Treatment optimization in asthma

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&

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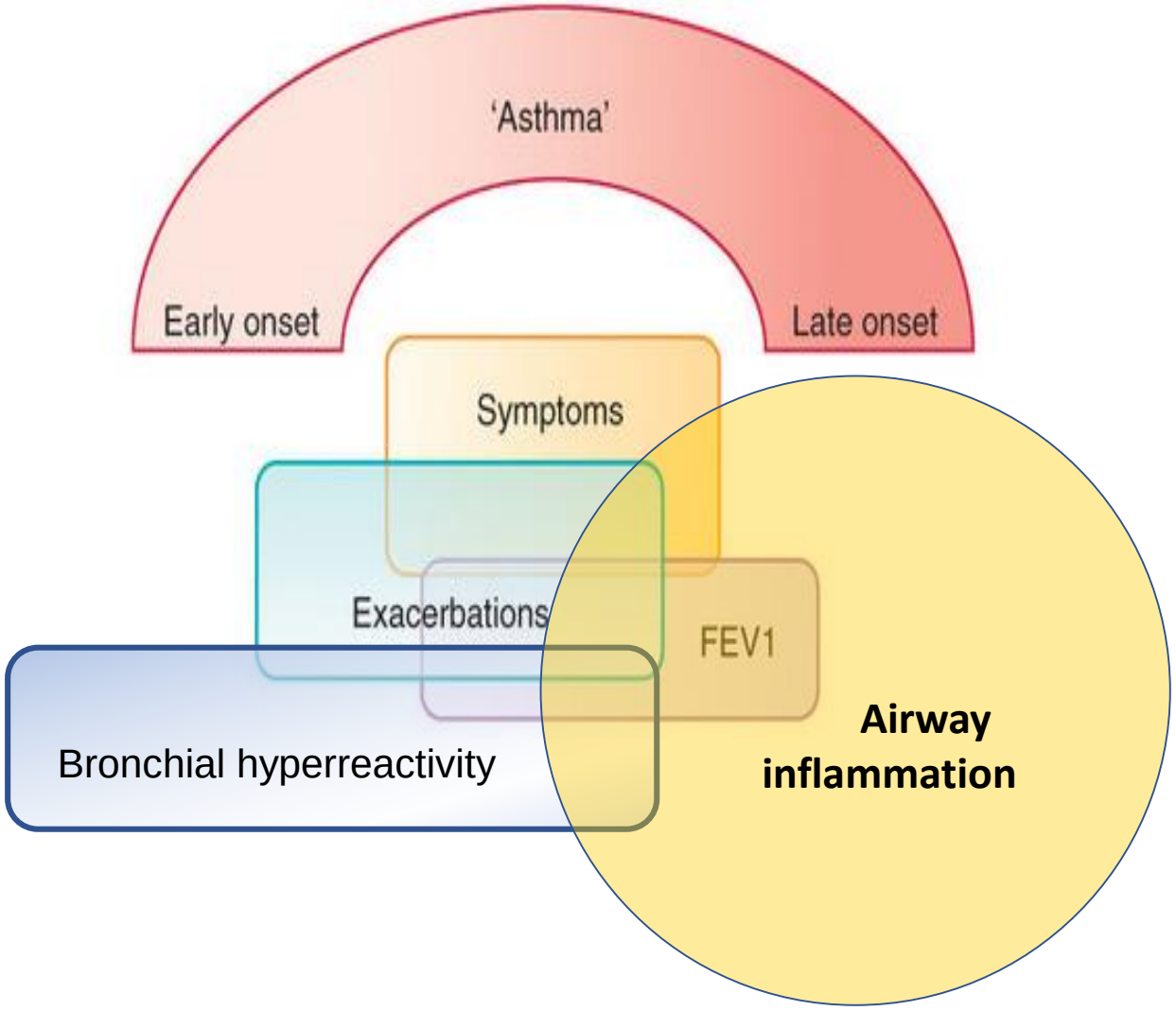
Disclosures: Professor Peter Howarth
GSK Global Medical Expert

Research support/ involvement	Clinical study involvement with GSK and Boehringer Ingelheim
Employee	Employee of GSK
Consultant	Part-time Professor of Allergy and Respiratory Medicine at Southampton University, UK
Major stockholder	Has share options in GSK
Speakers' bureau	No relevant conflicts of interest to declare
Honoraria	No relevant conflicts of interest to declare
Scientific Advisory Board	GSK

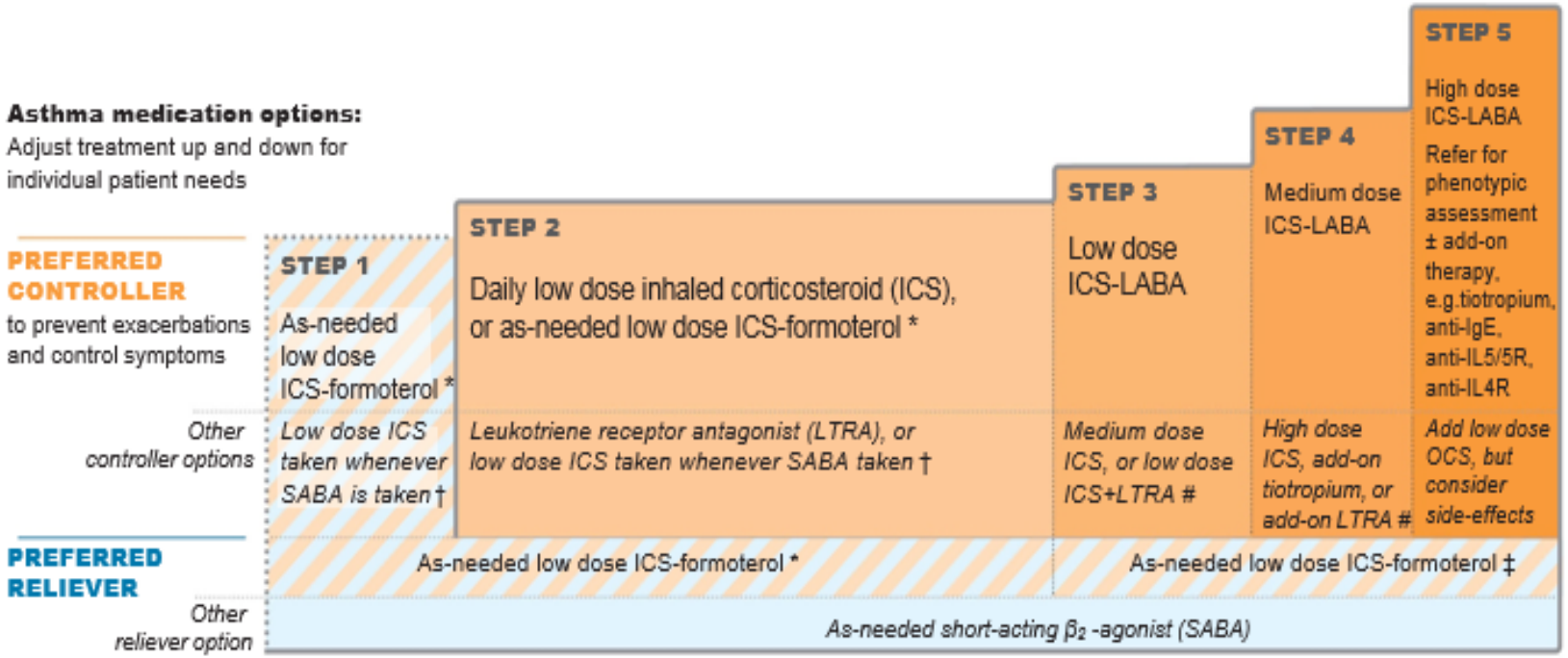
Asthma is an umbrella term that describes a clinical syndrome



Adapted from Wenzel S. Nature Medicine 2012;18:716–725

Global initiative for asthma 2019 (GINA 2019)

Adult asthma



* Off-label; data only with budesonide-formoterol (bud-form)

† Off-label; separate or combination ICS and SABA inhalers

‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy

\# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV >70% predicted

ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LTRA, leukotriene receptor antagonists; OCS, oral corticosteroid; SABA, short-acting β2-agonist

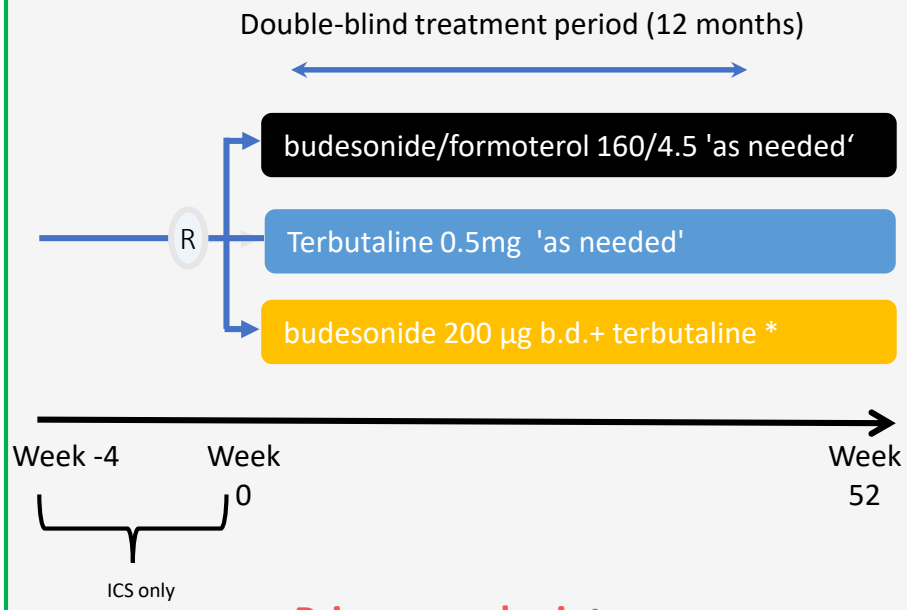
Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2019. Available from: www.ginasthma.org (Accessed April 2019).

Best treatment for mild asthma: SYGMA study

Patient population: patients in need of Step 2 treatment according to GINA

- Patients uncontrolled with SABA PRN
- Patients controlled with low stable dose of ICS or leukotriene antagonist + SABA PRN

SYGMA 1



Primary endpoint:

Well controlled asthma weeks (WCAW)

Budesonide/formoterol PRN vs SABA (superiority)

WELL CONTROLLED ASTHMA WEEK (WCAW) DEFINITION

Two or more of the following criteria must be fulfilled:

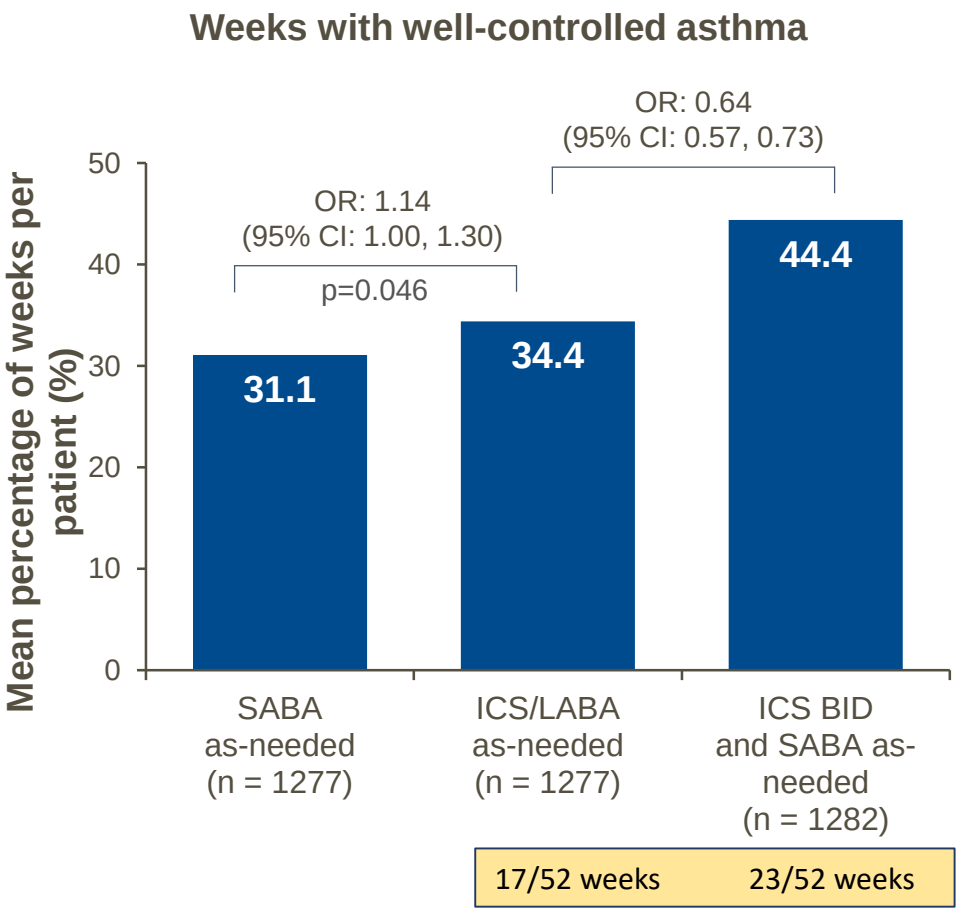
- ≤ 2 days with a daily asthma symptom score >1
- ≤ 2 days of as-needed medication use, up to a maximum of four occasions per week (multiple occasions per day are regarded as separate occasions)
- morning PEF ≥80% predicted every day.

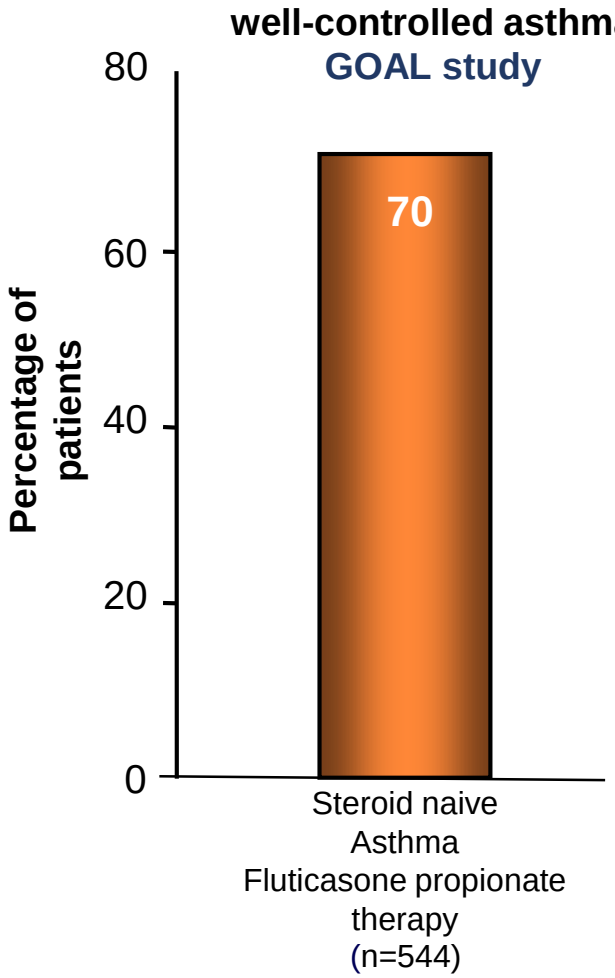
Both these must be fulfilled:

- no night-time awakenings due to asthma
- no additional inhaled and/or systemic corticosteroid treatment due to asthma

1. From the Global Initiative for Asthma. Global strategy for asthma management and prevention. Accessed 2018. Available from: https://www.ginasthma.org. 2. O'Byrne PM et al. Trials 2017; 18:12

Use of daily ICS and prn ICS/LABA in patients with mild asthma

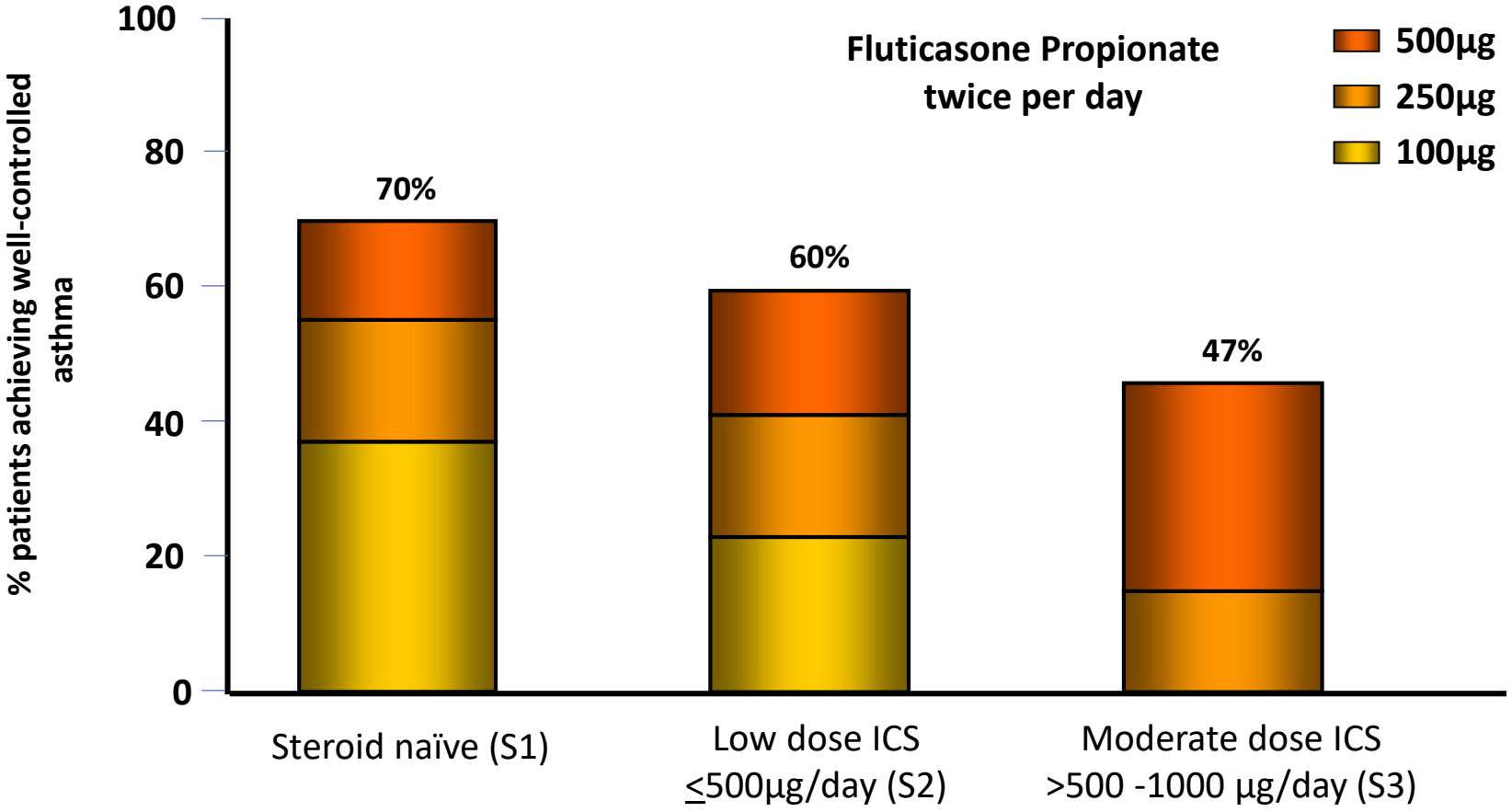




Increase in asthma-control

1. Adapted from O'Byrne PM, et al. *N Engl J Med.* 2018;378:1865–1876. 2. Adapted Bateman et al AJRCCM 2004; 170: 836–44

GOAL Study
'Well controlled' asthma after 1 year
(at least 87.5% of last 8 weeks)



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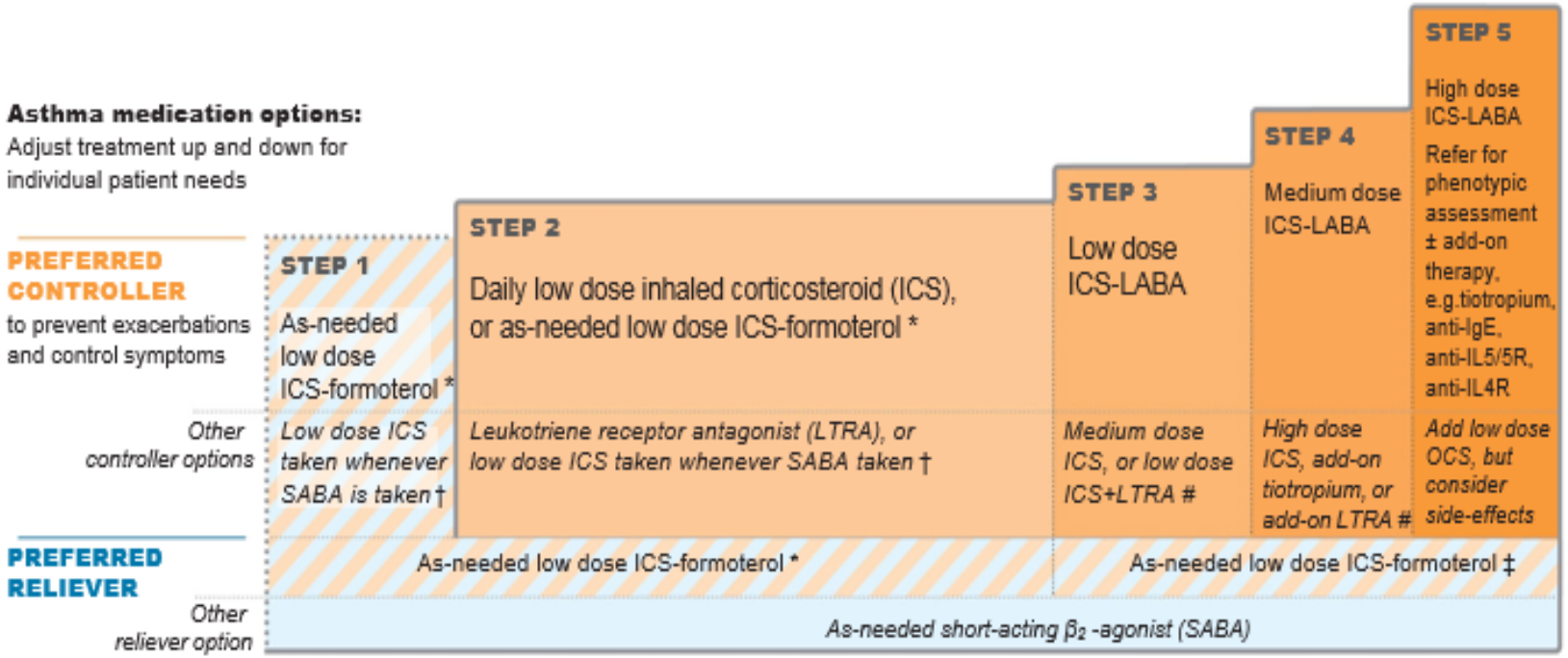
Adult asthma



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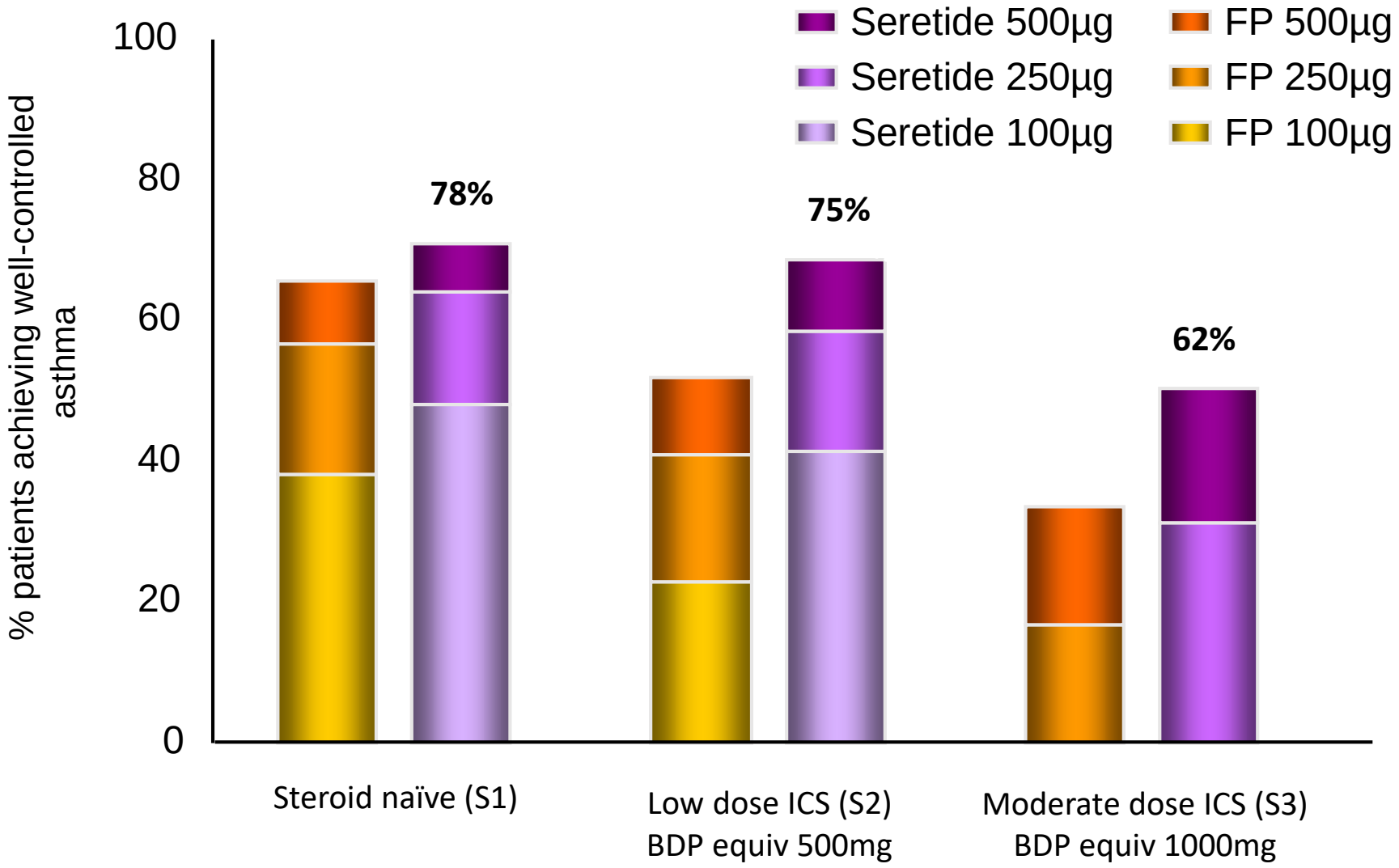
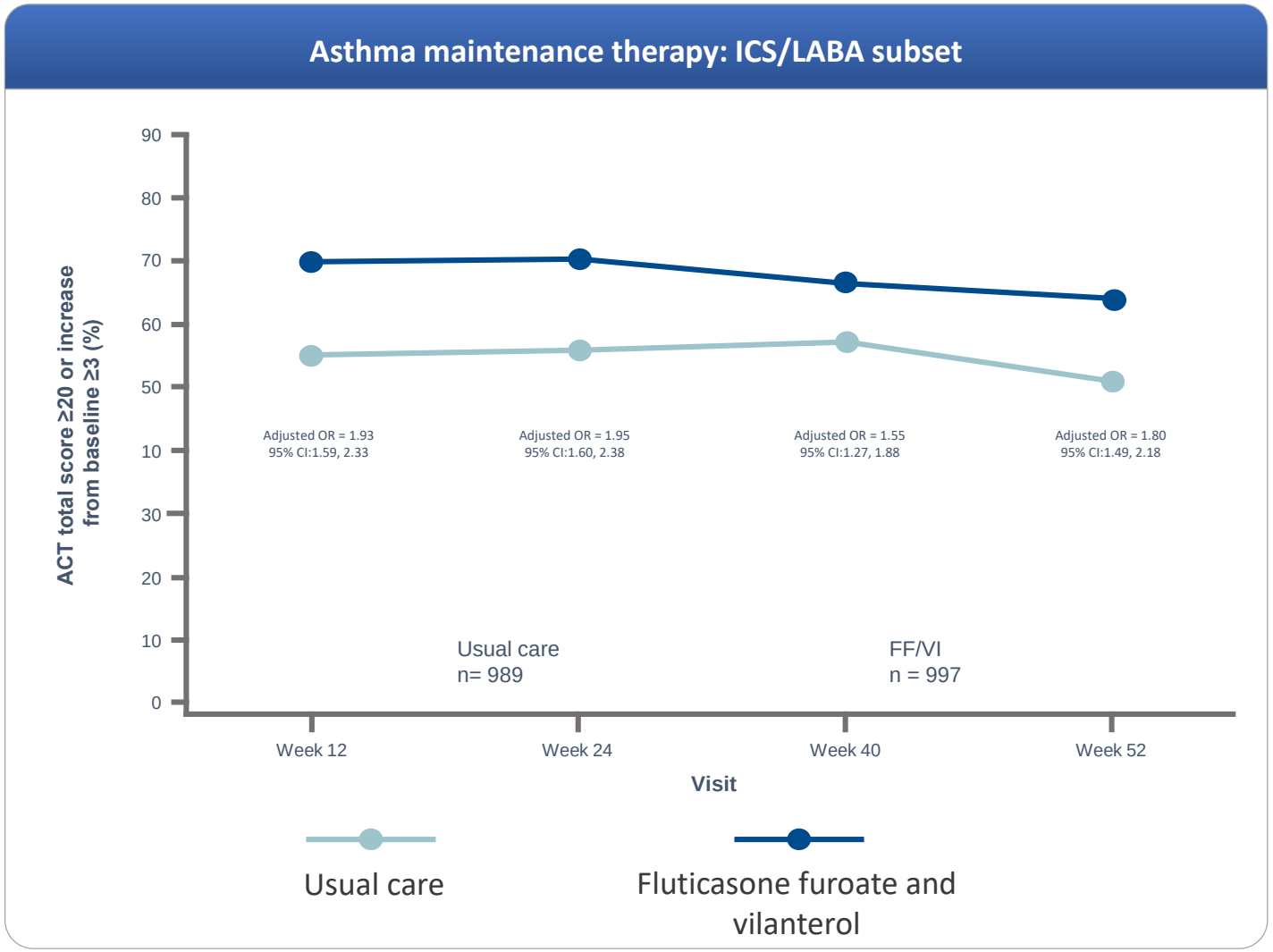


Adapted from Bateman et al AJRCCM 2004; 170: 836–44

Improved control with Relvar (FF/VI)* over other combination inhalers in clinical effectiveness study

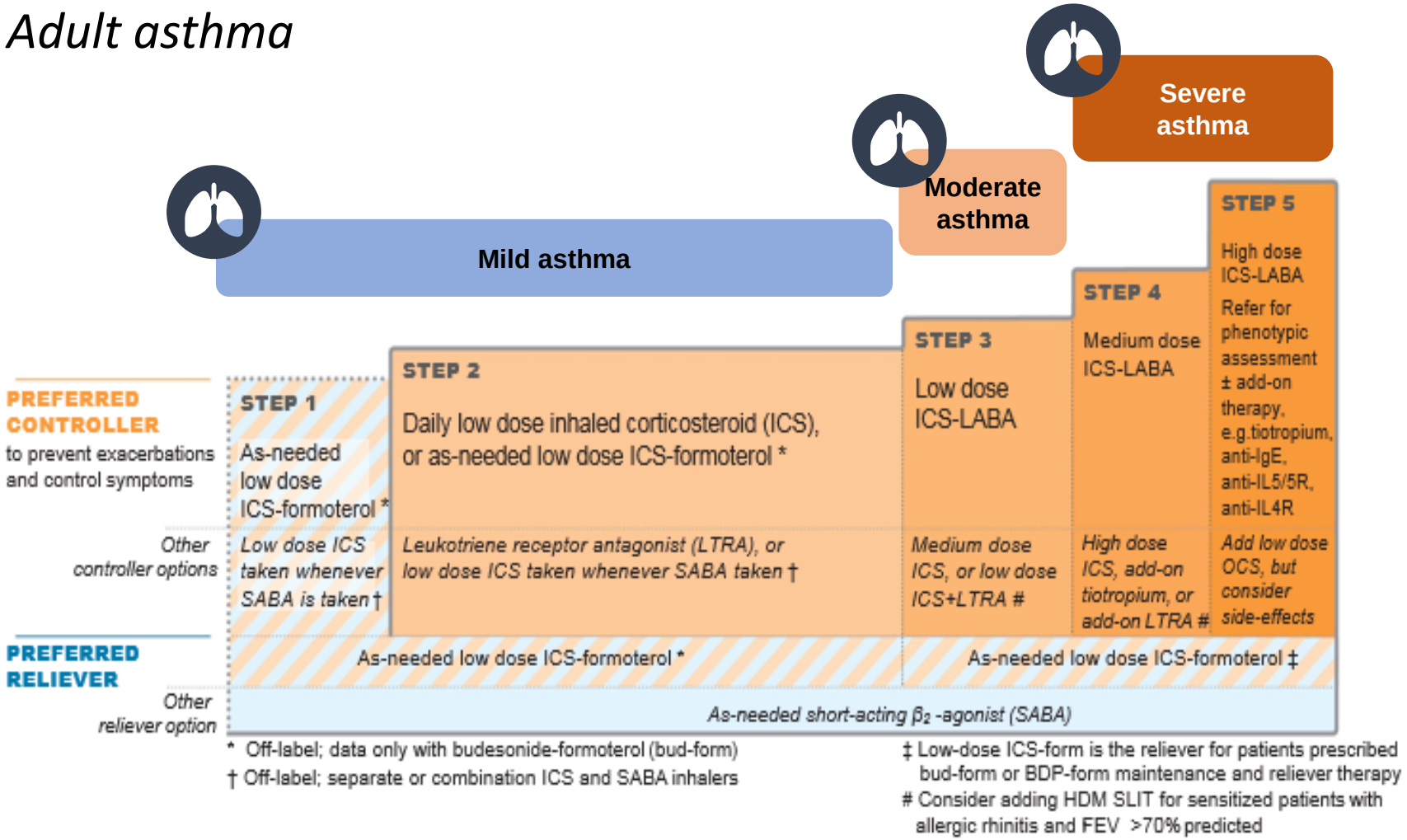


* FF, fluticasone furoate; VI, vilanterol.

Woodcock A, et al. *Lancet*. 2017;390:2247–2255.

Global initiative for asthma 2019 (GINA 2019)

Adult asthma



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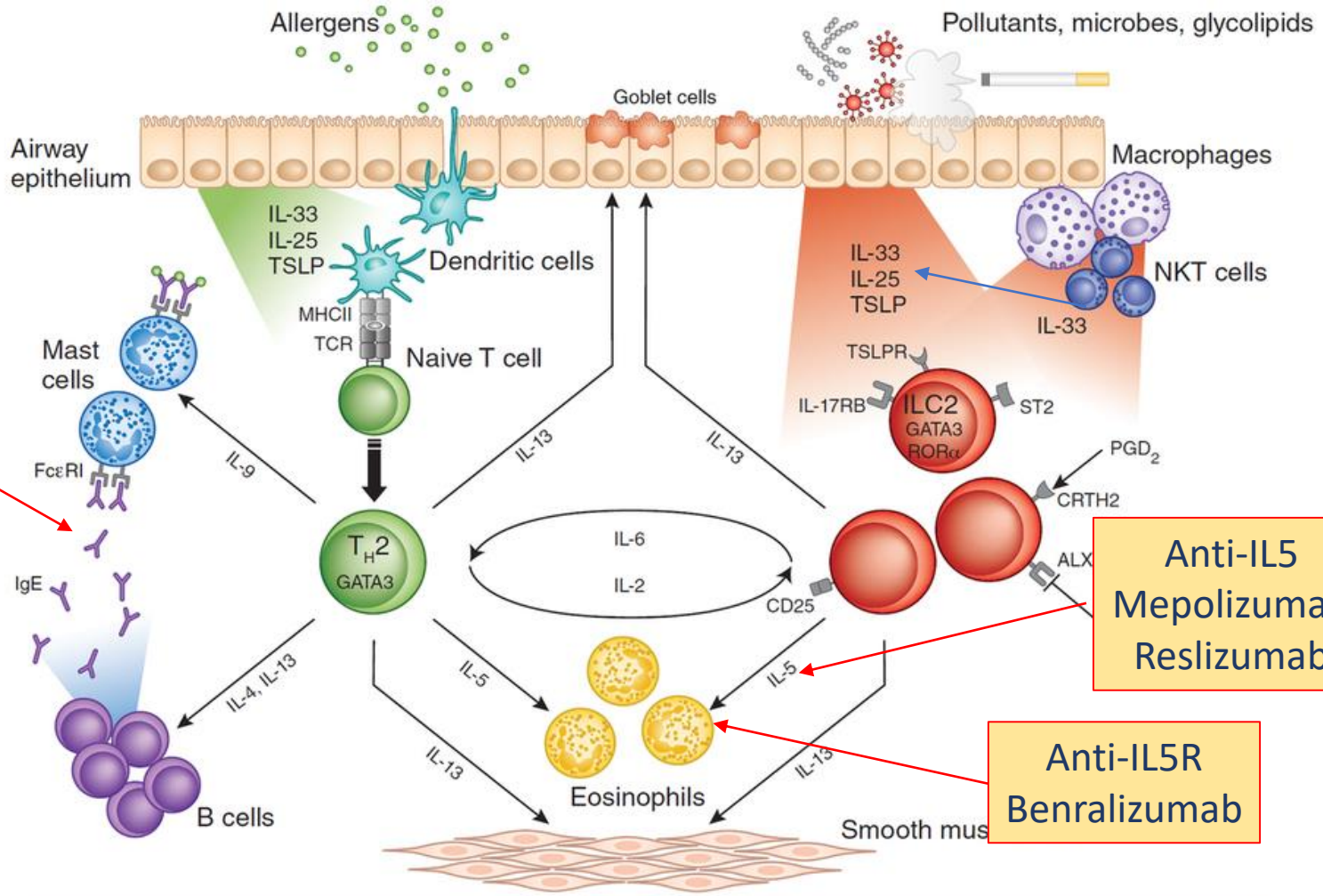
Type 2 airway inflammation and biologic directed targets



Anti-IgE
Omalizumab

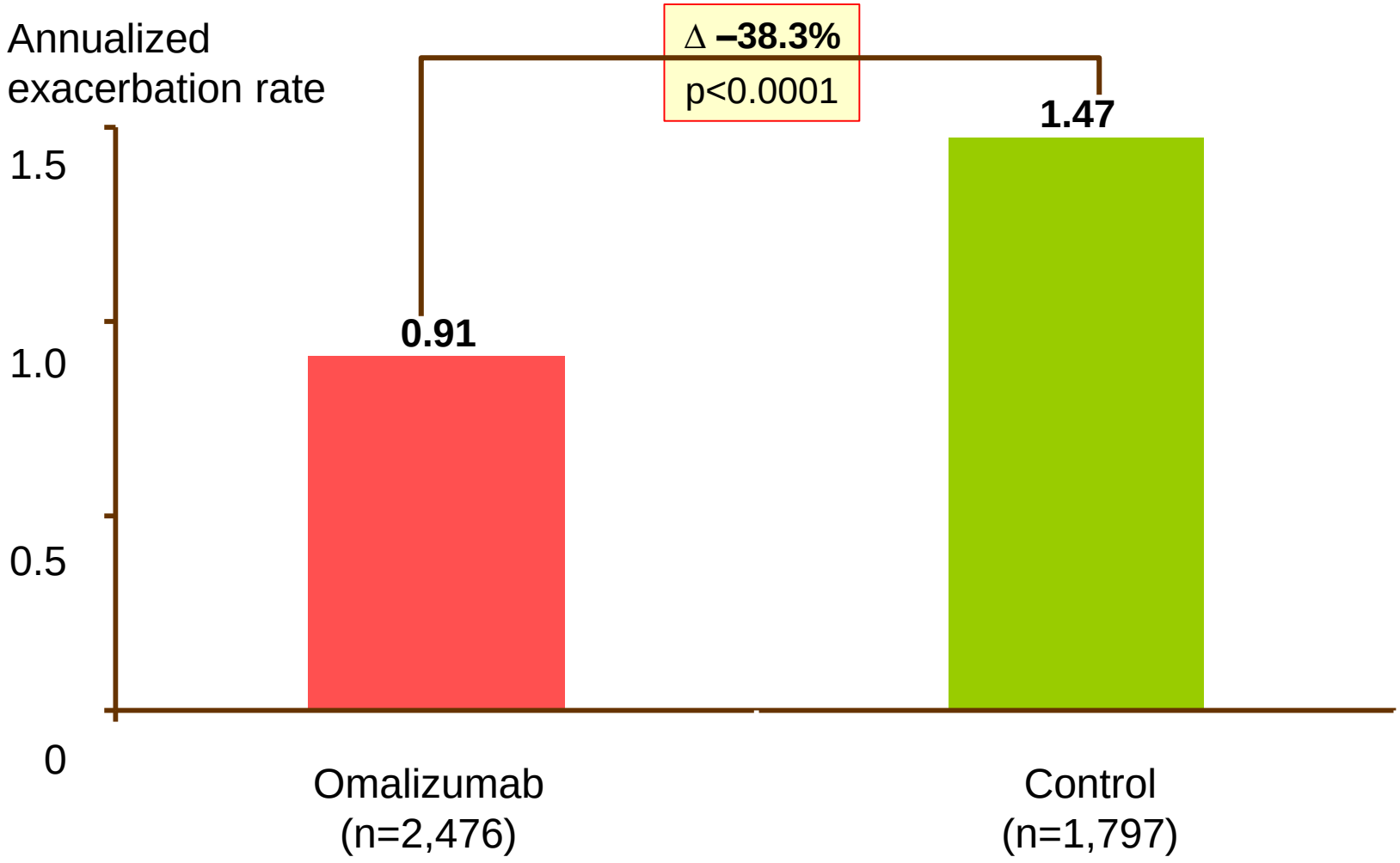
Anti-IL5
Mepolizumab
Reslizumab

Anti-IL5R
Benralizumab

Reslizumab is an investigational medicinal product, and it is unlicensed in Taiwan

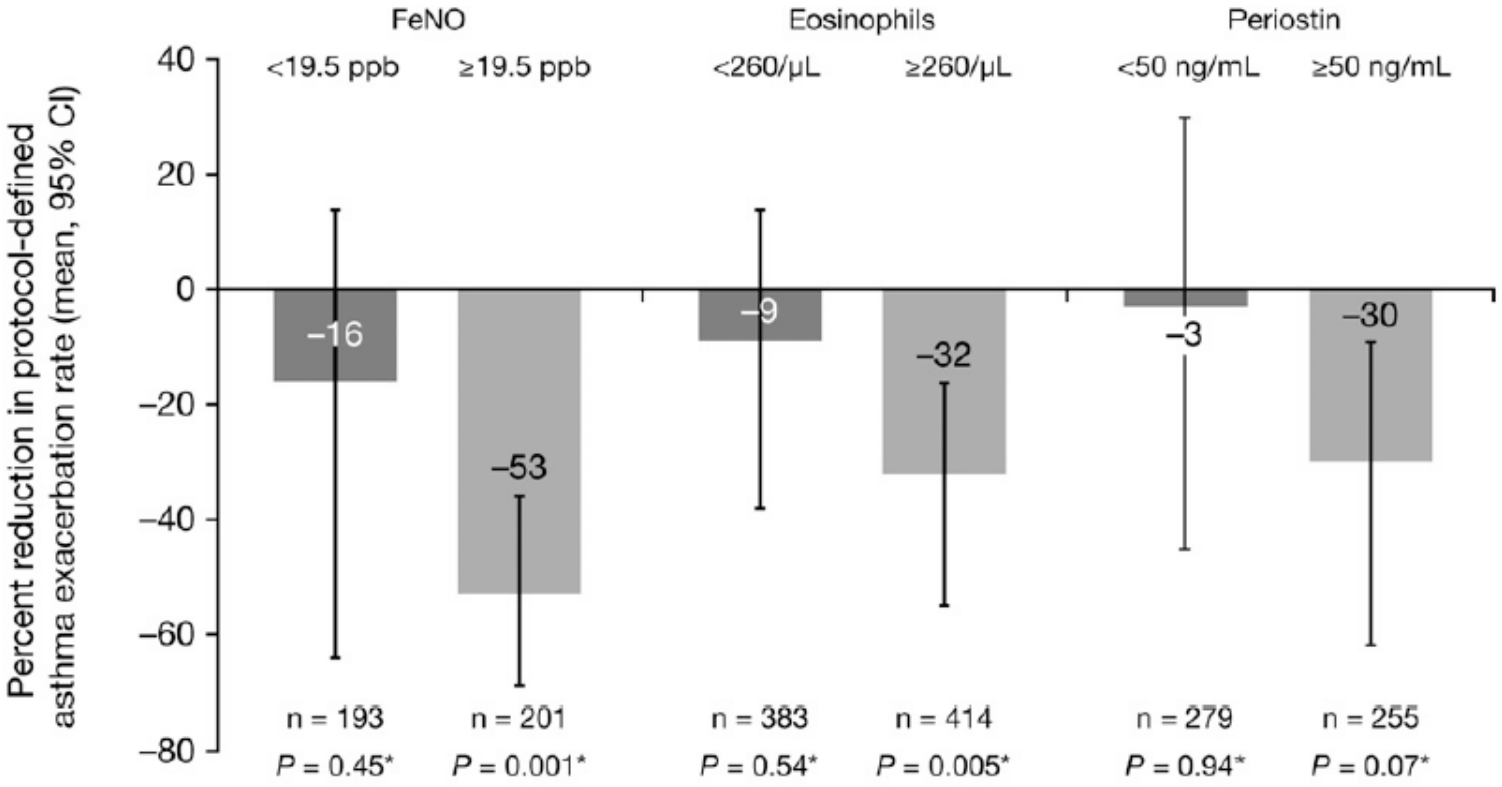
Brusselle et al. Ann Am Thorac Soc 2014:11(5);322-8

Omalizumab significantly reduces asthma exacerbation rate: pooled data



Adapted from Bousquet J, et al. Allergy 2005

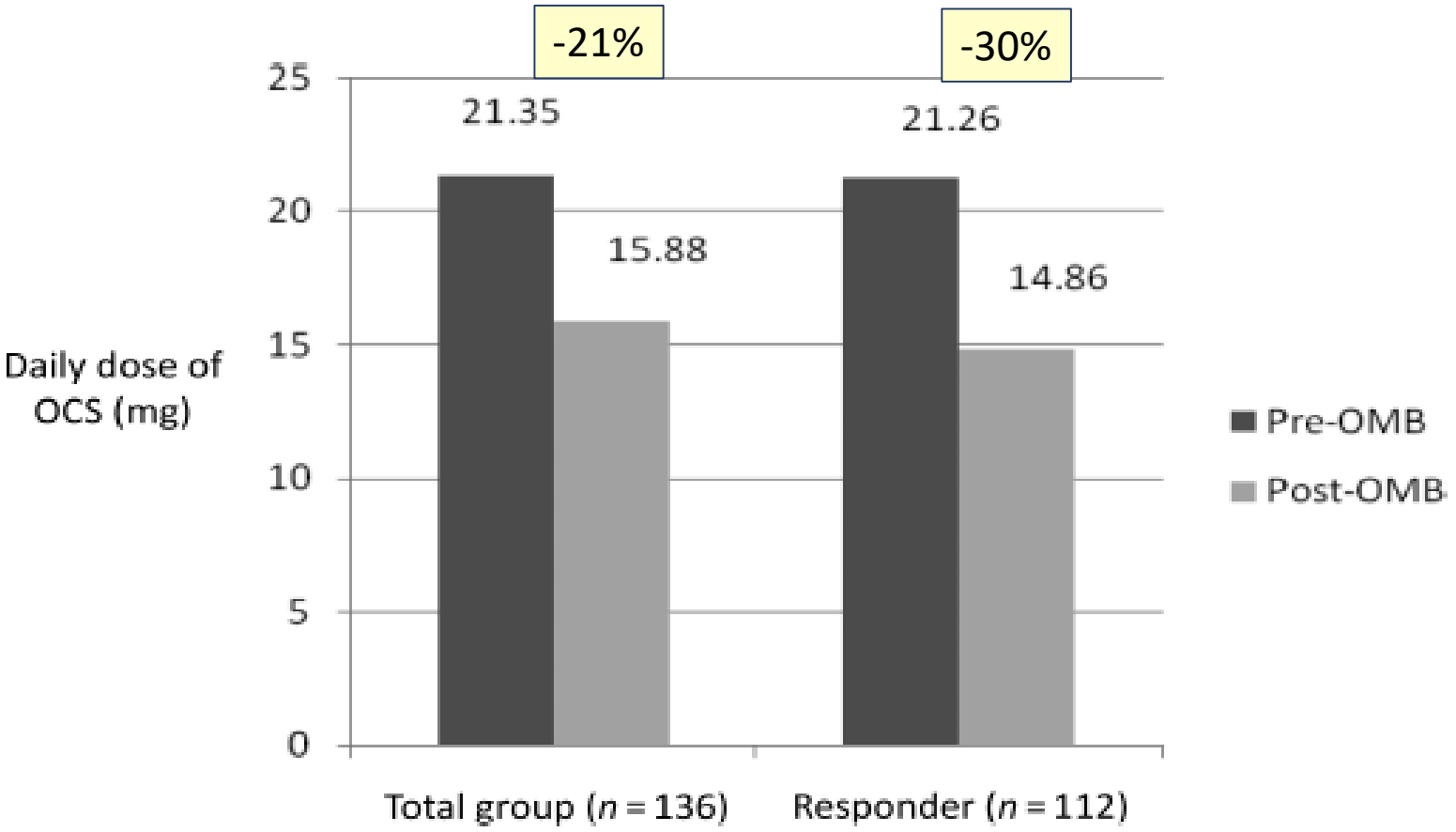
Omalizumab exacerbation reduction: Improved response with Th2 High Profiles



Exacerbation rates						
	Low FeNO at baseline	High FeNO at baseline	Low eosinophils at baseline	High eosinophils at baseline	Low periostin at baseline	High periostin at baseline
Omalizumab	0.60	0.50	0.65	0.70	0.73	0.66
Placebo	0.71	1.07	0.72	1.03	0.72	0.93

Hanania N et al AJRCCM 2013; 187: 804-11

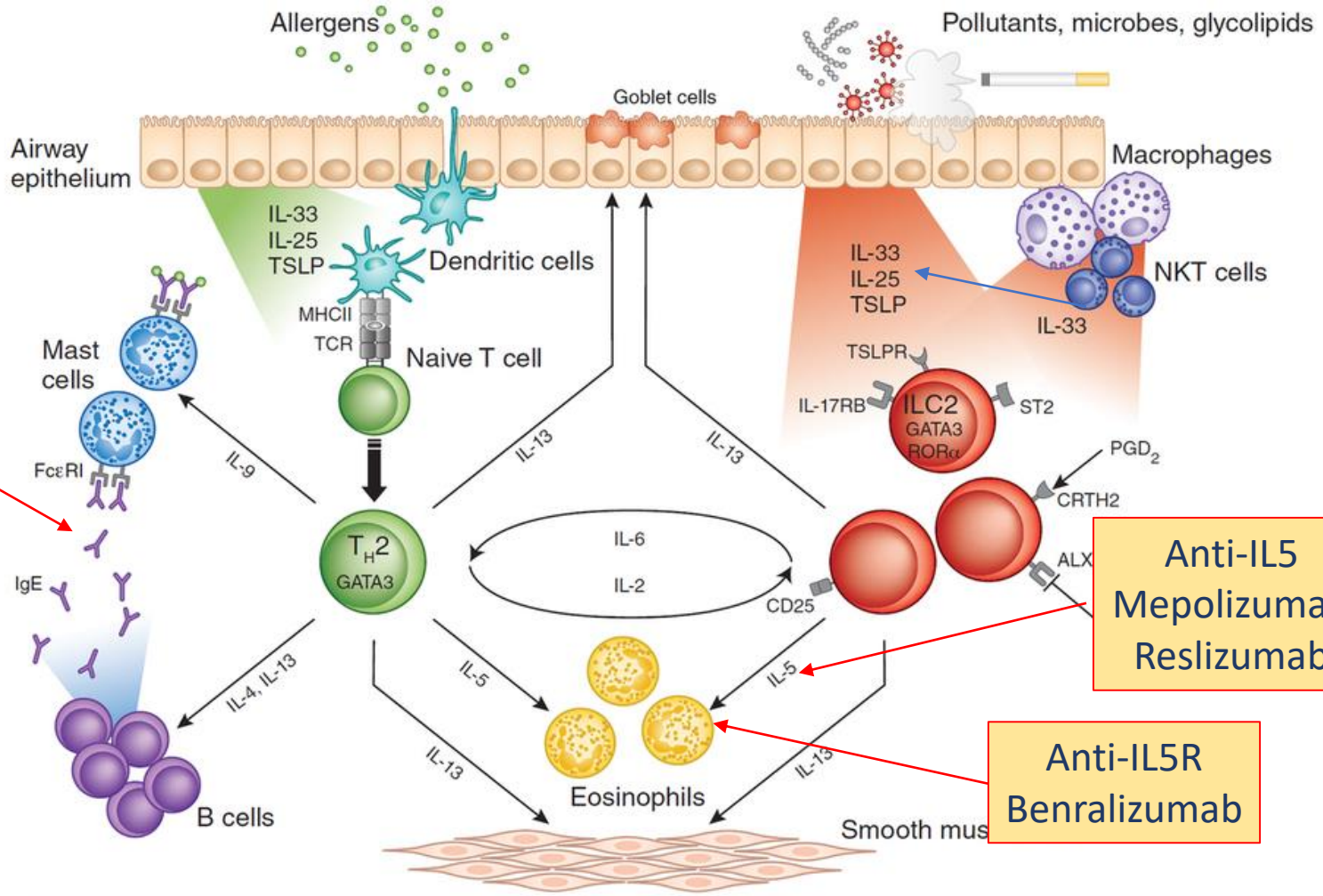
UK Apex study oral steroid sparing effect of Omalizumab



Daily dose of OCS (mg) in the 1 year pre- and post-OMB.

Barnes et al J Asthma 2013

Type 2 airway inflammation and biologic directed targets



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Omalizumab

Anti-IL5
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Reslizumab

Anti-IL5R
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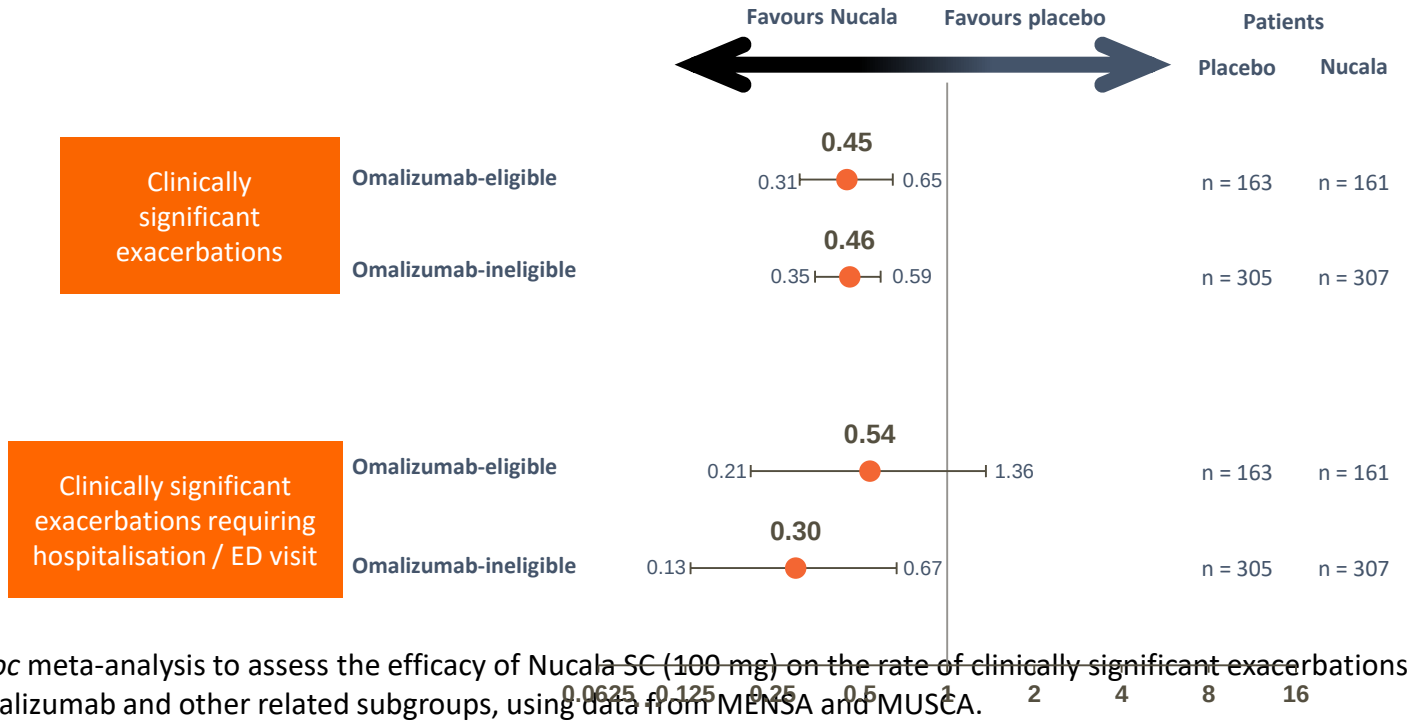
Brusselle et al. Ann Am Thorac Soc 2014:11(5);322-8

Mepolizumab reduces exacerbations in patients, irrespective of omalizumab eligibility

Compared with placebo, Nucala reduced the rate of clinically significant exacerbations in both the omalizumab-eligible (55% reduction) and the omalizumab-ineligible subgroups (54% reduction)



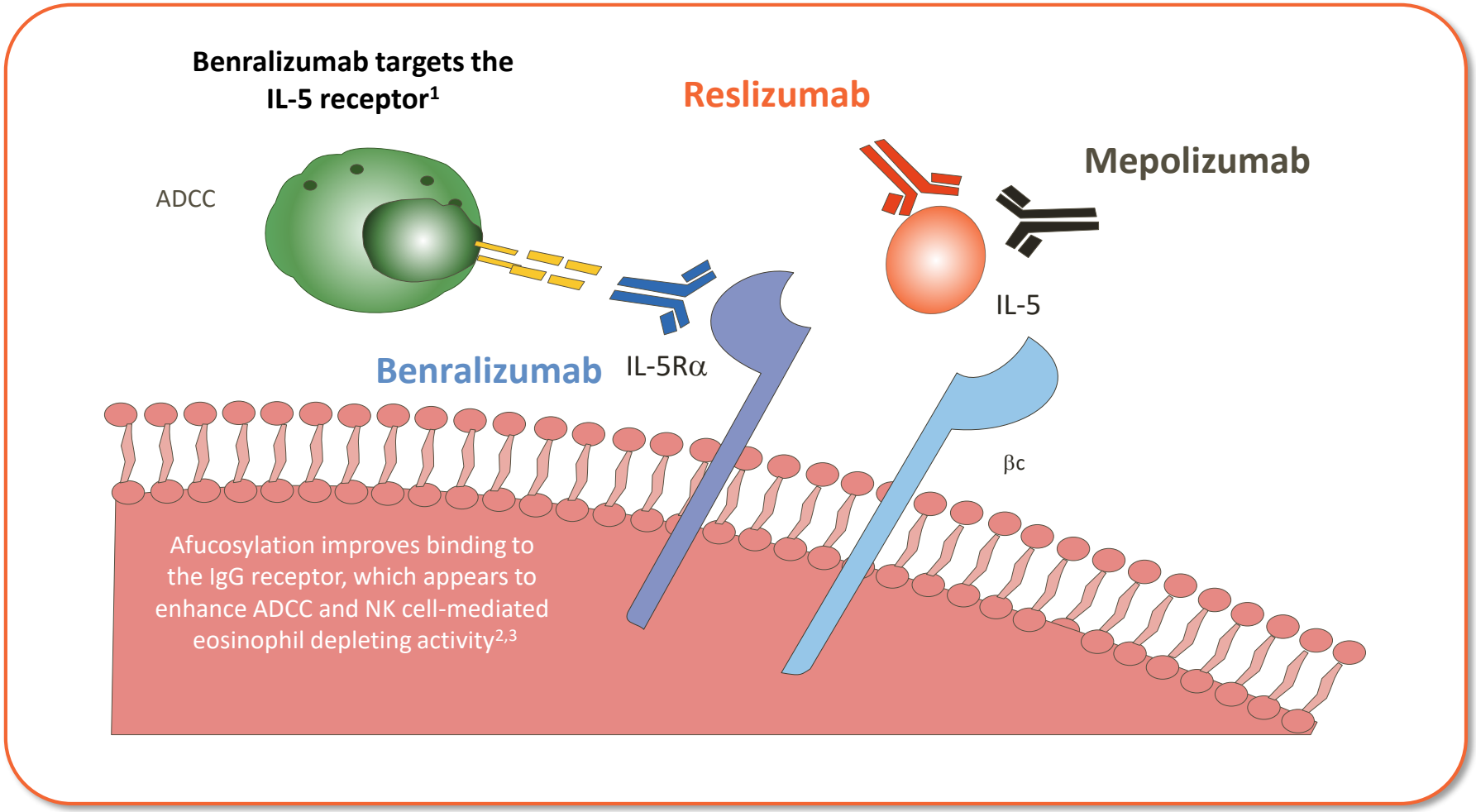
Post hoc meta-analysis to assess the efficacy of Nucala SC (100 mg) on the rate of clinically significant exacerbations in patients eligible for omalizumab and other related subgroups, using data from MENSA and MUSCA.
EU eligibility criteria defined as positive RAST score (≥1) for any of 5 aeroallergens: house dust mite, dog dander, cat dander, *Alternaria alternata*, German cockroach, and the following body weight and pre-treatment IgE combinations: ≥20–50 kg and ≥30–1,500 IU/mL; >50–60 kg and ≥30–1,200 IU/mL; >60–70 kg and ≥30–1,000 IU/mL; >70–80 kg and ≥30–900 IU/mL; >80–90 kg and ≥30–800 IU/mL; >90–125 kg and ≥30–600 IU/mL; >125–150 kg and ≥30–500 IU/mL.[1]

RAST, radioallergosorbent test.

1. GSK. Data on file. RFN/NLA/0159/18; 2. GSK. Data on file. RF/NLA/0246/18.

Monoclonal antibody therapies licenced for severe eosinophilic asthma

Reslizumab is an investigational medicinal product, and it is unlicensed in Taiwan



ADCC= Antibody dependent cell cytotoxicity, NKK = natural killer cells, IL-5 = interleukin 5

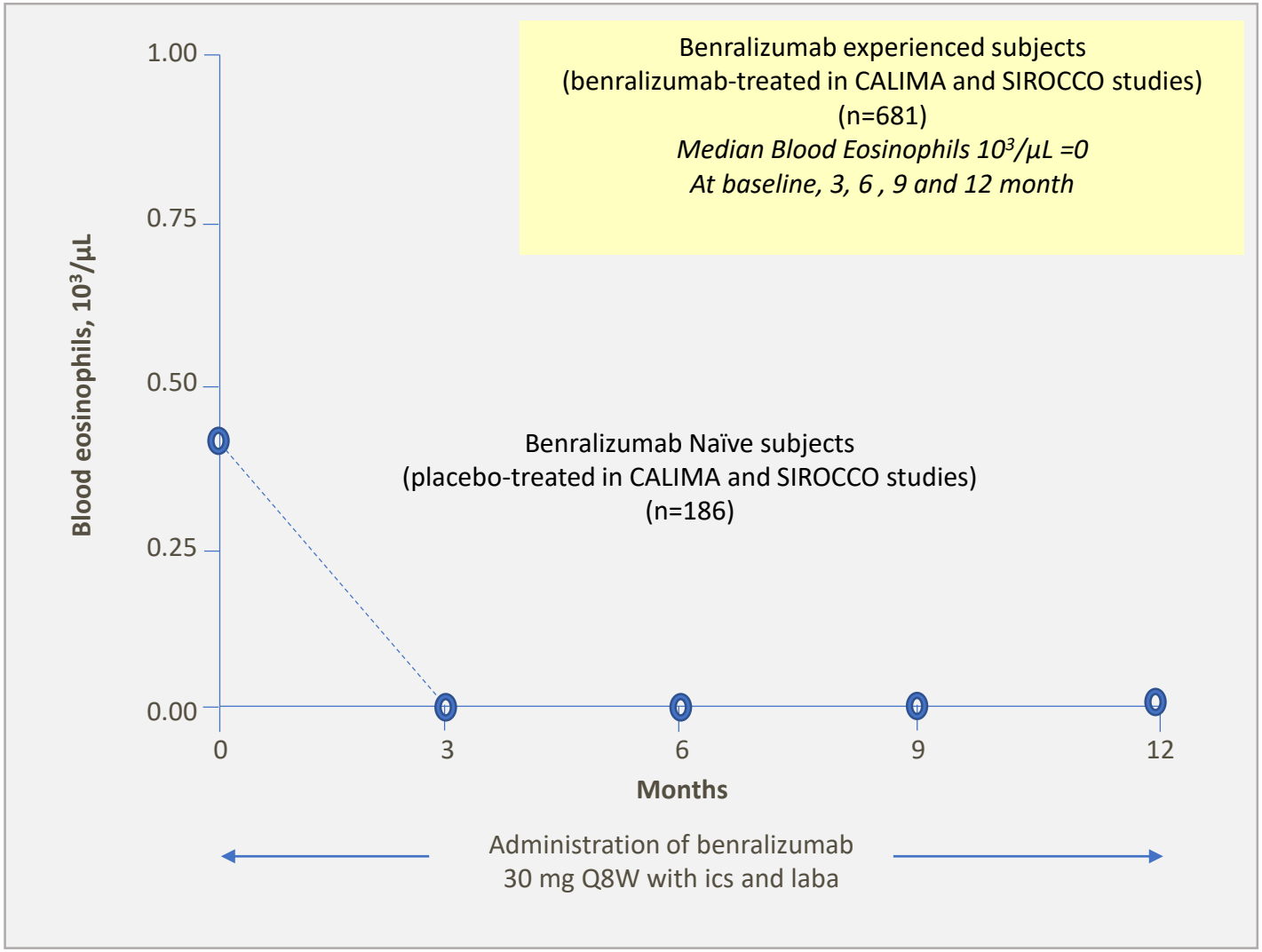
1. Varricchi G, et al. *Curr Opin Allergy Clin Immunol*. 2016;16:186–200; 2. Ghazi A, et al. *Expert Opin Biol Ther.* 2012;12:113–118; 3. Kolbeck R, et al. *J Allergy Clin Immunol* 2010;125:1344–1353.

Benralizumab in severe eosinophilic asthma

Blood eosinophils
BORA study

1 year extension from CALIMA and SCIROCCO studies

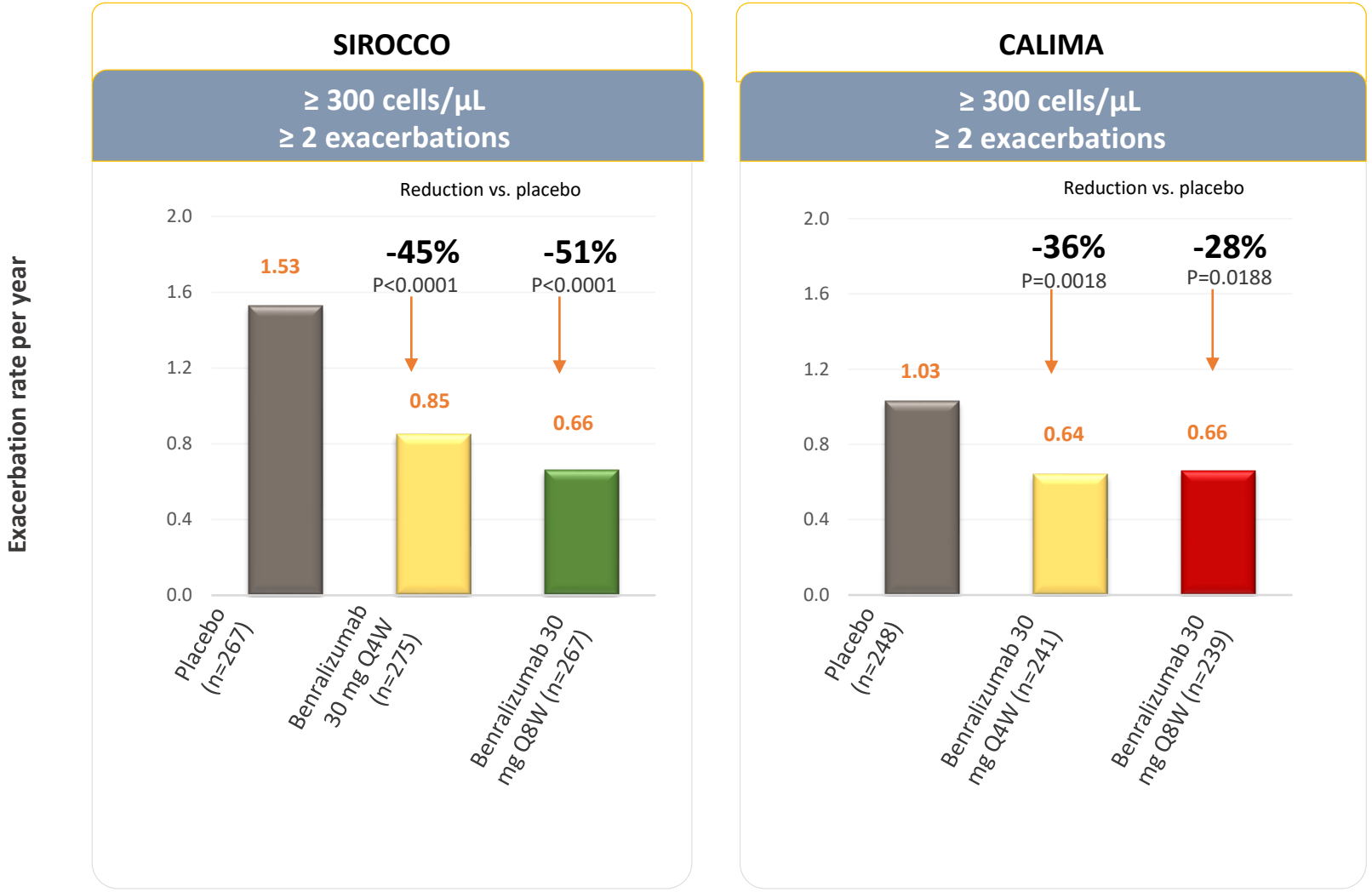
Trial recruitment Eosinophil Threshold: blood eosinophils ≥300 cells /µL



Busse et al Lancert Resp Med 2019; 7: 48-59.

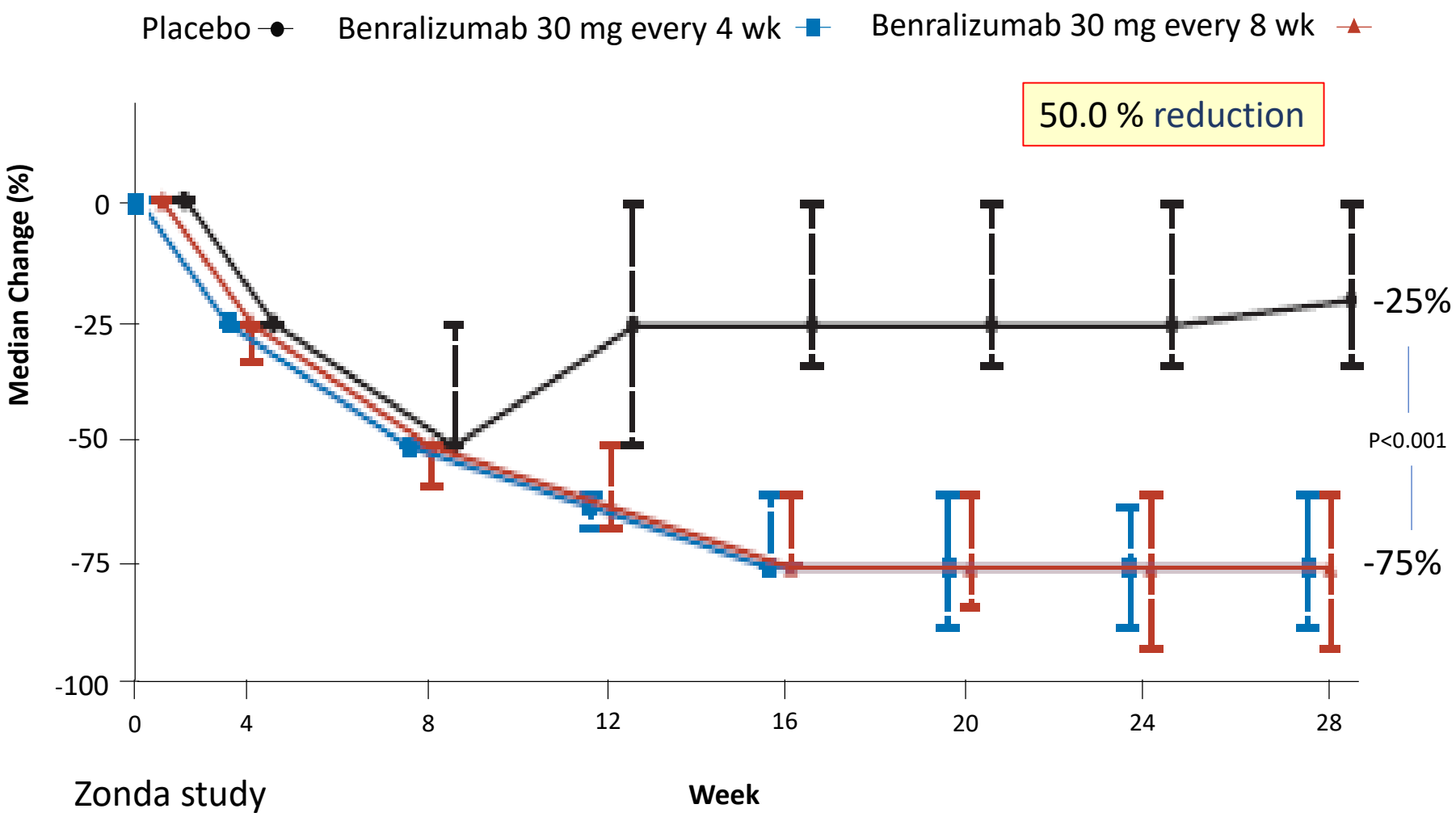
Benralizumab: impact on severe asthma exacerbations

Variable 28%-51%



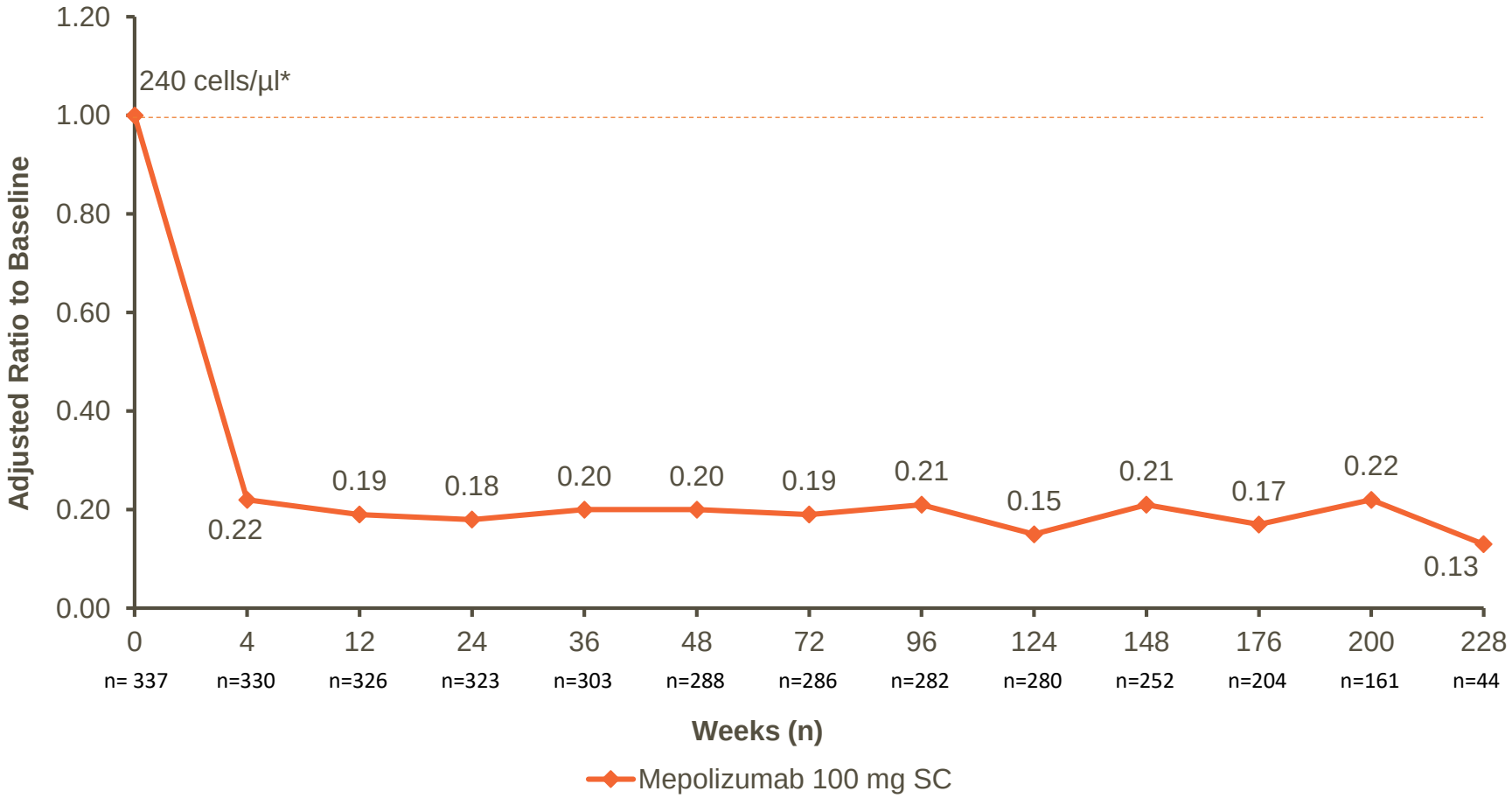
Supplement, FitzGerald JM, et al. *Lancet.* 2016;388(10056) 2128–2141; Supplement, Bleecker ER, et al. *Lancet.* 2016;388(10056):2115–2127

Influence of Benralizumab on oral steroid reduction in severe asthma



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

COLUMBA study: Sustained biological effect of mepolizumab in suppressing blood eosinophils



*Geometric Mean at baseline

Note: Where a result of Zero was recorded, a small value (i.e., minimum all non-missing results/2) was added prior to log transformation

SC: Subcutaneous

Khatri S, et al. *J Allergy Clin Immunol.* 2018;Oct 23. pii: S0091-6749(18)31479-9. [Epub ahead of print], GSK data on file.

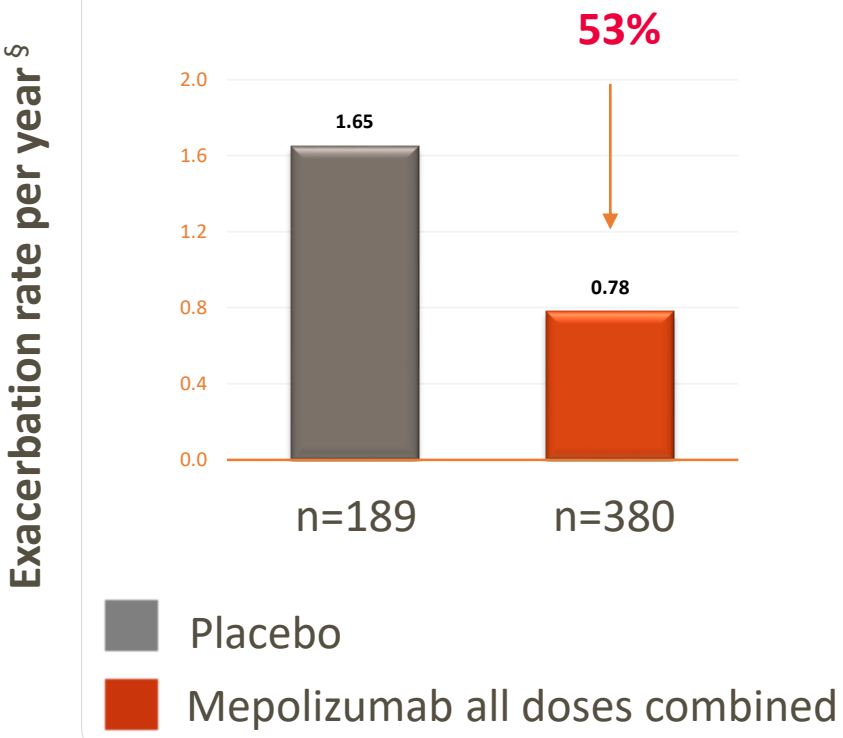
Mepolizumab: impact on asthma exacerbations

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

MENSA[1]

≥ 150 cells/µL
≥ 2 exacerbations

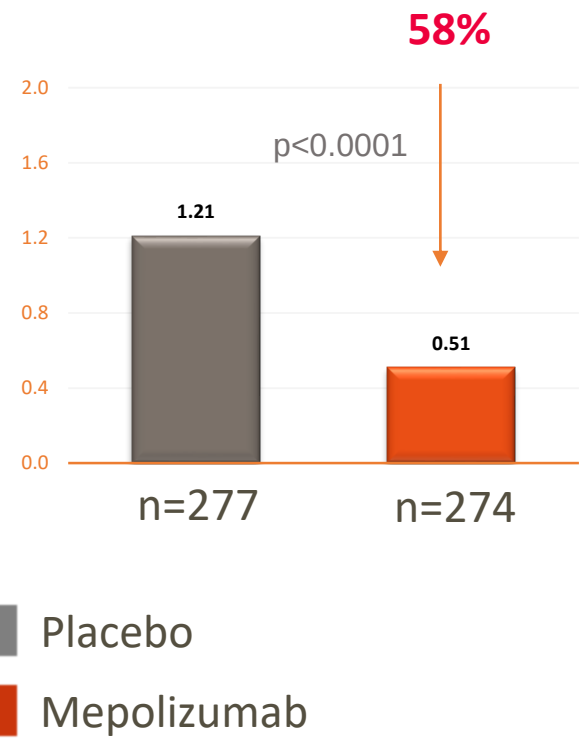
Reduction vs placebo at **32 weeks**



MUSCA[2]

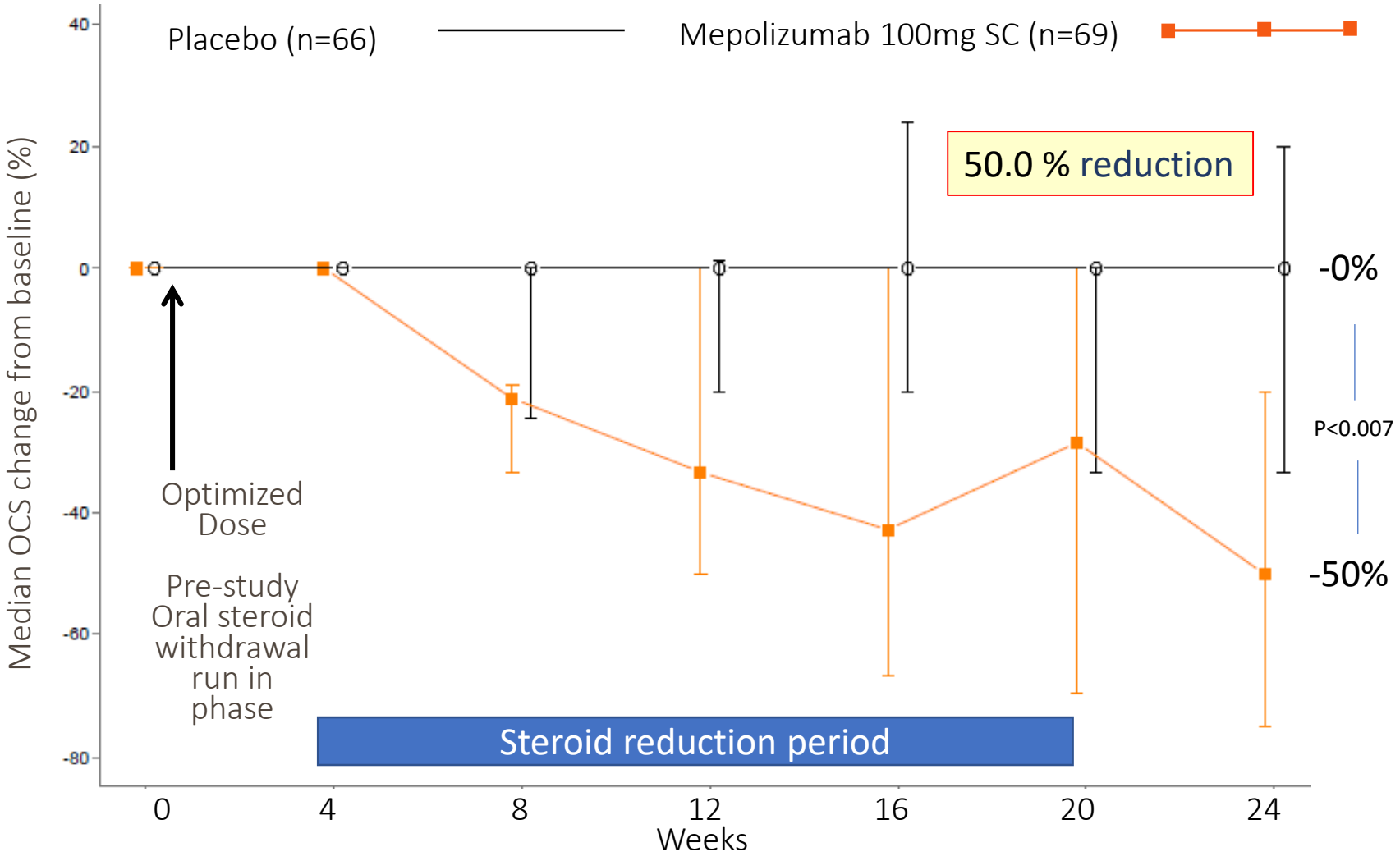
≥ 150 cells/µL
≥ 2 exacerbations

Reduction vs placebo at **24 weeks**



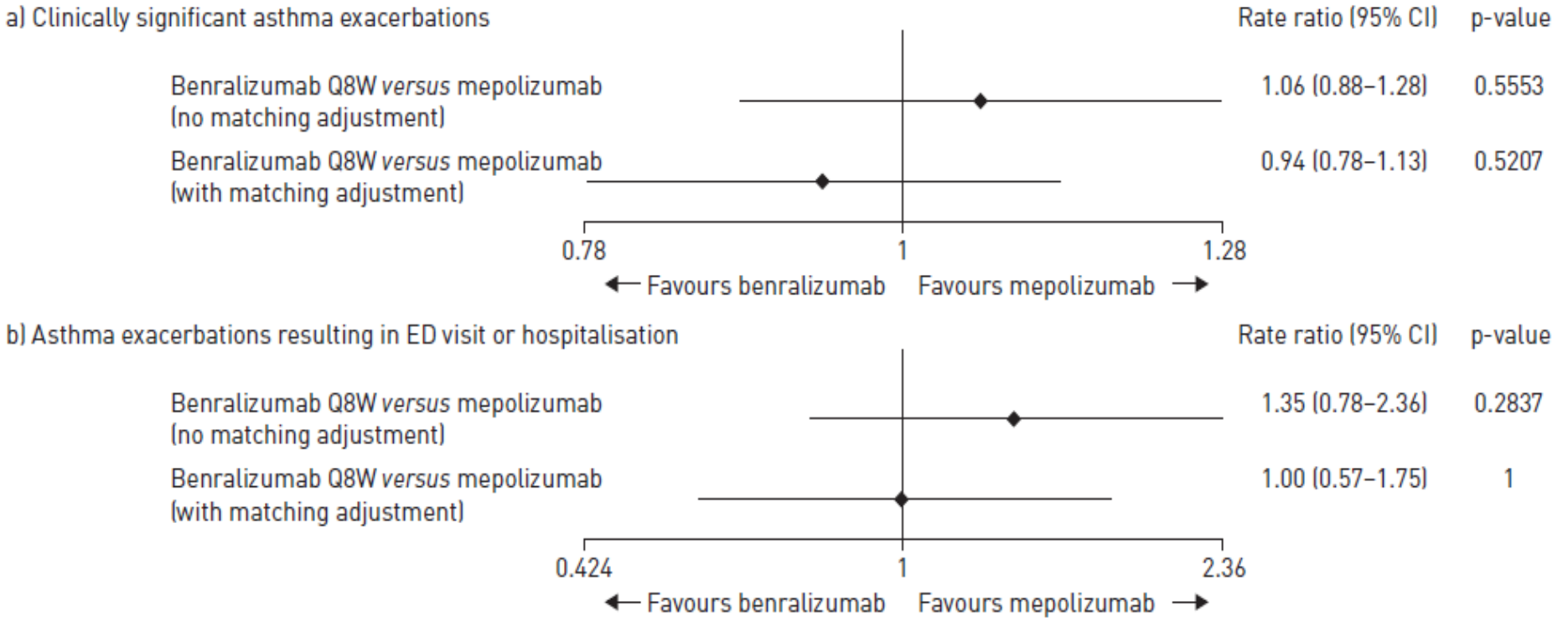
1. Ortega HG et al. Lancet Respir Med. 2016; 4(7): 549-556, 2. Chupp GL et al. Lancet Respir Med. 2017; 5(5): 390-400.

Influence of Mepolizumab on oral steroid reduction in severe asthma



Bel et al. N Engl J Med. 2014;371:1189-1197.

Indirect comparison of benralizumab versus mepolizumab for the treatment of severe asthma



Bourdin A, et al; Eur Respir J 2018; 52; 1801393

Anti-eosinophil monoclonals in severe asthma: heterogeneity between study populations

Characteristic	Mepolizumab 100 mg SC	Benralizumab 30 mg SC
Baseline blood eosinophils	≥150 cells/μL or ≥300 cells/μL in past year	≥300 cells/μL*
Exacerbation history	≥2 exacerbations in past year	≥2 exacerbations in past year
ICS dose	High	High
Maintenance OCS use	Allowed, any dose	Allowed, any dose
% predicted FEV_1	<80%	<80%
ACQ score	Not required	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.

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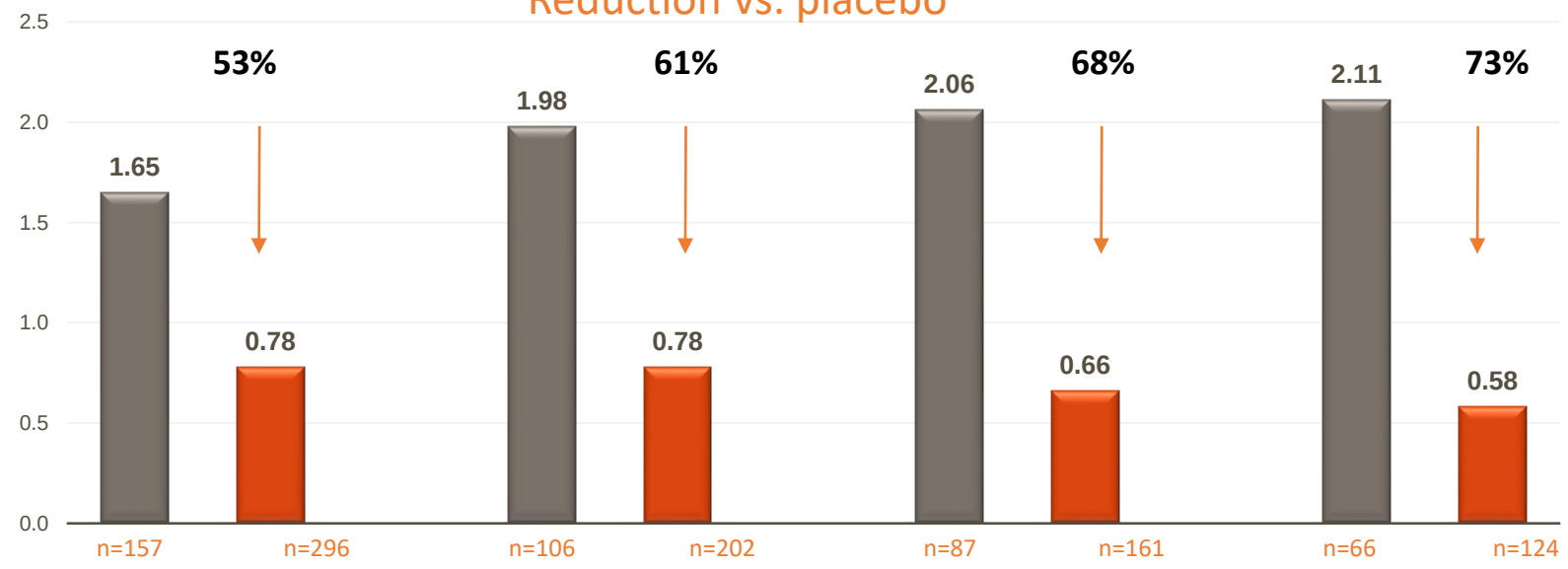
Busse W, et al . *J Allergy Clin Immunol.* 2019;143:190–200.e20.

Blood eosinophils a predictive biomarker of response to Mepolizumab

MENSA[1]

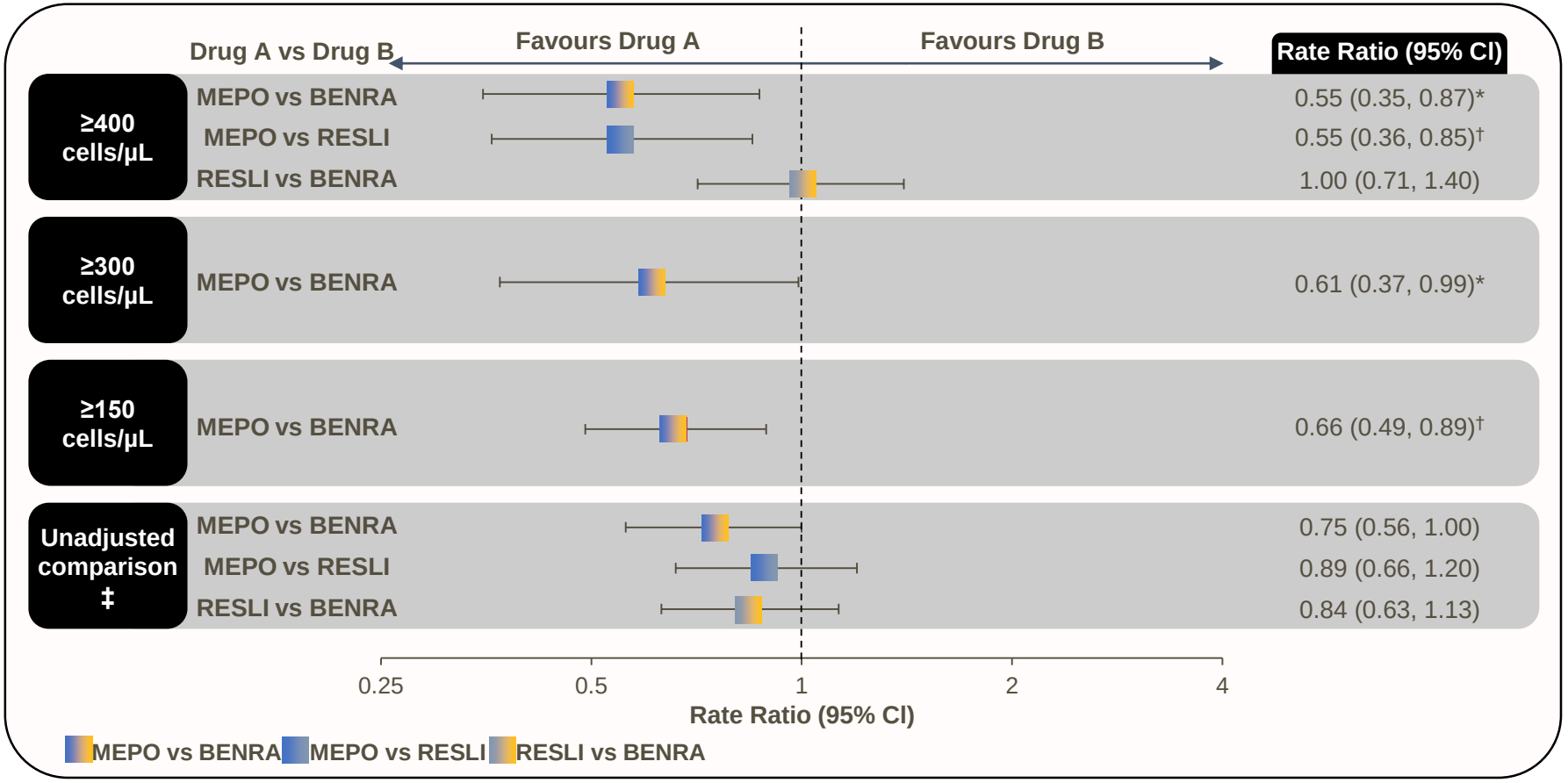
cells/µL

≥ 150	≥ 300	≥ 400	≥ 500



1. Adapted from Ortega HG, YanceySW, Mayer B, et al. Lancet Respir Med. 2016;4(7):549-556

Indirect comparisons of the rate of clinically significant exacerbations by baseline blood eosinophil subgroups



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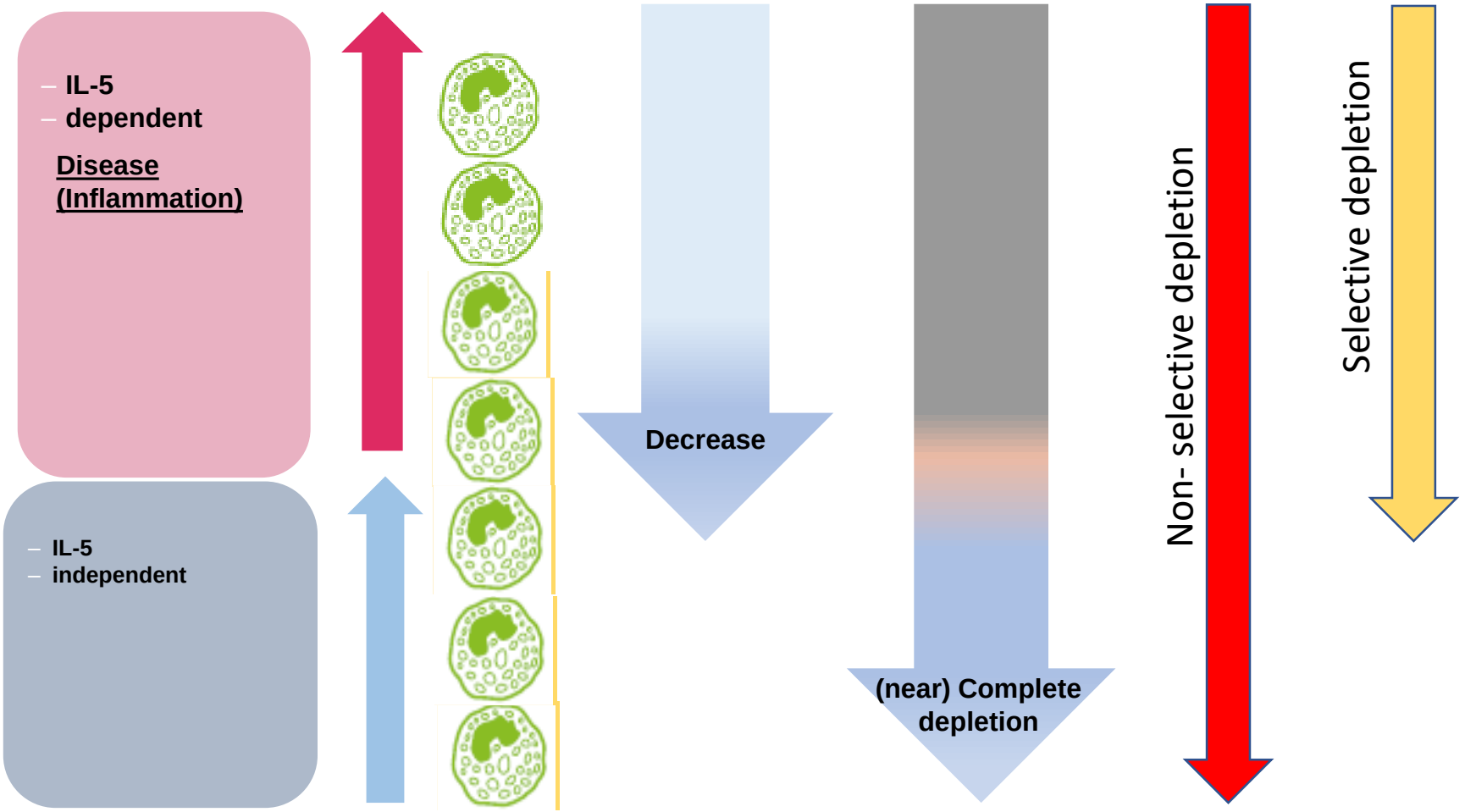
* $p < 0.05$, † $p < 0.01$, ‡ Raw data that have not been adjusted for ACQ, exacerbations and blood eosinophil threshold.
Note: No comparisons with reslizumab were possible below 400 cells/µL due to the inclusion criteria of those trials.

BENRA: benralizumab; MEPO: mepolizumab; RESLI: reslizumab.

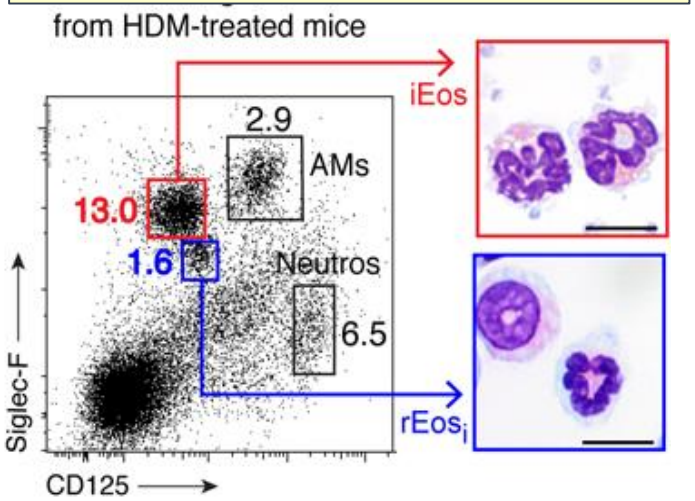
Busse W, et al. *J Allergy Clin Immunol.* 2019;143:190–200.e20.

What is desirable in an anti-eosinophil strategy?

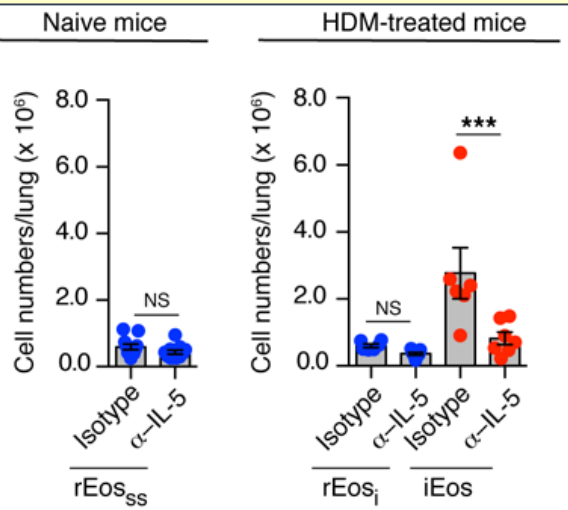


Murine Eosinophil heterogeneity: IL-5 dependent and IL5 independent

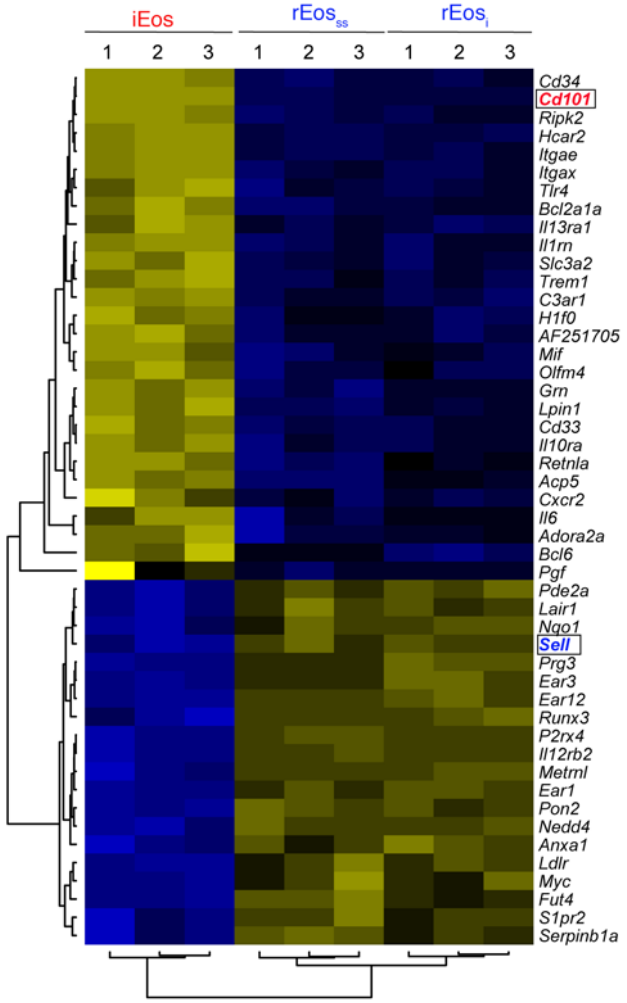
Two populations of eosinophils



Lung rEos not-modulated by anti IL-5



Different immune functions

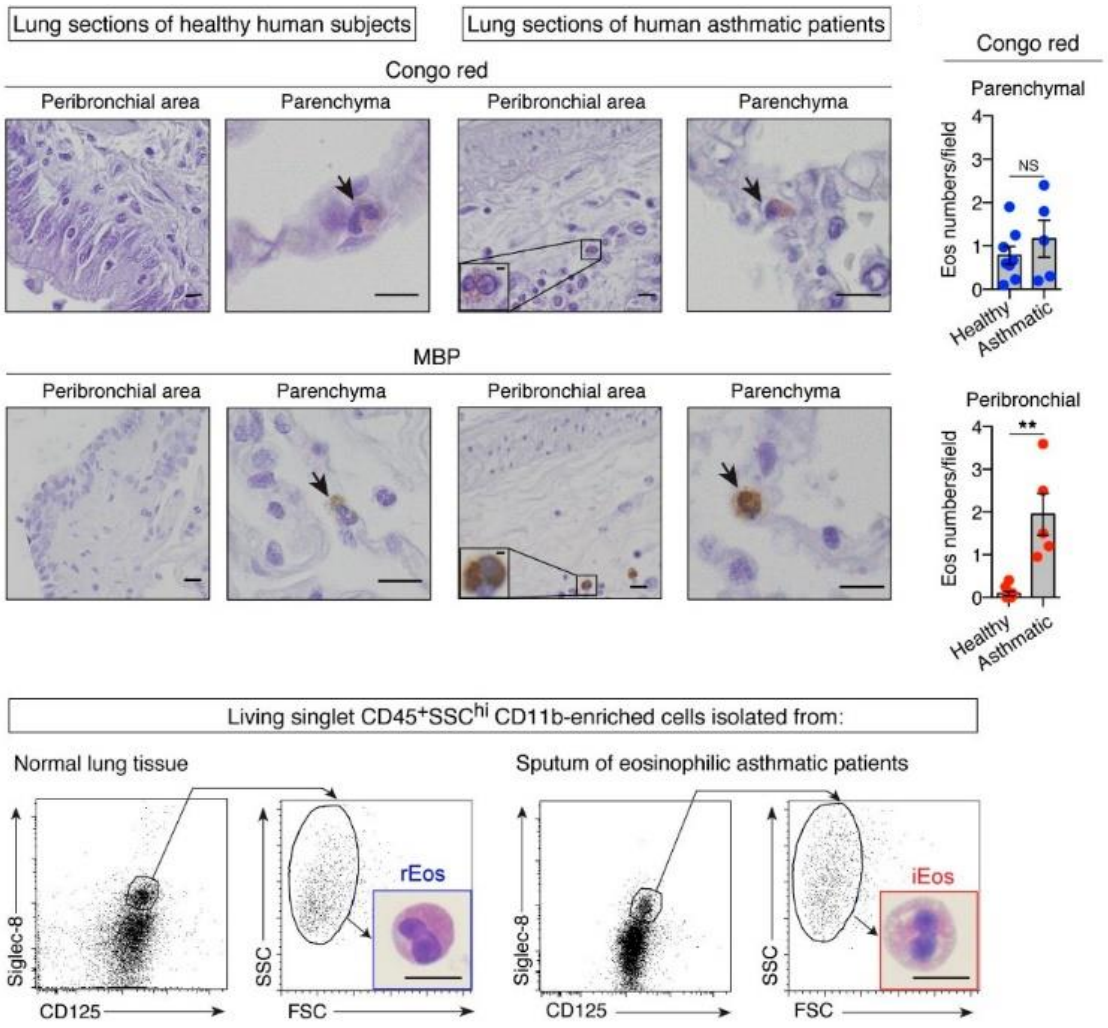


Inflammatory

Immune regulation & Homeostatic (↓ Th2)

Mesnil et al JCI 2016; 126: 3279-3295

Two eosinophil populations confirmed in human studies and both express CD125



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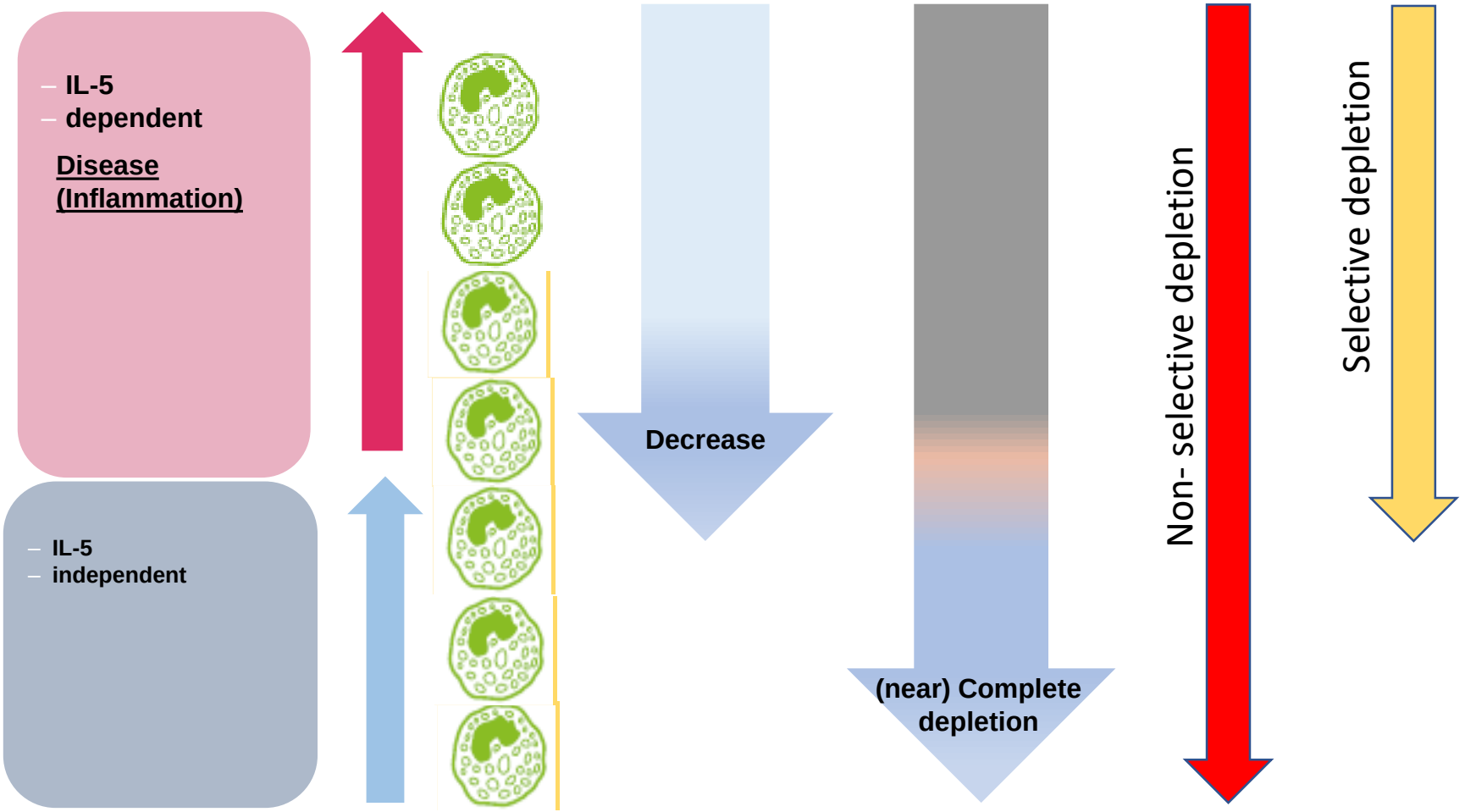
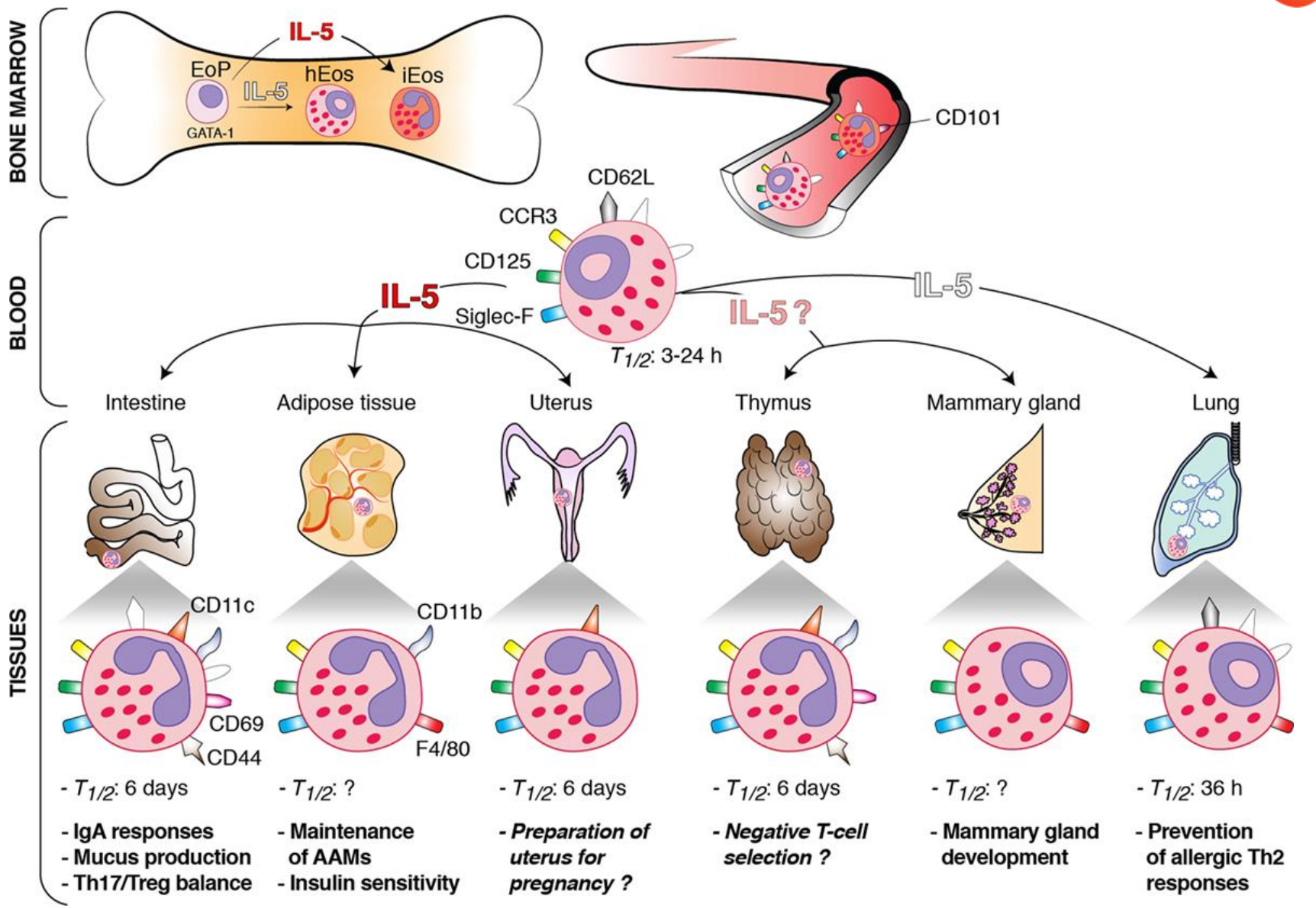
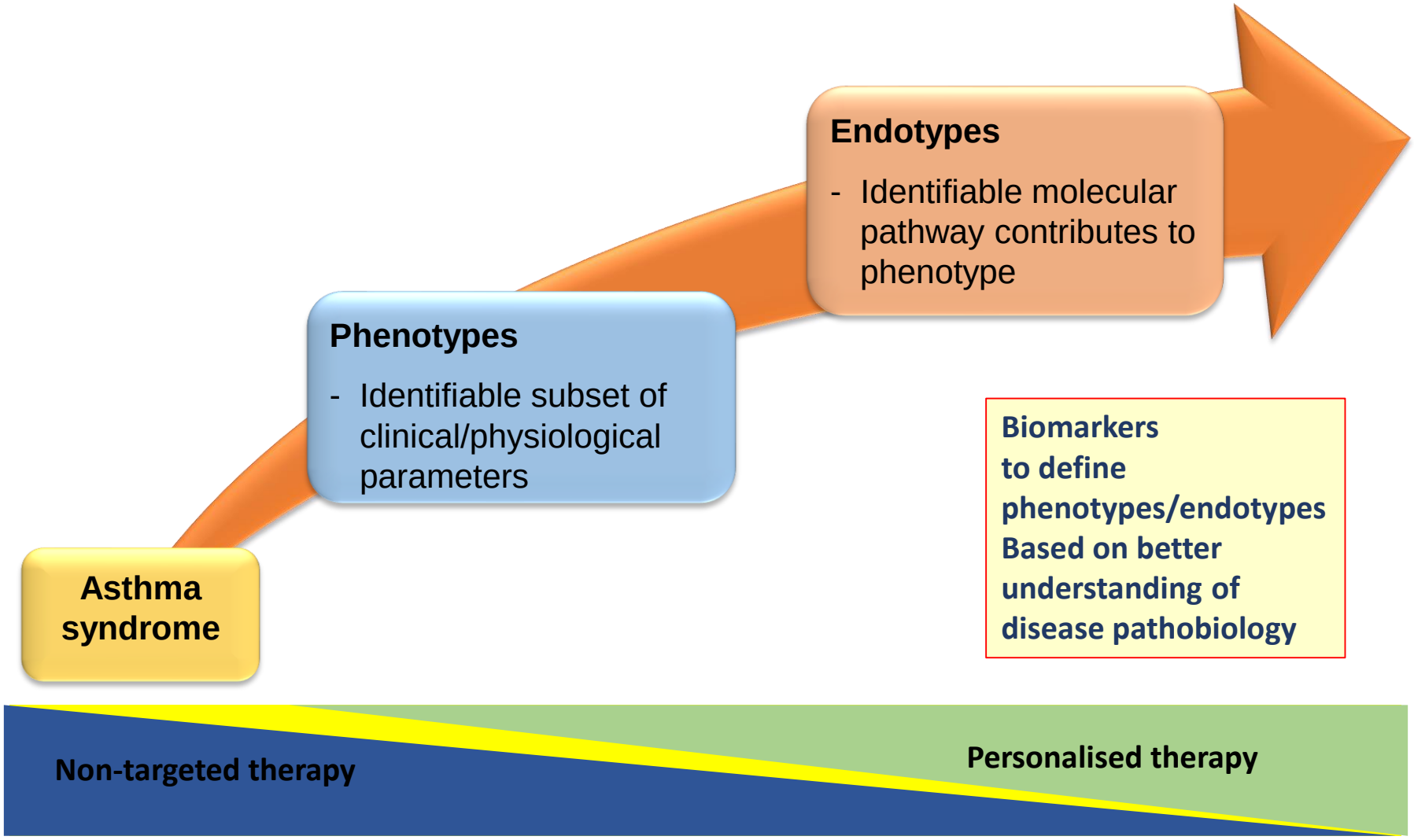


Potential role of resident eosinophils in health



Marichal et al Front Med 2017;4: 101

Personalised therapy the reflection of disease heterogeneity in severe uncontrolled asthma



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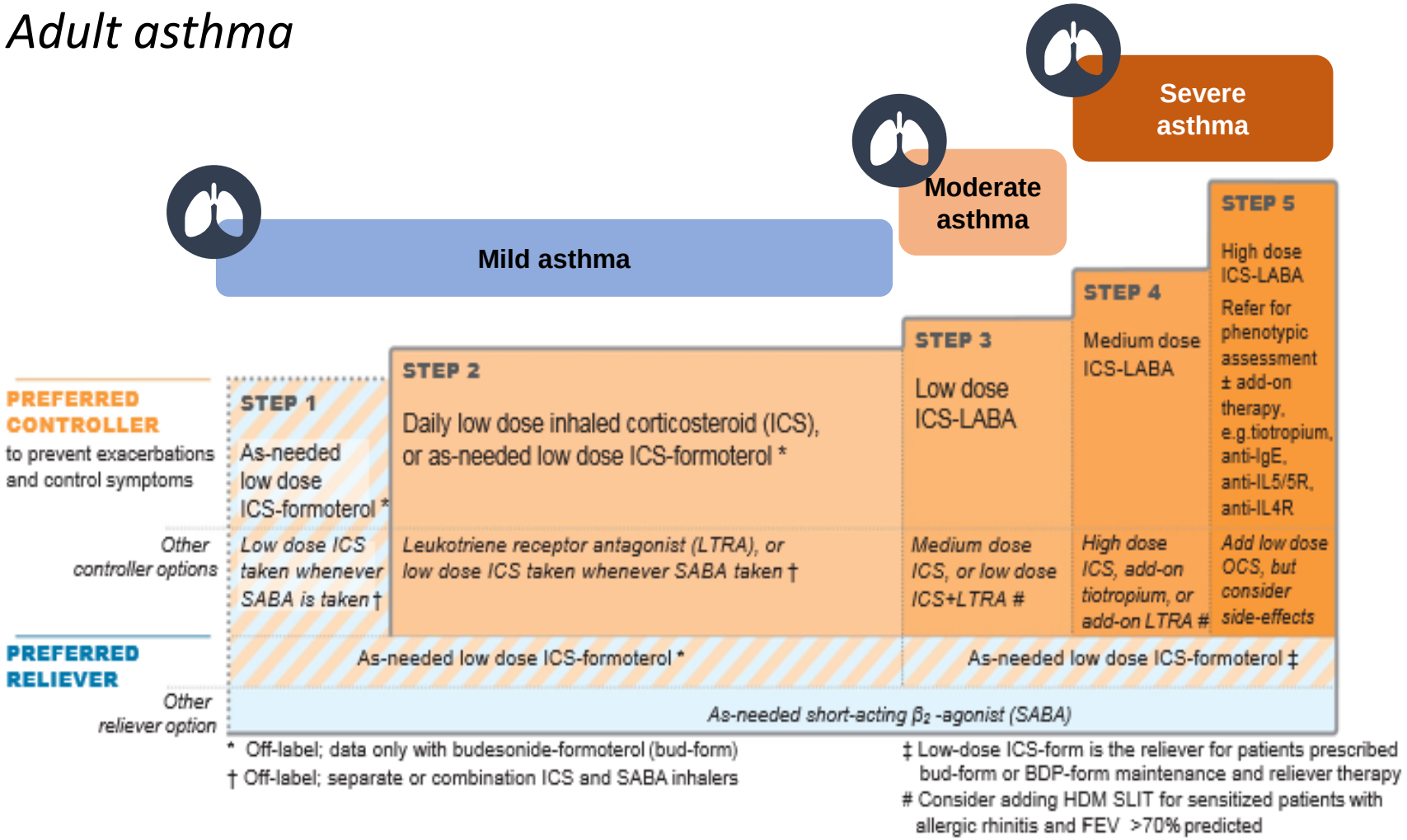


* Off-label; data only with budesonide-formoterol (bud-form)

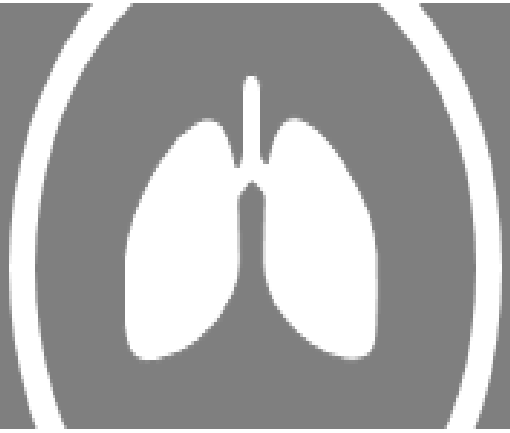
† Off-label; separate or combination ICS and SABA inhalers

‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy

Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV >70% predicted

ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LTRA, leukotriene receptor antagonists; OCS, oral corticosteroid; SABA, short-acting β2-agonist

Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2019. Available from: www.ginasthma.org (Accessed April 2019).



Thank you

Summary of adverse events for Nucala

	Mepolizumab (N = 368)
Any on-treatment AEs, n (%)*	53 (14)
Any AE related to mepolizumab, n (%)	53 (14)
Nervous system disorders	26 (7)
General disorders and administration site conditions	12 (3)
Musculoskeletal and connective tissue disorders	9 (2)
Skin and subcutaneous tissue disorders	9 (2)
Gastrointestinal disorders	6 (2)
Ear and labyrinth disorders	3 (<1)
Investigations	3 (<1)
Respiratory, thoracic and mediastinal disorders	2 (<1)
Cardiac disorders	1 (<1)
Immune system disorders	1 (<1)
Metabolism and nutrition disorders	1 (<1)
Not coded	4 (1)

	Mepolizumab (N = 368)
Any SAE related to mepolizumab, n (%)	2 (<1)
Hypersensitivity	1 (<1)
Pharyngeal swelling	1 (<1)
Fatal SAEs, n (%)	0
AEs related to mepolizumab leading to permanent discontinuation of mepolizumab, n (%)	9 (2)
Nervous system disorders	4 (1)
Gastrointestinal disorders	2 (<1)
Cardiac disorders	1 (<1)
Ear and labyrinth disorders	1 (<1)
General disorders and administration site conditions	1 (<1)
Immune system disorders	1 (<1)
Musculoskeletal and connective tissue disorders	1 (<1)
Respiratory, thoracic and mediastinal disorders	1 (<1)
Skin and subcutaneous tissue disorders	1 (<1)
Not coded	2 (<1)

Only data on mepolizumab- and GSK product-related AEs are collected during the study.
GlaxoSmithKline. Data on file. REF-27964.

Safety Overview of Relvar Ellipta

- The Phase III safety population for Relvar comprised **6,237** patients
- Safety and tolerability data from the pooled phase III safety data.

Very common AEs (≥1/10)	• Headache and nasopharyngitis
Other common AEs (≥1/100 to <1/10)	• Bronchitis, influenza, candidiasis of mouth and throat, cough, dysphonia, oropharyngeal pain, sinusitis, fractures, pyrexia, back pain, arthralgia, rhinitis, upper respiratory tract infection, pneumonia, abdominal pain and pharyngitis

- No dose adjustment is required for:
  - Patients with **renal impairment (腎功能不全)**
  - Patients with **hepatic impairment (肝功能不全)**
  - Patients aged **over 65 years（65歲以上）**

Mepolizumab(Nucala)簡易仿單

英文產品名稱：NUCALA Powder for Solution for Injection (Mepolizumab)
衛部菌疫輸字第001015號

中文產品名稱：舒肺樂凍晶注射劑

成分含量：注射劑，100毫克冷凍乾燥粉末，單劑小瓶裝，須泡製使用。

適應症與用途：表現型為嗜伊紅性白血球的嚴重氣喘且控制不良（severe refractory eosinophilic asthma）之成人患者之附加維持治療。

用法用量：NUCALA的建議劑量為每4週一次於上臂、大腿或腹部皮下注射100毫克。

禁忌症：NUCALA不可用於曾對mepolizumab或配方中之賦形劑產生過敏反應的患者。

警語和注意事項
過敏反應：
曾有在投予NUCALA之後發生過敏反應（如血管性水腫、支氣管痙攣、低血壓、蕁麻疹、皮疹）的報告。這些反應通常都是在投藥後數小時內發生，但有些病例會延遲發生（即數日後才發生）。如果發生過敏反應，應停用NUCALA。

急性氣喘症狀或惡化性疾病：

NUCALA不可用於治療急性氣喘症狀或急性惡化。切勿使用NUCALA治療急性支氣管痙攣或氣喘重積狀態。在開始使用NUCALA治療之後，如果患者的氣喘症狀仍未獲得控制或出現惡化的現象，應尋求醫療建議。

伺機性感染：帶狀皰疹

在對照性臨床試驗中，使用NUCALA治療的受試者有2個發生帶狀皰疹的嚴重不良反應病例，安慰劑組則無任何此類病例。在開始使用NUCALA治療之前，如果醫療條件適合，應考慮接種水痘疫苗。

降低皮質類固醇的劑量：

開始使用NUCALA治療時，切勿驟然停用全身性或吸入性皮質類固醇。如果適合降低皮質類固醇的劑量，應以逐步漸進的方式降低劑量，並應在醫師的直接監督之下進行。降低皮質類固醇的劑量可能會引發全身性戒斷症狀，並或使先前被全身性皮質類固醇壓制的症狀顯露出來。

寄生蟲（蠕蟲）感染：

嗜伊紅性白血球可能會涉及某些蠕蟲感染所引發的免疫反應。已知患有寄生蟲感染症的患者都被排除於臨床試驗之外。目前並不確知NUCALA是否會影響患者對寄生蟲感染的反應。對原先即患有蠕蟲感染症的患者，在開始使用NUCALA治療前應先治療其感染症。如果患者在接受NUCALA治療期間發生感染，並且對抗蠕蟲治療無法產生反應，應停止使用NUCALA治療，直到感染消退。

常見不良反應：頭痛、注射部位反應、背痛、疲倦等。

Relvar 簡易處方資訊

•英文產品名稱: Relvar® Ellipta® 92/22 mcg Inhalation Powder
•衛部藥輸字第026318號
•中文產品名稱:潤娃易®利達® 92/22 mcg乾粉吸入劑
•適應症與用途:慢性阻塞性肺病(COPD)患者之氣道阻塞症狀的維持治療，也適用於降低有惡化病史患者之COPD惡化。
•成份含量: fluticasone furoate/vilanterol 92 mcg/22 mcg
•用法用量: 每天於相同的時間吸入一次。每24小時不可使用Relvar® Ellipta®超過一次。
•劑型:乾粉吸入劑
•禁忌症:禁用於有嚴重乳蛋白過敏問題的患者，或已證實對fluticasone furoate、vilanterol或本品之任何賦形劑過敏的患者。
•警語和注意事項:發生氣喘相關死亡之風險升高的現象一般認為是一種LABA(包括vilanterol，即Relvar® Ellipta®的活性成分之一)的類別作用。其他內容請詳閱仿單。
•常見副作用: 頭痛、鼻咽炎, 上呼吸道感染
•不良事件通報程序：通報電話: (02) 23126836/ 郵箱: oax40892@gsk.com
•詳細處方資訊備索

葛蘭素史克藥廠 地址:100台北市忠孝西路一段66號24樓