Pro:

“The severe asthma patient with eosinophilic phenotype should always be treated with Anti-Interleukin-5 therapies”

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Disclosures

- Principal Investigator (Grant Funding): AstraZeneca, Chiesi, GSK, Novartis, Sanofi Aventis
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- Speaker: Astra-Zeneca, Genentech, GSK, Regeneron, Sanofi, Teva
- Royalties: Elsevier

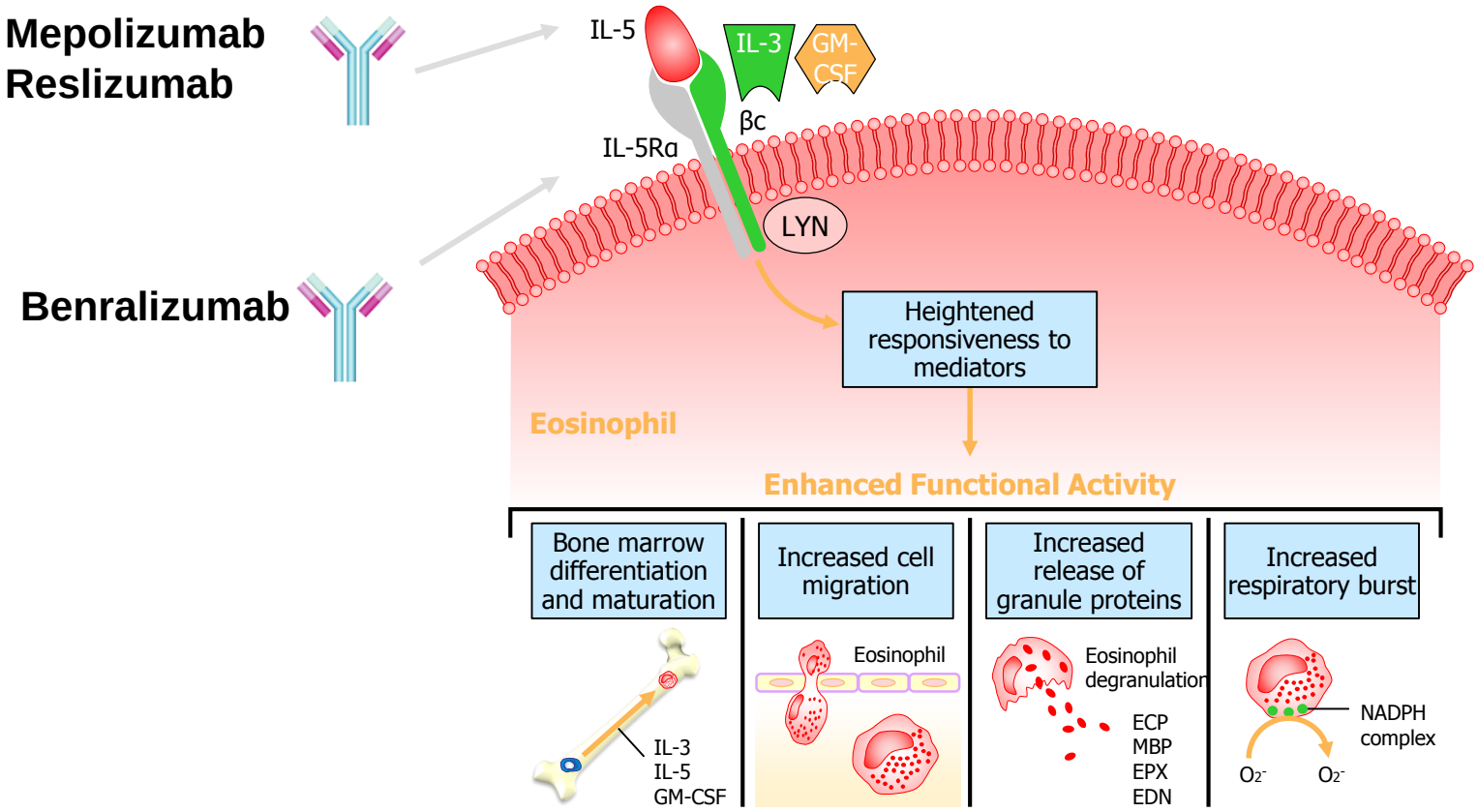
Objectives

- To comprehend the role of IL-5 in eosinophilic asthma
- Assess the efficacy and safety of anti-IL 5 monoclonal antibodies in the treatment of uncontrolled severe asthma

Pro Arguments: The severe asthma patient with eosinophilic phenotype should always be treated with Anti-Interleukin-5 therapies

- Severe uncontrolled eosinophilic asthma is the best identified phenotype associated with increased morbidity
- Anti-IL5 mAb (mepo, res, benra) are highly efficacious with an acceptable safety profile – the prototype of Precision Medicine!
- Anti-IL4R mAb (dupi) is highly efficacious as well and should be reserved for the T2 phenotype
- To advance the treatment of respiratory disease, we need to move away from the “lumping” approach as new targeted therapy becomes available

Targeting the Eosinophilic Phenotype - Anti-IL-5 or IL-5Rα



Varricchi G. et al.: Curr Opin Allergy Clin Immunol. 16: 186-200, 2016

The Eosinophil Phenotype is clearly linked to worse asthma control and increased risk of severe exacerbations

All patients with a recorded blood eosinophil count (n=130,248)

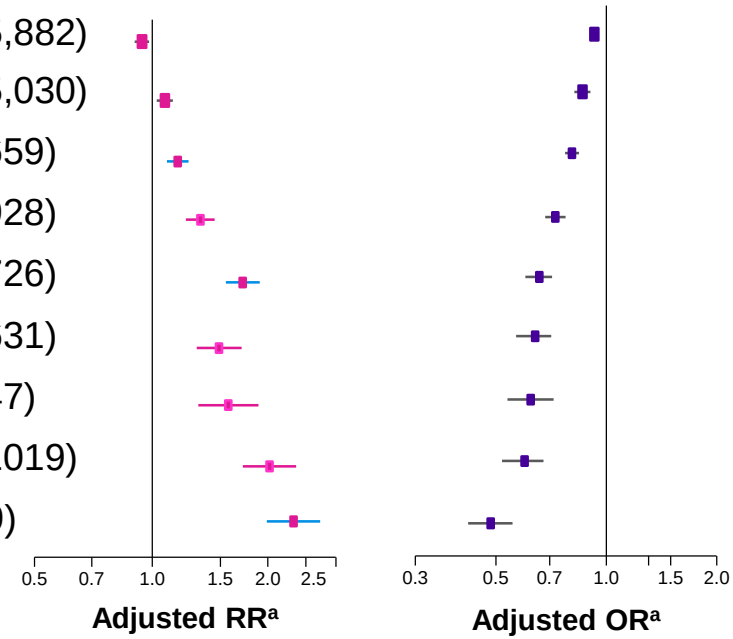
Severe Exacerbations

Increased

Overall Asthma Control

Decreased

201–300 cells per µL (n=25,882)
301–400 cells per µL (n=15,030)
401–500 cells per µL (n=8659)
501–600 cells per µL (n=4928)
601–700 cells per µL (n=2726)
701–800 cells per µL (n=1631)
801–900 cells per µL (n=947)
901–1000 cells per µL (n=1019)
>1000 cells per µL (n=1019)



Linear relationship between increasing blood eosinophil count and subsequent exacerbations over one year

[a]Data from medical records of asthmatics,12–80 years of age, with 2 years of continuous records, including 1 year before (baseline) and 1 year after (outcome) their most recent eosinophil count. Patients assigned to 9 eosinophil count categories compared with a reference category of 200 cells per µL or less (N=68,407). Adjusted for age, sex, body-mass index, smoking status and Charlson comorbidity index score.
[b]Sub-population of patients with available blood eosinophil counts to two decimal places.

OR=odds ratio; RR=rate ratio.

Adapted from Price DB, et al. *Lancet Respir Med.* 2015;3:849–858.

PRO ANTI-IL5 FOR EOSINOPHILIC ASTHMA

Anti-IL5 mAb (mepo, res, benra) are highly efficacious with an acceptable safety profile **– the prototype of Precision Medicine!**

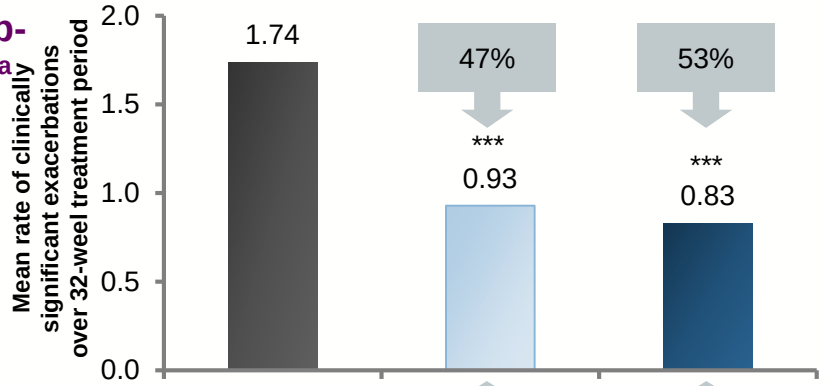
Mepolizumab (SC) Reduced Asthma Exacerbations, OCS Use, and Improved Lung Function in Patients with Severe Asthma with an Eosinophilic Phenotype

Placebo q4w | Mepolizumab 75 mg IV q4w | Mepolizumab 100 mg SC q4w

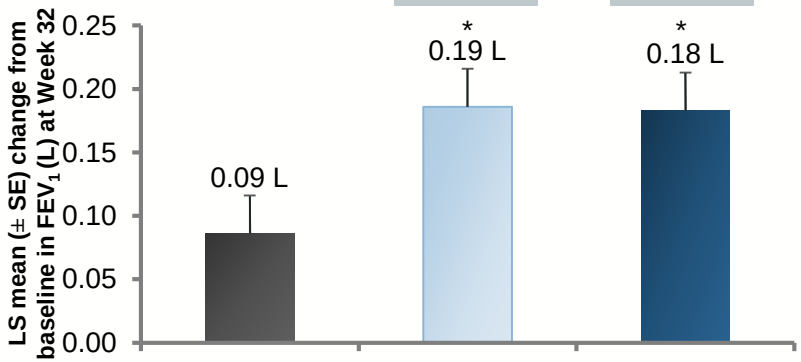
MENSA Phase 3 study (n=576) (ITT)[1]

(blood eosinophils ≥150/μL at screening or ≥300/μL in previous year)

No. of exacerb-ations[a]

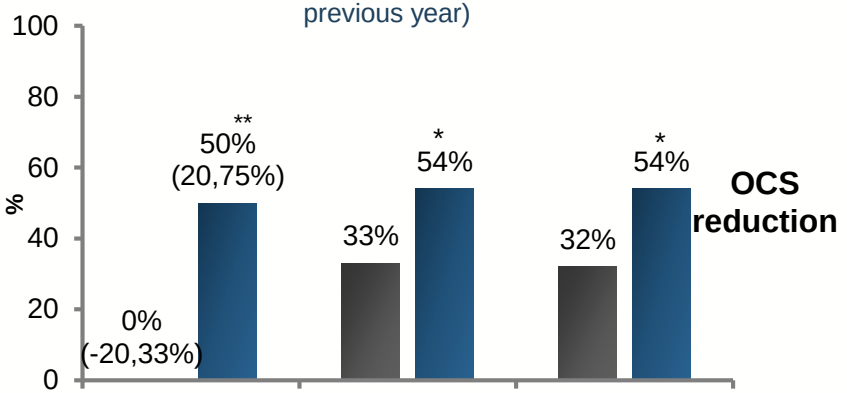


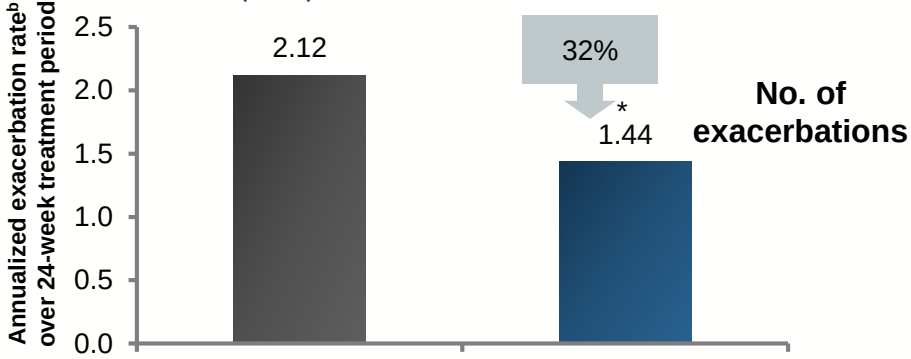
Change in FEV_1 (L)



SIRIUS Phase 3 study (n=135) (ITT)[2]

(blood eosinophils ≥150/μL at optimization phase or ≥300/μL during previous year)





- Mepolizumab also improved QoL and asthma control in patients with severe asthma with an eosinophilic phenotype[1,2]
- Most common AE with mepolizumab (n=263) versus placebo (n=257): Headache (19% vs 18%), injection-site reactions (8% vs 3%)[3]

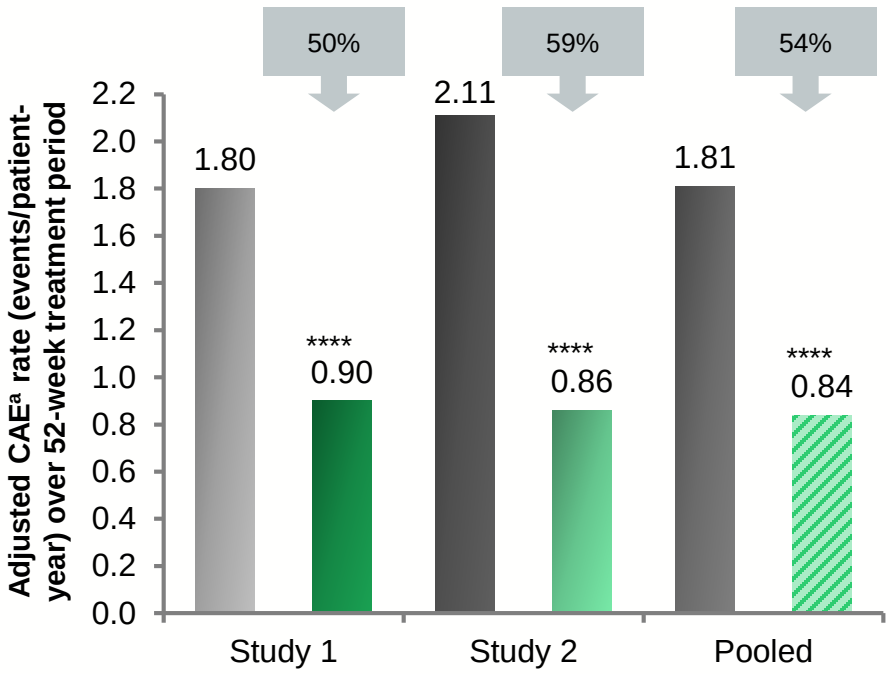
*p<0.05; **p<0.01; ***p<0.001. [a]Worsening of asthma requiring systemic corticosteroids for ≥3 days, or ER visit, or hospitalization; Worsening of asthma leading to the doubling (or more) of existing maintenance dose of OCS for ≥3 days, or emergency room visit, or hospitalization

1. Ortega HG, et al. *N Engl J Med*. 2014;371:1198–1207;
2. Bel EH, et al. *N Engl J Med*. 2014;371:1189–1197;

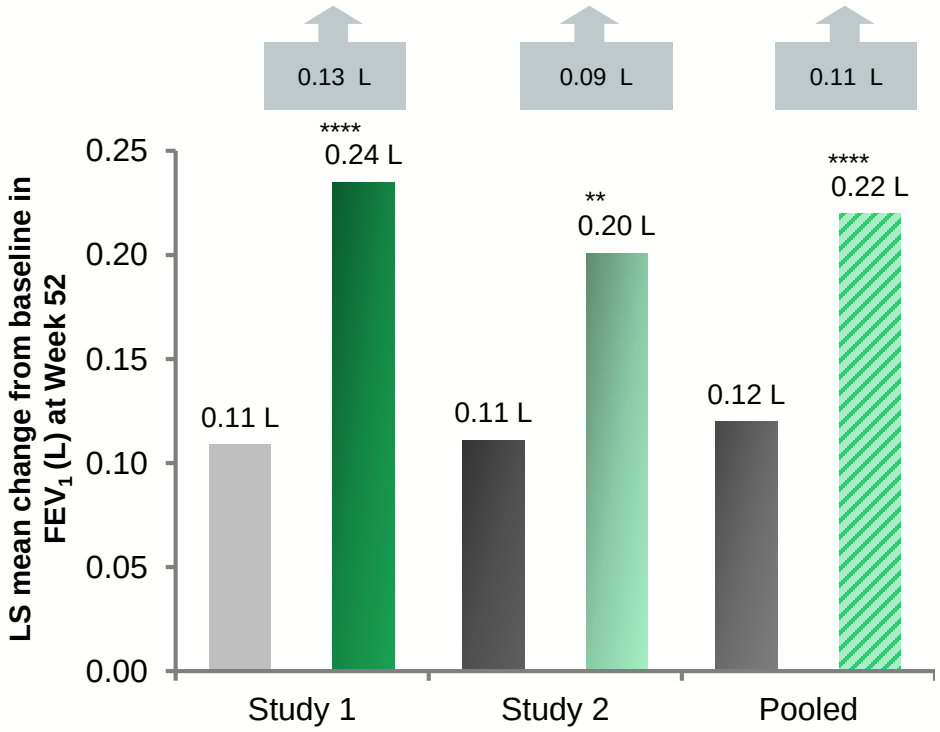
Reslizumab (IV) Reduced Exacerbations, and Improved Lung Function and QoL in Patients with Inadequately Controlled Asthma (Blood Eosinophils ≥400/µL)

Study 1: Placebo q4w (N=244) | Study 1: Reslizumab 3.0 mg/kg q4w (n=245) | Study 2: Placebo q4w (n=232) | Study 2: Reslizumab 3.0 mg/kg q4w (n=232)

Effect of reslizumab on annual exacerbation rate across Phase 3 studies (ITT)[1]



Effect of reslizumab on FEV_1 at Week 52 across Phase 3 studies (ITT)[1]



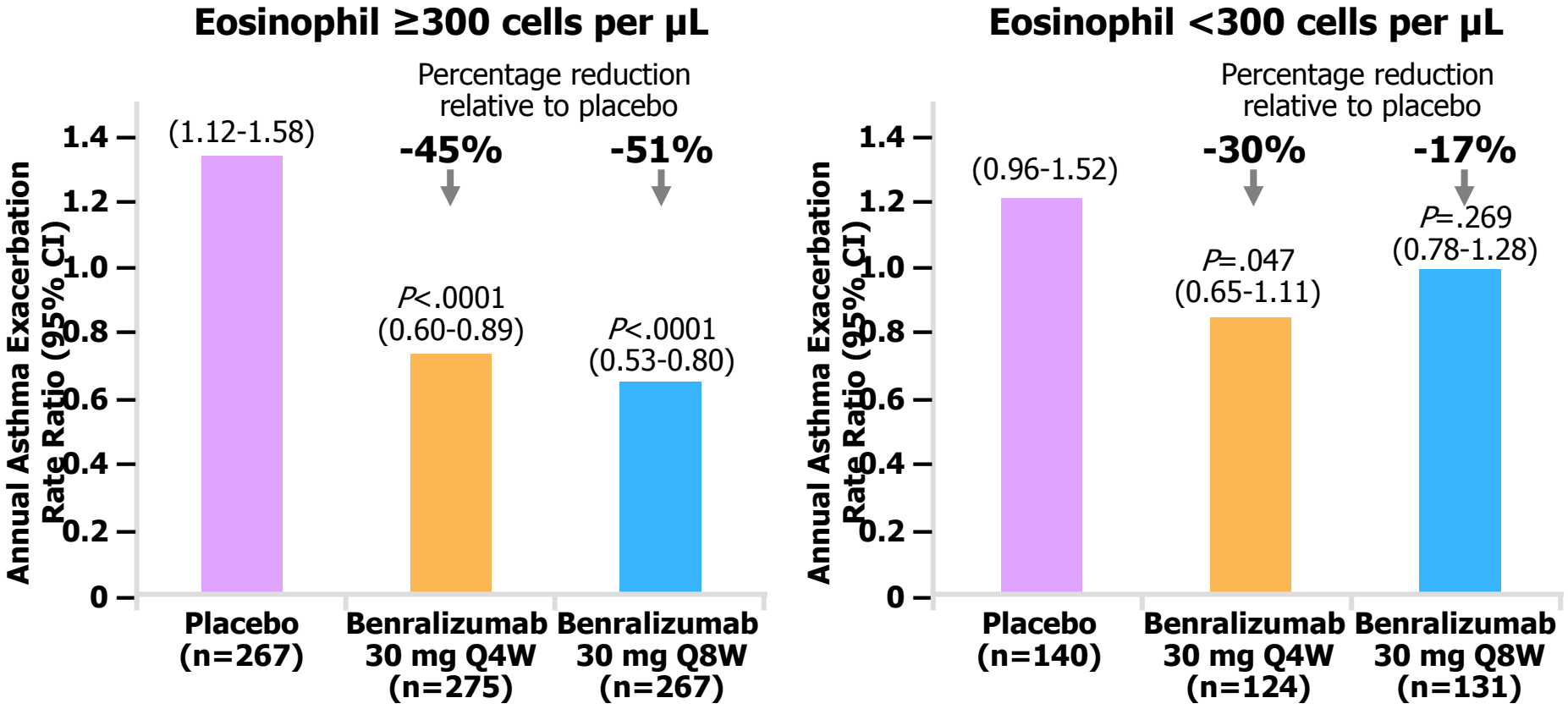
- Reslizumab also improved QoL in patients with severe asthma with an eosinophilic phenotype[1]
- In two Phase 3 trials, reslizumab SC did not meet its primary endpoint of significantly reducing CAEs and daily OCS dose[2]
- Most common AE with reslizumab (n=1131) vs placebo (n=730): Oropharyngeal pain (2.6% vs 2.2%)[3]

**p<0.01; ****p<0.0001
[a]Worsening of asthma requiring systemic corticosteroids in patients not already receiving treatment, or a two-times increase in dose of either ICS or systemic corticosteroids for ≥3 days, or the need for asthma-related emergency treatment
AQLQ, Asthma Quality of Life; CAE, clinical asthma exacerbation

1. Castro M, et al. *Lancet Respir Med.* 2015;3:355–366; 2. Teva press-release. http://www.tevapharm.com/news/teva_announces_top_line_results_from_phase_iii_studies_of_subcutaneously_administered_reslizumab_in_patients_with_severe_eosinophilic_asthma_01_18.aspx. Accessed February 2018; 3. Cinqair (reslizumab) Prescribing Information. Frazer, PA: Teva Respiratory, LLC. 2016

Benralizumab Reduced Frequency of Asthma Exacerbations (Primary Endpoint)

Annual asthma exacerbation rate estimates at 48 weeks according to baseline blood eosinophil concentrations

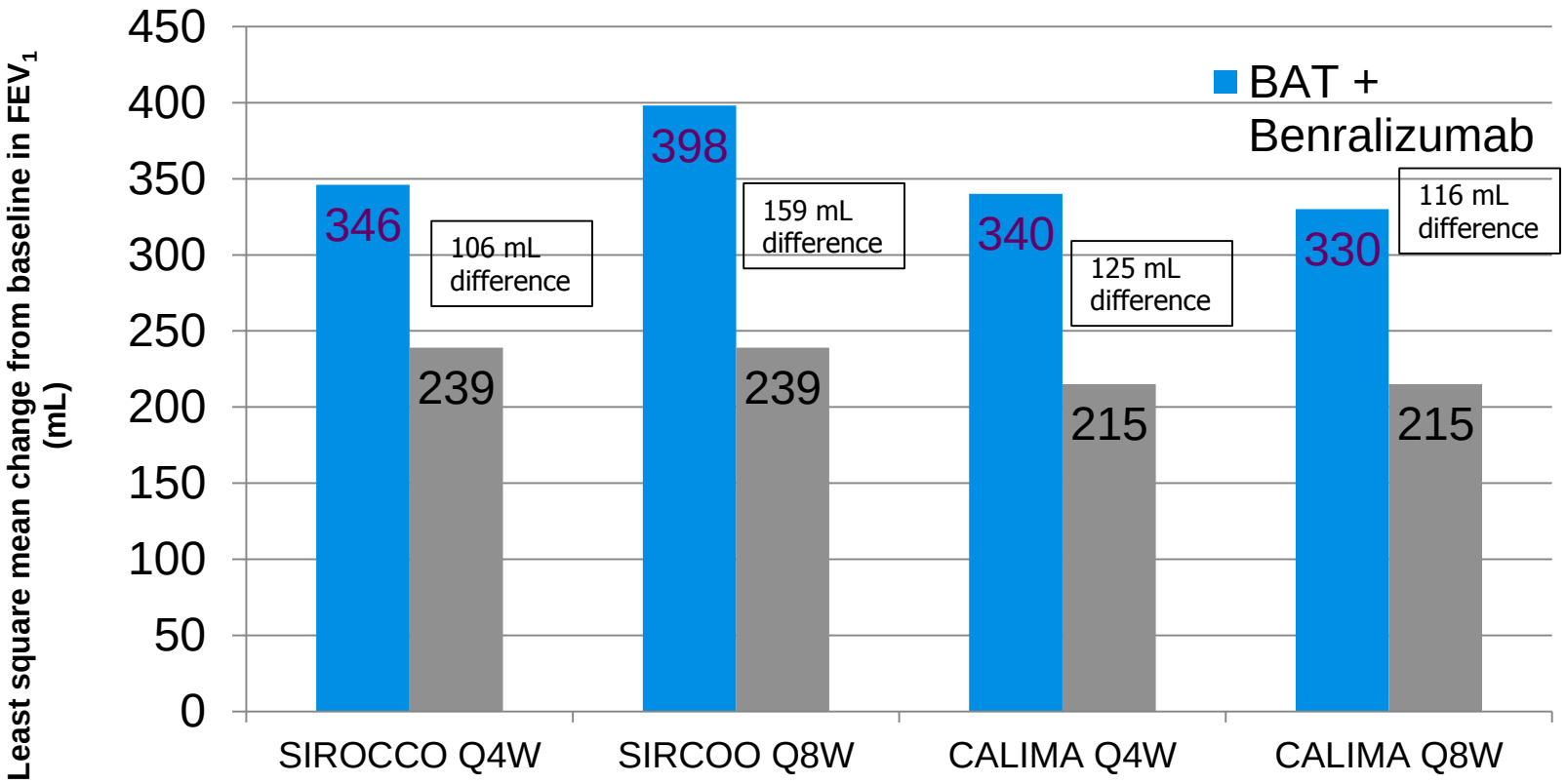


Bleecker ER, et al. *Lancet*. 2016;388(10056):2115-2127.

Benralizumab 30 mg SC is licensed for the treatment of severe eosinophilic asthma

Benralizumab Impact on FEV_1

Change from Baseline Over 48 Weeks (SIROCCO) or 56 Weeks (CALIMA)[1,2]



Data are for patients with a baseline blood eosinophil (EOS) level of ≥300 cells per µL. Patients were on background asthma therapy (BAT) of high-dose inhaled corticosteroids (ICS) plus long-acting beta agonists (LABA)

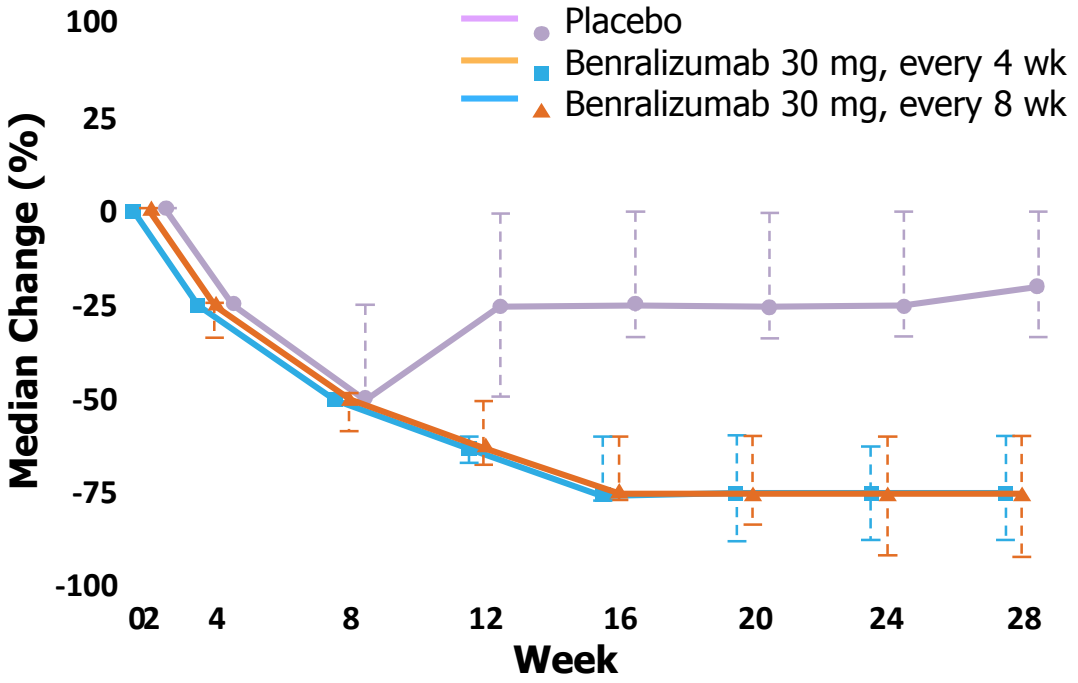
Bleecker ER, et al. *Lancet.* 2016; 388:2115-2127.
FitzGerald JM, et al. *Lancet.* 2016;388:2128-2141.

Benralizumab 30 mg SC is licensed for the treatment of severe eosinophilic asthma

Benralizumab Reduced Oral Glucocorticoid Dose in Severe Asthma (Primary Endpoint)

- 75% median reduction from baseline in the final oral glucocorticoid dose in patients who received either of the benralizumab regimens, vs 25% in the patients who received placebo (*P*<.001 for both comparisons)
- Other results:
  - Proportion of patients reducing OCS dose by 100%
  - Placebo 19% versus benralizumab 52%
  - Annual exacerbation rate was reduced by 70% relative to placebo (*P*<0.001)

Change from Baseline in Oral Glucocorticoid Dose



No. at Risk								
Benralizumab 30 mg Q4W	72	70	70	69	69	68	66	68
Benralizumab 30 mg Q8W	70	72	67	69	69	66	69	68
Placebo	74	75	73	74	74	73	73	72

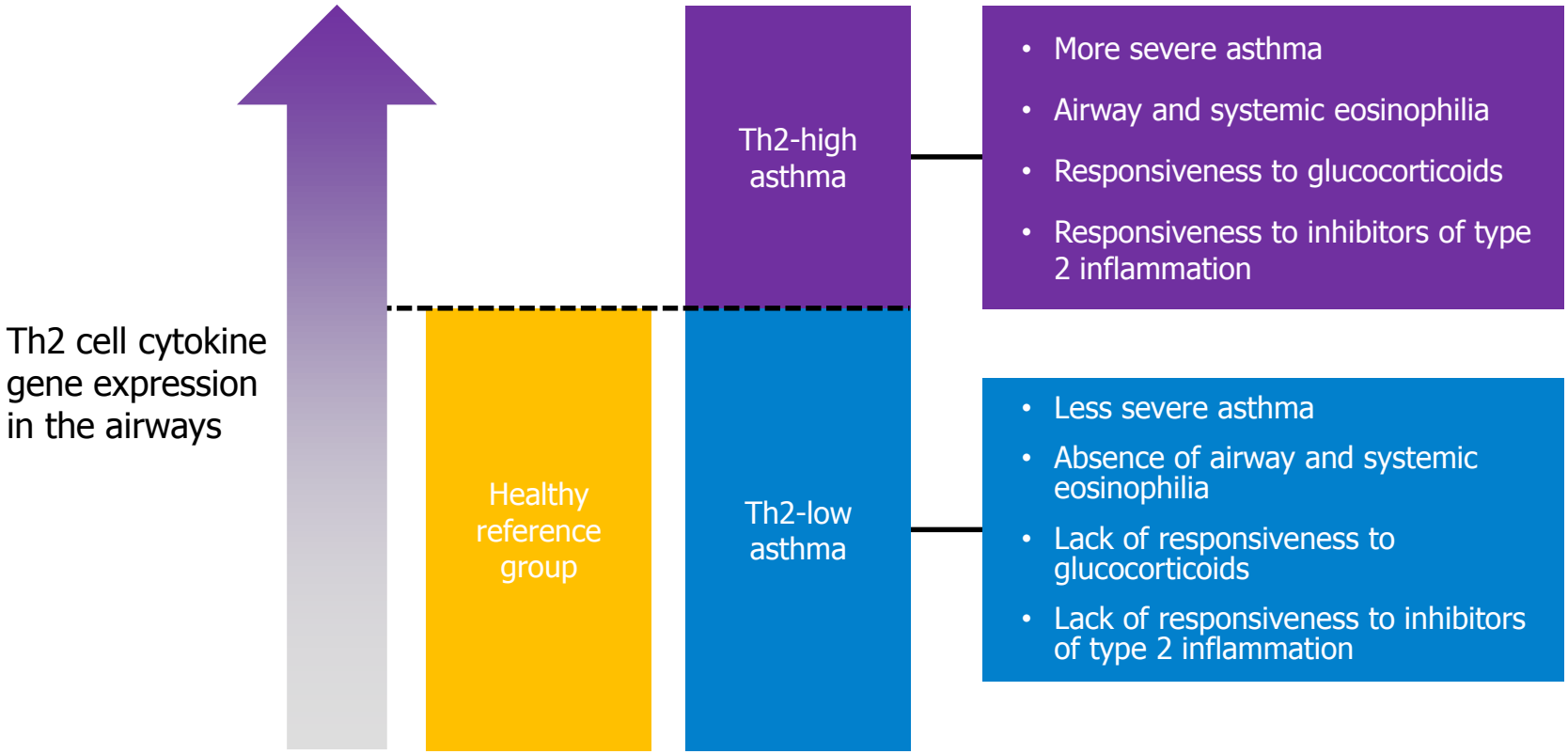
Nair P, et al. *N Engl J Med*. 2017;376:2448-2458.

Benralizumab 30 mg SC is licensed for the treatment of severe eosinophilic asthma

PRO ANTI-IL5 FOR EOSINOPHILIC ASTHMA

Anti-IL4R mAb (dupi) is highly efficacious as well and should be **reserved for the T2 phenotype**

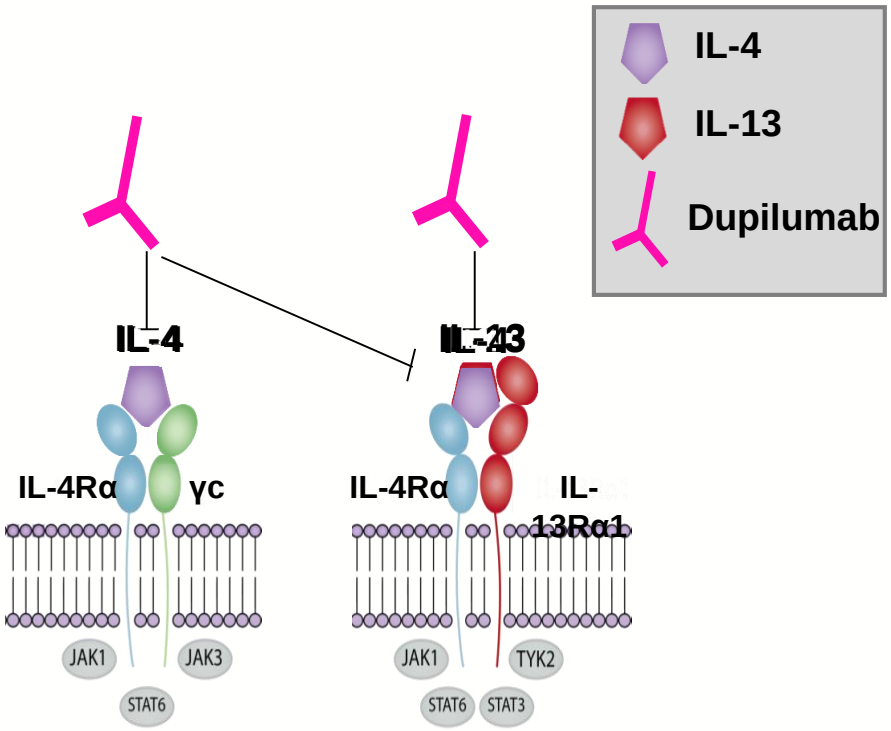
Phenotypes of asthma by Th2 cell cytokine gene expression



Fahy JV.: Nat Rev Immunol. 15: 57-65, 2015

Dupilumab Exerts its Mechanism of Action by Inhibiting IL-4 and IL-13

1. IL-4 and IL-13 bind to a shared subunit, IL-4Rα
2. Dupilumab, a human monoclonal IgG4 antibody, binds to IL-4Rα, blocking both IL-4 and IL-13 signalling
3. IL-4 and IL-13 pathways have unique and overlapping function



Type I Receptor

B cells, T cells, Monocytes, Eosinophils, Fibroblasts

Type II Receptor

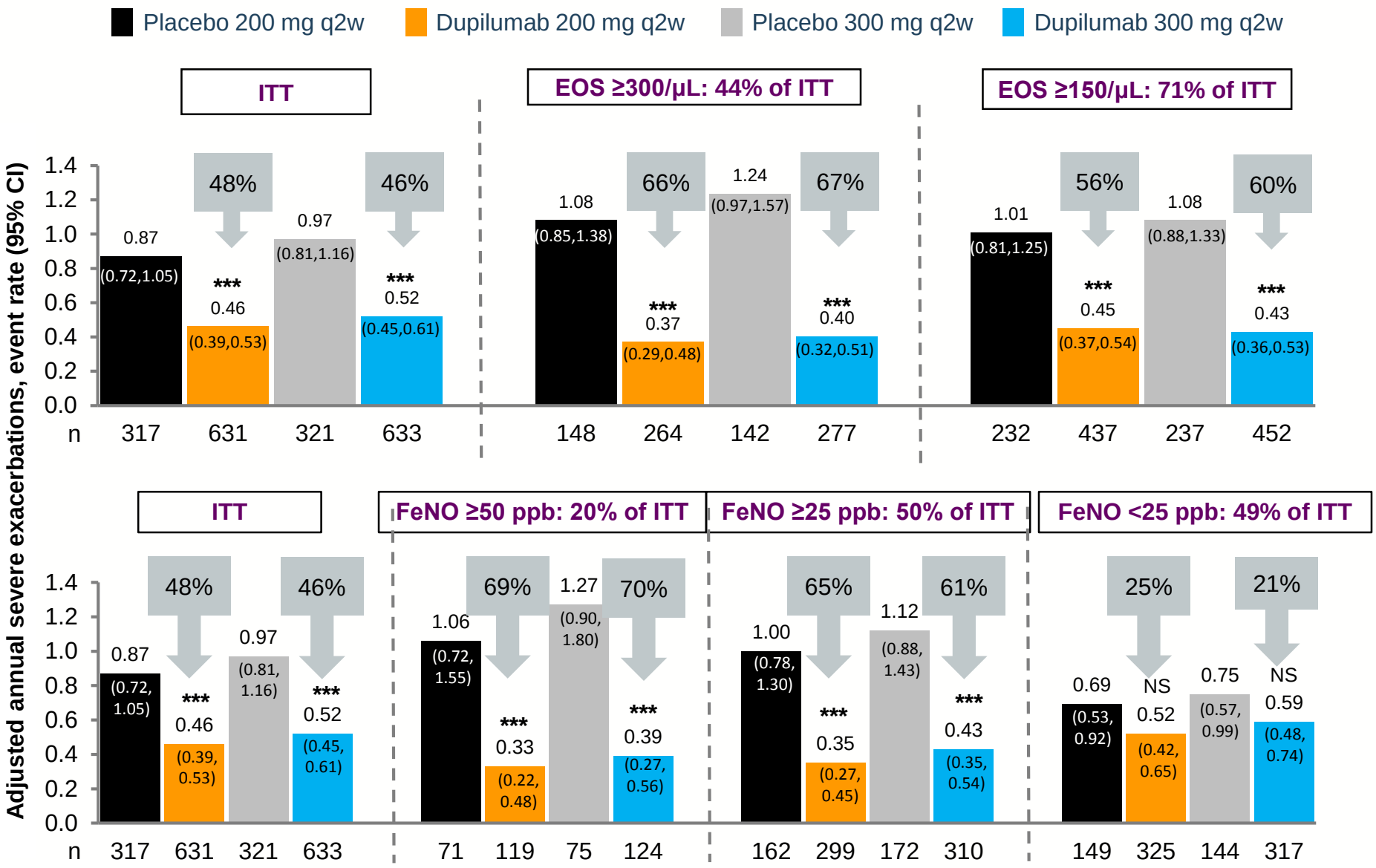
Epithelial cells, Smooth muscle cells, Fibroblasts, Monocytes, Activated B cells

Gandhi NA, et al. *Nat Rev Drug Discov.* 2016;15:35–50

γc, gamma chain; IL-4Rα, interleukin-4 receptor alpha; IL-13Rα, interleukin-13 receptor alpha 1; JAK, janus kinase; STAT, signal transducer and activator of transcription; TYK, tyrosine kinase

Dupilumab 200, 300 mg SC is licensed for the treatment of severe eosinophilic asthma

Phase 3 QUEST: Dupilumab (SC) Significantly Reduced the Rate of Severe Exacerbations across Range of Baseline EOS and FeNO Levels



***p<0.001

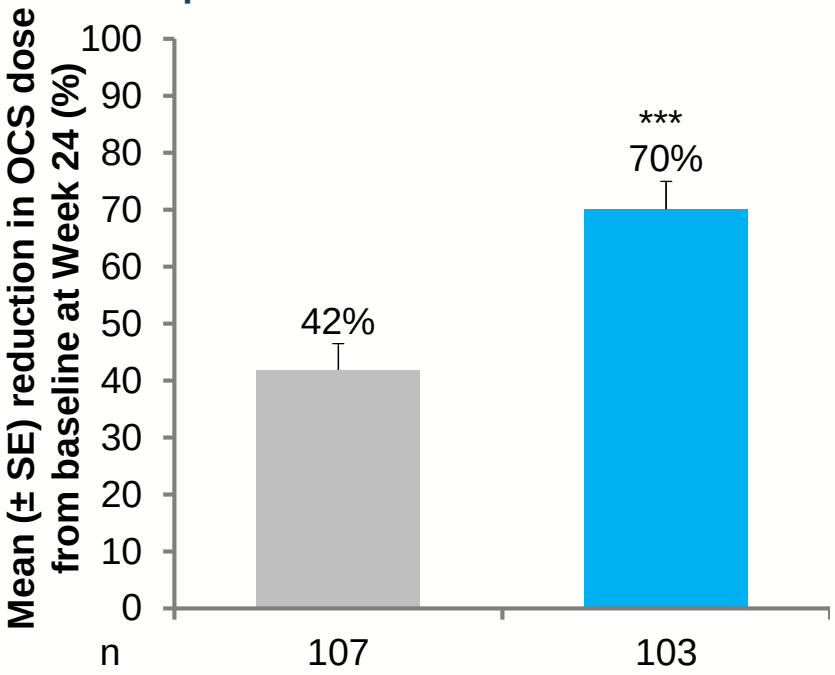
Castro M, et al. *N Engl J Med*. 2018, *ATS* 2018; Wenzel S, et al. *ATS* 2018

Dupilumab 200, 300 mg SC is licensed for the treatment of severe eosinophilic asthma

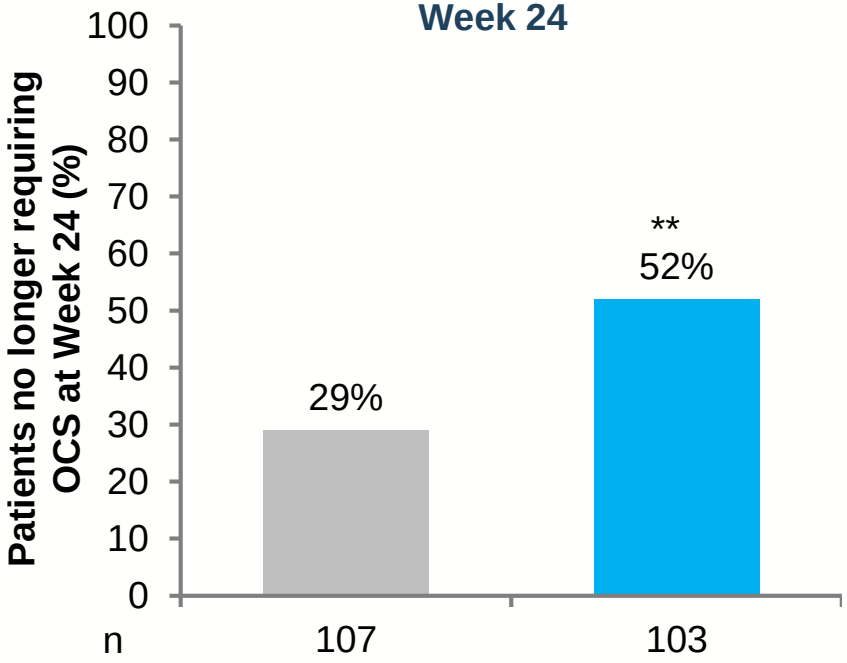
Phase 3 VENTURE: Dupilumab (SC) Significantly Reduced OCS Use at Week 24

Placebo 300 mg q2w Dupilumab 300 mg q2w

Mean percent reduction in OCS dose at Week 24



Proportion of patients no longer requiring OCS at Week 24



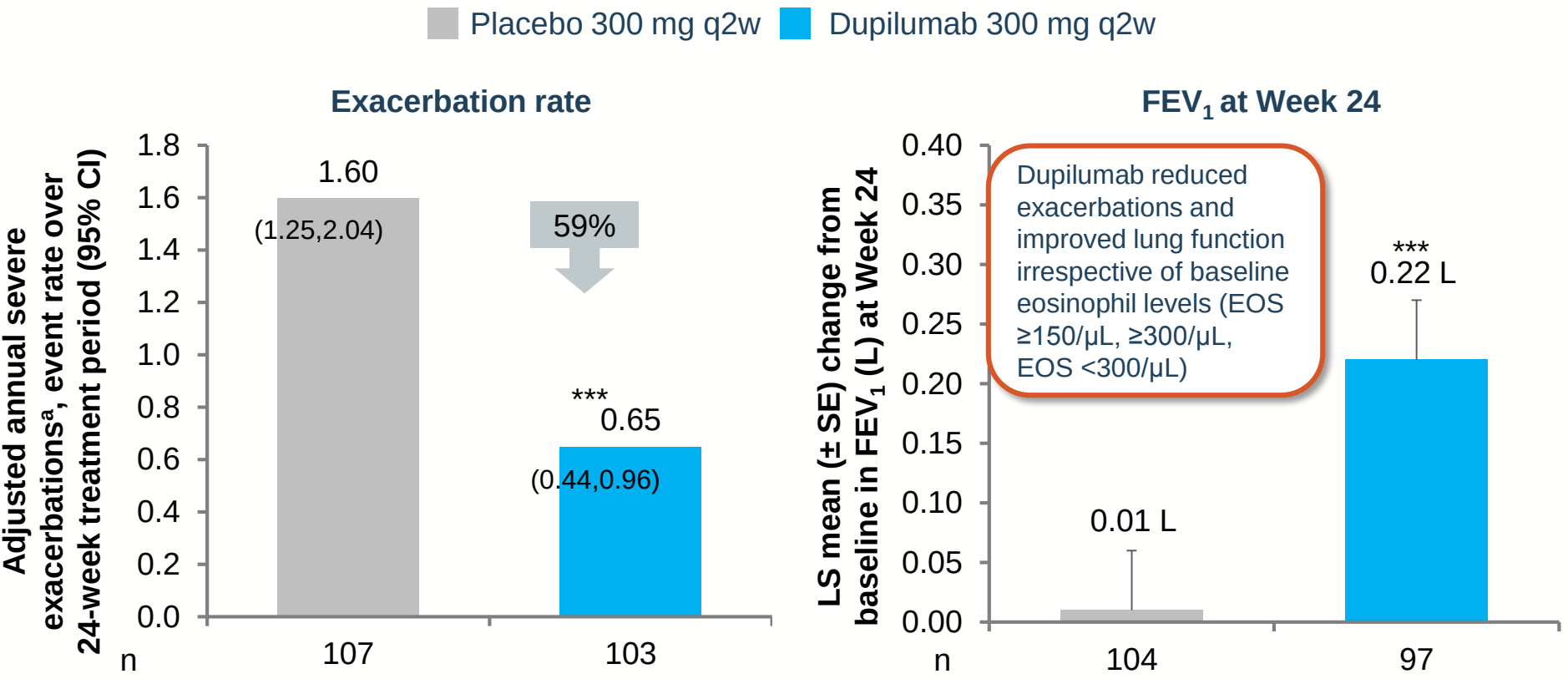
- **At Week 24, significantly more patients treated with dupilumab compared with placebo achieved:**
  - **≥50% reduction in OCS dose; 80% vs 53% (p<0.001)**
  - **Reduction of OCS dose to <5 mg/day relative to baseline; 72% vs 37% (p<0.001)**
  - **Maximum possible OCS dose reduction; 52% vs 30% (p=0.002)**

**p<0.01; ***p<0.001

Rabe KF, et al. *N Engl J Med*. 2018., *ATS* 2018

Dupilumab 200, 300 mg SC is licensed for the treatment of severe eosinophilic asthma

Phase 3 VENTURE: Dupilumab (SC) Significantly Reduced OCS Use and Exacerbations, and Improved Lung Function and Asthma Control



- **Asthma control:** Dupilumab also significantly improved asthma control (ACQ-5) (nominal p=0.002)[1]
- **Safety:**
  - QUEST, most common TEAEs were viral URTIs (18% vs19%) and ISR (HLT) (17% vs 8%, dupilumab vs placebo)[2]
  - VENTURE, most common TEAEs were eosinophilia[b] (14% vs1%) and ISR (HLT) (9% vs 4%, dupilumab vs. placebo)[3]

***p<0.001

[a]Deterioration of asthma leading to hospitalization, emergency room visit, or treatment for ≥3 days with systemic corticosteroids at ≥2 times the current dose

[b]Combination of 'Eosinophil count increase' and 'Eosinophilia'

HLT, High-Level Term; ISR, injection-site reactions; URTI, upper respiratory tract infection

1. Rabe KF, et al. *N Engl J Med*. 2018;
2. Castro M, et al *ATS* 2018; 3. Rabe K, et al. *ATS* 2018;

PRO ANTI-IL5 FOR EOSINOPHILIC ASTHMA

To advance the treatment of respiratory disease, we need to move away from the “lumping” approach as new targeted therapy becomes available

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

Assess and treat severe asthma phenotypes

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities)

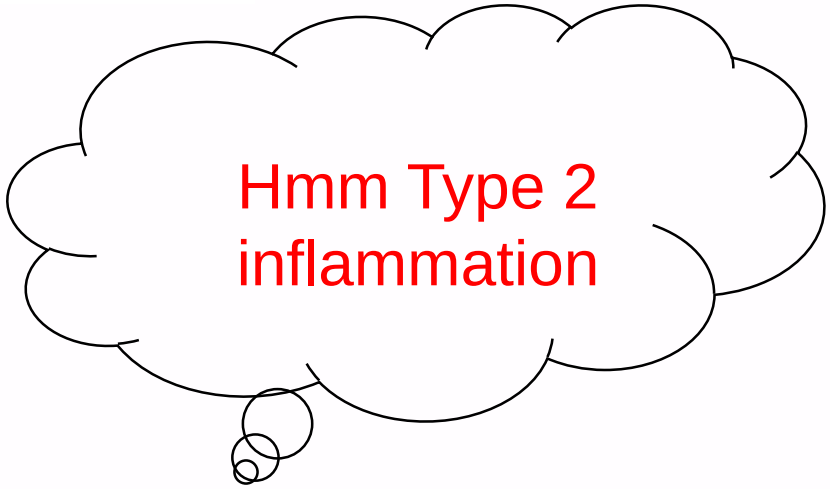
5 Assess the **severe asthma phenotype** and factors contributing to symptoms, quality of life and exacerbations

6a Consider ***non-biologic*** treatments

- ***Assess the severe asthma phenotype during high dose ICS treatment*** *(or lowest possible dose of OCS)*

Type 2 inflammation	
Could patient have Type 2 airway inflammation?	• Blood eosinophils ≥150/µl and/or • FeNO ≥20 ppb and/or • Sputum eosinophils ≥2%, and/or • Asthma is clinically allergen-driven and/or • Need for maintenance OCS (Repeat blood eosinophils and FeNO up to 3x, on lowest possible OCS dose)
Note: these are not the criteria for add-on biologic therapy (see **6b***)*	

- ***Investigate for comorbidities/differential diagnoses*** *and treat/refer as appropriate*
  - Consider: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins; CXR and/or HRCT chest; DLCO
  - Skin prick testing or specific IgE for relevant allergens, if not already done
  - Other directed testing (e.g. ANCA, CT sinuses, BNP, echocardiogram) based on clinical suspicion
- ***Consider need for social/psychological support***
- ***Involve multidisciplinary team care (if available)***
- ***Invite patient to enroll in registry (if available) or clinical trial (if appropriate)***



SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

Assess and treat severe asthma phenotypes *cont'd*

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities)

6b Consider ***add-on biologic Type 2*** targeted treatments

- Consider add-on Type 2-targeted biologic for patients with exacerbations or poor symptom control on high dose ICS-LABA, who:
  - have eosinophilic or allergic biomarkers, or
  - need maintenance OCS
- Consider **local payer eligibility criteria** and **predictors of response** when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

Which biologic is appropriate to start first?

Anti-IgE

*Is the patient eligible for **anti-IgE** for severe allergic asthma?*

- Sensitization on skin prick testing or specific IgE
- Total serum IgE and weight within dosage range
- Exacerbations in last year

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

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

no / *no*

Anti-IL5 / Anti-IL5R

*Is the patient eligible for **anti-IL5 / anti-IL5R** for severe eosinophilic asthma?*

- Exacerbations in last year
- Blood eosinophils ≥300/µl

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 ++

no / *no*

Anti-IL4R

*Is the patient eligible for **anti-IL4R***

… for severe eosinophilic/Type 2 asthma?

- Exacerbations in last year
- Blood eosinophils ≥150/µl or FeNO ≥25 ppb

… or because of need for maintenance OCS?

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

Eligible for none?
Return to section **6a**

Check local eligibility criteria for specific biologic therapies as these may vary from those listed

Other Biologics and Small Molecules Under Development for Type 2 Inflammatory Diseases

Agent	MoA	Mode of administration	Clinical phase	Patient populations
Asapiprant[1,2]	Prostaglandin D2 antagonist	?	Preclinical, 3 for allergic rhinitis	Allergic asthma, allergic rhinitis
RPC4046[3,4]	IL-13R antagonist/anti-IL-13 mAb	SC/IV	2 for EoE, 1 in asthma	Eosinophilic esophagitis, moderate-to-severe asthma
ADC3680/ADC3608 B[3]	CRTh2 antagonist	Oral	2	Inadequately controlled asthma
AMG-282/RG6149[3,5]	IL-33 antagonist/anti-IL-33 mAb	SC/IV	2 for asthma, 1 for CRSwNP	Mild atopic asthma, CRSwNP
ANB020[3,6]	IL-33 antagonist/anti-IL-33 mAb	SC/IV	2	Severe asthma (eosinophilic phenotype), peanut allergy, AD
SB010[3]	Anti-GATA3 DNAzyme	Oral	2	Mild asthma
GSK3772847[3]	IL-33 antagonist/anti-IL-33 mAb	IV	2	Moderate-to-severe asthma
MK-1029[3]	CRTh2 antagonist	Oral	2	Persistent asthma uncontrolled by montelukast
SAR440340/ REGN3500[3]	IL-33 antagonist/anti-IL-33 mAb	SC	2	Moderate-to-severe asthma
Timapiprant[3]	CRTh2 antagonist	Oral	2	Severe asthma of eosinophilic phenotype, moderate-to-severe AD
ABM125[7]	IL-25 antagonist	IV	3	Poorly controlled asthma after rhinovirus infection
Fevipiprant[3]	CRTh2 antagonist	Oral	3 for asthma, 2 in AD	Uncontrolled asthma, moderate-to-severe AD
Tezepelumab[3]	TSLP antagonist	SC	3	Inadequately controlled severe asthma
Lebrikizumab[3,13]	IL-13R antagonist/anti-IL-13 mAb	SC	**Discontinued in asthma**, 2 in AD	Uncontrolled asthma with ICS, moderate-to-severe AD
Tralokinumab[2,14]	IL-13R antagonist/anti-IL-13 mAb	SC	**Discontinued in asthma**, 3 in AD	Uncontrolled asthma, AD

Pro Arguments: The severe asthma patient with eosinophilic phenotype should always be treated with Anti-Interleukin-5 therapies

- Targeted phenotype therapy can lead to personalized medical therapy for asthma
- Doesn’t Richard Martin and National Jewish want to practice Precision Medicine?