22); 250 mg: 0.52 (2.36); 750 mg: 0.06 (2.76)

Figure 3. Exacerbation rates in patients with sputum eosinophils ≥3%

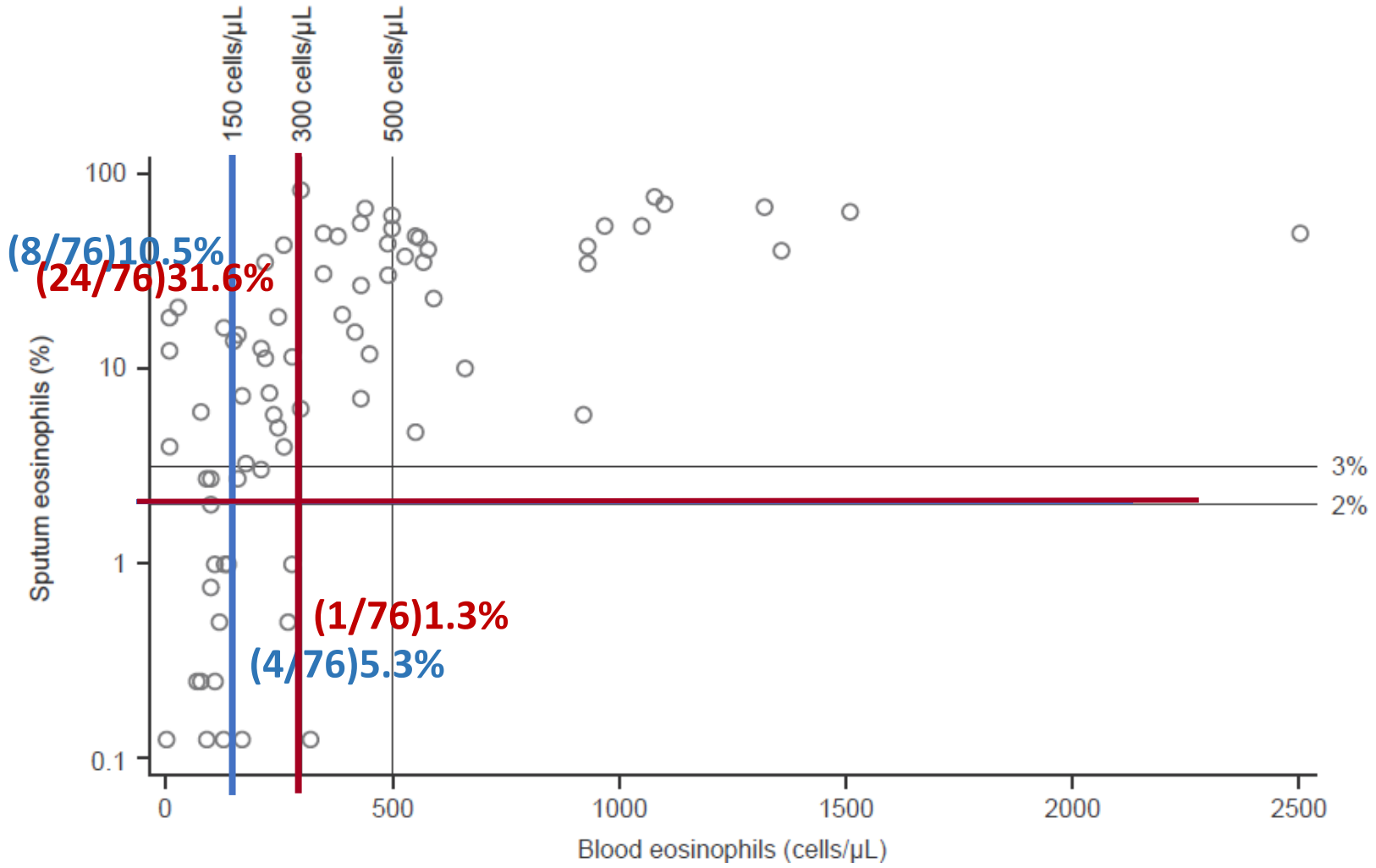


Rate ratio (95% CI): 75 mg: 0.29 (0.11, 0.72); 250 mg: 0.33 (0.15, 0.74); 750 mg: 0.31 (0.13, 0.73)

Prazma CM, Presented at the ATRS 2018 Meeting, San Diego, CA, USA, May 18–23, 2018

Discordance between local & systemic eosinophilia

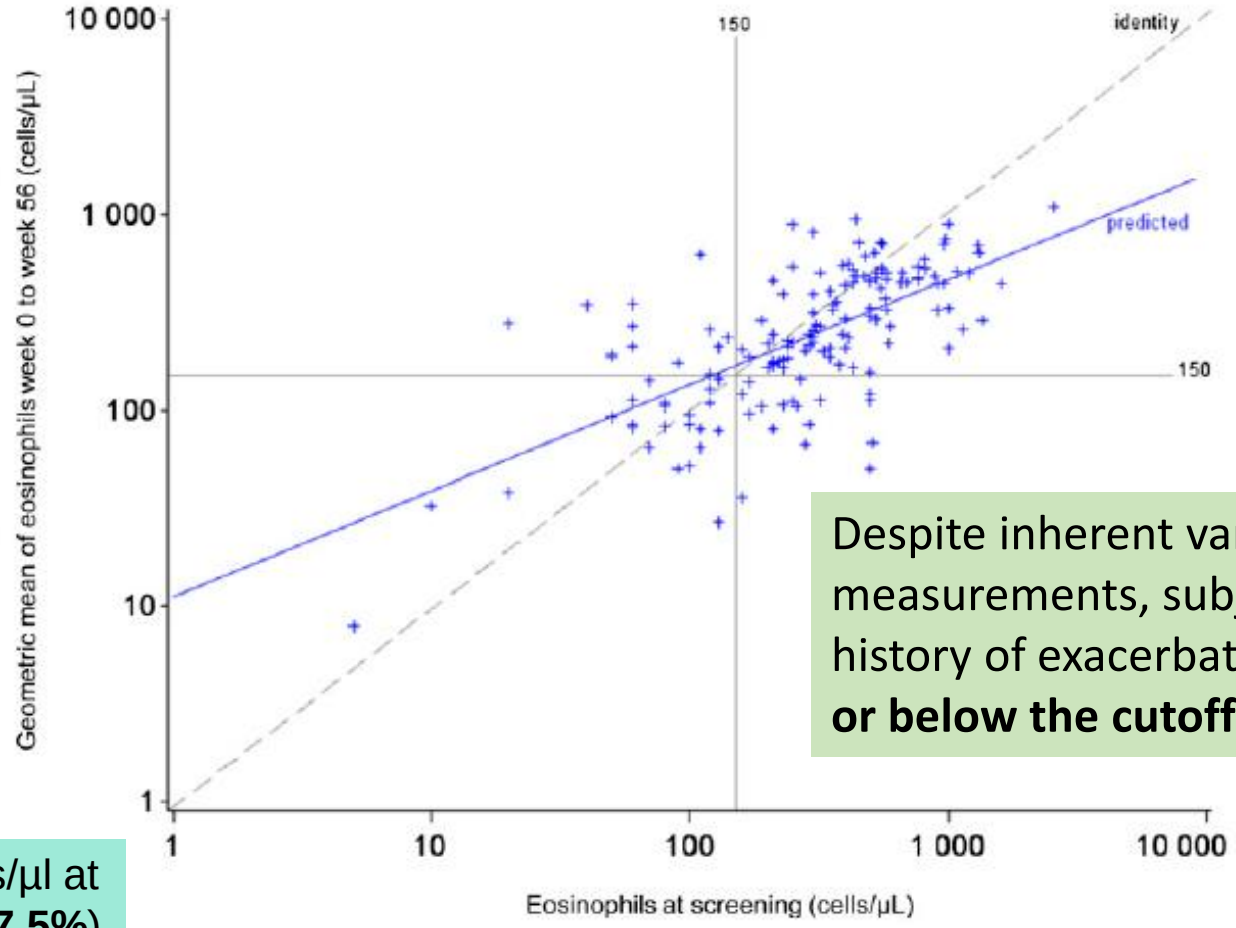
76 paired samples in DREAM



Ortega et al. J Allergy Clin Immunol 2015;136:825-6.

Screening eosinophils are predictive of the eosinophil count in the following year

Placebo subjects enrolled in the DREAM study



Subjects with ≥150 cells/µl at screening (n=115),

98 (**85%**) remained at ≥150 cells/µl in the following year

Despite inherent variability of blood eosinophil measurements, subjects on high dose ICS and with a history of exacerbations tend to **remain either above or below the cutoff value**.

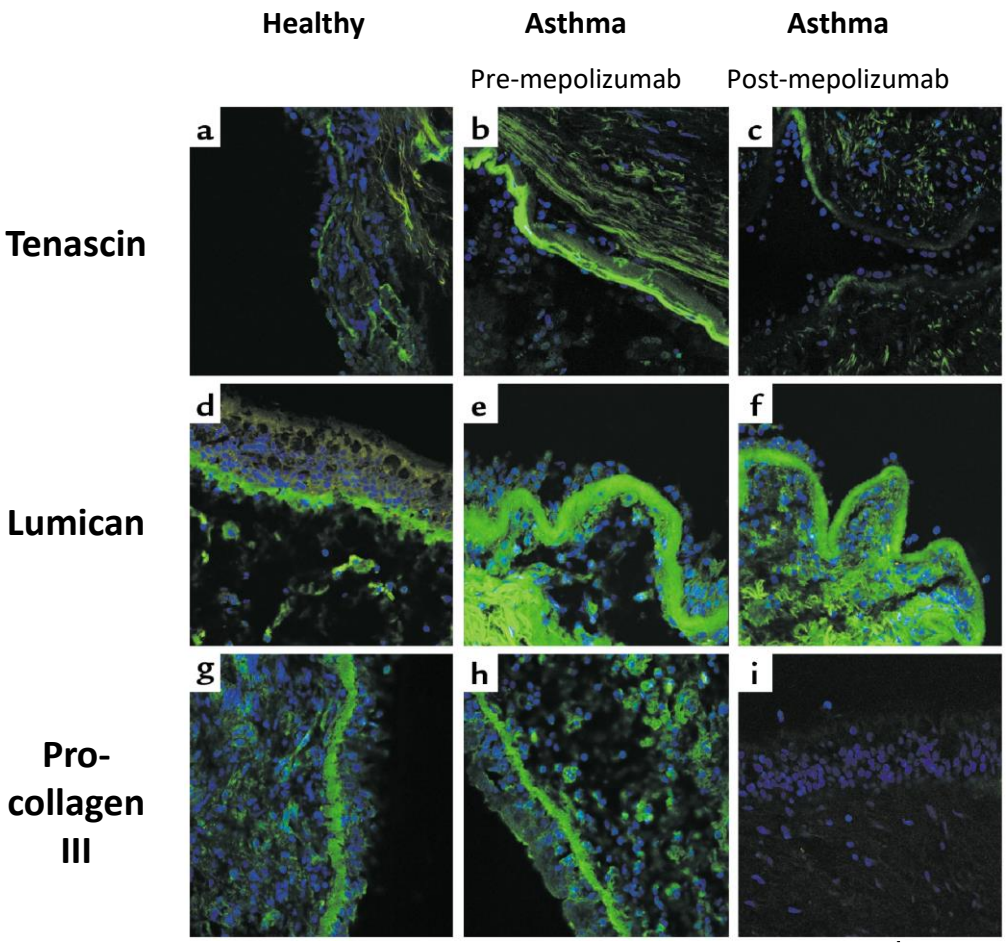
Subjects with <150 cells/µl at screening (n=40), 27 (**67.5%**) remained <150 cells/µl in the following year

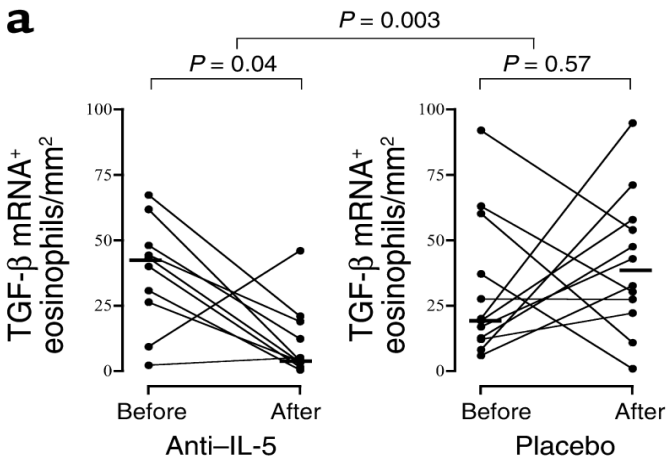
Katz, et al. Ann Am Thorac Soc Vol 11, No 4, pp 531–536, May 2014. DOI: 10.1513

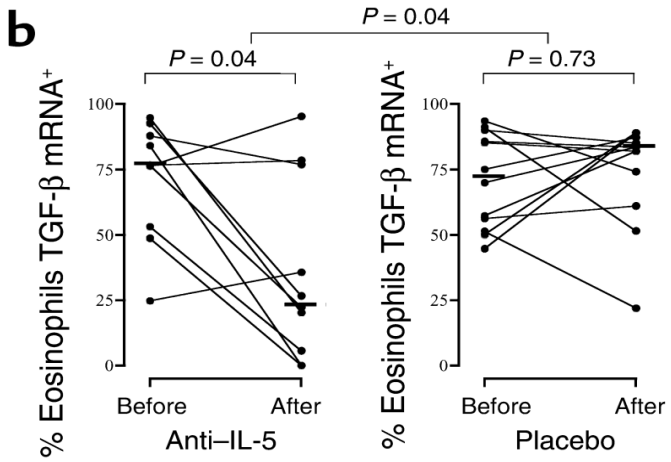
Anti-IL5 may reverse eosinophil-derived TGF-β mediated airway remodeling in asthma

Mepolizuamb reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of atopic asthma

- Randomized, double-blind, placebo-controlled study
- Bronchial biopsies were obtained before and after 3 infusions of mepolizumab in 24 atopic asthmatics





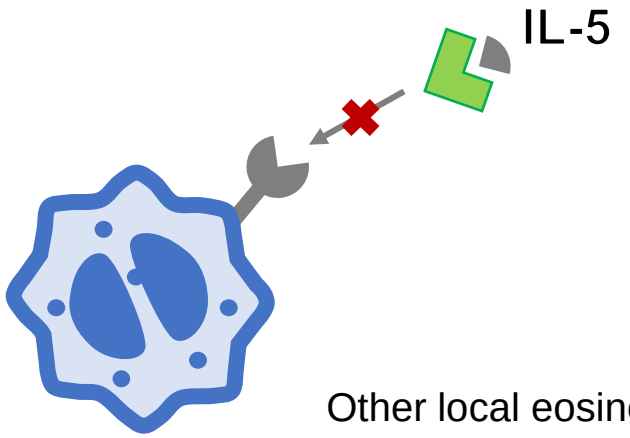


Flood-Page P *et al. J Clin Invest*. 2003 Oct;112(7):1029-36

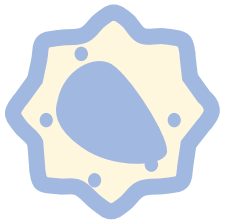
Indirect Treatment Comparison

Mechanism of action: IL-5 cytokine targeted versus eosinophil targeted

Anti-IL-5 MOA[1-4]
indirect

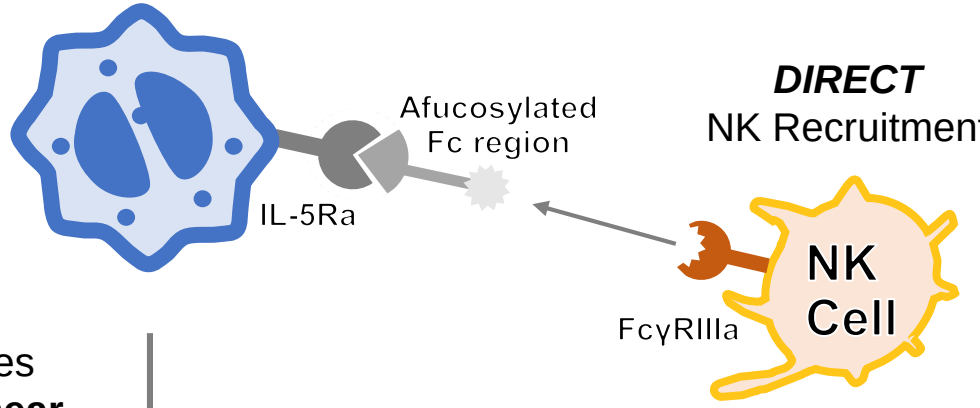


Other local eosinophil activating factors may render clearance by anti-IL-5 ***incomplete***[3,4]

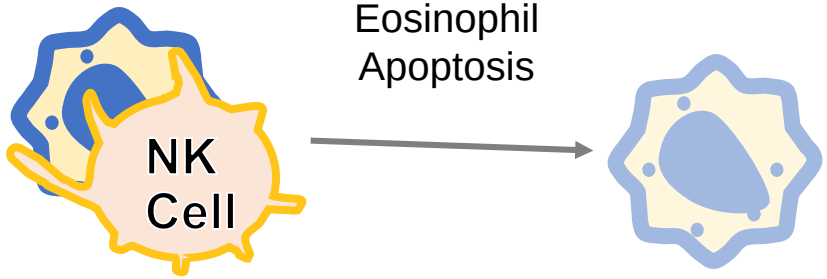


PASSIVE
Eosinophil Apoptosis

Benralizumab MOA[5-7]
Enhanced Antibody-Dependent Cell-mediated Cytotoxicity (ADCC)



Benralizumab induces **direct**, **rapid***, and **near complete** depletion of eosinophils via its enhanced ADCC MOA



*Benralizumab induces eosinophil apoptosis within 6 hours *in vitro*[7]; blood eosinophils were depleted within 24 hours in a clinical study[6]
IL-5 = interleukin 5; IL-5Ra = interleukin 5 receptor alpha; MOA = mechanism of action; NK = natural killer.

1. Patterson MF, et al. *J Asthma Allergy*. 2015;8:125-134; 2. Busse WW, et al. In: Lee JJ, Rosenberg HF, eds. Eosinophils in Health and Disease. London, UK: Academic Press; 2013: 587-591; 3. Flood-Page P, et al. *Am J Respir Crit Care Med.* 2003.167:199-204; 4. Sehmi R et al. *Clin Exper Allergy.* 2016;793-802; 5. Kolbeck R et al. *JACI* 2010;125:1344-1353; 6. Laviolette M et al. *J Allergy Clin Immunol.* 2013;132:1086-1096; 7. Dagher R et al. International Eosinophil Society 10th Biennial Symposium, Gothenburg, Sweden, Friday, 21 July 2017

A network meta-analysis and indirect treatment comparison comparing anti-IL5 treatments in severe eosinophilic asthma

Mepolizumab (100mg Q4W SC)	Reslizumab (3mg/kg Q4W IV)	Benralizumab (30mg Q8W SC)
MENSA (NCT01691521)[1] MUSCA (NCT02281318)[2]	Castro M et al. *Am J Respir Crit Care Med* 2011[5] NCT01270464[6] NCT01508936[7] NCT01287039[8] NCT01285323[8]	SIROCCO (NCT01928771)[3] CALIMA (NCT01914757)[4]

In addition, two meta-analyses were identified including subgroup analyses relevant for this analyses, but not reported in the individual study publications:

- a meta-analysis of SIROCCO and CALIMA[9]
- a meta-analysis of NCT01287039 (Study 1) and NCT01285323 (Study 2)[10]

1. Ortega HG et al. N Engl J Med. 2014;371:1198–207; 2. Chupp GL et al. Lancet Respir Med. 2017;5:390-400; 3. Bleecker ER et al. Lancet. 2016; 388: 2115–27; 4. FitzGerald JM et al. Lancet. 2016; 388: 2128–41; 5. Castro M et al. Am J Respir Crit Care Med 2011;184:1125–32; 6. Bjermer L et al. Chest. 2016 ;150(4):789-98; 7. Corren J et al. Chest. 2016;150(4):799-810; 8. Castro M et al. Lancet Respir Med. 2015 ;3(5):355-66; 9. FitzGerald JM et al. Lancet Respir Med. 2018 ;6(1):51-64; 10. Brusselle G et al. ERJ Open Res. 2017;3(3): 00004-2017. doi: 10.1183/23120541.00004-2017

Heterogeneity between studies

Key differences in study inclusion criteria

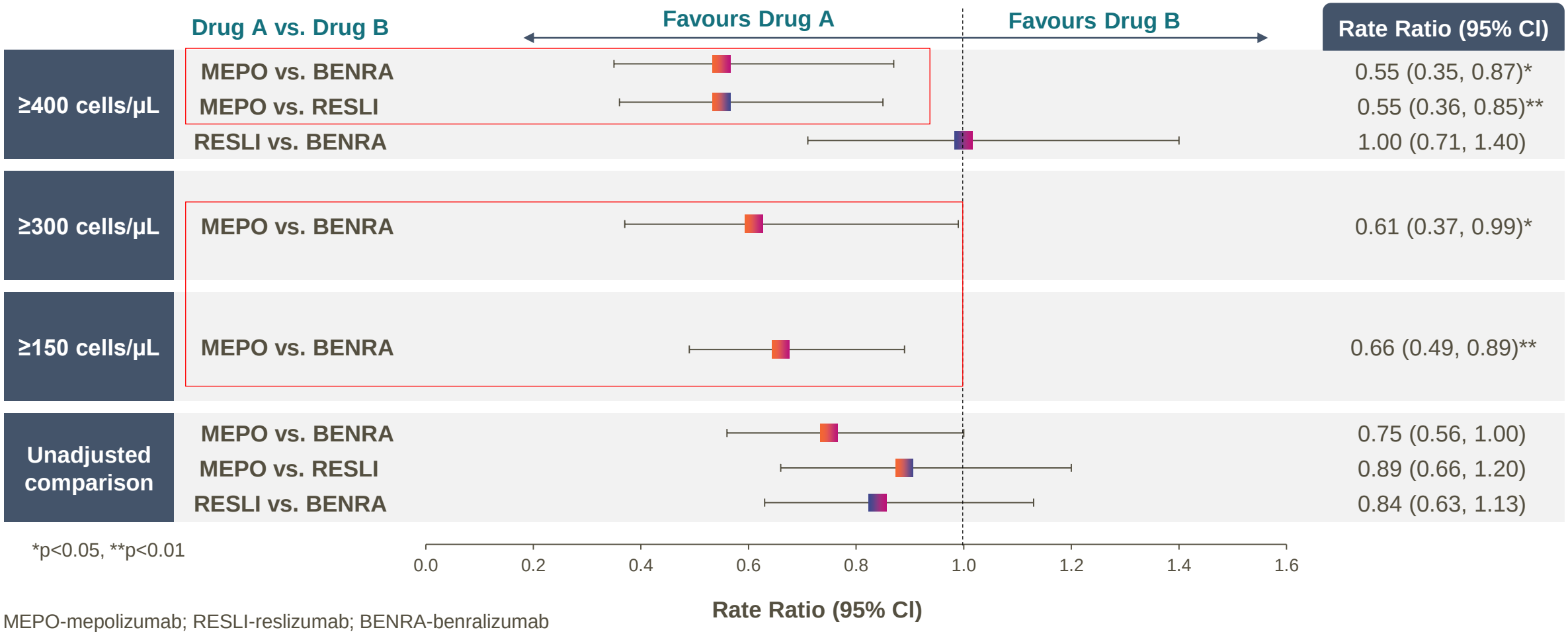
Characteristic	Mepolizumab	Reslizumab	Benralizumab
Baseline blood eosinophils	**≥150 cells/μL or ≥300 cells/μL in past year**	**≥400 cells/μL**	**≥300 cells/μL***
Exacerbation history	≥2 exacerbations in past year	≥1 exacerbation in past year	≥2 exacerbations in past year
ICS dose	**High** (≥18 years: ≥880 μg/day fluticasone; ≥12 and ≤17 years: ≥440 μg/day fluticasone or equivalent)	**Medium-high** (≥440 μg/day fluticasone or equivalent)	**High** (≥500 μg/day fluticasone dry powder formulation or equivalent)
Maintenance OCS use	Allowed, any dose	Allowed, ≤10mg prednisolone/day	Allowed, any dose
%predicted FEV_1	<80% (<90% for age <18)	Not required	<80% (<90% for age <18)
ACQ score	Not required	ACQ-7 ≥1.5	ACQ-6 ≥1.5

*Inclusion criteria for benralizumab studies were wider for blood eosinophil and ICS dose. However, results were reported for the ≥300 cells/μL and high ICS dose patient population

GSK Data on File RF/NLA/0129/18 (1)

Clinically significant exacerbations

Comparisons of the rate of clinically significant exacerbations by baseline blood eosinophil subgroups and in the ITT population

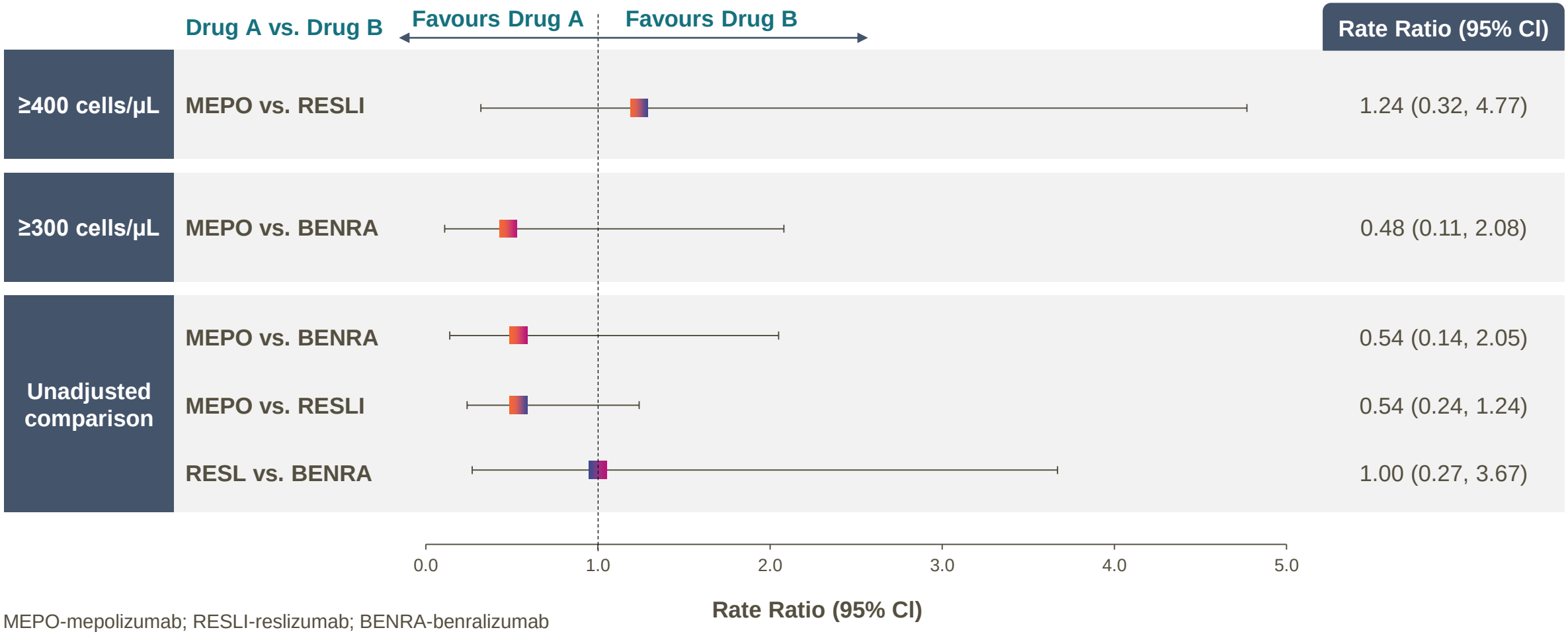


MEPO-mepolizumab; RESLI-reslizumab; BENRA-benralizumab

GSK Data on File RF/NLA/0129/18 (1)

Exacerbations requiring ER visit and/or hospitalization

Comparisons of the rate of exacerbations requiring ER visit/hospitalization by baseline blood eosinophil subgroups and in the ITT population

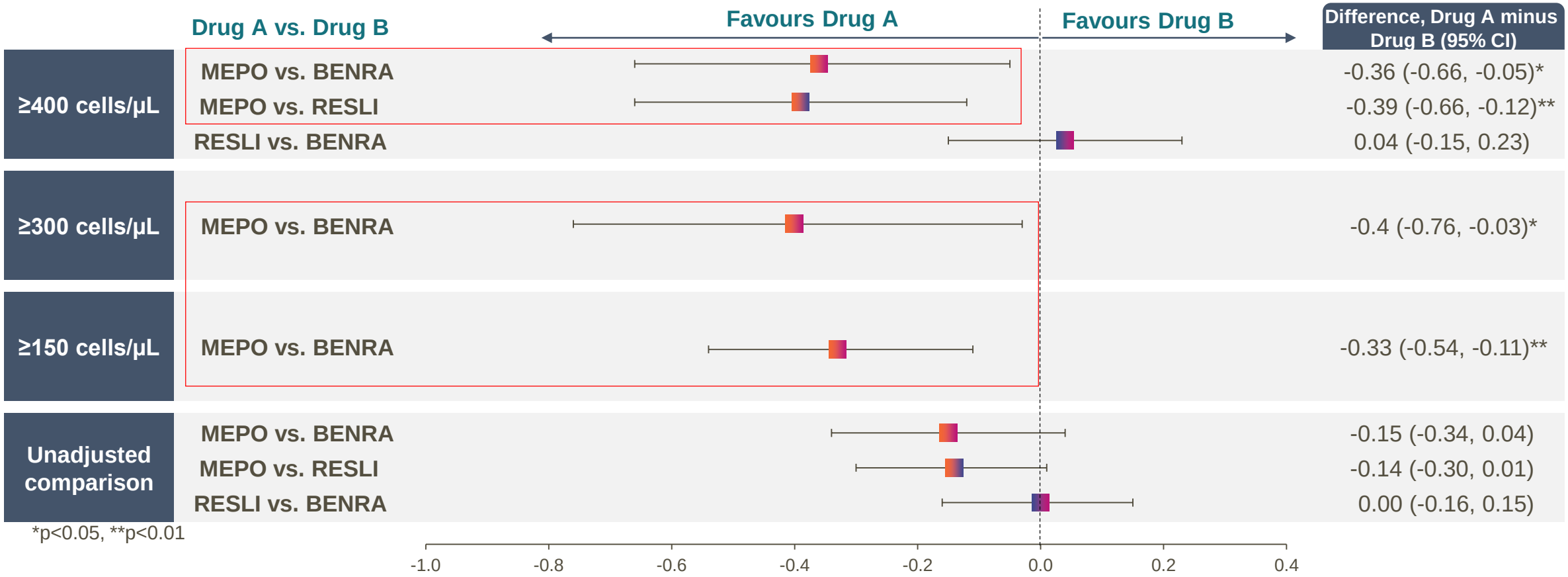


MEPO-mepolizumab; RESLI-reslizumab; BENRA-benralizumab

GSK Data on File RF/NLA/0129/18 (1)

Asthma Control Questionnaire (ACQ)

Comparisons of the change from baseline in ACQ score by baseline blood eosinophil subgroups and in the ITT population



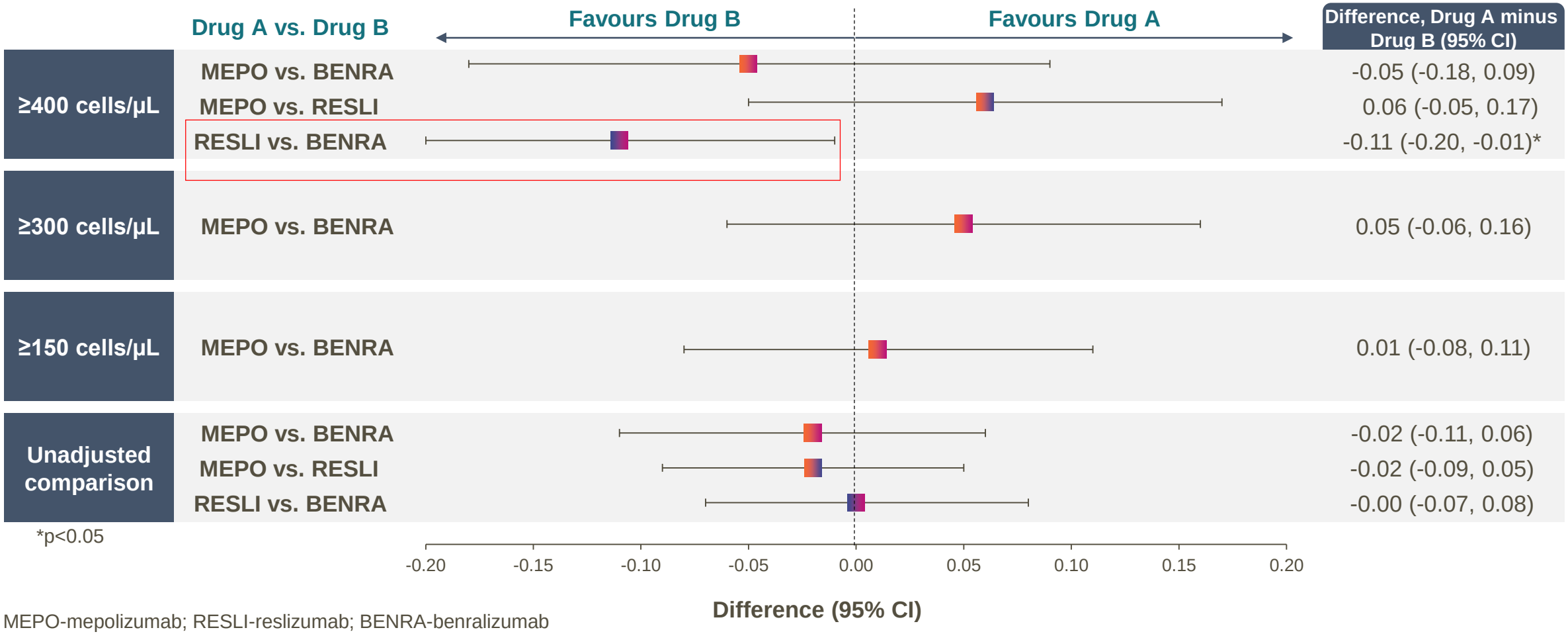
Different ACQ's were used: Mepo-ACQ-5; Benra-ACQ-6; Resli-ACQ-7

MEPO-mepolizumab; RESLI-reslizumab; BENRA-benralizumab

GSK Data on File RF/NLA/0129/18 (1)

Pre-bronchodilator FEV_1 (L)

Comparisons of the change from baseline in pre-bronchodilator FEV_1 score by baseline blood eosinophil subgroups and in the ITT population



MEPO-mepolizumab; RESLI-reslizumab; BENRA-benralizumab

GSK Data on File RF/NLA/0129/18 (1)

Summary

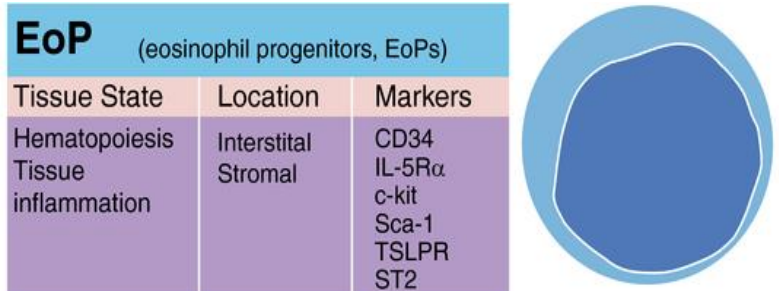
		Mepo vs Benra	Mepo vs. Resli	Benra vs. Resli
Subgroup		**Primary analysis**		
Clinically Significant Exacerbation	≥400	Mepo significantly superior	Mepo significantly superior	No difference
	≥300	Mepo significantly superior	No data on reslizumab	
	≥150	Mepo significantly superior	No data on reslizumab	
Asthma Control	≥400	Mepo significantly superior	Mepo significantly superior	No difference
	≥300	Mepo significantly superior	No data on reslizumab	
	≥150	Mepo significantly superior	No data on reslizumab	
ER visit, hospitalization	≥400	No data on benralizumab	No difference	No data on benralizumab
	≥300	No difference	No data on reslizumab	No data on reslizumab
Secondary Analysis				
FEV_1	≥400	No difference	No difference	Benra significantly superior
	≥300	No difference	No data on reslizumab	
	≥150	No difference	No data on reslizumab	

ER-Emergency room; FEV_1- Forced expiratory volume in 1 second

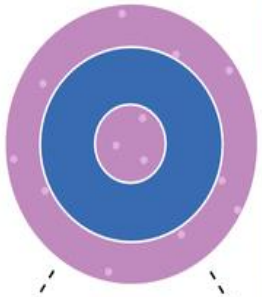
GSK Data on File RF/NLA/0129/18 (1)

level of EOS
benefit or risk for 0,
good EOS vs. bad EOS

Eosinophil Heterogeneity



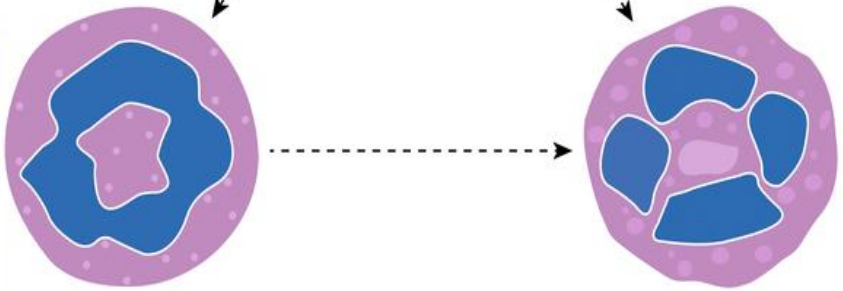
EoP (eosinophil progenitors, EoPs)		
Tissue State	Location	Markers
Hematopoiesis Tissue inflammation	Interstital Stromal	CD34 IL-5Rα c-kit Sca-1 TSLPR ST2



Steady State (hEos, $rEos_{ss}$)		
Tissue State	Location	Markers
Homeostasis Steady state tissues Epithelial quiescence	Interstital	Siglec-F^{med} $CD101^{low}$ CD62L IL-5Rα

Homeostatic, regulatory eosinophils (rEos)

Inflammatory, infiltrating eosinophils (iEOS)

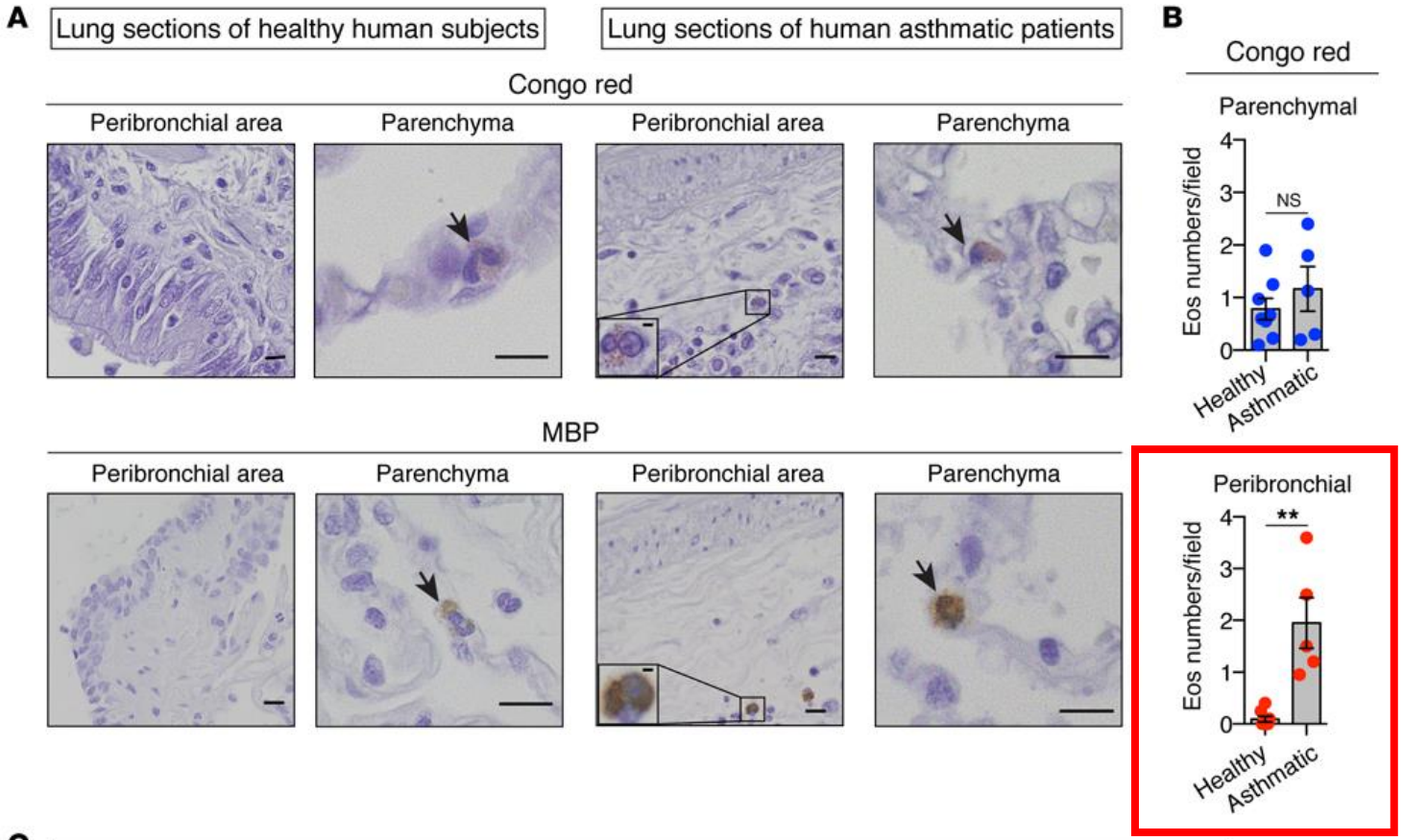


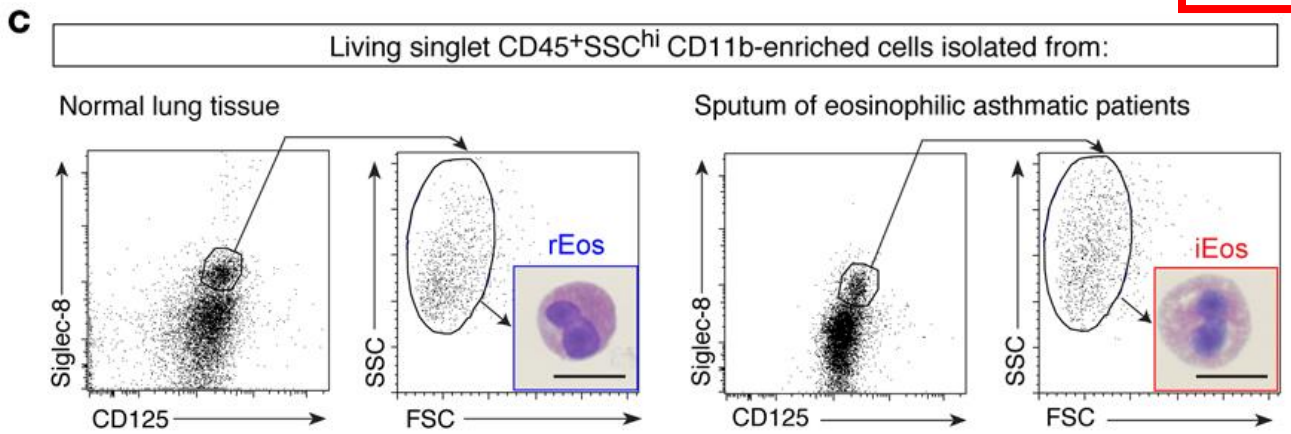
Type1 (hEos, $rEos_i$, devEos, LP eos)		
Tissue State	Location	Markers
Type1/DAMPs immune response Injury and repair Development/ Branching morphogenesis	Sub-epithelial Interstitial Stromal Lamina propria Perivascular	Siglec-F^{med} $CD11^{low/-}$ $CD101^{low}$ CD62L TLR7/8 IL-5Rα

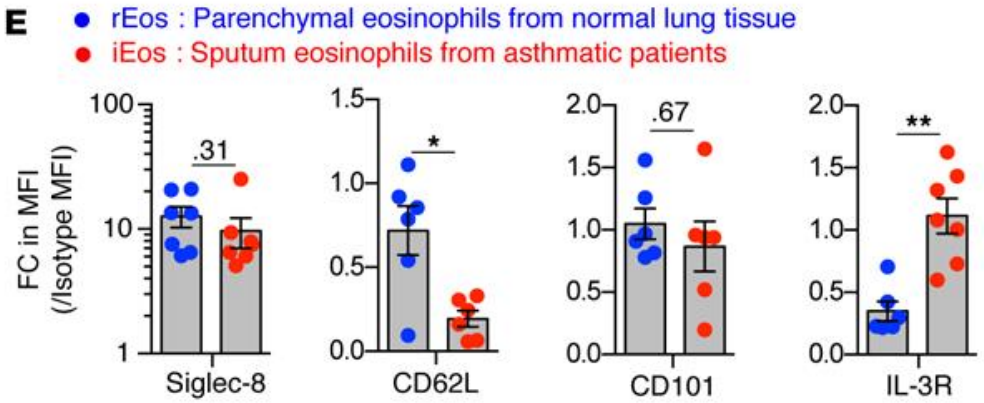
Type2 (iEos, vEos, IE eos, devEos, hEos)		
Tissue State	Location	Markers
Type2 immunity Remodeling and resolution Epithelial shedding and turnover Development/ Epithelialization	Intra-, Trans-epithelial Mucosal Airway lumens Adipose	Siglec-F^{high} $CD11c^{low}$ $CD101^{hgh}$ C5αR1 ST2 IL-5Rα

Abdala-Valencia et al J Lekoc Biol 2018 Jul;104(1):95-108

Localization, morphology, and phenotype of lung rEos and iEos in humans

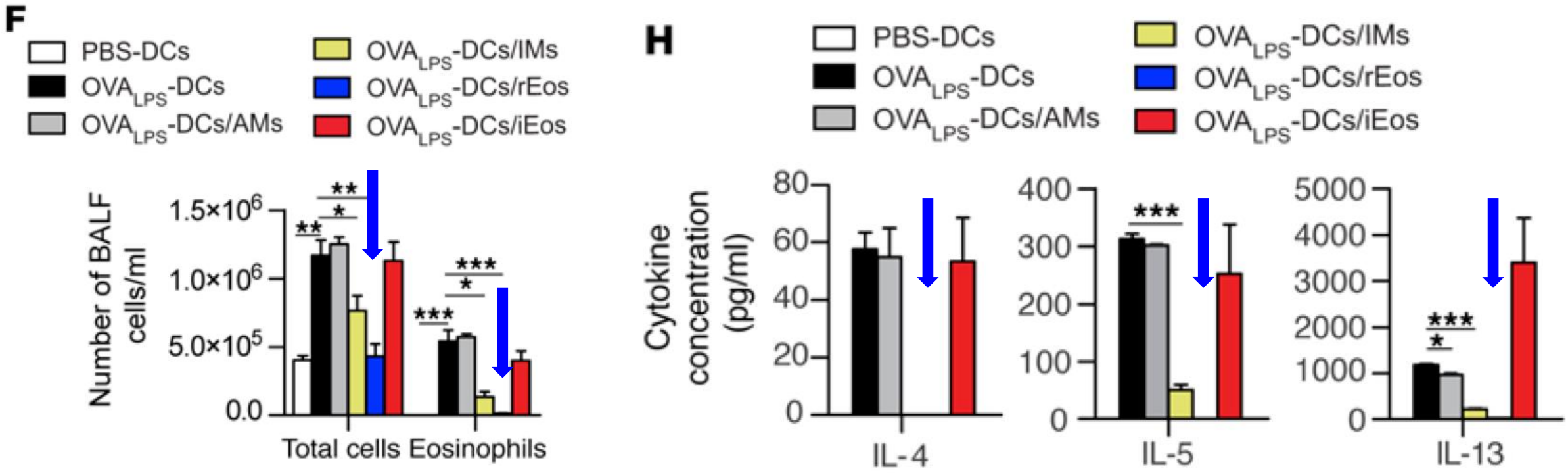






Mesnil et al JCI 2016; 126: 3279-3295

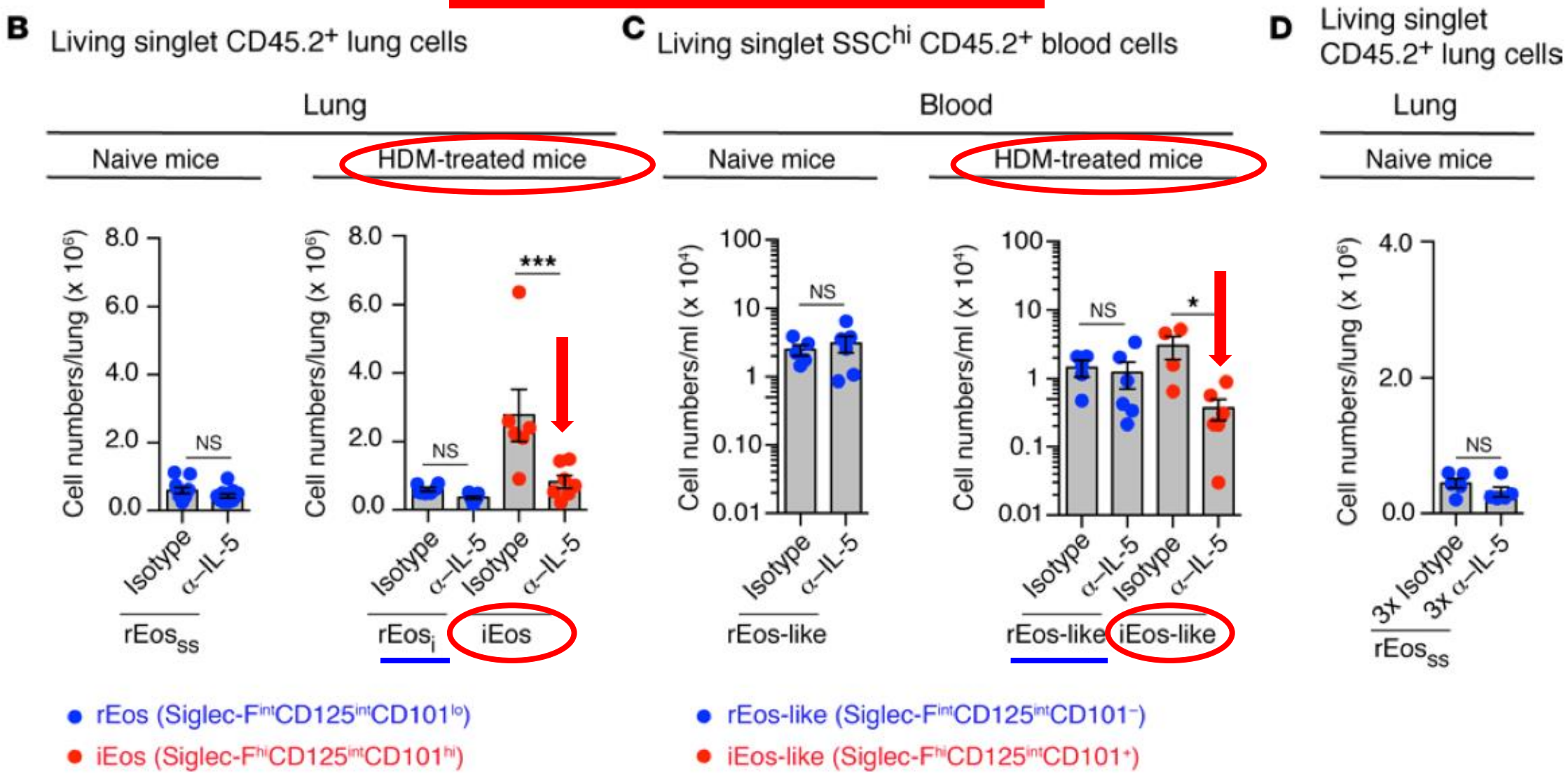
Immunosuppressive functions of rEos



Mesnil et al JCI 2016; 126: 3279-3295

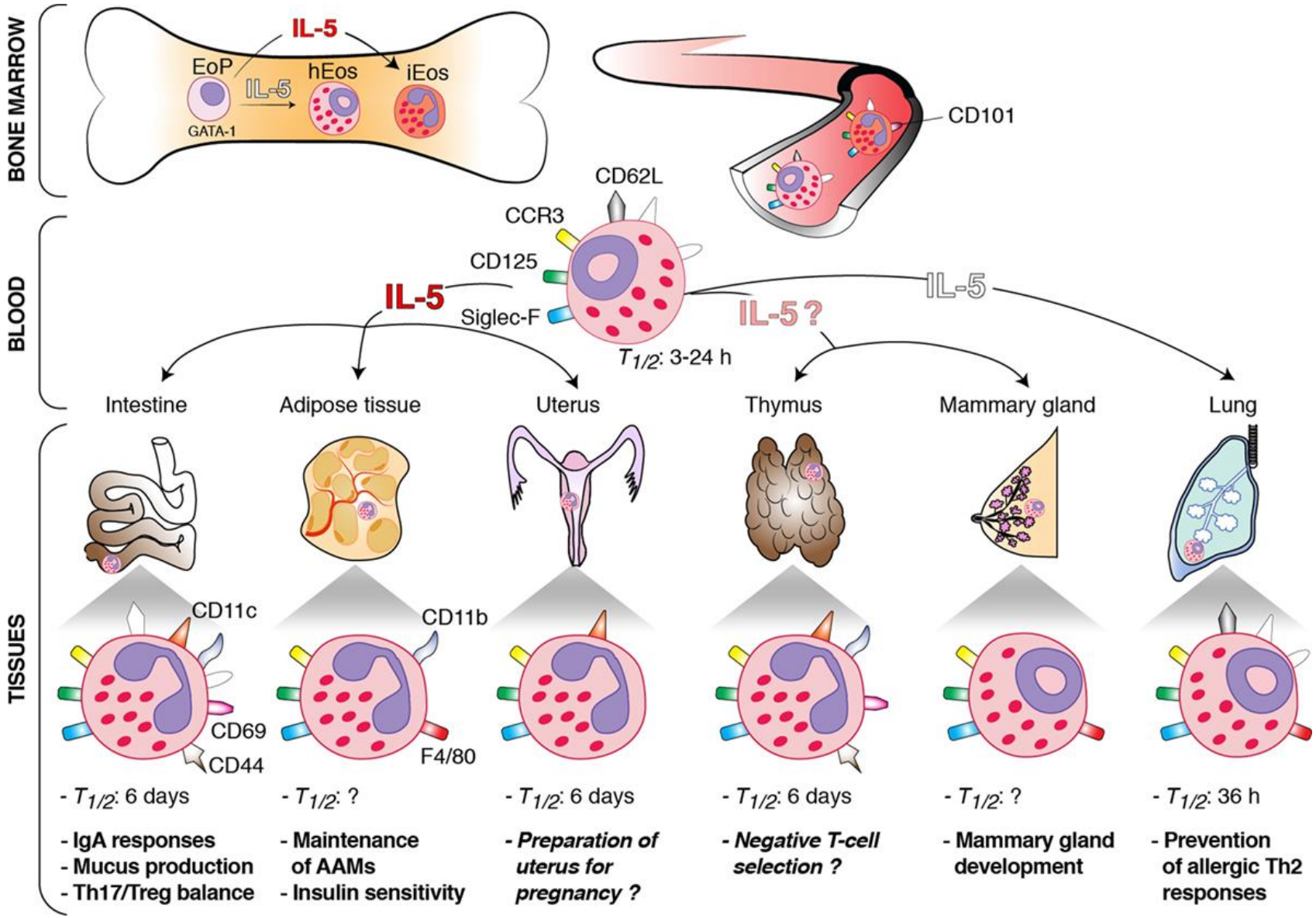
Sensitivity and responsiveness of eosinophil subsets to α-IL-5 treatments

The effect of α-IL-5Rα?



Mesnil et al JCI 2016; 126: 3279-

Potential role of resident eosinophils in health



Marichal et al Front Med 2017;4: 101

Summary: Mepolizumab in severe eosinophilic asthma*

** Eosinophilic asthma criteria: Peripheral blood eosinophil count of 150 cells/µl on entry or 300 cells/ µl in last year*

Decrease in Exacerbations**

Study	Subjects on mepolizumab (n)	Dose and duration	Severe Exacerbation Reduction
MENSA[1]	194	100mg SC for 32 weeks	53%
MUSCA[2]	274	100mg SC for 24 weeks	58%

Improvement in quality of life

MUSCA STUDY[2]: SGRQ
Treatment difference (mepolizumab–placebo) 95% CI
–7.7 (–10.5, –4.9)
Responder analysis
Odds ratio (95% CI)
2.2 (1.6 to 3.2)

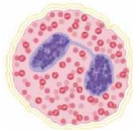
MENSA STUDY[1]: SGRQ
Treatment difference (mepolizumab–placebo) 95% CI
–7.0 (–10.2, –3.8)
Responder analysis
Odds ratio (95% CI)
2.1 (1.3 to 3.2)

Reduction in oral steroids

SIRIUS study[3]
Median dose reduction
- Mepolizumab 50%
- Placebo 0%

P=0.007

Severe Eosinophilic asthma



Improvement in FEV_1**

MENSA study[1]: 98 ml
MUSCA study[2]: 120ml

Improvement in ACQ**

MENSA study[1]: - 0.44
MUSCA study[2]: -0.40

** All impacts over and above that of Placebo in randomised, placebo-controlled, double-blind trials

1. Ortega HG et al. *N Engl J Med*. 2014;371(13):1198-1207, 2. Chupp et al. *Lancet Respir Med*. 2017;5:390–400, 3. Bel EH, et al. *N Engl J Med.* 2014;371:1189-1197.

Thank you for your attention