«Terapie biologiche per l'infiammazione di tipo 2 nell'asma grave e nelle comorbilità di tipo 2»

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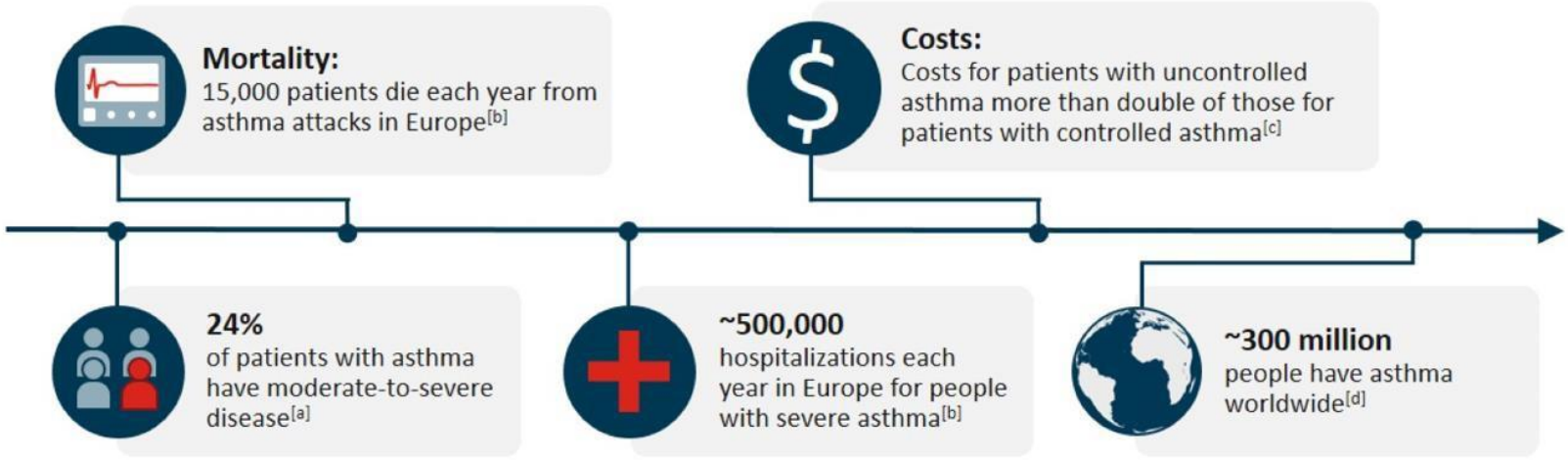
Serious Consequences of Severe Asthma



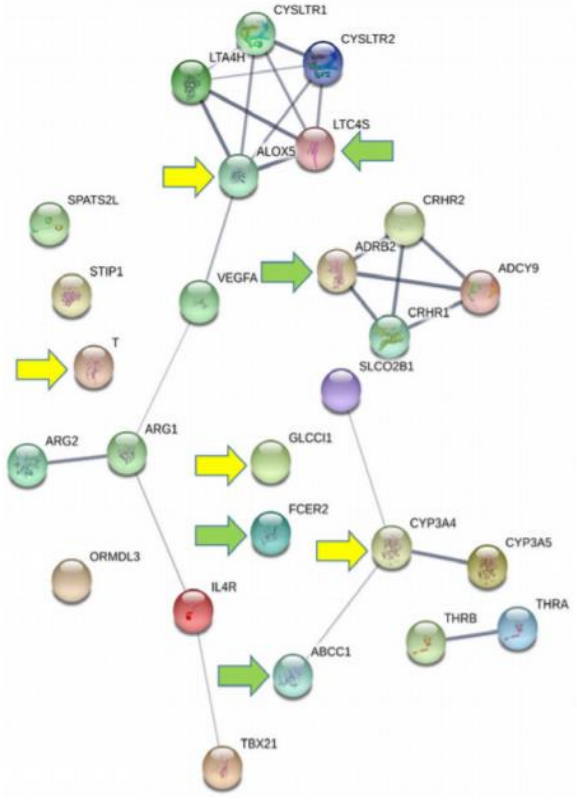
Severe allergic asthma is a **chronic condition**, which, when **uncontrolled**, has a **serious impact** on QoL, morbidity, mortality, and health expenditure

a. GINA. Global Strategy for Asthma Management and Prevention, 2020;4S-12S; b. europeanlung.org; c. Sullivan SD, et al. *Allergy*. 2007;62:126-133; d. World Health Organization. Global surveillance, prevention and control of chronic respiratory diseases. A comprehensive approach. 2007.

Pharmacogenetic Factors Affecting Asthma Treatment Response. Potential Implications for Drug Therapy

- Based on replicated studies covering a significant number of patients, at least **four genes show potential for pharmacogenomics implementation in asthma therapy.**

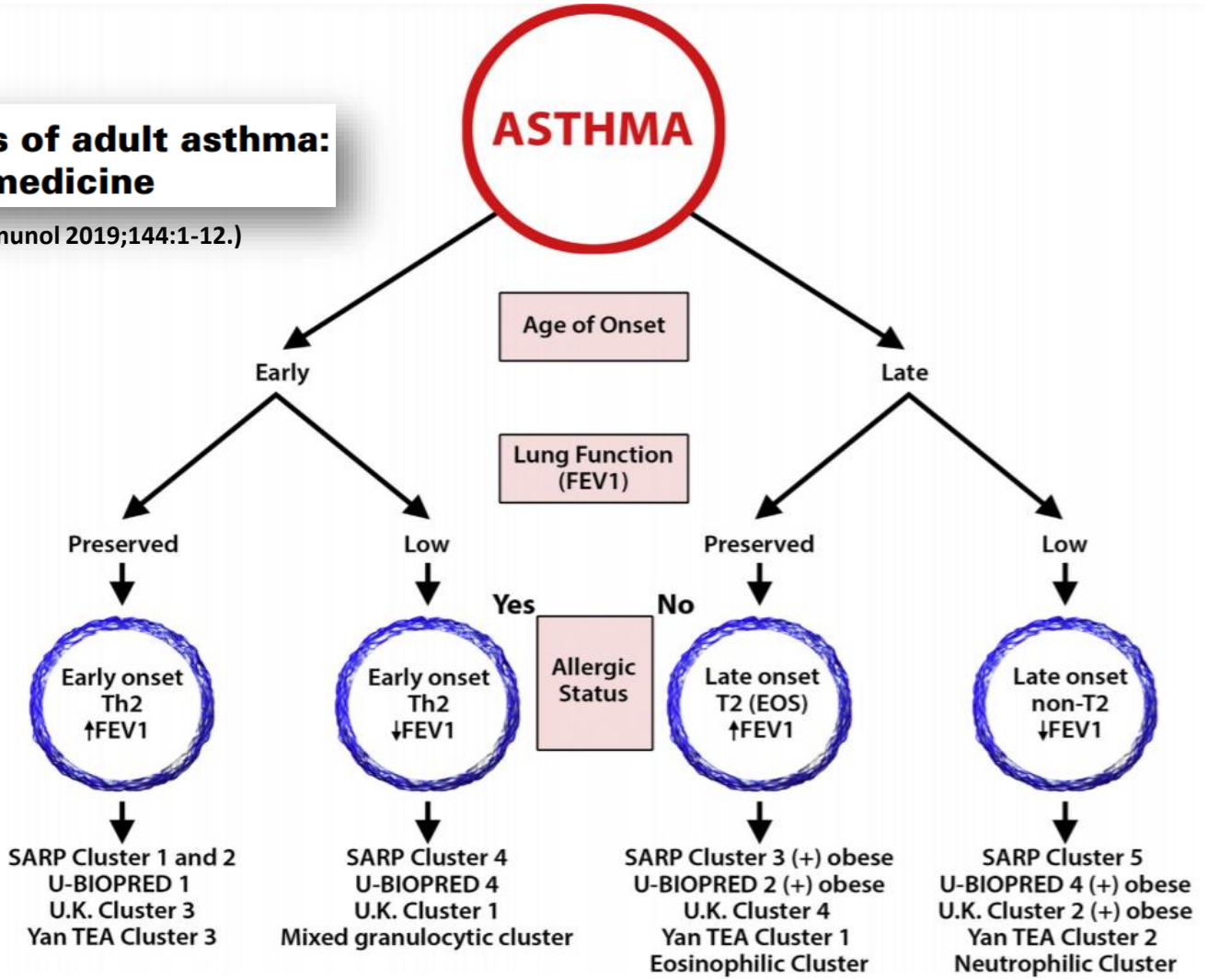
- These genes are related to the response to inhaled corticosteroids (**FCER2**), antileukotriene agents **(ABCC1** and **LTC4S**) and beta-agonists (**ADRB2**).



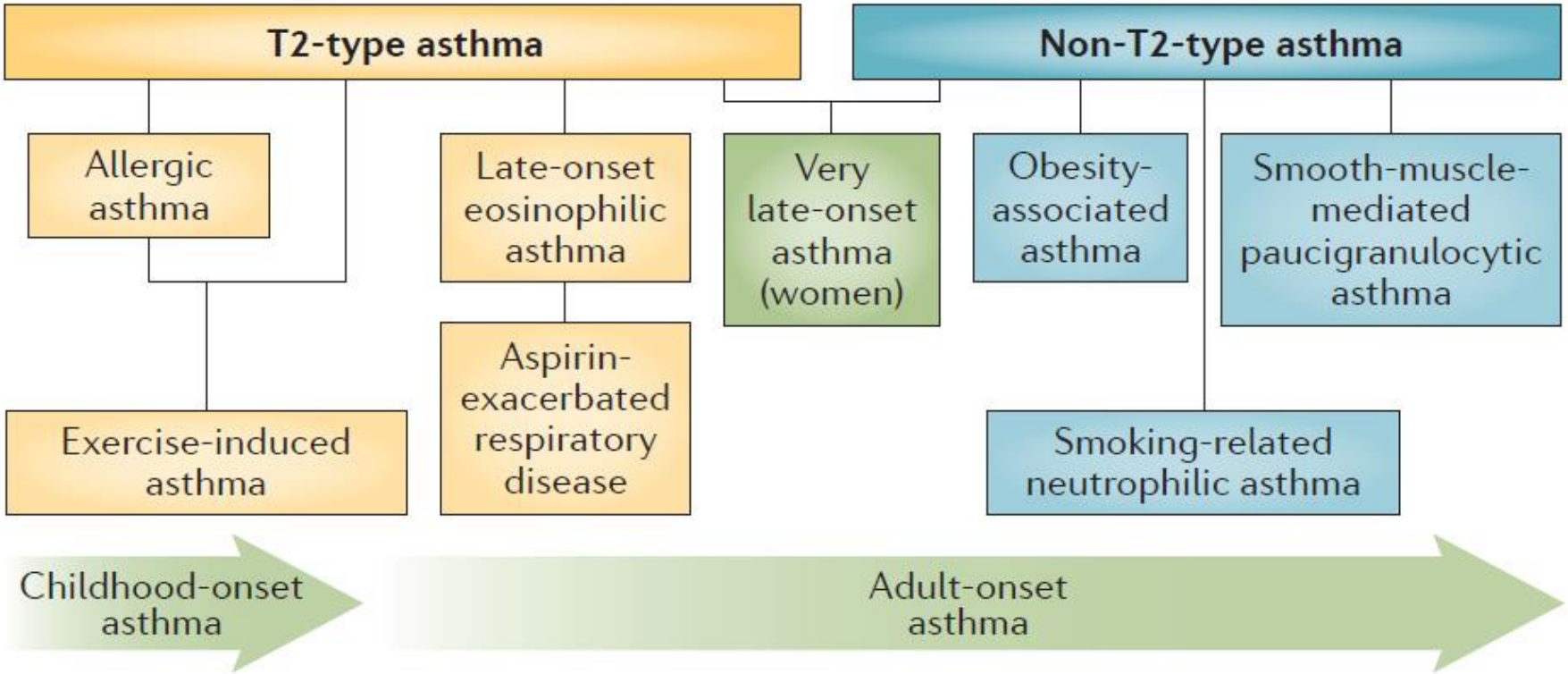
Phenotypes and endotypes of adult asthma: Moving toward precision medicine

(Kaur R & Chupp G, (J Allergy Clin Immunol 2019;144:1-12.)

Diagram showing similarities between asthma phenotypes in cluster analysis studies using age of onset and lung function.

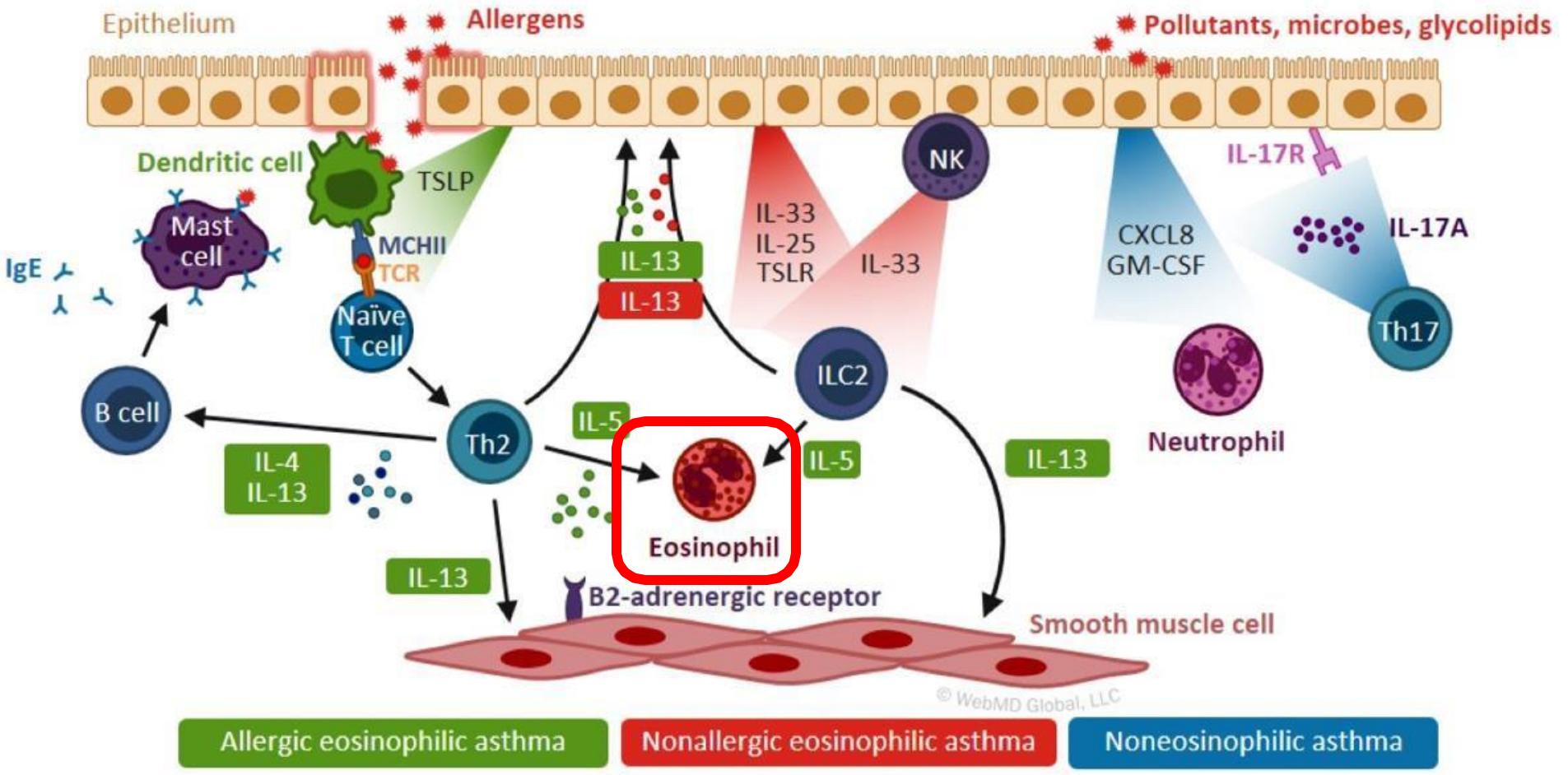


ASTHMA SUBPHENOTYPES



(Holgate ST, Wenzel S, Postma DS, Weiss ST, Renz H, Sly PD. *Nature Rev Dis Primers* 1:15025, 2015)

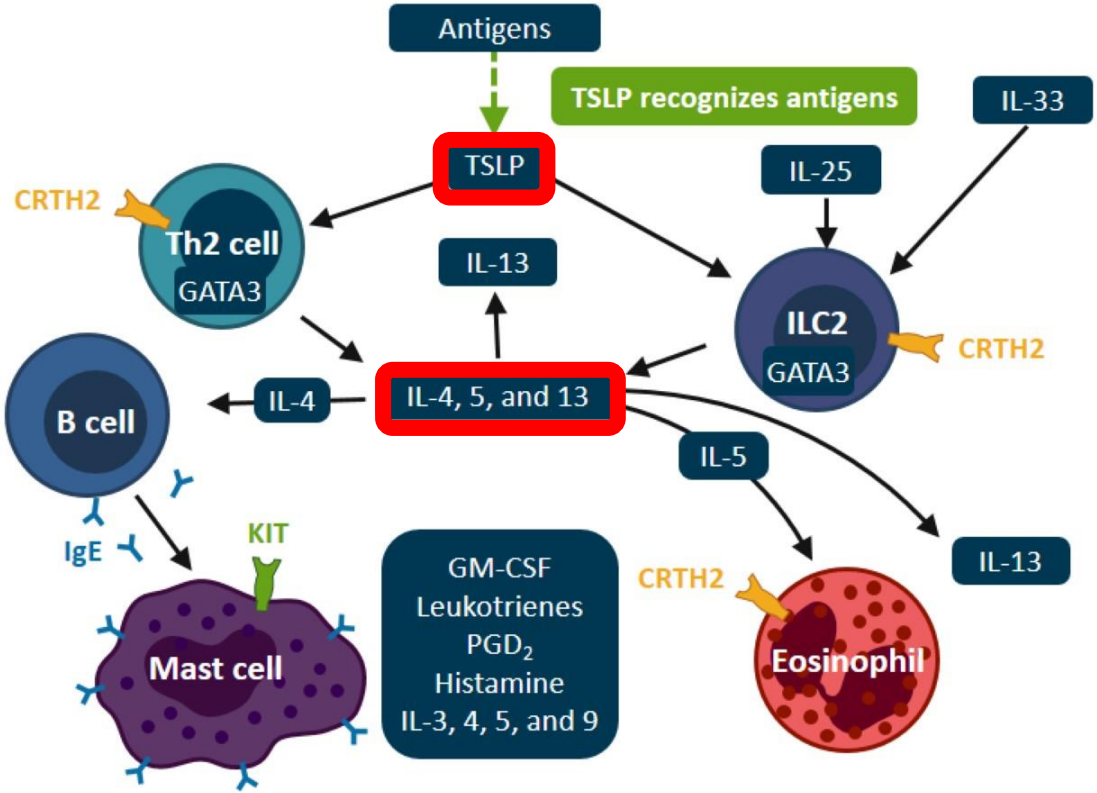
Current Paradigm Of Asthma Immunology



Brusselle GG, et al. *Nat Med*. 2013;19:977-979; Carr TF, et al. *Am J Respir Crit Care Med*. 2018;197:22–37.

Inflammatory Mechanisms in Severe Asthma

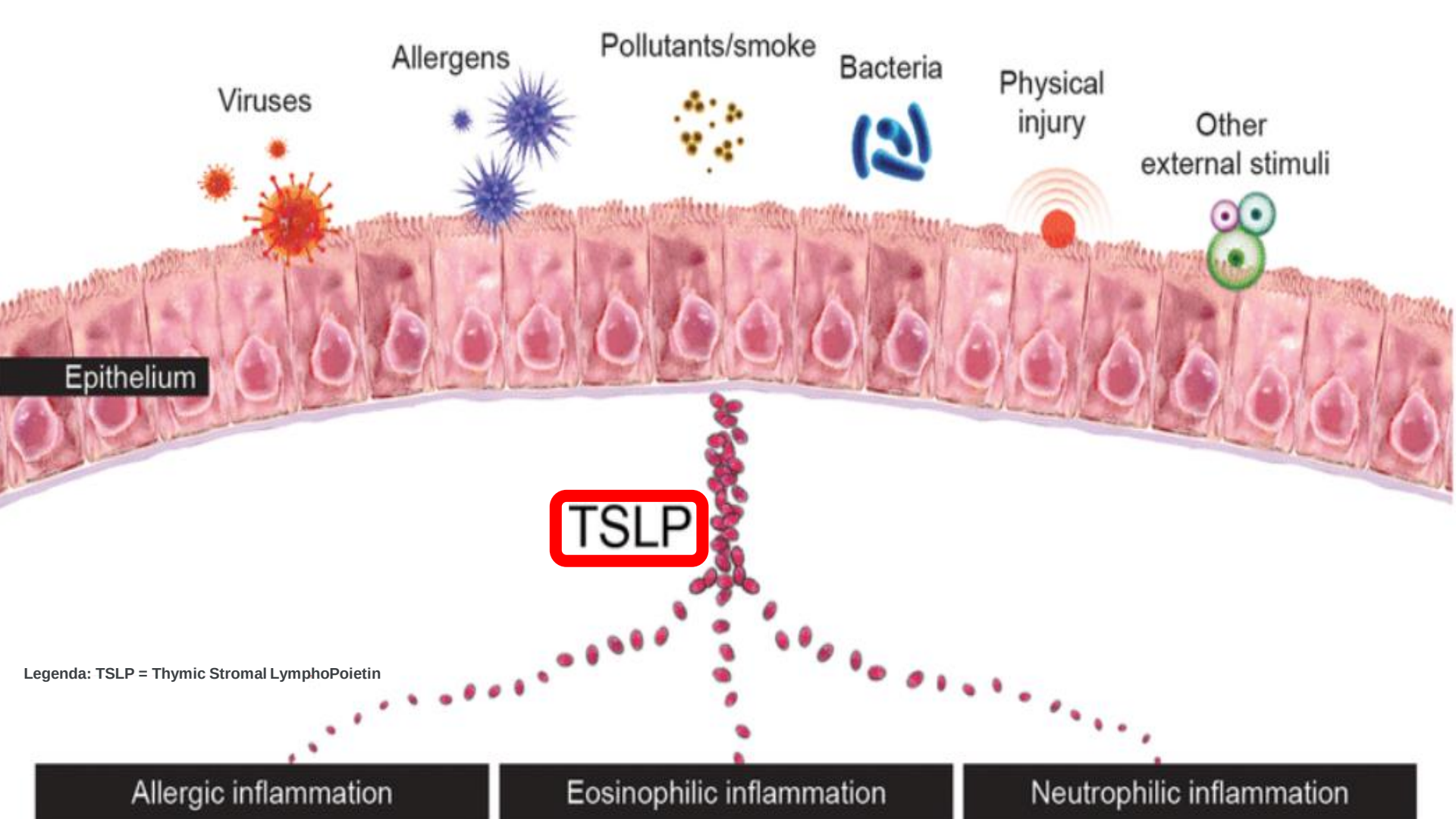
Type 2 Inflammation



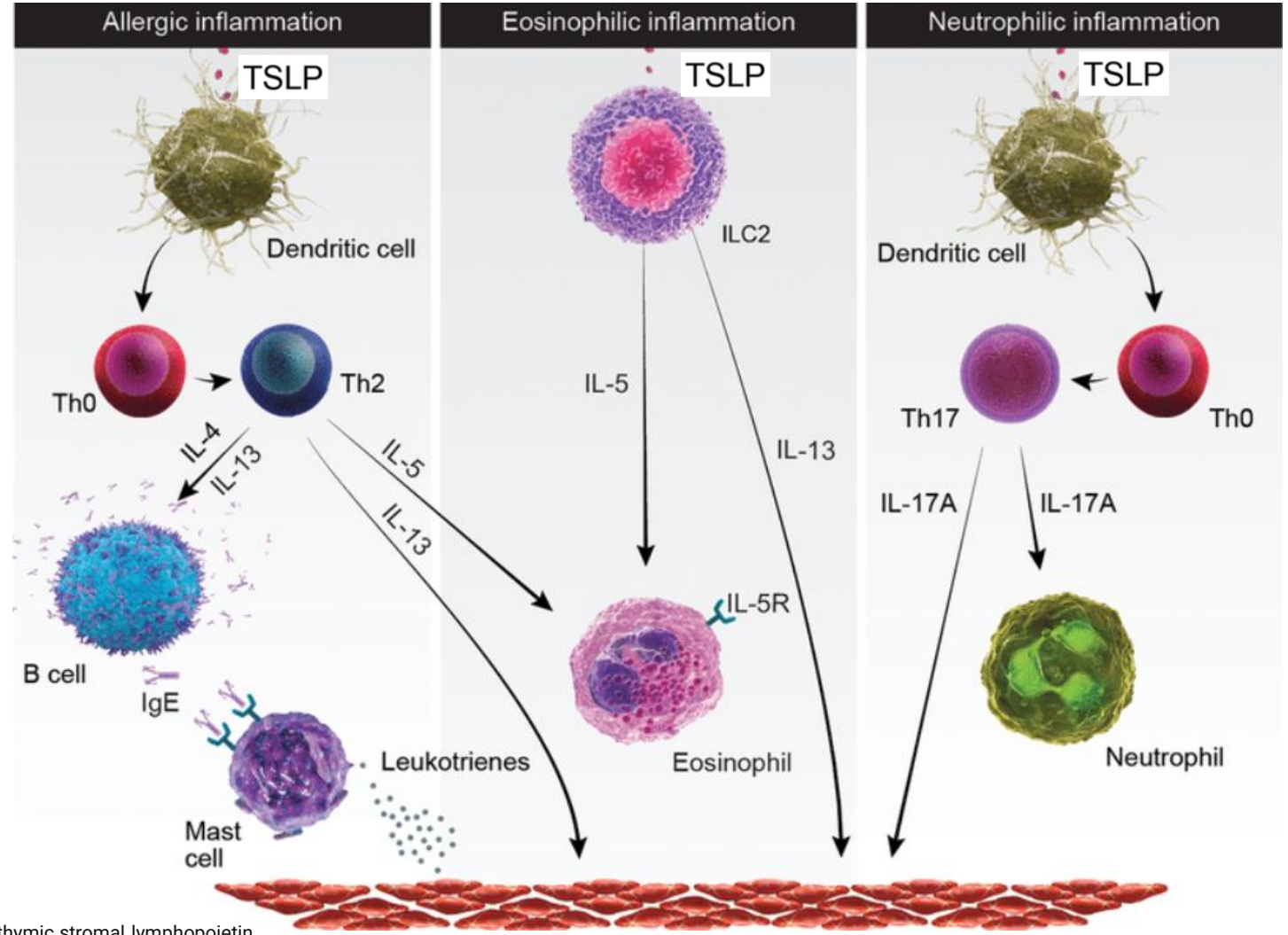
The T2-inflammatory pathway with contributions from adaptive and innate immune responses leads to production of the T2 cytokines IL-4, IL-5, and IL-13 and eosinophils activation.

Israel E, et al. *N Engl J Med.* 2017;377:965-976.

TSLP = Thymic Stromal LymphoPoietin



Legenda: TSLP = Thymic Stromal LymphoPoietin



TSLP, thymic stromal lymphopoietin

Downstream Mediators Trigger Type 2 Asthma

Cytokine Activity

IL-4

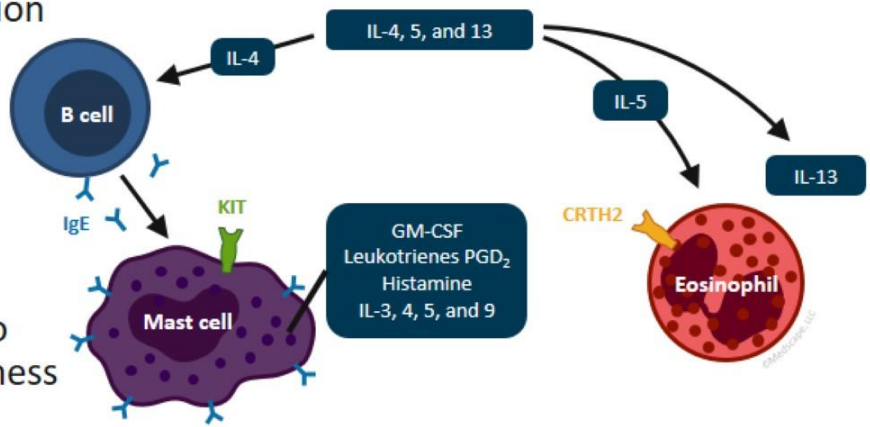
- Stimulates B-cell production of IgE and activates mast cells

IL-5

- Activates eosinophils

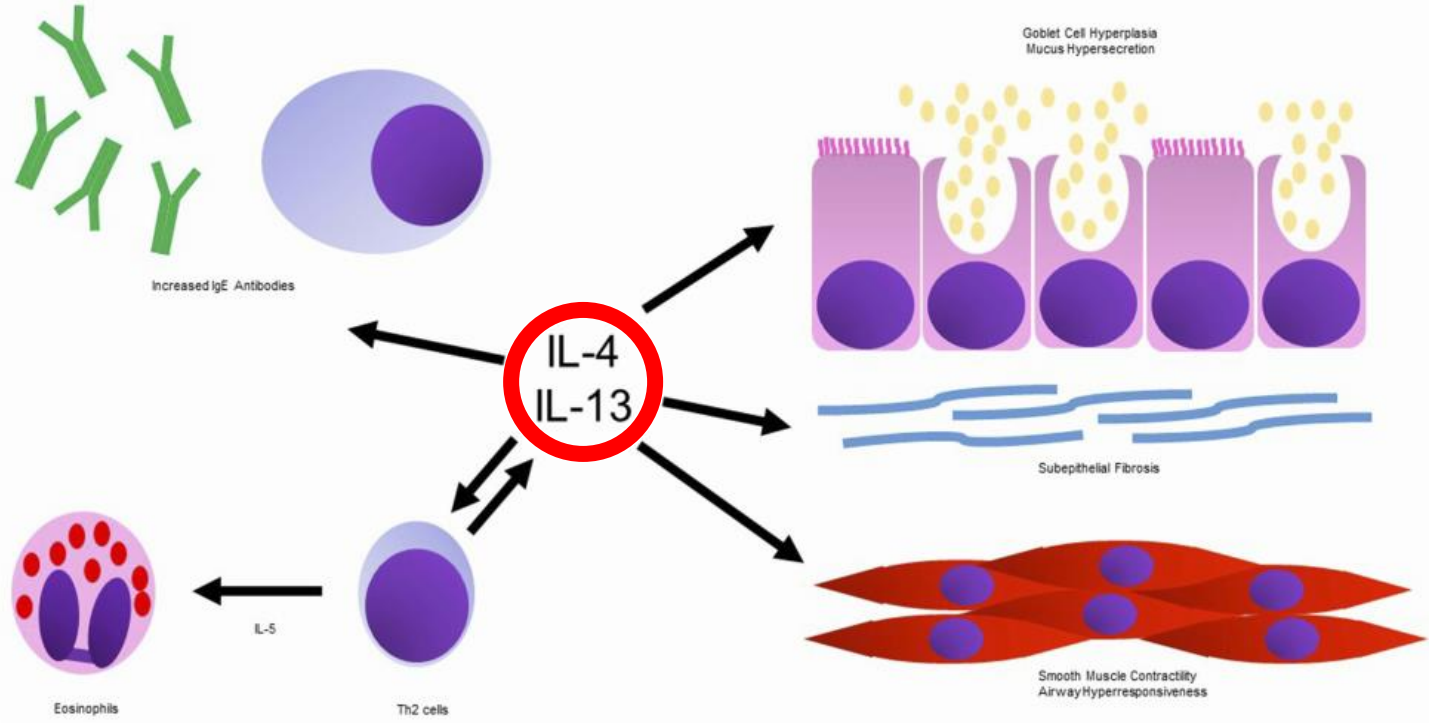
IL-13

- Acts on smooth muscle to induce hyper-responsiveness and remodeling
- Stimulates epithelium to ↑ cytokine production
- Stimulates mucus production



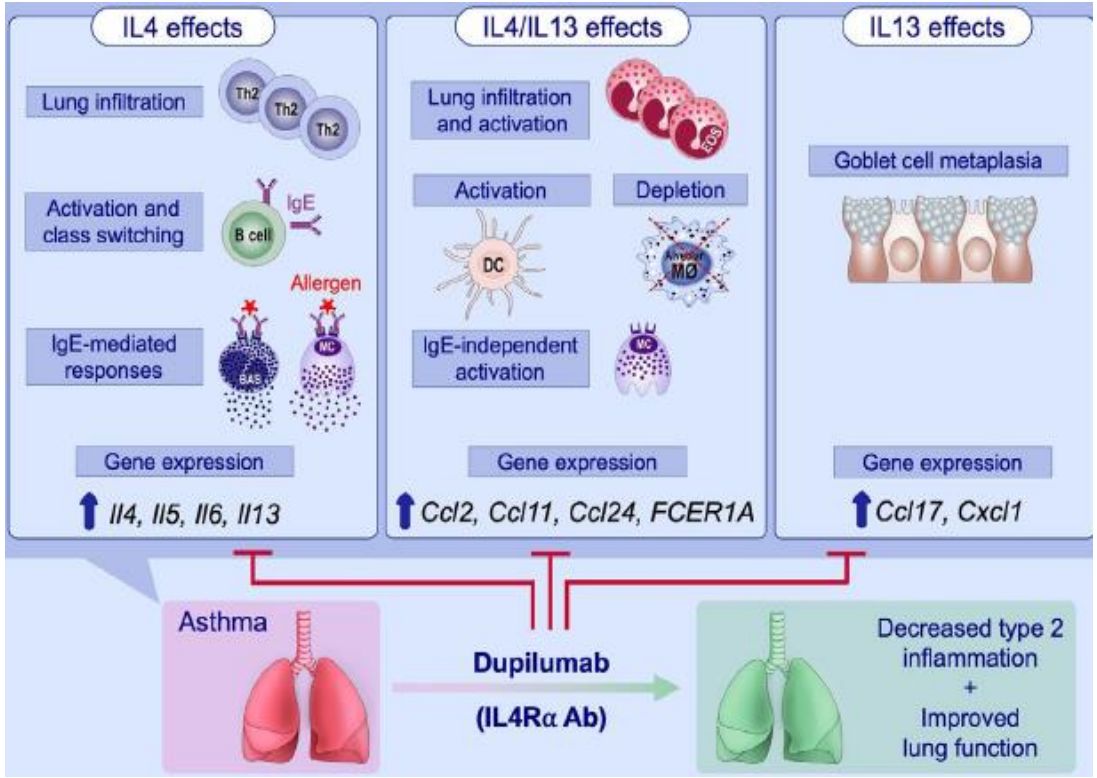
Israel E, et al. *N Engl J Med*. 2017;377:965-976.

Asthma related actions of interleukin-4 and interleukin-13



(Brooks GD:
"Updated Evaluation of Dupilumab in the Treatment of Asthma: Patient Selection and Reported Outcomes",
Therapeutics and Clinical Risk Management 2020:16 181–187)

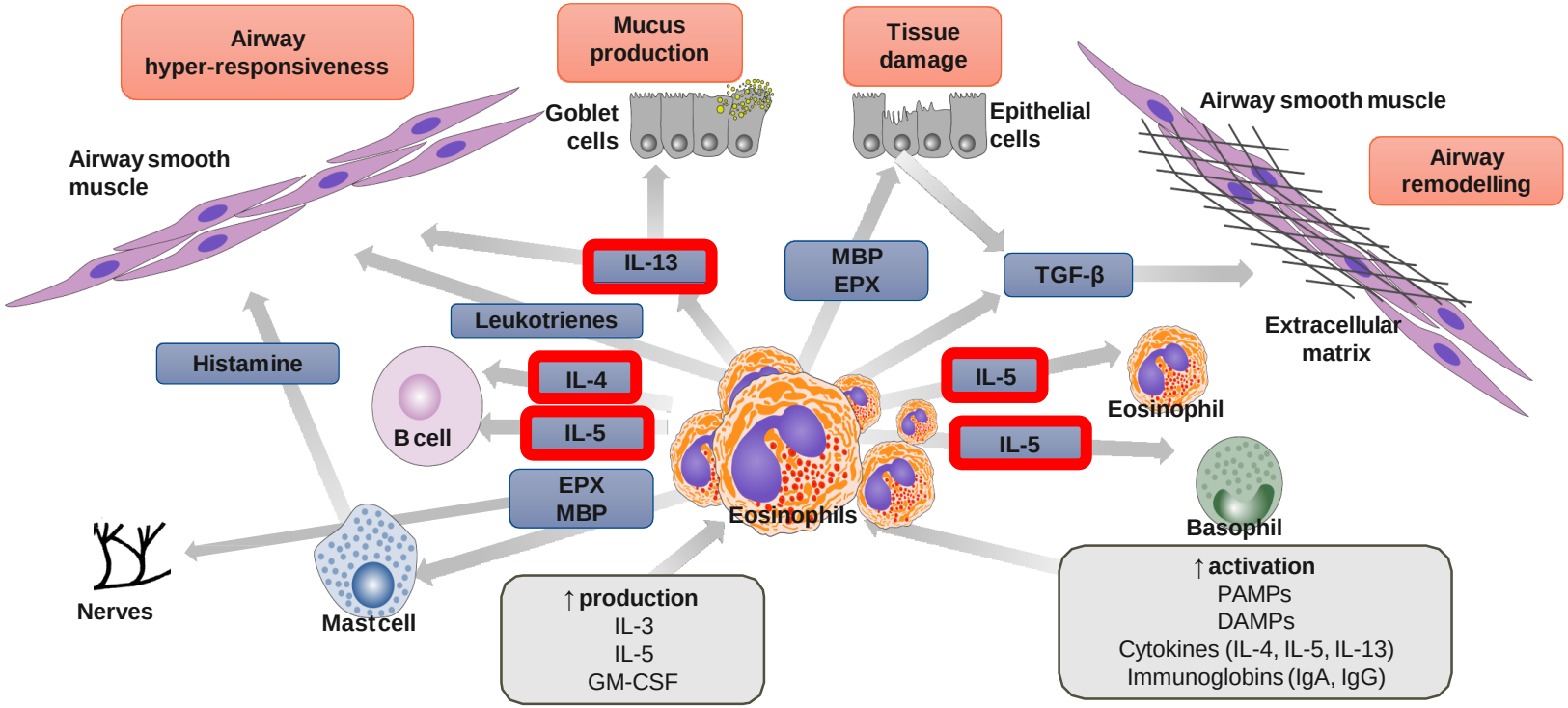
Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4Rα antibody, is required to broadly inhibit type 2 inflammation



…Only dual IL-4/IL-13 blockade prevented eosinophil infiltration into lung tissue without affecting circulating eosinophils, demonstrating that tissue, but not circulating eosinophils, contributes to disease pathology.

(Le Floc'h A. et al., Allergy. 2020;75:1188–1204)

Interleukin-5 & Eosinophils in the Pathophysiology of Severe Asthma



EPX: eosinophil peroxidase; DAMP: damage-associated molecular pattern; Ig: immunoglobulin; MBP: major basic protein; PAMP: pathogen-associated molecular pattern; TGF-β: transforming growth factor beta 1.

Image adapted from: 1. McBrien CN, Menzies-Gow A. *Front Med (Lausanne)*. 2017;4:93. 2. Menzella F, *et al. J Asthma Allergy.* 2015;8:105–14.
3. Varricchi G, *et al. Front Immunol.* 2017;8:242. 4. Drake MG, *et al. Sci Transl Med.* 2018;10:eaar8477.

Allergic bronchopulmonary aspergillosis (ABPA)

Allergic rhinitis

Bronchiectasis

COPD

Respiratory infection

Non-allergic rhinitis

Migraine

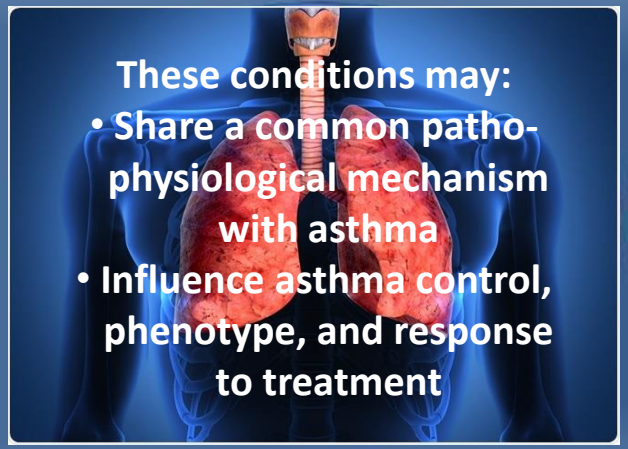
CRSwNP

Hyperventilation

Anxiety

Panic attacks

Allergic conjunctivitis



Psychiatric disorders

Skin disorders

Depression

Atopic dermatitis

Snoring

Metabolic syndrome

Sleep disorders

Food allergies

Gastrointestinal reflux disease (GERD)

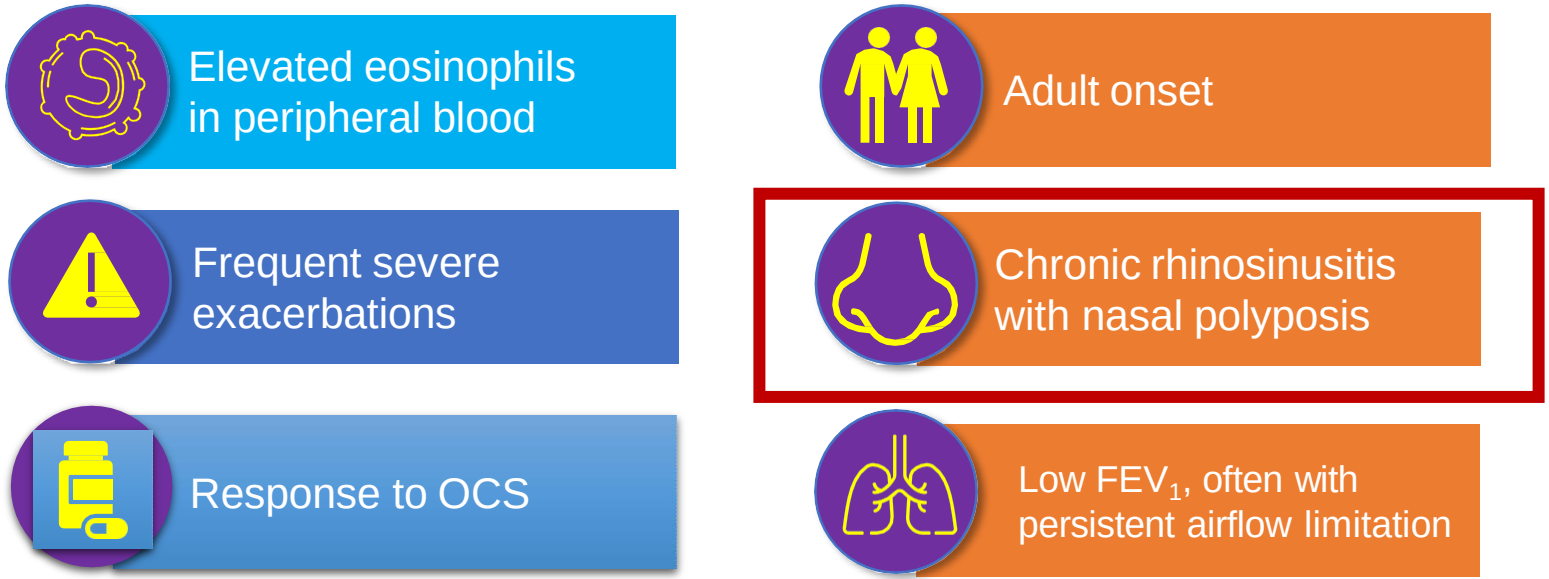
Obesity

Obstructive sleep apnea

Asthma comorbidities

* COPD: Chronic obstructive pulmonary disorder

Most Consistently Identifiable Features Associated With Severe Eosinophilic Asthma



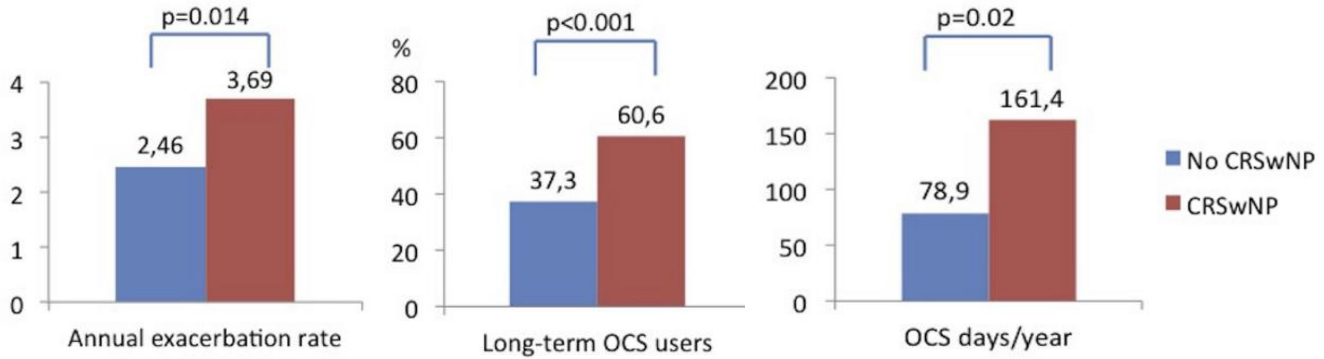
de Groot J et al. *ERJ Open Res*. 2015;1:00024-2015.

Major comorbidities

Patients with diseases driven by Type 2 inflammation can have an increased prevalence of other Type 2 inflammatory diseases

4. Bousquet J, et al. *Allergy*. 2008;63(Suppl. 86):8–160.
5. Vandeplas G. *Clin Transl Allergy*. 2015;5(Suppl. 4).
6. Porsbjerg C, et al. *Respirology*. 2017;22:651–661.
7. Ceylan E, et al. *Respirology*. 2007;12:272–276.
8. Stevens W, et al. *J Allergy Clin Immunol Pract*. 2016;4:565-572.
9. Kennedy JL, et al. *Am J Rhinol Allergy*. 2016;30:407–413.
10. Whiteley J, et al. *Curr Med Res Opin*. 2016;32:1645-1651.
11. Castro M, et al. *NEJM*. 2018;378:2486-2496.

Chronic rhinosinusitis with nasal polyps impact in severe asthma patients: Evidences from the Severe Asthma Network Italy (SANI) registry



695 patients with severe asthma enrolled in 66 SANI centers were analyzed.

The prevalence of CRSwNP was **40.6%**.

(Canonica GW et al., Respiratory Medicine 166 (2020) 2 april)

	Studies	Study participants with AD (n)	Prevalence % (95% CI) The **mean prevalence** of asthma among patients with atopic dermatitis was **25.7%**.	Studies	Study participants with AD (n)	OR (95% CI)
Sex						
Female	14	74,283	24.1 (18.8-29.9)	-	-	-
Male	13	6,380	27.9 (20.5-36.0)	-	-	-
Age						
Children <18	90	468,096	26.3 (23.5-29.1)	46	185,894	2.78 (2.50-3.10)
Adults >18	31	93,574	21.8 (18.4-25.4)	10	25,921	2.85 (1.67-4.85)

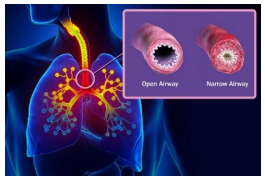
Ravnborg N. et al. :
Prevalence of asthma in patients with atopic dermatitis: a systematic review and meta-analysis,
***Journal of the American Academy of Dermatology* (2020)**

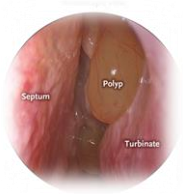
Chronic rhinosinusitis with nasal polyps impact in severe asthma patients: Evidences from the Severe Asthma Network Italy (SANI) registry

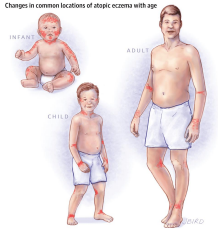
(Canonica GW et al., Respiratory Medicine 166 (2020) 2 april)

Demographic and clinical characteristics of SANI population.

	All the patients (n = 695)	Patients with CRSwNP (n = 282)	Patients without CRSwNP (n = 413)	p values
Mean age, years	54.9 ± 16.6	54.9 ± 12.9	55.13 ± 13.7	0.836
Female, %	60.6	61.3	60.0	0.731
Mean age of asthma onset, years	33.7 ± 16.6	34.5 ± 15.9	33.0 ± 17.2	0.290
Atopy, %	75.9	72.6%	79.8	0.184
BMI (mean, Kg/m^2)	26.6 ± 16.7	27.1 ± 22.8	25.9 ± 4.8	0.390
Annual exacerbation rate, mean	3.03 ± 5.55	3.69 ± 7.43	2.46 ± 3.00	0.014
FEV_1% predicted, mean	73.6 ± 20.4	74.4 ± 19.3	73.0 ± 21.4	0.440
Prevalence of atopic dermatitis, %	5.9	8.6	3.4	0.019
Prevalence of bronchiectasis, %	15.5	20.9	11.9	0.001
Prevalence of GERD, %	26.9	27.5	24.6	0.572
FE_{NO} (mean, ppb)	44.3 ± 48.9	54.4 ± 53.8	34.6 ± 28.3	<0.0001
Blood eosinophils (mean, cells/mcl)	492.3 ± 612.5	513.6 ± 607.2	471.9 ± 618.2	0.466
Serum IgE (mean, kU/l)	459.2 ± 850.1	379.4 ± 394.7	533.3 ± 1114.1	0.058







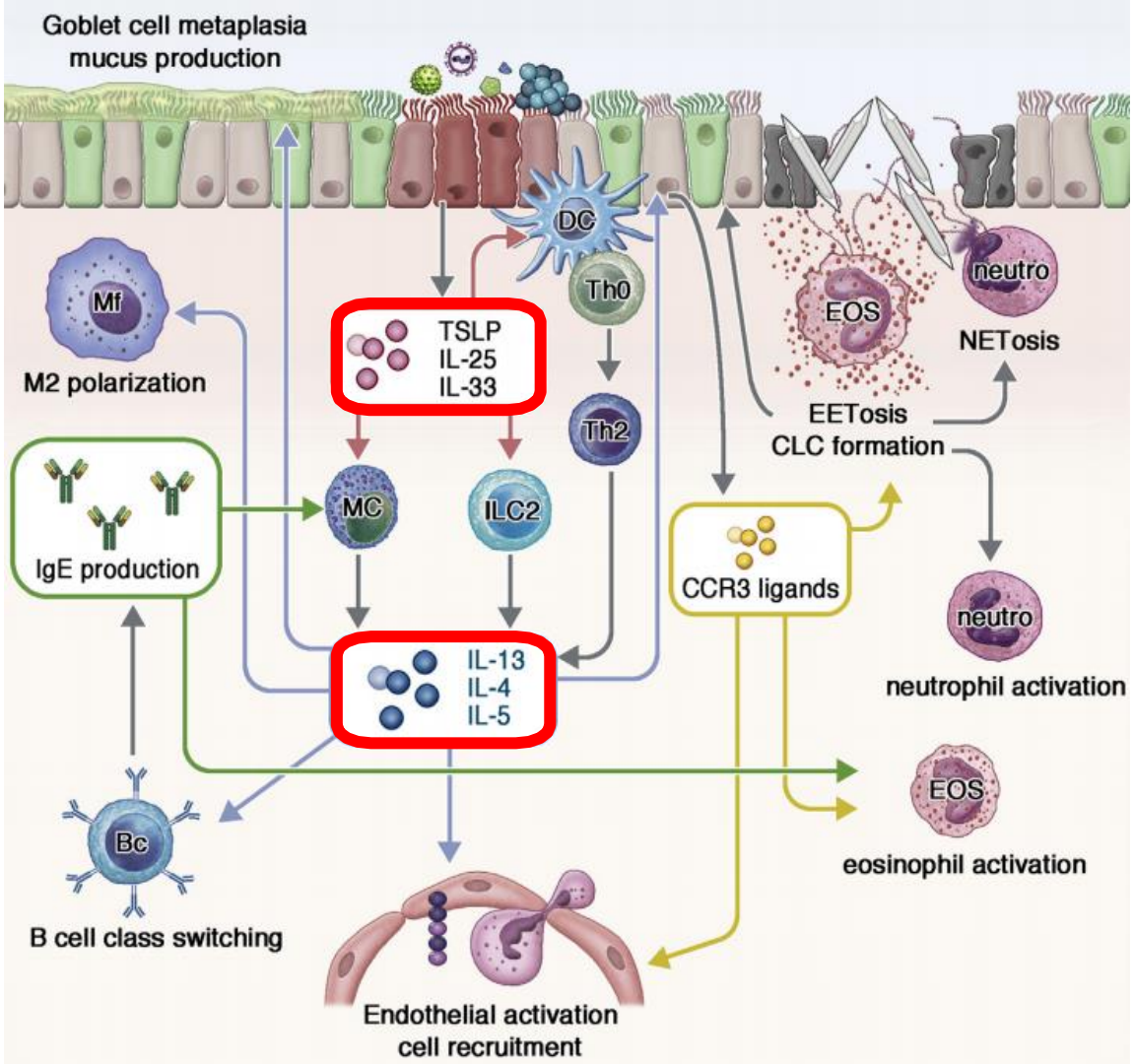
Atopic dermatitis was significantly more frequent in patients with CRSwNP (8.6%) than in subjects without nasal polyposis (3.4%).

Type 2 Comorbidities and Asthma Exacerbations

Independent baseline predictors of ≥ 2 asthma attacks during year 1 of a 2-year follow-up

	Adjusted OR (95% CI)
Rhinitis	1.14 (1.03, 1.27)
CRSwNP	1.60 (1.46, 1.76)
AD	1.13 (1.02, 1.25)

Blakely JD, et al. *J Allergy Clin Immunol Pract*. 2017;5:1015-1024.

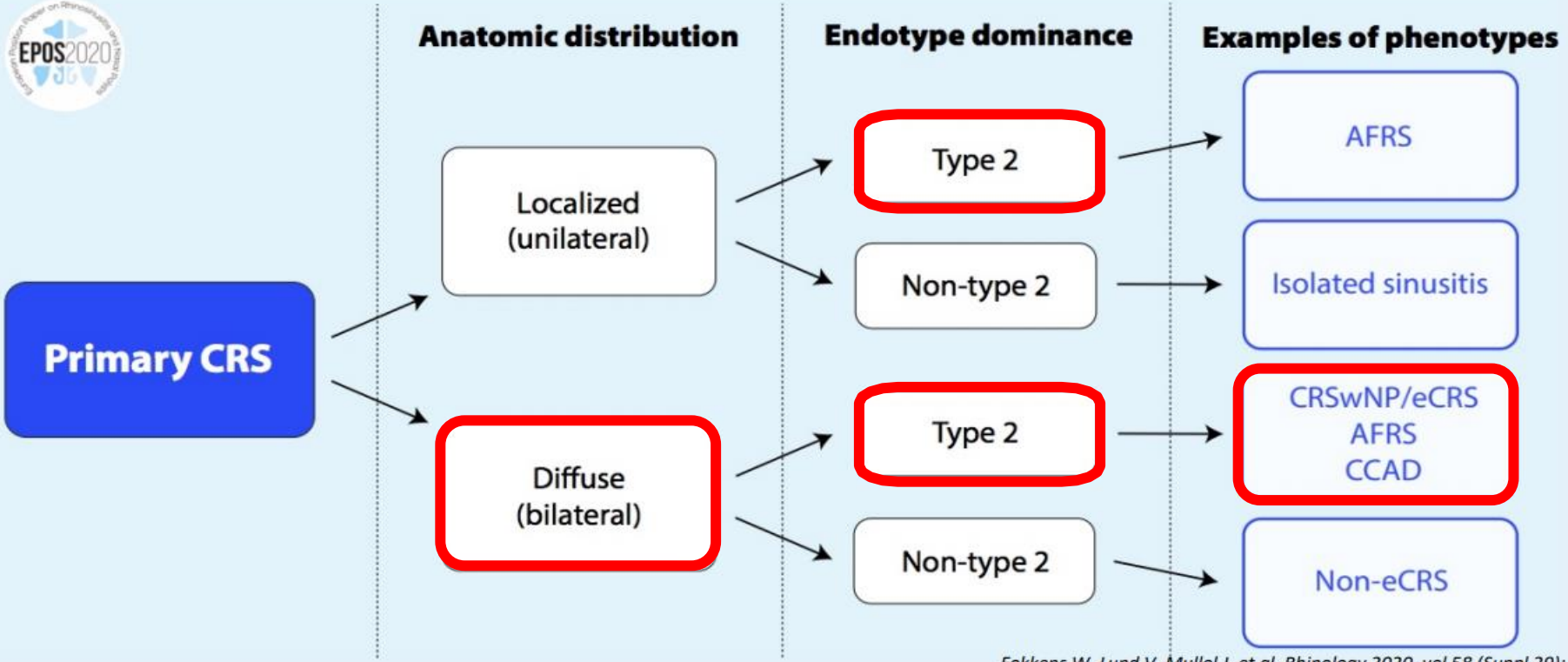


Biologics and their targets in type 2 inflammation in CRSwNP.

Target cytokines in type 2 immune reactions

(Bachert C et al., J Allergy Clin Immunol 2020; 145:725-39)

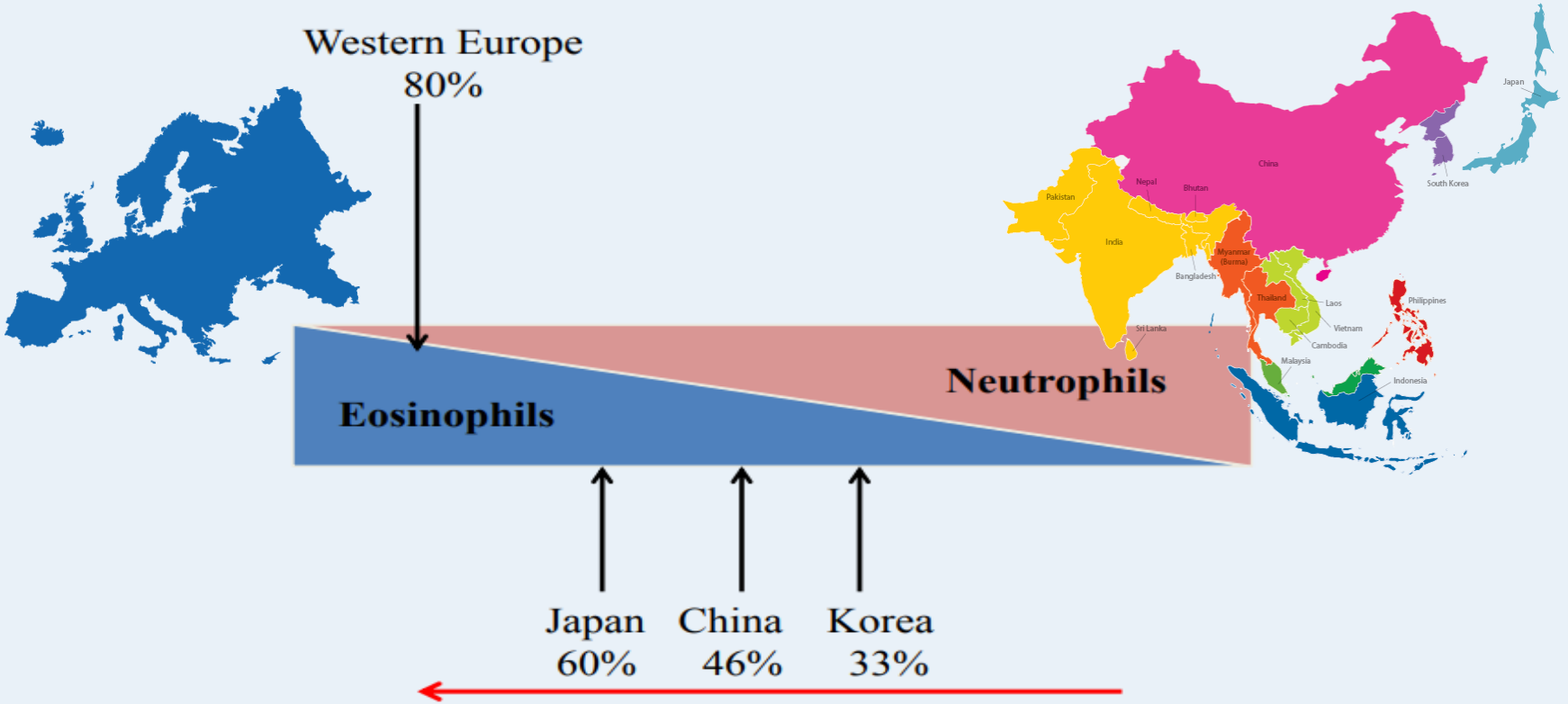
New Classification of CRS

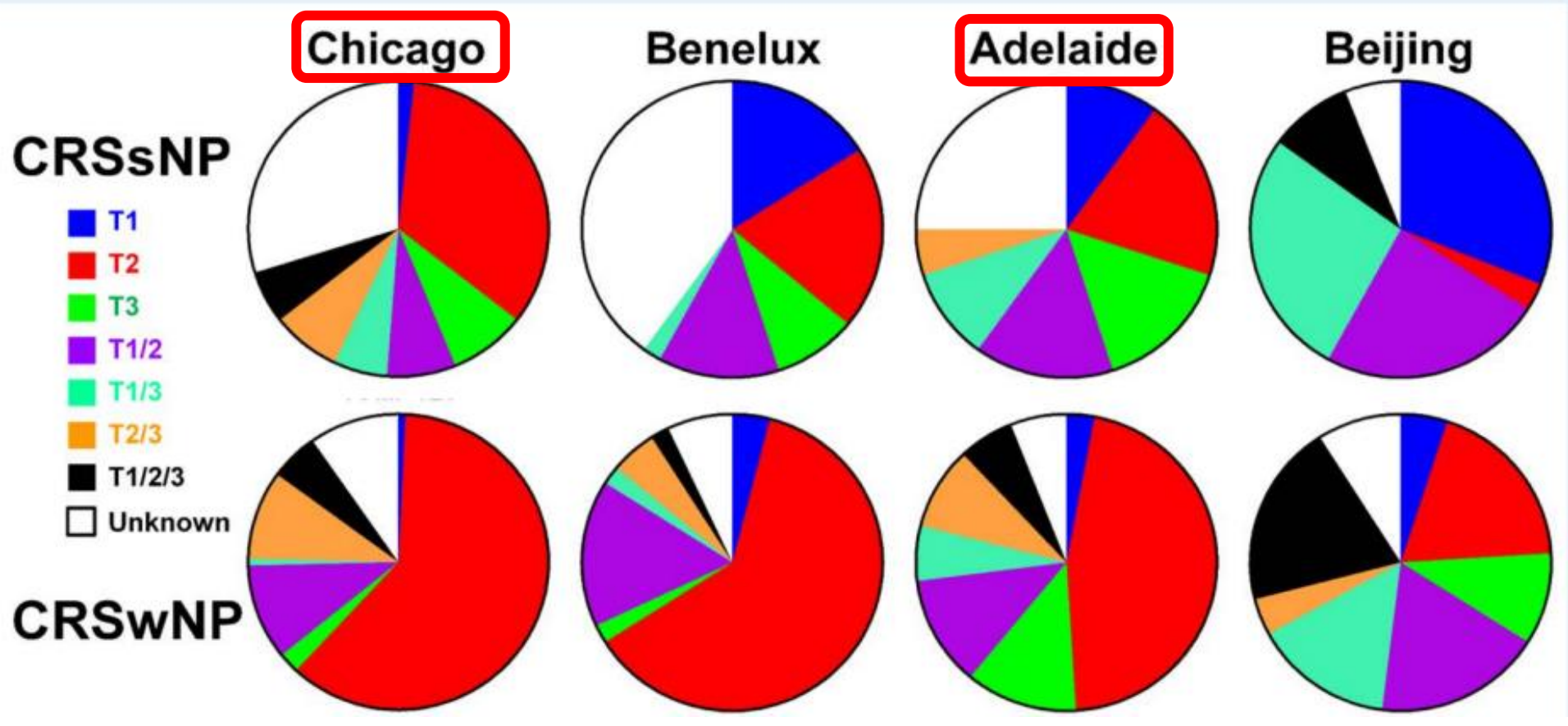


Fokkens W, Lund V, Mullol J, et al. Rhinology 2020, vol 58 (Suppl 29): 1-464.
web: www.epos2020.com, rhinologyjournal.com

Eosinophilia in NP- Western world view?

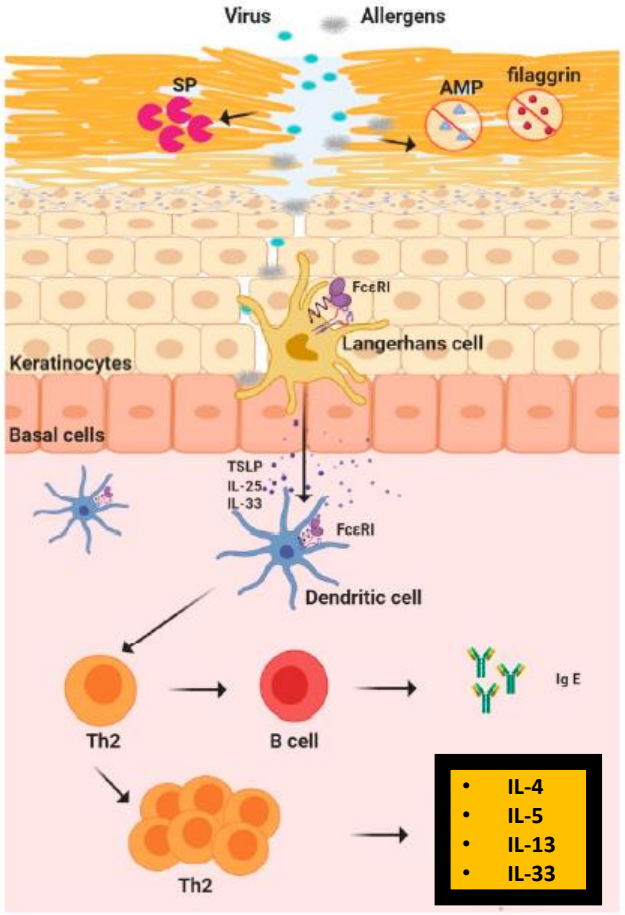
after *Nakayama et al Rhinology 2011;49:392-*





Kato A et al., unpublished. 2018 (updated)
Wang X and Bachert C al., *J Allergy Clin Immunol.* 2016

Skin barrier abnormalities and immune dysfunction are the main features of atopic dermatitis



Skin barrier abnormality

filaggrin ↓
ceramides ↓
antimicrobial peptides (AMP) ↓
serine protease (SP) inhibitors ↓

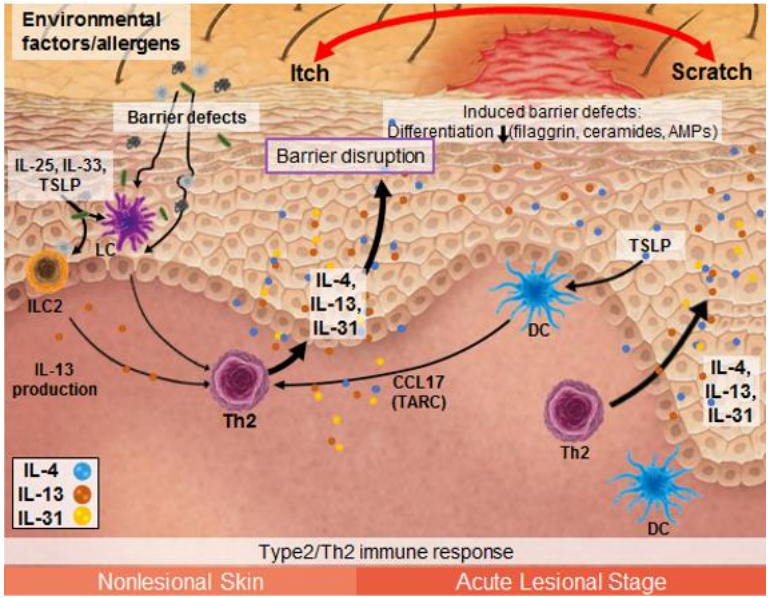
serine protease (SP) ↑
tight junction (TG) disorder ↑

Immune dysfunction

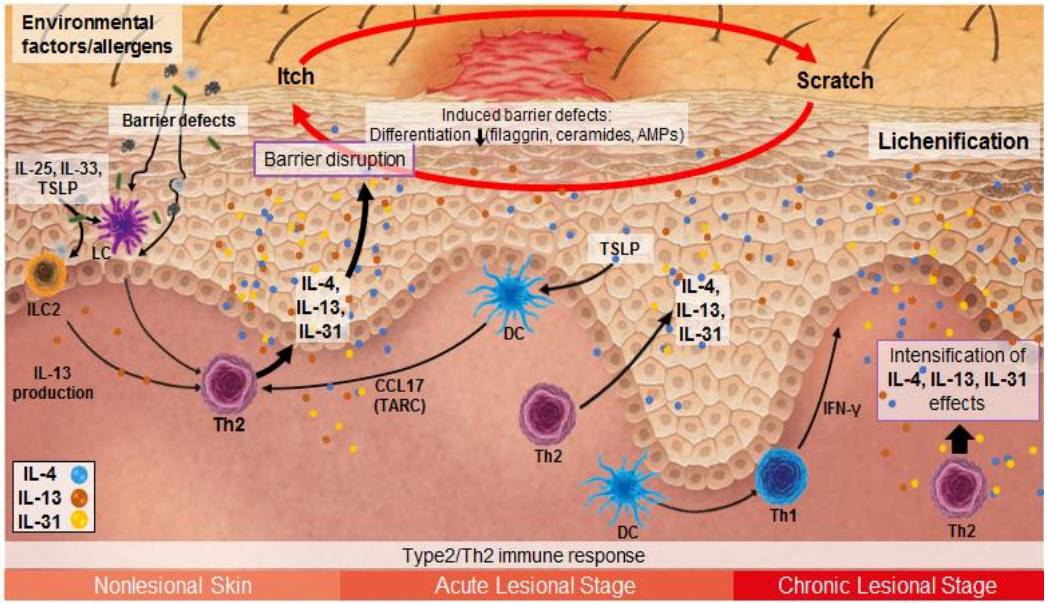
IgE levels ↑
sensitization to allergens ↑
Th2 cytokines ↑
FcεRI expression ↑
thymic stromal lymphopoietin (TSLP) ↑

(Yang G et al., Int. J. Mol. Sci. **2020**, 21, 2867)

In Acute Skin Lesions, Atopic Dermatitis Inflammation Is Associated With Increased Type 2 (including Th2) Cells

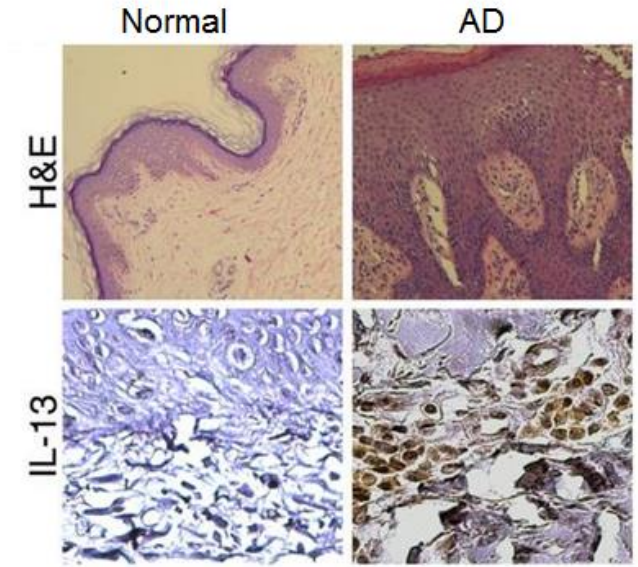


In Chronic Skin Lesions, Type 2 (Including Th2) Signaling Persists With an Increase in Th1 Activation

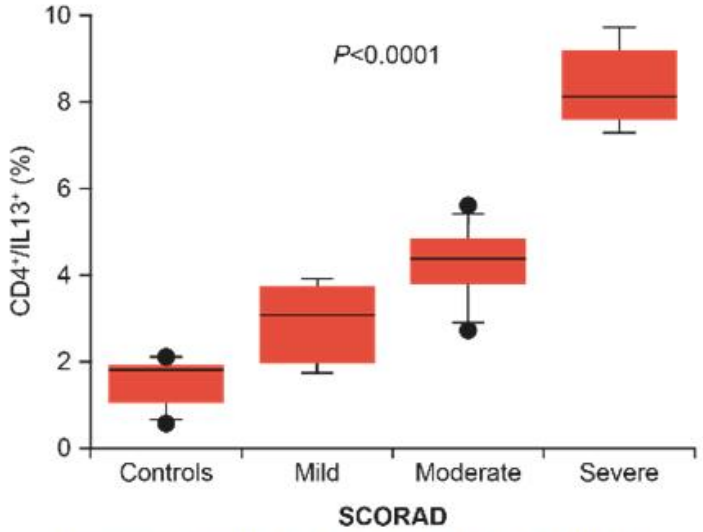


Noda S, Krueger JG, Guttman E. *J Allergy Clin Immunol* 2015;135:324–336.
Gandhi NA, Bennett BL, Graham NM *et al. Nat Rev Drug Discov* 2016;15:35–50.
Wynn TA. *Nat Rev Immunol* 2015;15:271–282.

IL-13 Cytokine Levels Correlate With Disease Severity



Increased level of IL-13$^+$ staining in skin from patients with AD compared with normal skin[1]

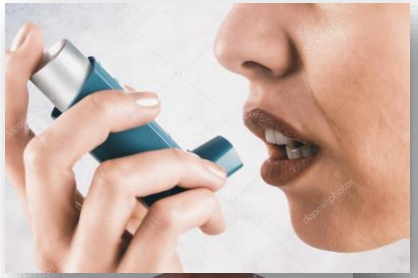


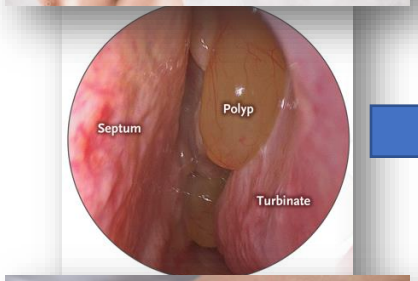
Increased levels of CD4$^+$IL-13$^+$ T cells in peripheral blood correlate with disease severity in pediatric patients[2]

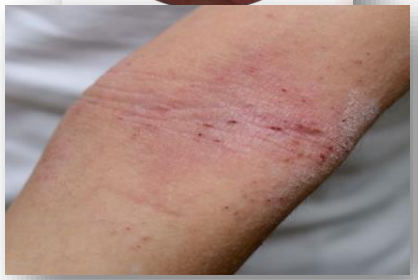
SCORAD, Scoring of Atopic Dermatitis.

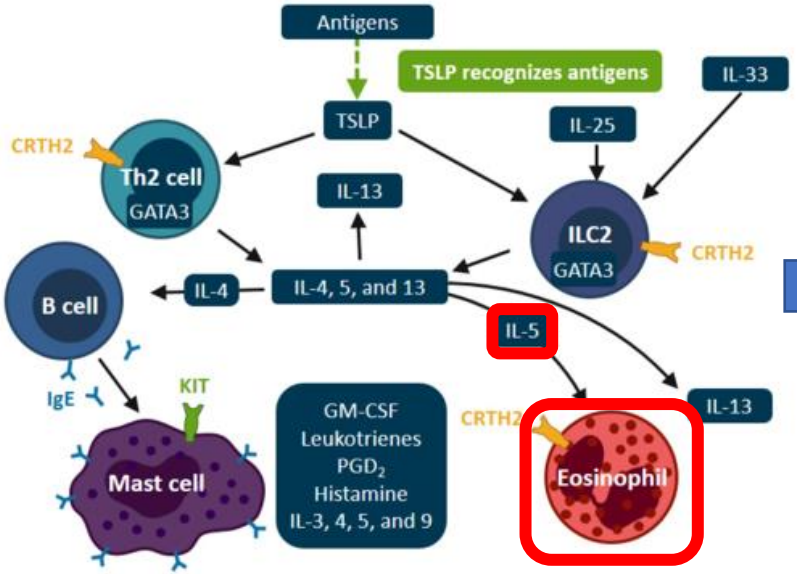
1. Geskin LJ *et al. Blood* 2015;125:2798–2805. 2. La Grutta S *et al. Allergy* 2005;60:391–395.

The Emerging Role of the Type 2 Inflammatory Cascade : A systemic disease?









Global Initiative for Asthma (GINA)

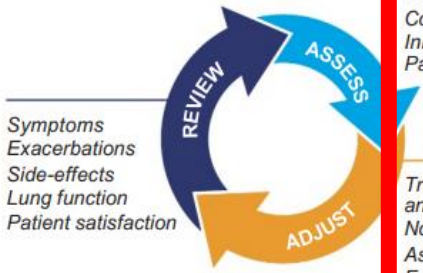
What's new in GINA 2021?

Updated 26 April 2021

GINA Global Strategy for Asthma Management and Prevention

Adults & adolescents 12+ years

Personalized asthma management
Assess, Adjust, Review
for individual patient needs



CONTROLLER and **PREFERRED RELIEVER**
(Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-formoterol
RELIEVER: As-needed low-dose ICS-formoterol			

CONTROLLER and **ALTERNATIVE RELIEVER**
(Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

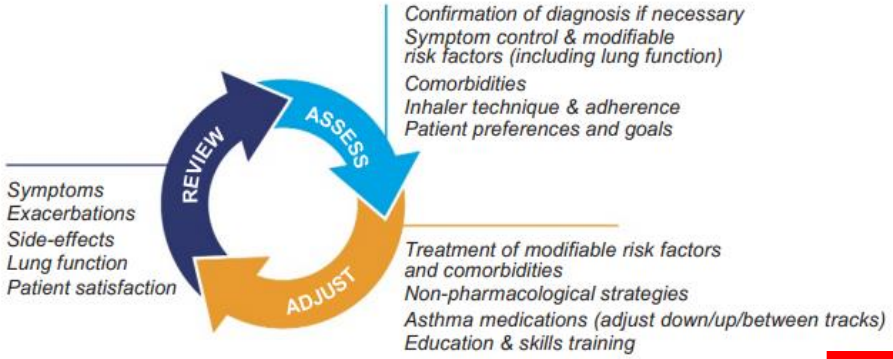
STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-LABA
RELIEVER: As-needed short-acting β2-agonist				

Other controller options for either track

	Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT	*Medium dose ICS, or add LTRA, or add HDM SLIT*	*Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS*	*Add azithromycin (adults) or LTRA; add low dose OCS but consider side-effects*

Adults & adolescents 12+ years

Personalized asthma management
Assess, Adjust, Review
for individual patient needs



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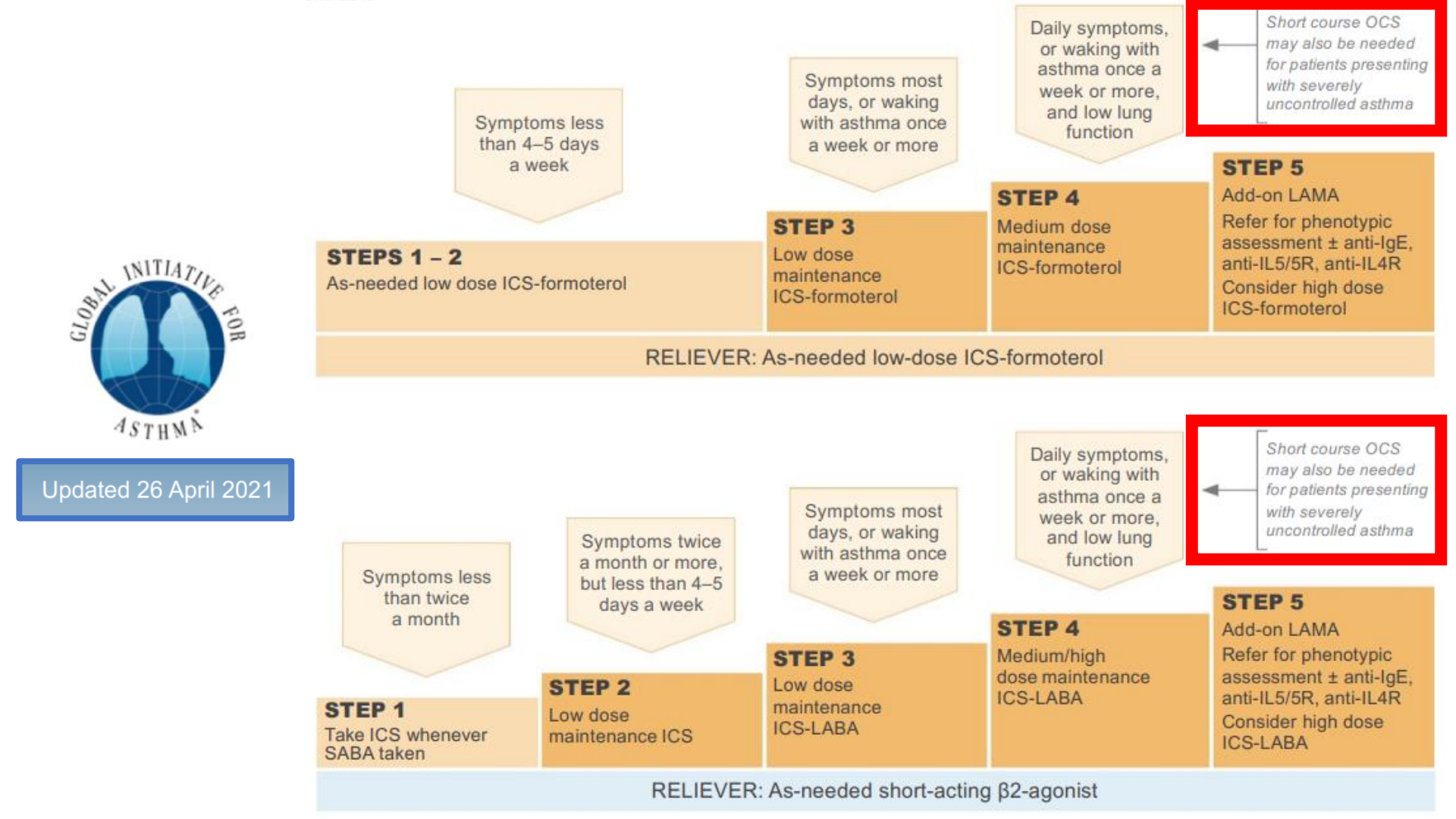
RELIEVER: As-needed low-dose ICS-formoterol			

CONTROLLER and **ALTERNATIVE RELIEVER**
(Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-LABA
RELIEVER: As-needed short-acting β2-agonist				

Other controller options for either track

	Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT	*Medium dose ICS, or add LTRA, or add HDM SLIT*	*Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS*	*Add azithromycin (adults) or LTRA; add low dose OCS but consider side-effects*


Symptoms less than 4–5 days a week
Symptoms most days, or waking with asthma once a week or more
Daily symptoms, or waking with asthma once a week or more, and low lung function
Short course OCS may also be needed for patients presenting with severely uncontrolled asthma
STEPS 1 – 2
As-needed low dose ICS-formoterol
STEP 3
Low dose maintenance ICS-formoterol
STEP 4
Medium dose maintenance ICS-formoterol
STEP 5
Add-on LAMA
Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R
Consider high dose ICS-formoterol
RELIEVER: As-needed low-dose ICS-formoterol
Updated 26 April 2021
Symptoms less than twice a month
Symptoms twice a month or more, but less than 4–5 days a week
Symptoms most days, or waking with asthma once a week or more
Daily symptoms, or waking with asthma once a week or more, and low lung function
Short course OCS may also be needed for patients presenting with severely uncontrolled asthma
STEP 1
Take ICS whenever SABA taken
STEP 2
Low dose maintenance ICS
STEP 3
Low dose maintenance ICS-LABA
STEP 4
Medium/high dose maintenance ICS-LABA
STEP 5
Add-on LAMA
Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R
Consider high dose ICS-LABA
RELIEVER: As-needed short-acting β2-agonist

20 to 60% of Patients With Severe or Uncontrolled Asthma Use OCS Therapy on a Regular Basis[1,2]

In Real-World Evidence Studies

15-22% of patients with severe asthma who received **long-term[a] or frequent short-term courses of OCS**[3-5]

42-64% of patients with severe asthma who received **long-term[a] OCS**[6-9]

[a]Long-term use encompasses any prolonged use of OCS that is not a short-term, acute course / burst of OCS to treat an asthma exacerbation. Long-term use is described in the literature as the following: maintenance OCS use, regular OCS use, daily OCS use and chronic OCS use. OCS = oral corticosteroid.

1. Bleecker ER et al. *Am J Respir* Crit Care Med. 2020;201:276-293; 2. Voorham J et al. *Allergy.* 2019;74:273-283; 3. Broder MS et al. *Ann Allergy Asthma Immunol*. 2017;118:629-647; 4. Phipatanakul W et al. *Am J Resp Crit Care Med.* 2017;195:1439-1448; 5. Moore WC et al. *J Allergy Clin Immuno*l. 2011;128:328-336; 6. Wang E et al. Chest. 2020;157:790-804; 7. Heffler E et al. *J Allergy Clin Immunol Pract*. 2019;7:1462-1468; 8. Shaw DE et al. *Eur Resp J*. 2015;46:1308-1321; 9. Sweeney J et al. *Thorax*. 2012;67:754-756.

Oral Corticosteroid-Related Adverse Events Are Common and Affect Multiple Organs in Patients With Asthma

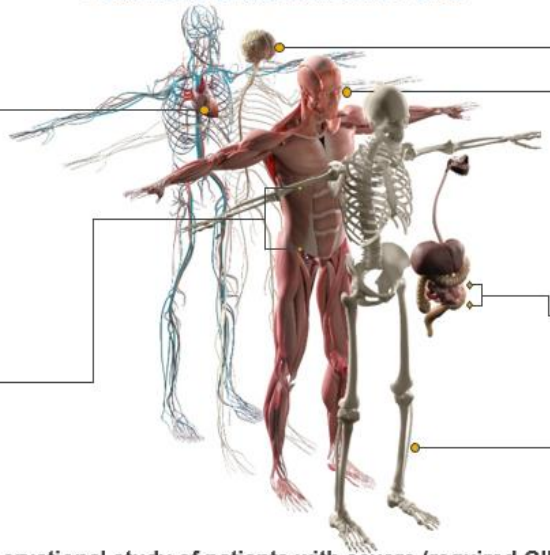
Odds of OCS-Related Morbidity (Severe vs. Mild/Moderate Asthma; n=4783)

Real World Evidence from OPCRD

Hypertension
OR, 1.35; p=0.001 (34% vs. 29%)

Cardiovascular disease
OR, 1.36; p=0.035 (10% vs. 7%)

Metabolic disorders:
Type II diabetes
OR, 1.46; p=0.006 (10% vs. 7%)
BMI >30 kg/m^2
OR, 1.36; p<0.001 (42% vs. 35%)



Psychiatric disorders
OR, 1.43; p<0.001 (38% vs. 31%)

Cataracts
OR, 1.89; p<0.001 (9% vs. 5%)

Dyspeptic disorders
OR, 3.99; p<0.001 (65% vs. 34%)

Osteoporosis
OR, 5.23; p<0.001 (16% vs. 4%)

Cross-sectional observational study of patients with severe (required GINA Step 5 treatment and ≥4 OCS prescriptions/year in 2 consecutive study years) and mild or moderate (GINA Step 2-3) asthma. Results are based on data from the OPCRD, a UK respiratory database (N=7195)

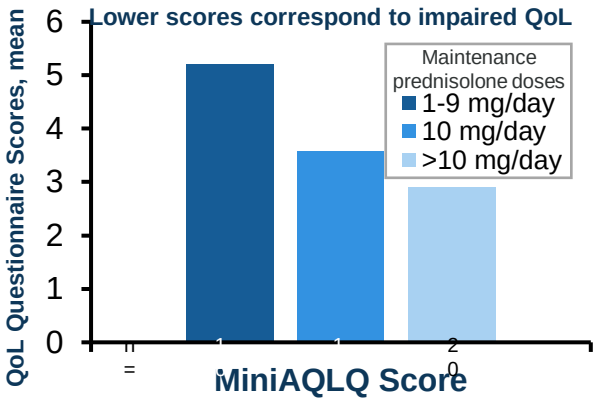
Note: Similar rates observed as OPCR database, in addition to high rates of osteopenia (35%) and obstructive sleep apnea (11%).
BMI = body mass index; GINA = Global Initiative for Asthma; OCS = oral corticosteroids; OPCRD = Optimum Patient Care Research Database; OR = odds ratio.
Sweeney J et al. *Thorax*. 2016;71:339-346.

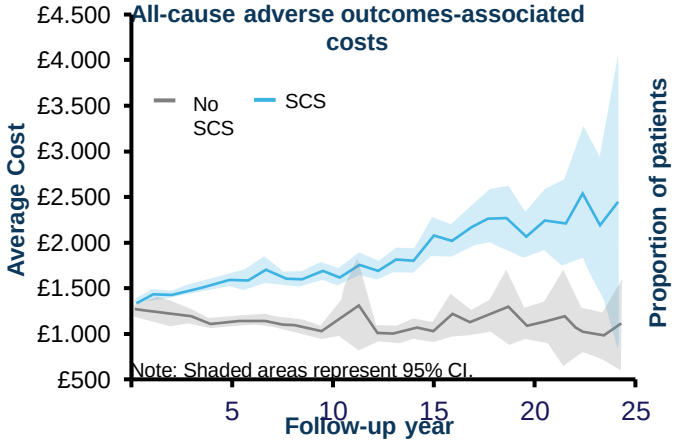
OCS Use is Associated With Reduced Quality of Life, Increased Health Care Cost and Mortality Risk

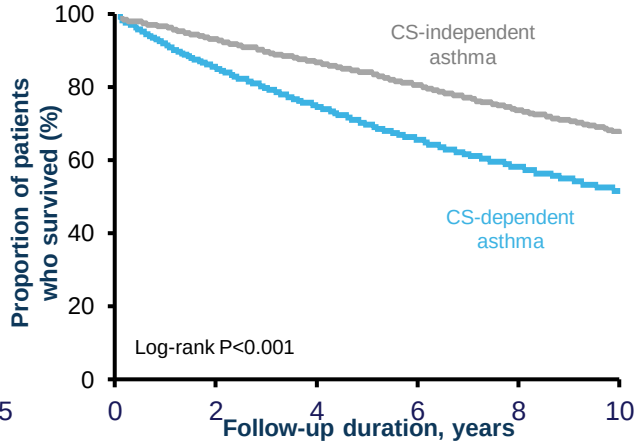
Increased OCS dose related to decreased quality of life[1]

1.5 to 2.2x increased SCS-related economic burden[2]

2.2x increased SCS-related mortality risk[3]



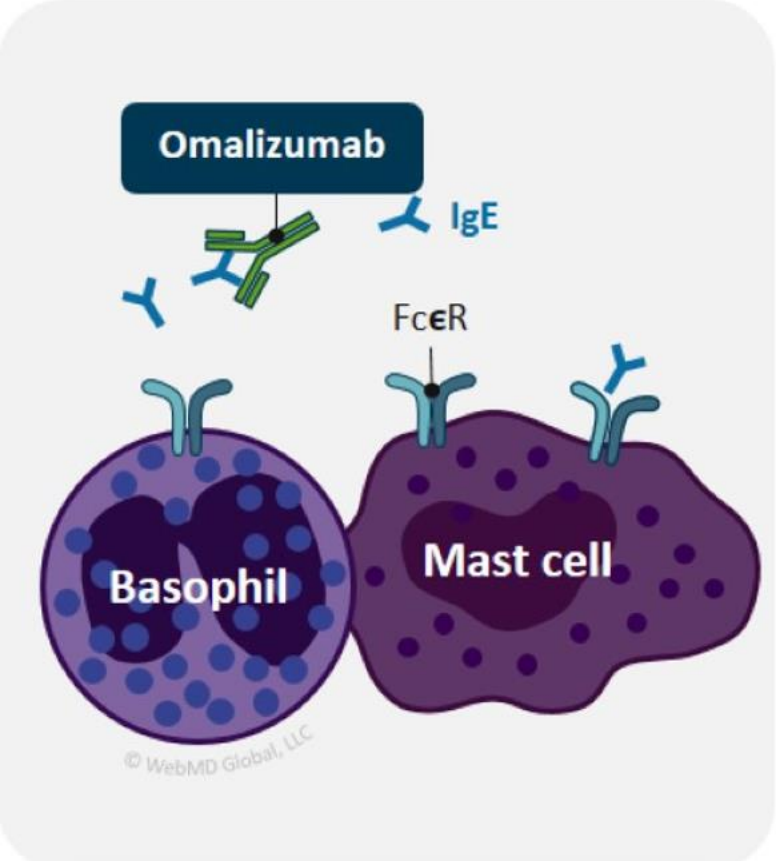


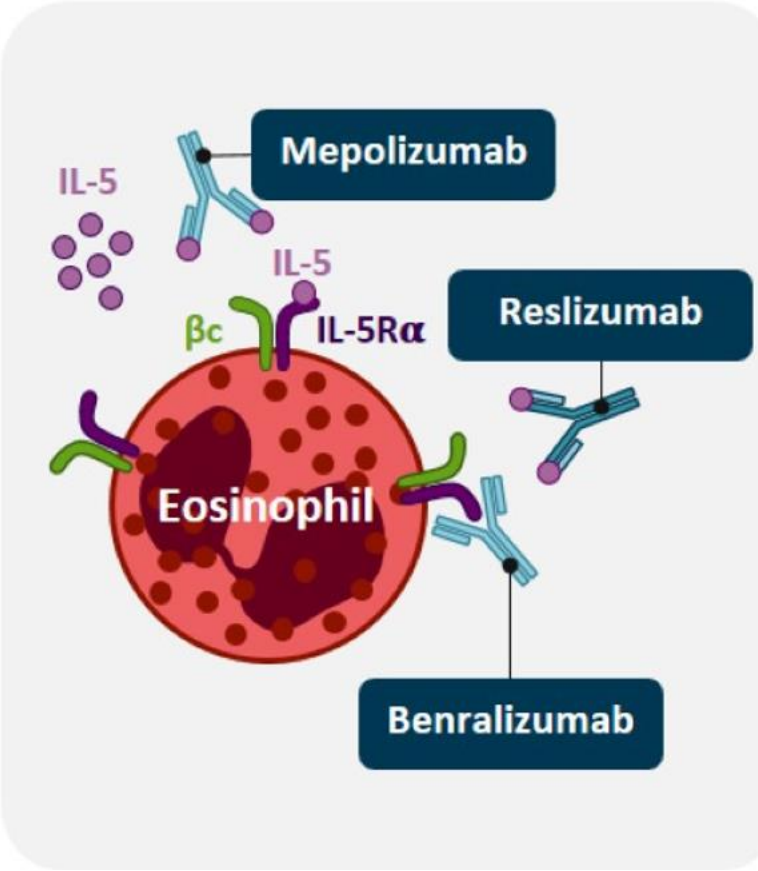


MiniAQLQ = Mini Asthma Quality of Life; OCS = oral corticosteroid(s); QoL = quality of life; SCS = systemic corticosteriod.

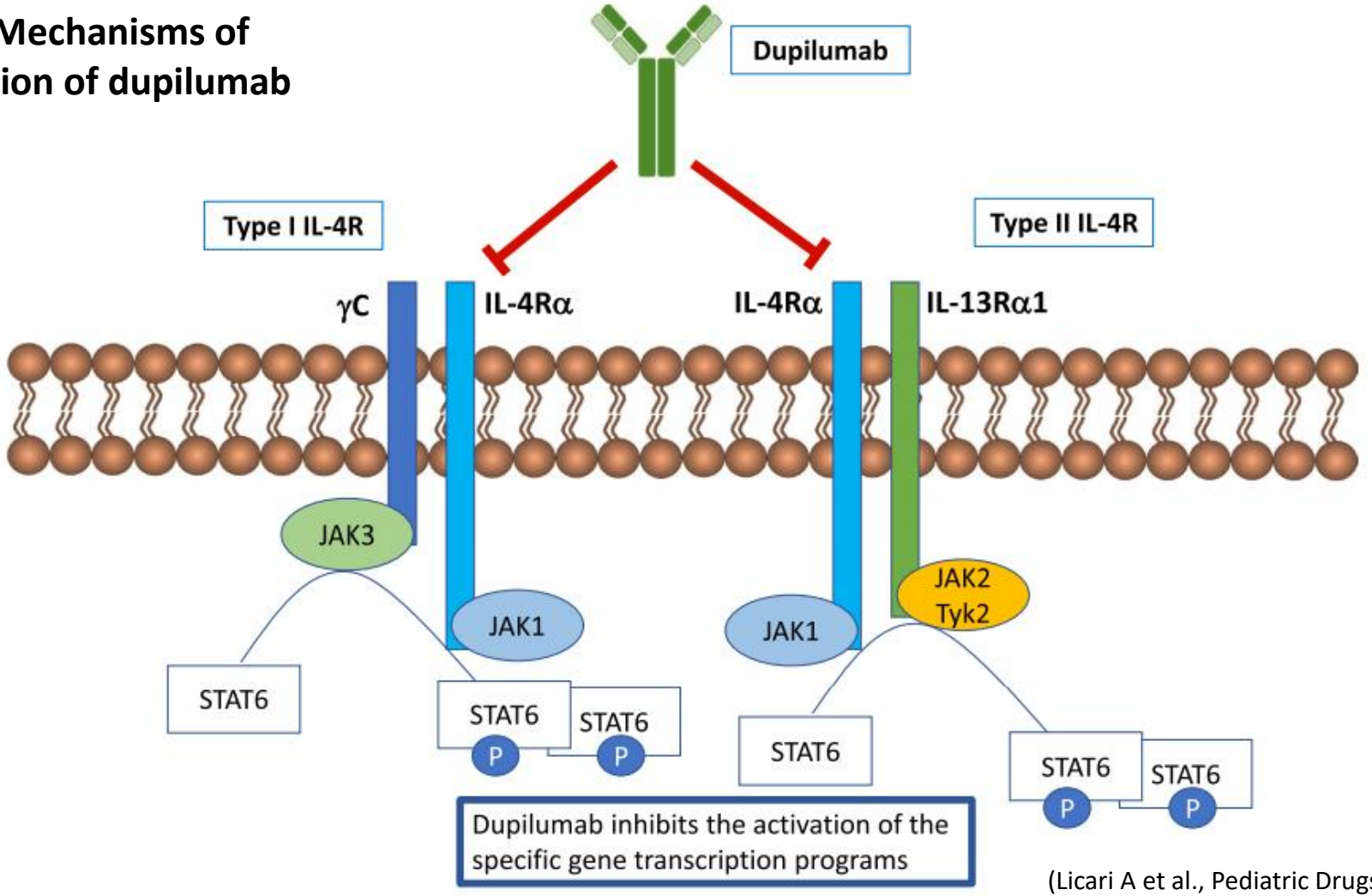
1. Hyland ME et al. *Eur Respir J*. 2018;52:1800618; 2. Voorham J et al. Article and supporting information. *Allergy*. 2019;74:273-283; 3. Lee H et al. *Eur Respir J.* 2019;54:1900804.

Novel Biologic Agents



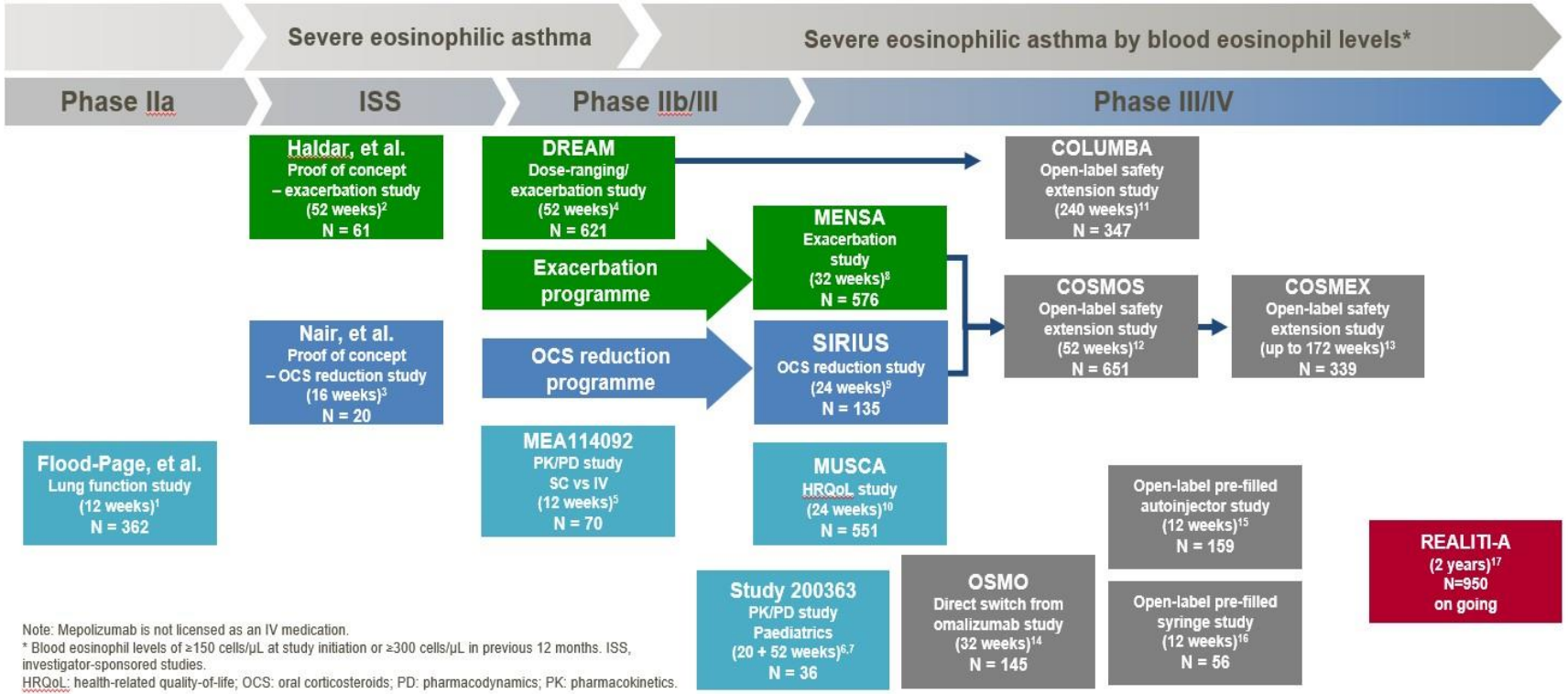


Mechanisms of action of dupilumab



(Licari A et al., Pediatric Drugs 2020)

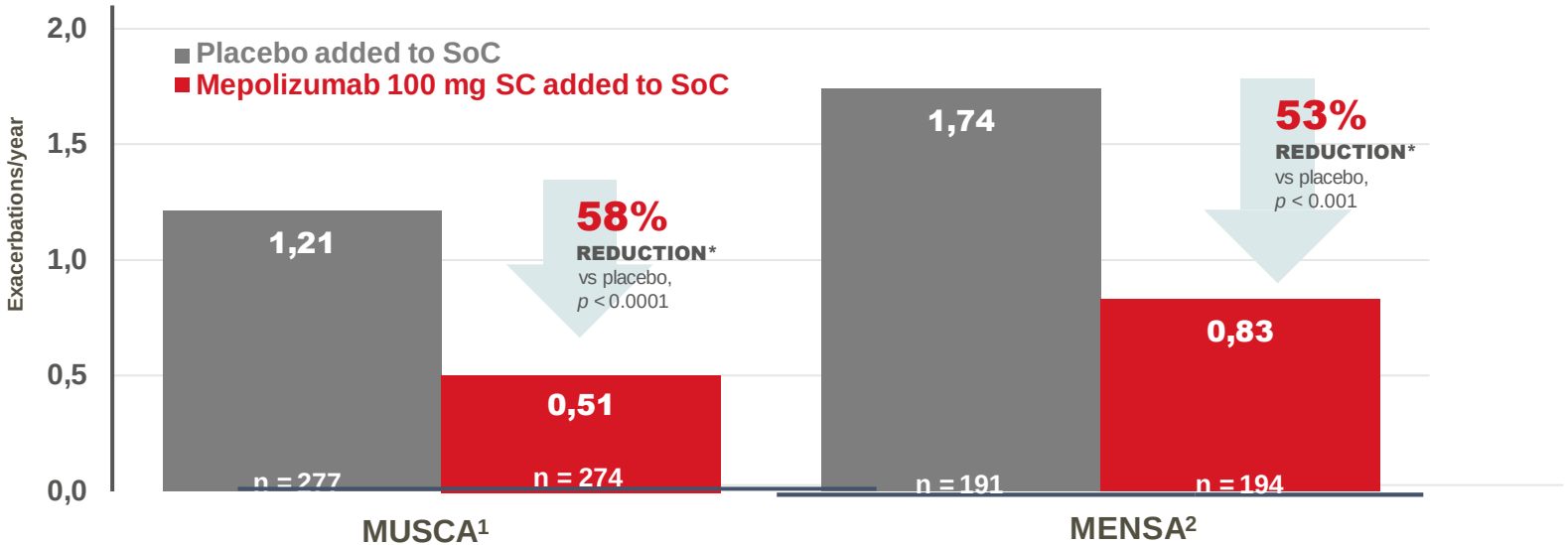
Programma di sviluppo clinico di mepolizumab negli adulti/adolescenti



Note: Mepolizumab is not licensed as an IV medication.
* Blood eosinophil levels of ≥150 cells/µL at study initiation or ≥300 cells/µL in previous 12 months. ISS, investigator-sponsored studies.
HRQoL: health-related quality-of-life; OCS: oral corticosteroids; PD: pharmacodynamics; PK: pharmacokinetics.

1. Flood-Page P, Swenson C, Faiferman I, et al., Am J Respir Crit Care Med. 2007;176:1062–1071; 2. Haldar P, Brightling CE, Hargadon B, et al., N Engl J Med. 2009;360:973–984; 3. Nair P, Pizzichini E, Kjarsgaard M, et al., N Engl J Med. 2009;360:985–993; 4. Pavord ID, Korn S, Howarth P et al., Lancet. 2012;380:651–659; 5. Pouliquen et al. Int J Clin Pharmacol Ther. 2015 Dec; 53(12): 1015–1027; 6. Gupta A et al, Pediatr Pulmonol. 2019 Sep 9. doi: 10.1002/ppul.24508; 7. Gupta A et al, J Allergy Clin Immunol. 2019 Nov;144(5):1336-1342.e7; 8. Ortega HG, Liu MC, Pavord IP, et al., N Engl J Med. 2014;371:1198–1207; 9. Bel EH, Wenzel SE, Thompson PJ, et al., N Engl J Med. 2014;371:1189–1197; 10. Chupp GL, Bradford ES, Albers FC, et al., Lancet Respir Med. 2017;5:390–400; 11. Khatri S, Moore W, Gibson PG, et al., J Allergy Clin Immunol. 2019;143:1742–1751; 12. Lugogo N, Domingo C, Chanez P, et al., Clin Ther. 2016;38:2058–2070; 13. Khurana S et al, Clin Ther. 2019 Oct;41(10):2041-2056.e5; 14. Chapman KR et al. Allergy. 2019 Sep;74(9):1716-1726; 15. Bernstein D, Pavord IP, Chapman KR, et al., J Asthma. 2019;28:1–12; 16.Bel EH;Journal of Asthma;2020;57;755-764; 17.

Mepolizumab: Powerful reductions in exacerbations

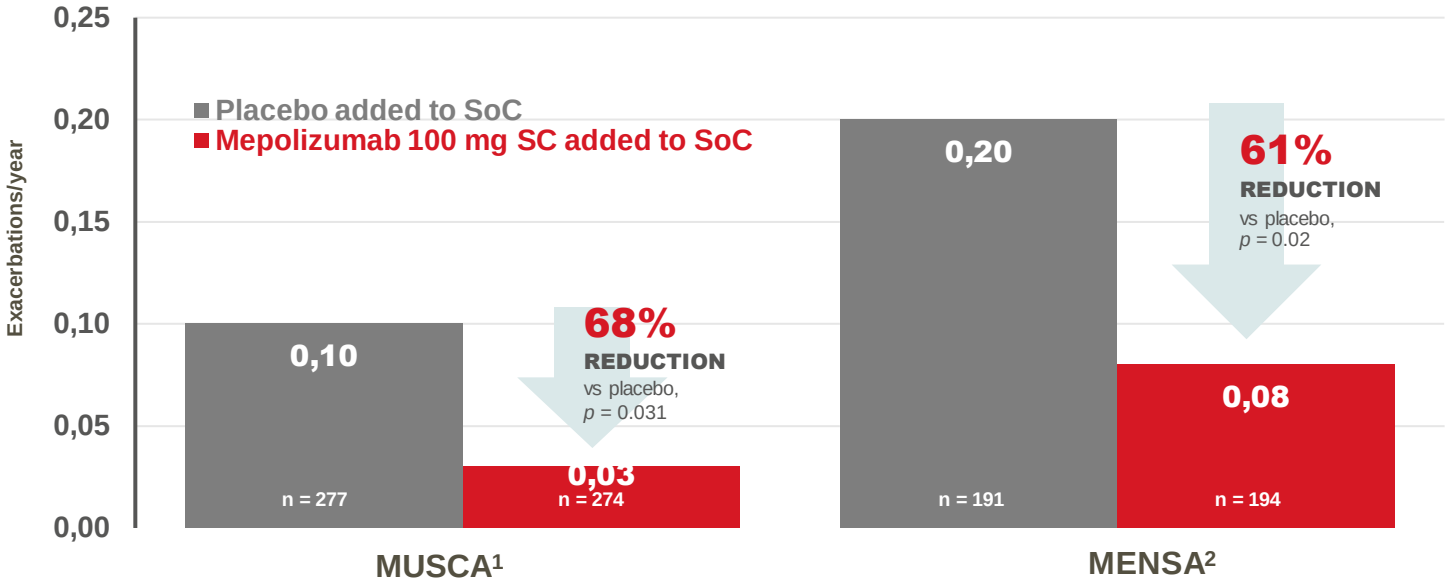


Mepolizumab significantly reduced the rate of clinically significant exacerbations vs placebo

- Additional study endpoint.
- SC, subcutaneous; SoC, standard of care.

1. Chupp GL, et al. *Lancet **Respir** Med*. 2017;5:390–400;
2. Ortega HG, et al. *N Engl J Med*. 2014;371:1198–1207.

Mepolizumab: reductions in exacerbations requiring hospitalisation / ED visit



Mepolizumab significantly reduced the rate of exacerbations requiring hospitalisation / ED visit vs placebo

ED, Emergency Department; SC, subcutaneous; SoC, standardof care.

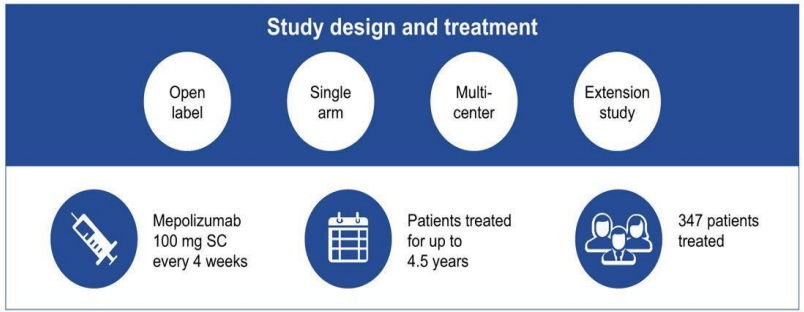
1. Chupp GL, et al. *Lancet Respir Med*. 2017;5:390–400;

2. Ortega HG, et al. *N Engl J Med*. 2014;371:1198–1207.

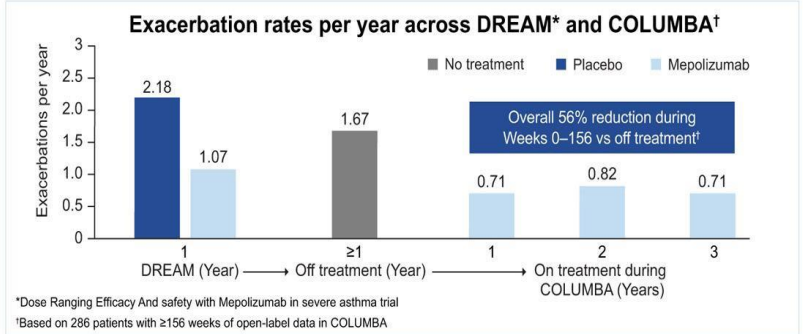
Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma

COLUMBA: Long-term safety and durability of mepolizumab response in patients with severe eosinophilic asthma

Study design and treatment



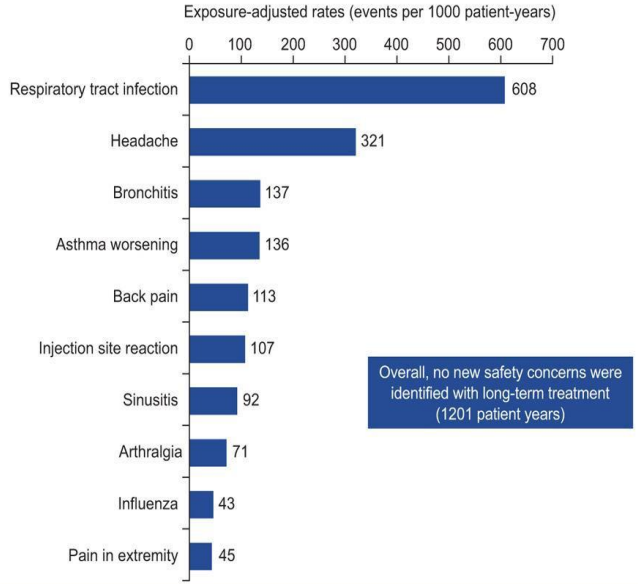
Exacerbation rates per year across DREAM* and COLUMBA†



*Dose Ranging Efficacy And safety with Mepolizumab in severe asthma trial

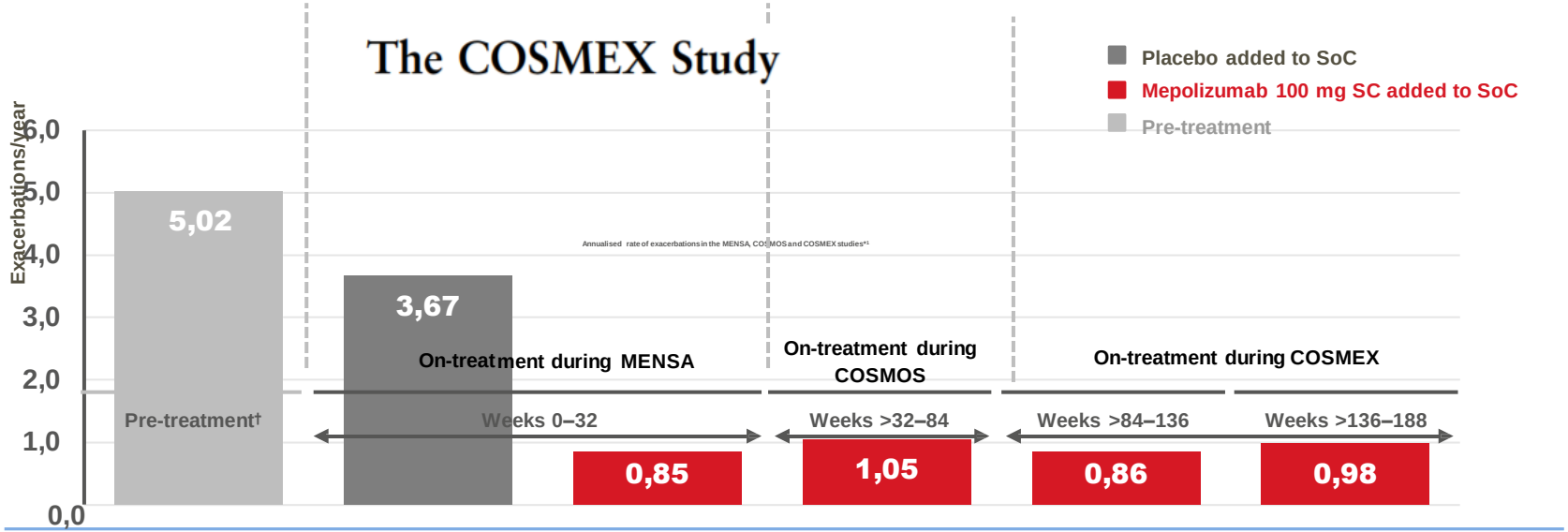
†Based on 286 patients with ≥156 weeks of open-label data in COLUMBA

On-treatment AEs occurring in >10% of patients during COLUMBA



(Khatri et al., J Allergy Clin Immunol 2018)

Mepolizumab Durability: sustained exacerbation reduction for up to 4.8 yrs



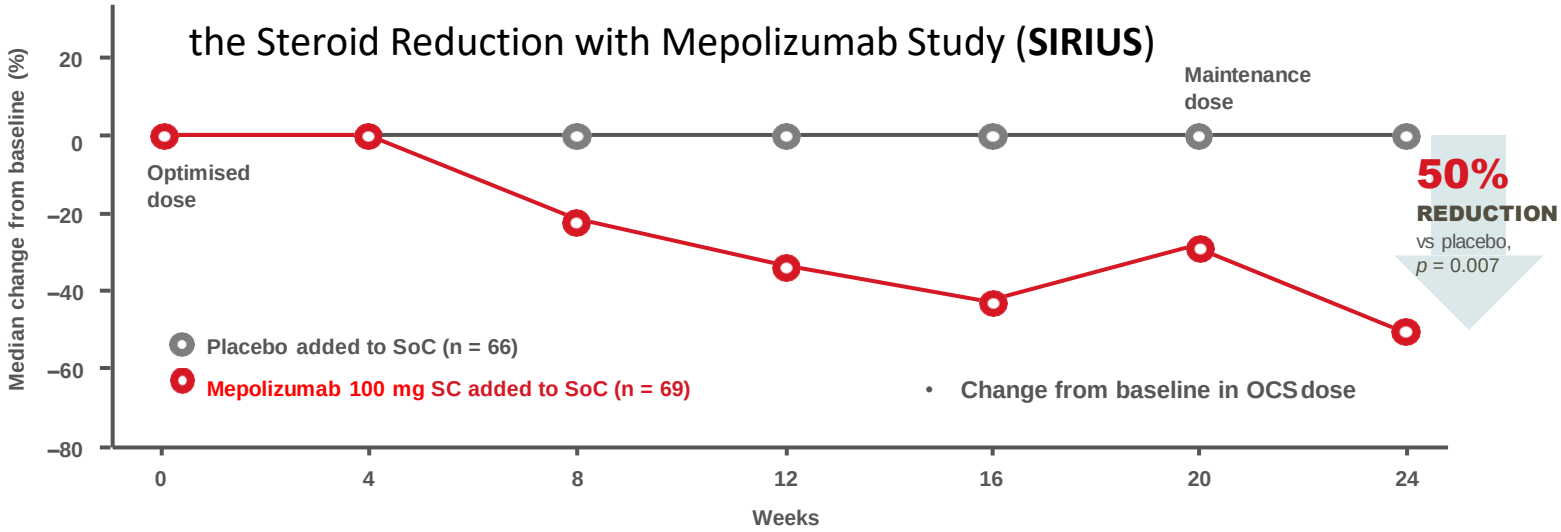
In patients with the most severe forms of severe eosinophilic asthma,‡ Mepolizumab provided up to 4.8 years of sustained exacerbation reduction

* In total, 95 patients with ≥188 weeks of continuous reporting across MENSA, COSMOS and COSMEX with ≤12 weeks between last dose in COSMOS and first dose in COSMEX are summarised (MENSA: placebo [n = 24], Nucala [n = 71]). The Nucala group in MENSA includes both patients treated with 100 mg SC and 75 mg IV doses (75 mg IV dose is not an approved dose of Nucala).[2] Analyses include clinically significant exacerbations from MENSA and all exacerbations from COSMOS and COSMEX. † Pre-treatment refers to the 12 months prior to enrolment in MENSA; ‡ Defined as life-threatening / seriously debilitating asthma prior to enrolment in Phase III trials: ≥1 intubation in lifetime, ≥1 hospitalisation or ≥3 exacerbations in prior year, OCS dose ≥10 mg at randomisation, FEV_1 ≤50% predicted and ACQ-5 score ≥3 or SGRQ score ≥60[1].

ACQ-5, Asthma Control Questionnaire – 5 questions; FEV_1, forced expiratory volume in 1 second; IV, intravenous; OCS, oral corticosteroid; SC, subcutaneous; SGRQ, St George's Respiratory Questionnaire; SoC, standard of care.

1 Ortega HG et al, N Engl J Med. 2014;371:1198-207; Lugogo N et al, Clin Ther 2016; 38; 2058-2070; Khurana S et al, Clin Ther. 2019 Oct;41(10):2041-2056.e5

Mepolizumab:
Powerful reduction in OCS dose



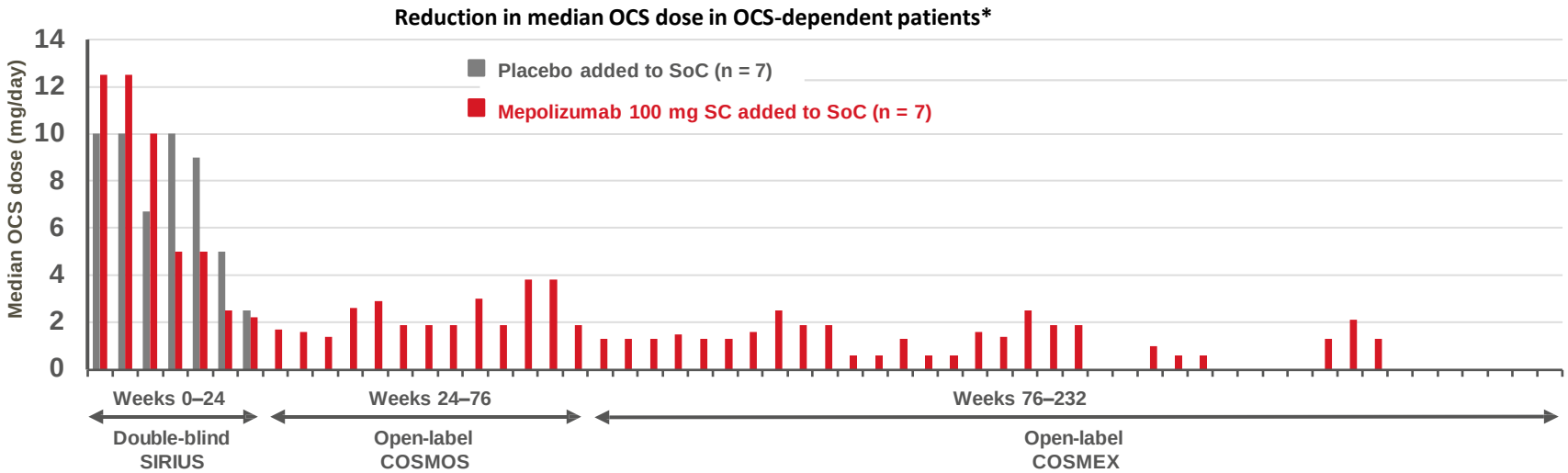
In patients with OCS-dependent asthma, Mepolizumab significantly reduced daily OCS dose by 50% vs placebo, while maintaining asthma control*

* At Week 24 when added to high-dose ICS and additional maintenance treatment (secondary study endpoint).

ICS, inhaled corticosteroid; OCS, oral corticosteroid; SC, subcutaneous; SoC, standard of care.

Bel EH, et al. *N Engl J Med*. 2014; 371:1189–1197.

Mepolizumab: Lasting reduction in OCS dose up to 4.8 years



In patients with the most severe forms of severe eosinophilic asthma and OCS-dependence,† Mepolizumab demonstrated durable OCS dose reduction for up to 4.8 years

The co-primary endpoints in COSMEX were frequency of adverse events and exacerbation rates.

* A total of 14 patients with ≥232 weeks of continuous reporting across SIRIUS, COSMOS and COSMEX with ≤12 weeks between the last dose in COSMOS and the first dose in COSMEX are summarised (SIRIUS: placebo [n = 7], Nucala [n = 7]).

† COSMEX enrolled patients with a history of life-threatening / seriously debilitating asthma prior to enrolment in Phase III trials: ≥1 intubation in lifetime, ≥1 hospitalisation or ≥3 exacerbations in prior year, OCS dose ≥10 mg at randomisation, FEV_1 ≤50% predicted and ACQ-5 score ≥3 or SGRQ score ≥60. ACQ-5, Asthma Control Questionnaire – 5 questions; FEV_1, forced expiratory volume in 1 second; OCS, oral corticosteroid; SC, subcutaneous; SGRQ, St George's Respiratory Questionnaire; SoC, standard of care.

Bel EH et al, N Engl J Med. 2014;371:1189-97; Lugogo N et al, Clin Ther 2016; 38; 2058-2070; Khurana S et al, Clin Ther. 2019 Oct;41(10):2041-2056.e5

WINDWARD programme : benralizumab Phase III in asthma

ZONDA
Efficacy and safety study of benralizumab to reduce OCS use in patients with uncontrolled asthma on high-dosage ICS/LABA and chronic OCS therapy

CALIMA
Efficacy and safety study of benralizumab in adults and adolescents with asthma inadequately controlled on medium- to high-dosage ICS/LABA

SIROCCO
Efficacy and safety study of benralizumab added to high-dosage ICS/LABA in patients with uncontrolled asthma

BORA
Safety extension study of benralizumab in asthmatic adults and adolescents on ICS/LABA

BISE
Efficacy and safety study of benralizumab in adults with mild to moderate persistent asthma

GREGALE
Functionality and reliability of the APFS in an at-home setting and performance of the APFS after use

PONENTE
Efficacy and safety study of benralizumab to reduce OCS use with a faster steroid tapering schedule in patients with uncontrolled asthma on high-dosage ICS/LABA and chronic OCS therapy

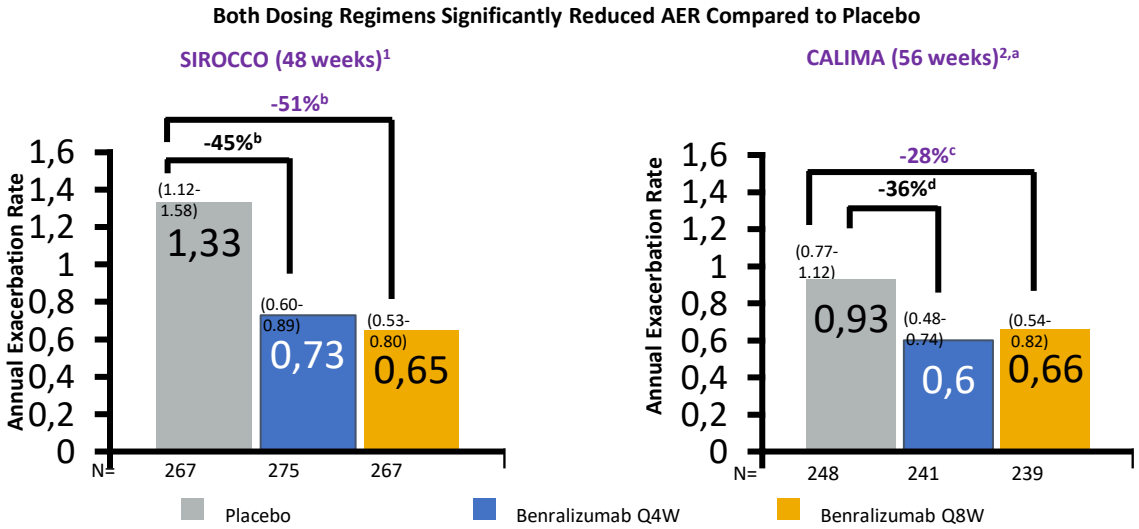
ANDHI/ AIP
Efficacy and safety study of repeat dosing of benralizumab on top of standard of care asthma therapy in adults and adolescents with severe uncontrolled asthma

MELTEMI
Safety extension study of benralizumab in asthmatic adults and adolescents on ICS/LABA

SOLANA
Study to evaluate the onset of effect and time course of change in lung function with benralizumab in patient with severe uncontrolled asthma and eosinophilic inflammation

GRECO
Study to assess functionality, reliability, and performance of a single-use auto-injector with benralizumab administered at home

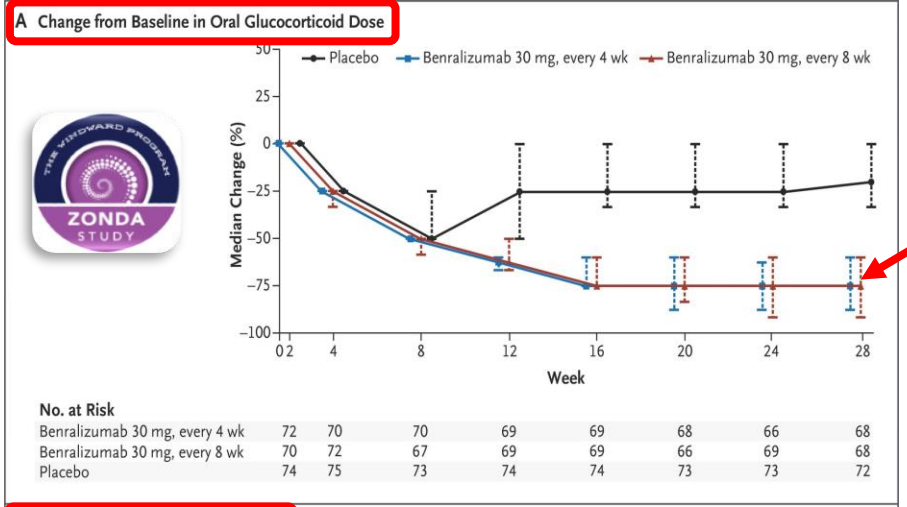
SIROCCO and CALIMA: Benralizumab Significantly Reduced AER (EOS ≥300 cells/µL, High-Dosage ICS plus LABA)

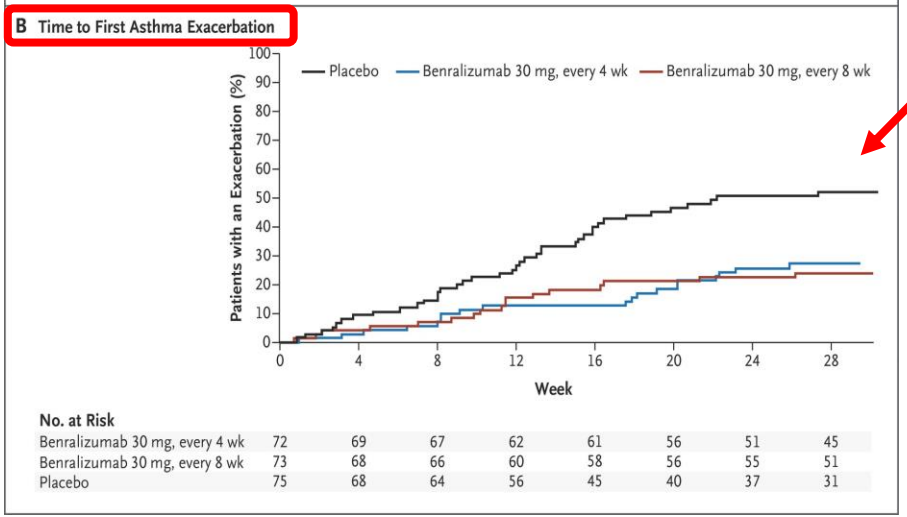


[a]Data for CALIMA from high-dosage ICS cohort. Analysis via negative binomial model, including covariates treatment group, region, number of exacerbations in the previous year, and use of maintenance oral corticosteroids. [b]p<0.0001; [c]p=0.0188; [d]p=0.0018. Notes: Values above bars represent 95% CI

AER = annual exacerbation rate; EOS = baseline blood eosinophil count; ICS = inhaled corticosteroid; Q4W = every 4 weeks; Q8W = every 8 weeks.

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





Median daily OCS dosage was reduced by 75% from baseline with benralizumab compared to 25% with placebo

Exacerbation Reduction in Benralizumab Patients in ZONDA Despite Reduced OCS Dependence.

Conclusions :

Benralizumab showed significant, clinically relevant benefits, as compared with placebo, on oral glucocorticoid use and exacerbation rates.

(Nair et al., N Engl J Med , Volume 376(25):2448-2458 , June 22, 2017)

Study Design

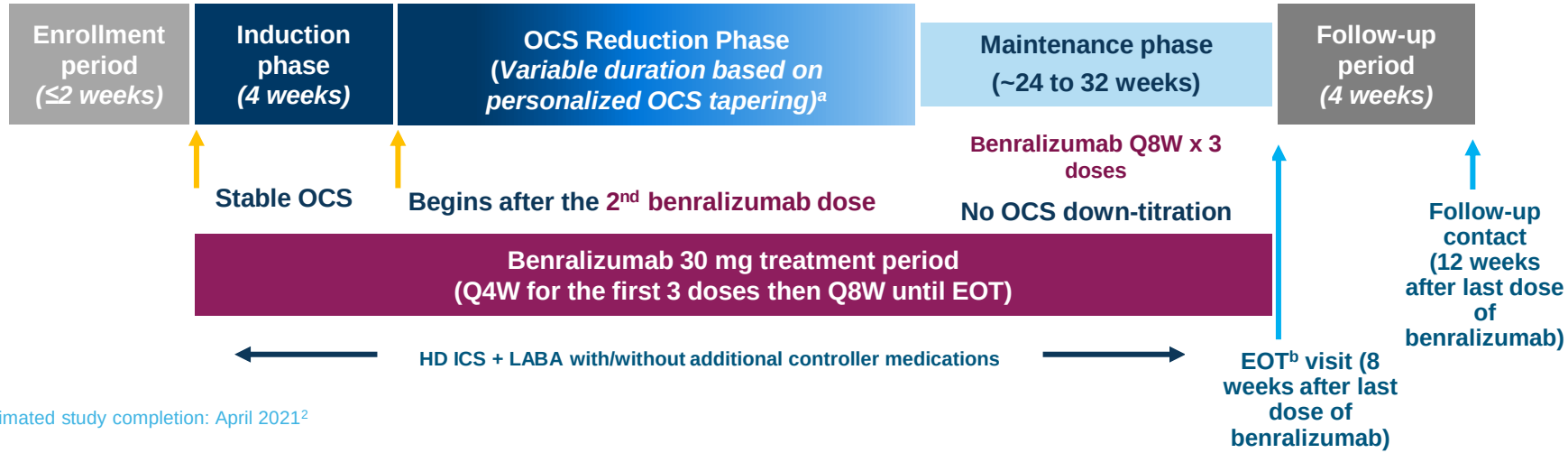
Multicenter, open-label study of benralizumab in OCS-dependent patients with asthma

Objectives

- To evaluate how quickly and safely OCS doses can be tapered to physiological doses (≥5 mg/day prednisone or equivalent)
- To demonstrate how to manage AI and how to taper OCS dose if AI is present

Population (N=598)[1,2]

EOS ≥150 cells/μL *or* EOS ≥300 cells/μL in past 12 months



Estimated study completion: April 2021[2]

[a]Guided by schema of OCS reduction defined in the study protocol; [b]EOT will vary from 32 to 42 weeks depending on patients baseline OCS dose and other factors.

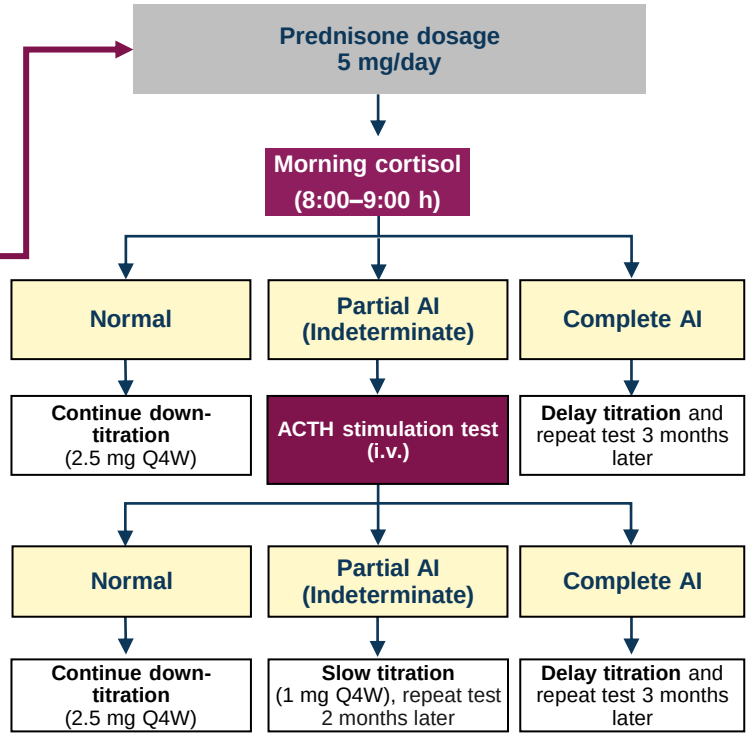
AI = adrenal insufficiency; EOS = eosinophils; EOT = end of treatment; HD = high-dose; ICS = inhaled corticosteroid; LABA = long-acting β2 agonist; OCS = oral corticosteroids; Q4W = every 4 weeks; Q8W = every 8 weeks.

1. Menzies-Gow A et al. *ERJ Open Res.* 2019;5:00009-2019; 2. Study NCT03557307. ClinicalTrials.gov website.

Algorithm for OCS-Tapering and Evaluation of Adrenal Function

Fast reductions from high OCS doses to 7.5mg/d followed by individualized tapering based on adrenal function

Baseline OCS dose (mg/day)	OCS reduction to reach a prednisone dose of:			
	20 mg/d	10 mg/d	7.5 mg/d	5 mg/d
>20	5 mg/d Q1W	5 mg/d Q2W	2.5 mg/d Q2W	2.5 mg/d Q4W
>10 to ≤20		5 mg/d Q2W	2.5 mg/d Q2W	2.5 mg/d Q4W
>7.5 to ≤10			2.5 mg/d Q2W	2.5 mg/d Q4W
>5 to ≤7.5				2.5 mg/d Q4W

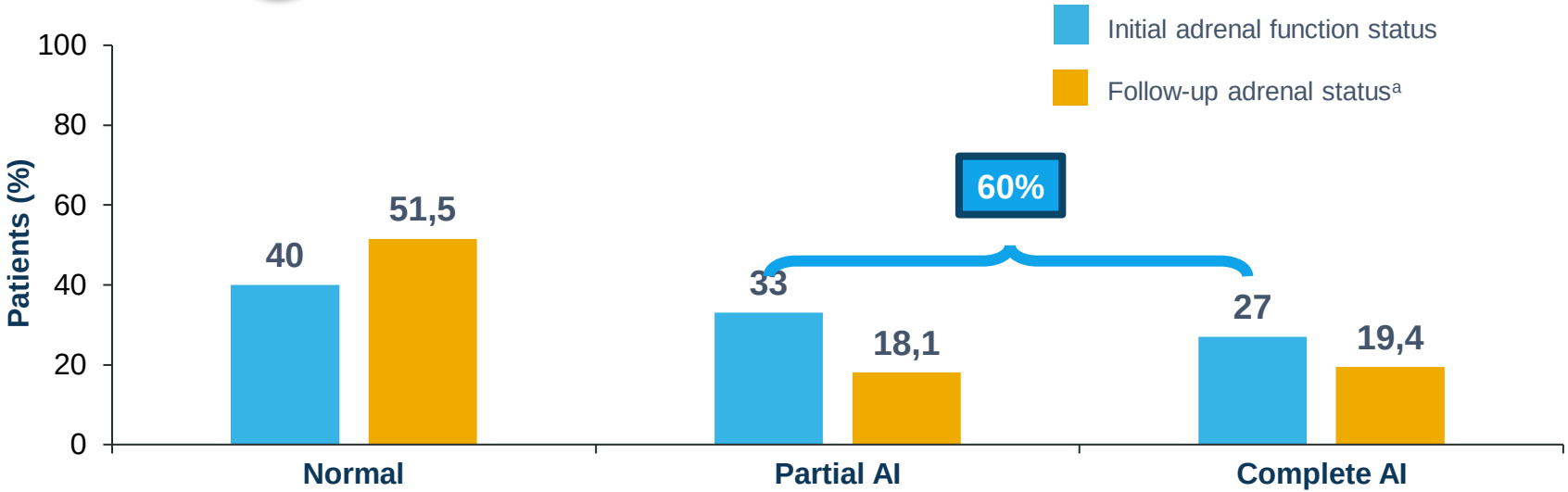


Note: If there are signs/symptoms of AI, physicians should reduce OCS more slowly (1 mg/Q4W), regardless of cortisol concentrations but no further tapering in the OCS dosage in the case of complete AI.
ACTH = adrenocorticotropic hormone; AI = adrenal insufficiency; d = day; HPA = hypothalamic-pituitary-adrenal; IV = intravenous; OCS = oral corticosteroid(s); Q1W = every 1 weeks; Q2W = every 2 weeks; Q4W = every 4 weeks.

Menzies-Gow A et al. *ERJ Open Res*. 2019;5:00009-2019.

Adrenal Function Status During OCS Reduction Phase

Although AI was commonly observed (60%), OCS dose was still reduced, when managed appropriately



Note: 68 patients with incomplete or missing adrenal function status information: 48 did not reach a stable daily OCS dosage of 5 mg and, therefore, did not undergo testing and 20 had indeterminate cortisol, but not ACTH evaluation to complete full adrenal function status. Therefore, percentages are based on N=530.

[a]58 patients with partial or complete AI (34 and 24 patients, respectively) at initial testing did not have adrenal function status completed at final HPA testing, leading to 141 patients with partial AI and 119 with complete AI being tested for adrenal function status at final HPA axis testing.

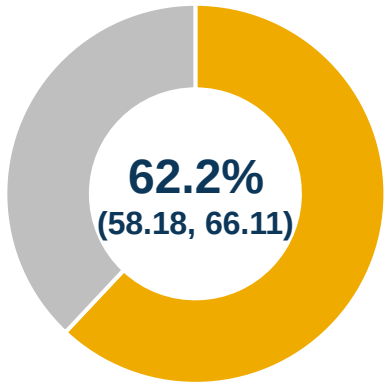
ACTH = adrenocorticotropic hormone; AI = adrenal insufficiency; m = months; OCS = oral corticosteriod.

Menzies-Gow A et al. Poster presented at: Virtual AAAAI Annual Meeting; February 26-March 1, 2021. Poster L45.

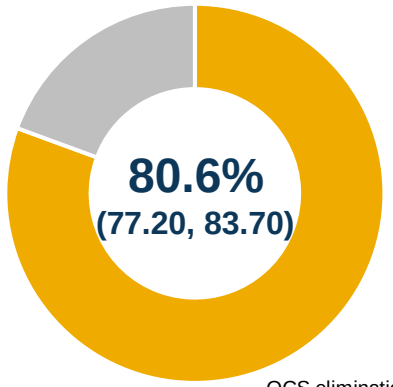
PRIMARY ENDPOINTS
Elimination or Reduction of OCS

The majority of OCS-dependent asthma patients eliminated or reduced OCS dose

100% reduction in OCS dose[a]



100% reduction or daily OCS doses of ≤5 mg, if AI[a]



Note: Data are provided with 95% confidence interval calculated using the Clopper-Pearson exact method. Analyses were descriptive only; no formal hypotheses were tested.
[a]Sustained over at least 4 weeks without worsening of asthma. [b]If reason for further reduction was AI.
AI = adrenal insufficiency; OCS = oral corticosteriod.
Menzies-Gow A et al. Poster presented at: AAAAI Annual Virtual Meeting; February 26-March 1, 2021. Poster L45.

dupilumab

Type 2, including Th2-mediated diseases

ATOPIC DERMATITIS

BRONCHIAL ASTHMA

Additional Indications

NASAL POLYPOSIS

Type 2, including Th2-mediated diseases

dupilumab

BRONCHIAL ASTHMA

- Liberty Asthma Quest
- Liberty Venture Asthma

Additional Indications

NASAL POLYPOSIS

- Liberty NP Sinus 24
- Liberty NP Sinus 52

Atopic Dermatitis Dupilumab Programme :

LIBERTY CLINICAL TRIAL PROGRAM IN ATOPIC DERMATITIS — A Broad Phase 3 Program in Adults With Moderate-to-Severe AD

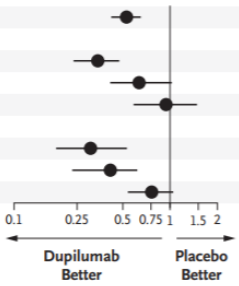
	Study	Design[1]	Population	N
1 Monotherapy	SOLO 1	Treatment period of 16 weeks	Patients inadequately controlled with or inadvisable for topical medications	671
	SOLO 2			708
	SOLO-CONTINUE	Treatment period of 36 weeks after completion of SOLO 1 or 2	Patients who achieved IGA 0-1 or EASI-75 at week 16 in SOLO 1 or 2	475
2 Concomitant administration with TCS	CHRONOS	Treatment period of up to 52 weeks (endpoints at 16 and 52 weeks)	Patients inadequately controlled with topical medications	740
	CAFÉ	Treatment period of 16 weeks	Severe patients only Uncontrolled or ineligible to oral CSA[2]	330
3 Open label extension	OLE	Open label extension for up to 3 years allowing use of topical therapy as needed	Patients who participated to previous studies	2600

Liberty Asthma Quest

Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma

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)

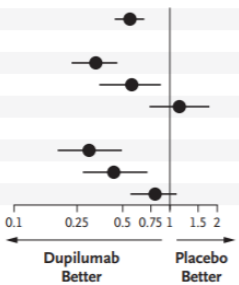
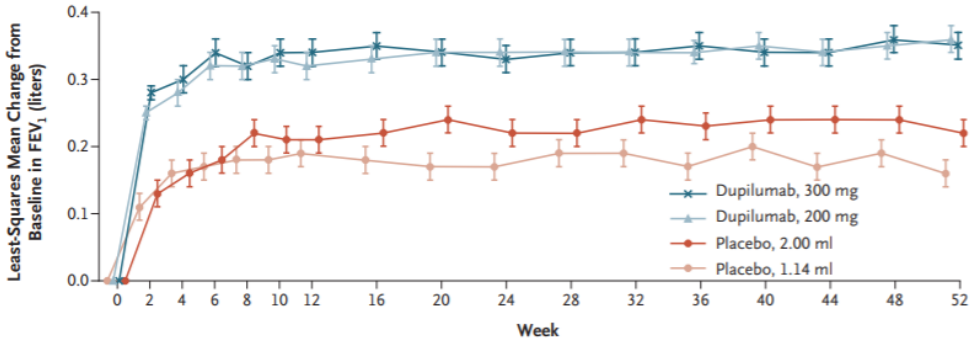


Figure 1. Forest Plots of the Risk of Severe Asthma Exacerbations in the Intention-to-Treat Population and in Subgroups Defined According to Baseline Blood Eosinophil Count and Baseline FE_{NO}.

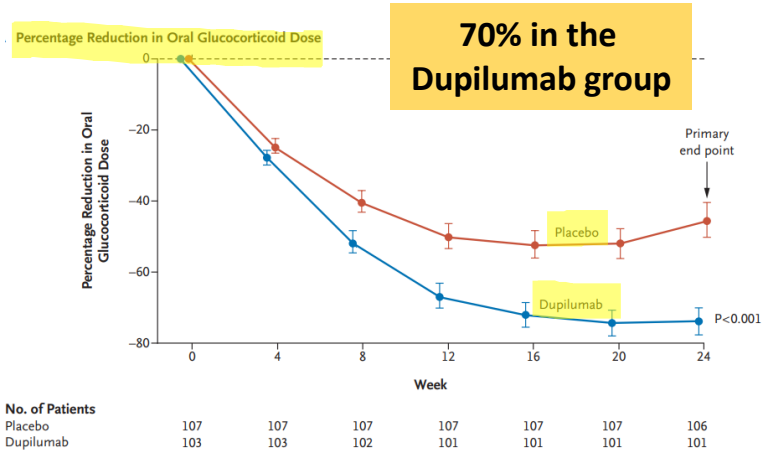


In conclusion, we found that dupilumab effectively treated patients with moderate-to-severe asthma, providing a significant reduction in the rate of severe exacerbations, rapid and sustained improvement in lung function and asthma control, and symptom relief. The most robust results were observed in patients with elevated type 2 immune characteristics, including eosinophil counts and FE_{NO}.

Castro M, Corren J, Pavord ID, et al. N Engl J Med 2018;378:2486-96.

Liberty Asthma Venture

Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma



70% in the Dupilumab group

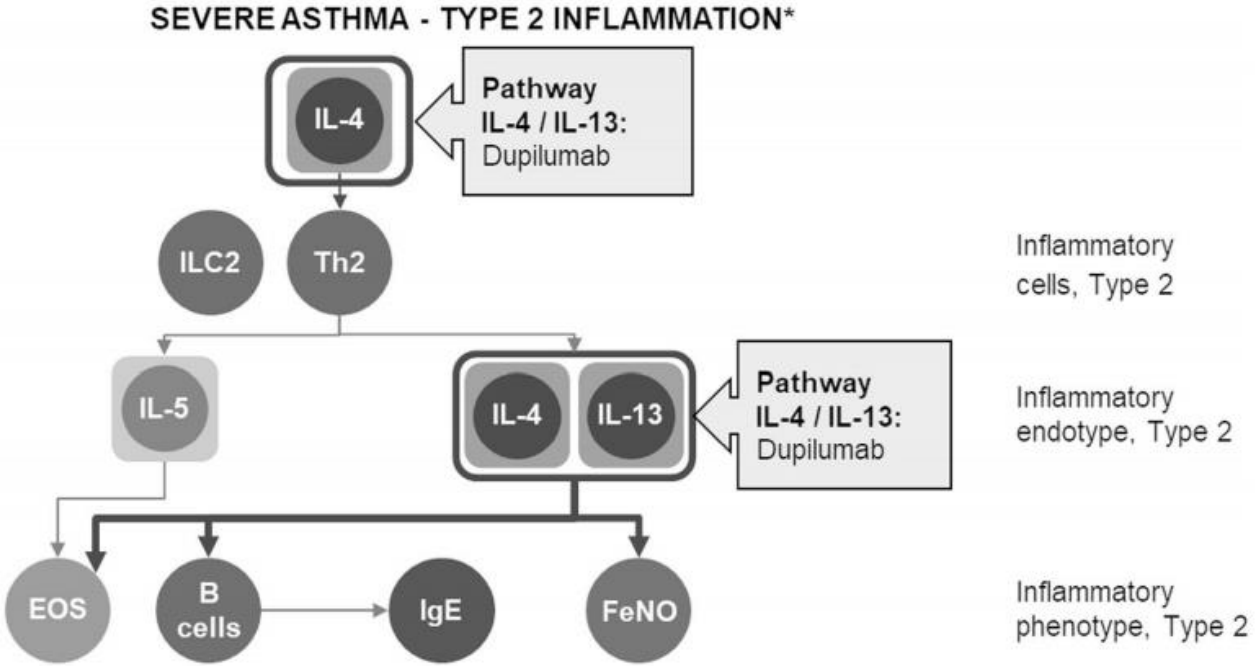
The patients on dupilumab were more successful at reducing their oral steroid dose than the placebo group. The least square mean reduction in glucocorticoid dose was 70.1% in the dupilumab group and 41.9% in the placebo group ($p<0.001$). The median dose reduction was 100% in the dupilumab group and 50% in the placebo group. Treatment with dupilumab was also associated with fewer severe asthma exacerbations, greater FEV_1 improvement, and improved asthma control (ACQ-5) compared to placebo.

CONCLUSIONS:

In patients with glucocorticoid-dependent severe asthma, dupilumab treatment reduced oral glucocorticoid use while decreasing the rate of severe exacerbations and increasing the FEV1 .

Rabe KF, Nair P, Brusselle G, et al., N Engl J Med. 2018; 378 (26):2475–2485.

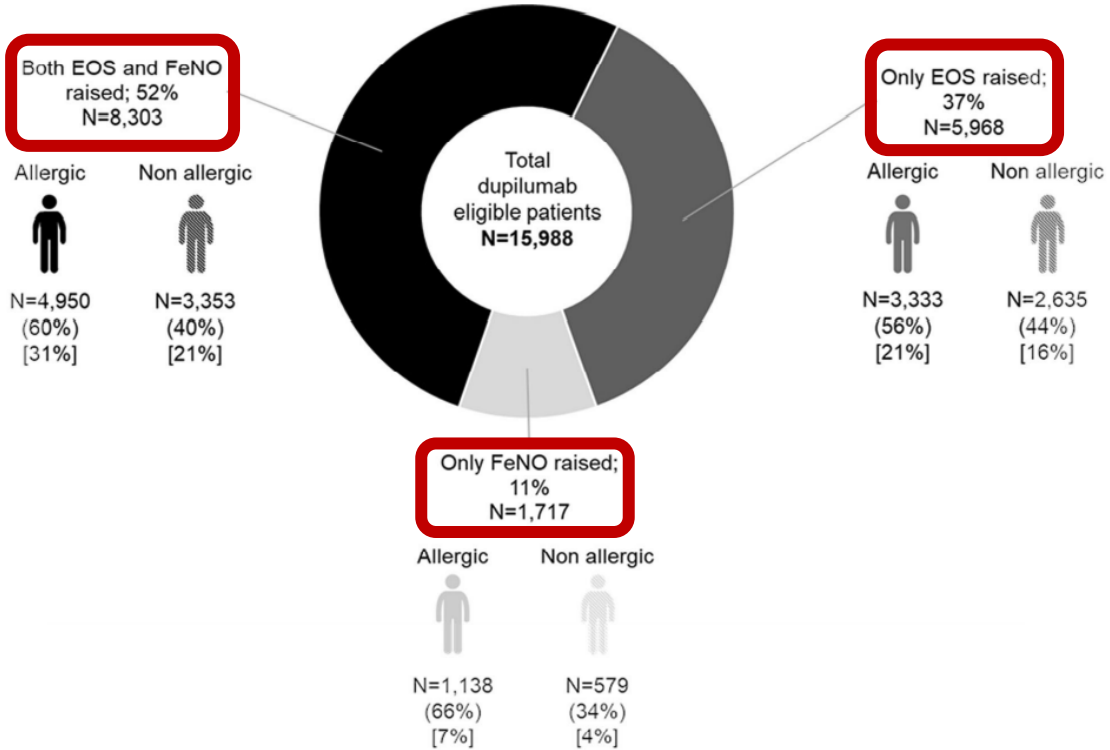
Defining type 2 asthma and patients eligible for dupilumab in Italy: a biomarker-based analysis



Dupilumab is the first biologic approved and specifically indicated for the treatment of uncontrolled severe asthma with Type 2 inflammation: asthma that includes allergic (anti-IgE) and/or eosinophilic (anti-IL5) phenotypes

(Canonica et al. Clin Mol Allergy (2021) 19:5)

Defining type 2 asthma and patients eligible for dupilumab in Italy: a biomarker-based analysis

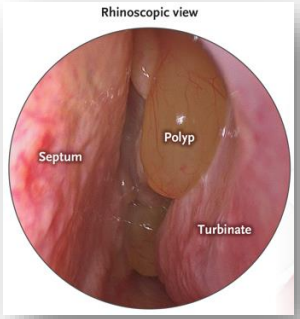


Overview of estimated Italy dupilumab-eligible patient population.

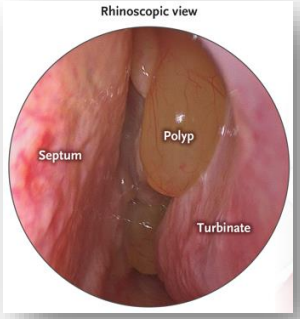
(Canonica et al. Clin Mol Allergy (2021) 19:5)

Efficacy of Biologics on Moderate to Severe Persistent Asthma with Type 2-High Phenotype

Agent	↓ Exacerbations	↑ Lung function	OCS ↓	Special feature
Omalizumab (IgE)	25%	±	–	Aged >6 y; also approved for CIU
Mepolizumab (IL-5)	50%	+	++	Greatest experience of anti–IL-5s; also approved for EGPA
Reslizumab (IL-5)	50%	++	–	Weight-base dose (intravenously)
Benralizumab (IL-5R)	50%	++	++	Every 8 wk and IL-5R
Dupilumab (IL-4/IL-13)	50%	++	++	Eosinophils, FeNO; also approved for AD and CRSwNP



CRSwNP Treatments



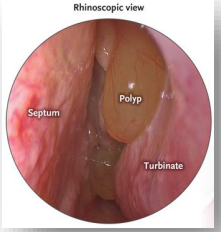
INCS[a,b]

Oral GCS[a,c]

Surgery[a,d]

Treatment limitations: medication side effects, surgery risks, reoccurrence of disease

a. Stevens WW, et al. *J Allergy Clin Immunol Pract*. 2016;4:565-572; b. Aukema AA, et al. *J Allergy Clin Immunol*. 2005;115:1017-1023; c. Van Zele T, et al. *J Allergy Clin Immunol*. 2010;125:1069-1076.e4; d. Patel ZM, et al. *Int Forum Allergy Rhinol*. 2017;7:119-127; e. Chen S, et al. *Curr Med Res Opin*. 2020;36:1897-1911.



Biologics for chronic rhinosinusitis with nasal polyps

IL-5 upregulated in NP[1]

1997	2000	2001	2004	2005
IL-5 delays eosinophil apoptosis[2]	Eosinophil dominated inflammation[3]	Total IgE and SE-IgE elevated[4]	SE-IgE antibodies related to AERD[5]	Local IgE formation[6]

Recognition of type 2 cytokines and IgE in CRSwNP and the development of biologic therapies over time

2006	2011	2013	2016	2017	2019
Reslizumab[7] PoC trial	Mepolizumab[8] PoC trial	Omalizumab[9] PoC trial	Dupilumab[10] Phase 2 trial	Mepolizumab[10] Phase 2 trial	Dupilumab[12] Phase 3 trials

Phase 3 Development

Mepolizumab
Omalizumab
Benralizumab

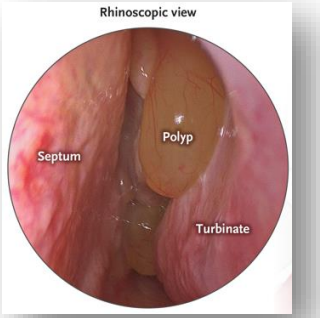
(Bachert C et al., J Allergy Clin Immunol 2020;145:725-39)

PROGETTO ARIA - Rinite Allergica e suo impatto sull'Asma

Consensus Multidisciplinare ARIA-ITALIA: poliposi nasale e farmaci biologici

Carlo Lombardi[1] e Giovanni Passalacqua[2] per ARIA-ITALIA e Società Scientifiche aderenti*

Riccardo Asero[3], Diego Bagnasco[2], Francesco Blasi[4], Matteo Bonini[5], Mario Bussi[6], Rikki F. Canevari[7], Giorgio Walter Canonica[8], Paolo Castelnuovo[9], Lorenzo Cecchi[10], Lorenzo Cosmi[11], Matteo Gelardi[12], Enrico Heffler[8], Luciana Indinnimeo[13], Massimo Landi[14], Amelia Licari[15], Francesco Liotta[11], Alberto Macchi[16], Luca Malvezzi[17], Gianluigi Marseglia[15], Claudio Micheletto[18], Antonino Musarra[19], Diego Peroni[20], Giorgio Piacentini[21], Venerino Poletti[22], Luca Richeldi, [23], Angela Santoni[24], Michele Schiappoli[25], Gianenrico Senna[25], Adriano Vaghi[26], Alberto Villani[27]

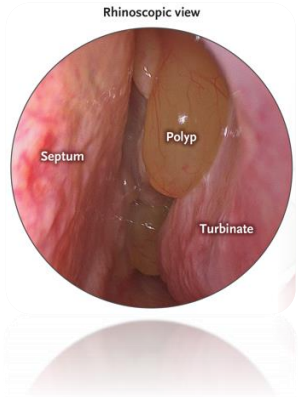


*Documento approvato da: AAIITO: Ass. Allergologi Immunologi Italiani Territoriali e Ospedalieri; AICNA: Accademia Italiana di Citologia Nasale; AIPO: Associazione Italiana Pneumologi Ospedalieri; IAR: Italian Academy of Rhinology; SIAAIC: Soc. Italiana di Allergologia Asma e Immunologia Clinica; SIAIP: Soc. Italiana di Allergologia e Immunologia Pediatrica; SIICA: Soc. Italiana di Immunologia Clinica e Allergologia; SIMRI: Soc. Italiana Malattie Respiratorie Infantili; SIO: Soc. Italiana di Otorinolaringoiatria; SIP: Soc. Italiana di Pediatria; SIP/IRS: Soc. Italiana di Pneumologia/Italian Respiratory Society

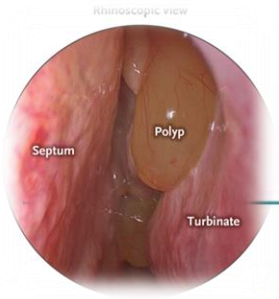
http://www.progetto-aria.it/aim.htm

Consensus Multidisciplinare ARIA-ITALIA: poliposi nasale e farmaci biologici

AUTORE, Anno (ref)	FARMACO (stato)	DOSE	DUR.	ETA	Attivi/ Plac	RISULTATI PRINCIPALI
Gevaert, 2013 (26)	Omalizumab **Fase III conclusa**	150-375 mg/mese (S.C.)	16 sett	42-56	15/8	Riduzione del total nasal polyp score Riduzione del Lund-Macay TC score
Gevaert, 2011 (28)	Mepolizumab **Fase ii in corso**	750 mg e.v 2 somministrazioni a distanza di 28 gg	8 sett.	35-50	20/10	Riduzione del total nasal polyp score
Bachert, 2016 (29)	Mepolizumab	750 mg e.v. ogni 4 settimane	25 sett	18-70	53/54	Riduzione della proporzione di pazienti che necessitano di nuovo intervento chirurgico. Riduzione VAS, total nasal polyp score; punteggio SNOT22
Gevaert, 2006 (30)	Reslizumab **No studi registrativi in corso**	1-3 mg/Kg e.v. unica dose	12 sett	18-63	16/8	Riduzione del total nasal polyp score in solo metà dei pz e solo x 4 settimane
Bachert 2016 (31)	Dupilumab **Approvato EMA-FDA**	600 mg load + 300 mg/w s.c.	16 sett	35-65	30/30	Riduzione del total nasal polyp score Riduzione del Lund-Macay TC score
Bachert 2019 (32)	Dupilumab	300 mg s.c./2 wks	24 sett	30-65	143/133	Riduzione significativa dello score endoscopico, TC, SNOT e VAS a 6 mesi
Bachert 2019 (32)	Dupilumab	300 mg s.c. /2wks O 300 mg sc/2 wks per 24 sett. Poi ogni 4 sett	52 sett	30-65	150-153/153	Riduzione significativa dello score endoscopico, TC, SNOT e VAS a 6 mesi. Ulteriore miglioramento a 12 mesi. Riduzione numero interventi, riduzione OCS



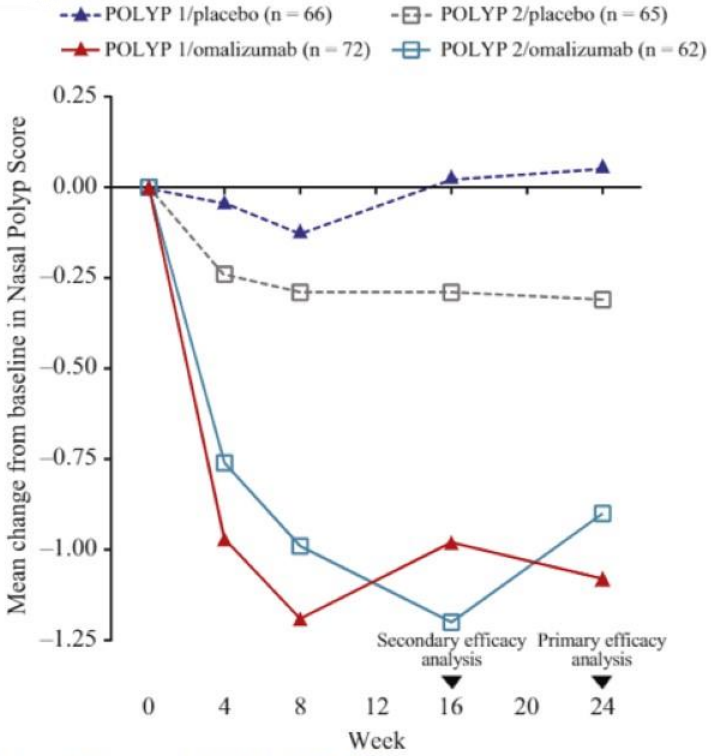
http://www.progetto-aria.it/



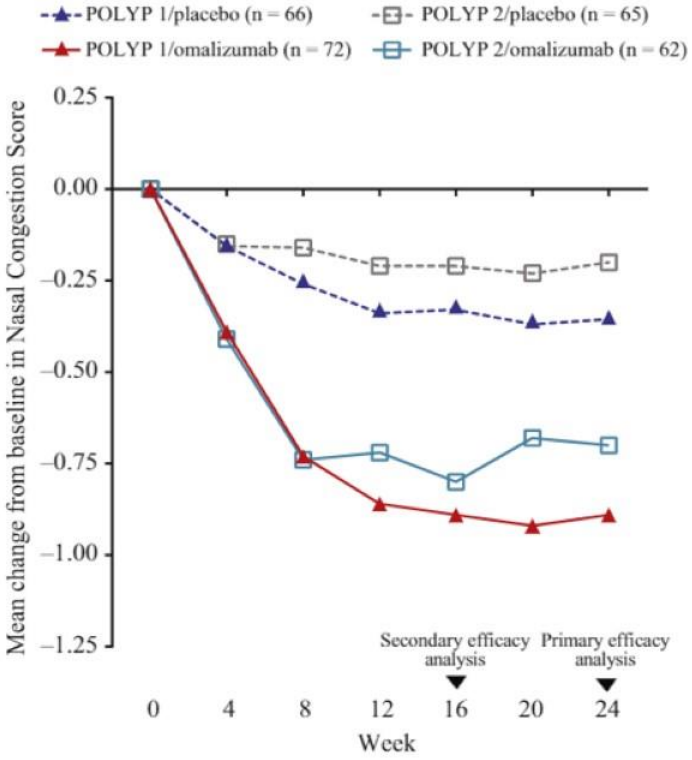
Omalizumab in Severe CRSwNP

POLYP1 and POLYP2 Studies

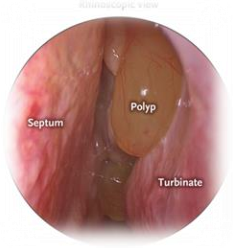
Nasal Polyp Score



Nasal Congestion Score



Gevaert P, et al. *J Allergy Clin Immunol.* 2020;146:595-605.



MEPOLIZUMAB

Gevaert et al[4]	Baseline	8 wk
NPS	5.2 (5.5)	−1.30
Improvement % patients		50%
CT scan improvement		>50% (<20%)
Blood eosinophil counts (10^3/mL)		−332

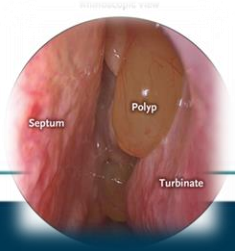
Bachert et al[4]	Baseline		25 wk
% of patients requiring surgery	100%		30% (10%)
% of patients improved by >1 point in NPS			50% (27%)
SNOT-22 questionnaire	51.5 (49.5)		−13.2
Blood eosinophil counts (cells/μL)	500 (470)		−330
PnIF (L/min)	101		+26.7
Nasal polyposis severity VAS scores	Rhinorrhea	6.2	−2.4
	Mucus in throat	6.0	−2.1
	Nasal blockage	7.9	−1.8
	Loss of smell	9.0	−1.9

Note: Baseline blood eosinophil counts did not affect the responder rate and could not be used to identify responders.

Gevaert P, Lang-Loidolt D, Stammberger H, Van Zele T, Holtappels G, Tavernier J, et al. Nasal interleukin-5 levels determine the response to anti-interleukin-5 treatment in nasal polyp patients. J Allergy Clin Immunol 2006;118:1133-41.
Gevaert P, van Bruaene N, Cattaert T, van Steen K, Van Zele T, Acke F, et al. Mepolizumab, a humanised anti-IL-5 monoclonal antibody, as treatment option for severe nasal polyposis. J Allergy Clin Immunol 2011;128:989-95.
Bachert C, Sousa AR, Lund VJ, Scadding GK, Gevaert P, Nasser S, et al. Reduced need for surgery in severe nasal polyposis with mepolizumab: a randomised trial. J Allergy Clin Immunol 2017;140:1024-31.

(Bachert C et al., J Allergy Clin Immunol 2020; 145:725-39)

Mepolizumab for Severe CRSwNP



SYNAPSE Study

- **52-week trial with 4-week add-on mepolizumab 100 mg SC in adults with CRSwNP vs placebo treated with INCS**
- **Total endoscopic NPS and nasal obstruction VAS score significantly improved ($P < .001$) with mepolizumab (n = 206) vs placebo (n = 201)**

Secondary endpoints

- 57% reduction in surgery
- Improvements in SNOT-22 and VAS scores
- Decreased use of SCS

No new safety issues; nasopharyngitis most common AE

Hopkins C, et al. *Eur Respir J*. 2020;56:4616.

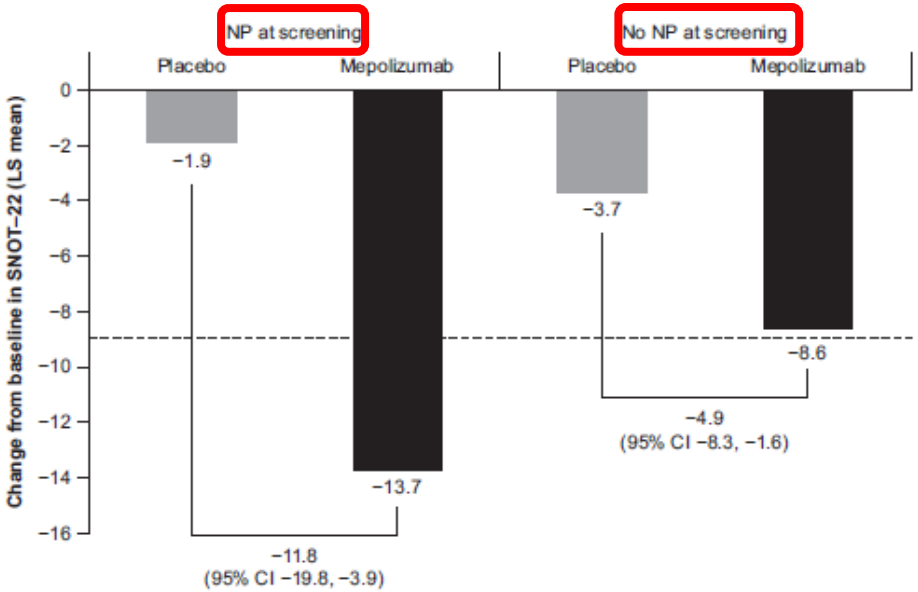
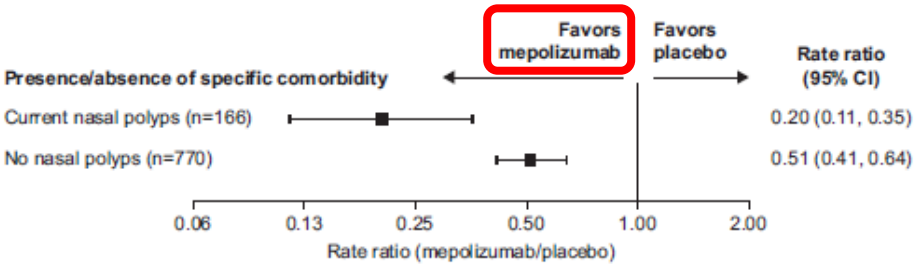


FIG 1. Change from baseline in the SNOT-22 score* at week 24 in MUSCA patients with SEA with or without NP. *LS*, Least squares. *Analyzed using mixed model repeated measures adjusted for baseline value, number of exacerbations in the year before the study, baseline maintenance oral corticosteroid therapy, region, and baseline % predicted prebronchodilator FEV_1. The dashed line as positioned represents the established MCID (from baseline) for SNOT-22 (−8.9 points).

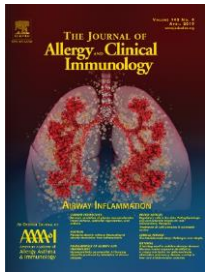


Severe eosinophilic asthma with nasal polyposis: A phenotype for improved sinonasal and asthma outcomes with mepolizumab therapy

Results from a post hoc analysis of the MUSCA study and a meta-analysis of MUSCA and MENSA

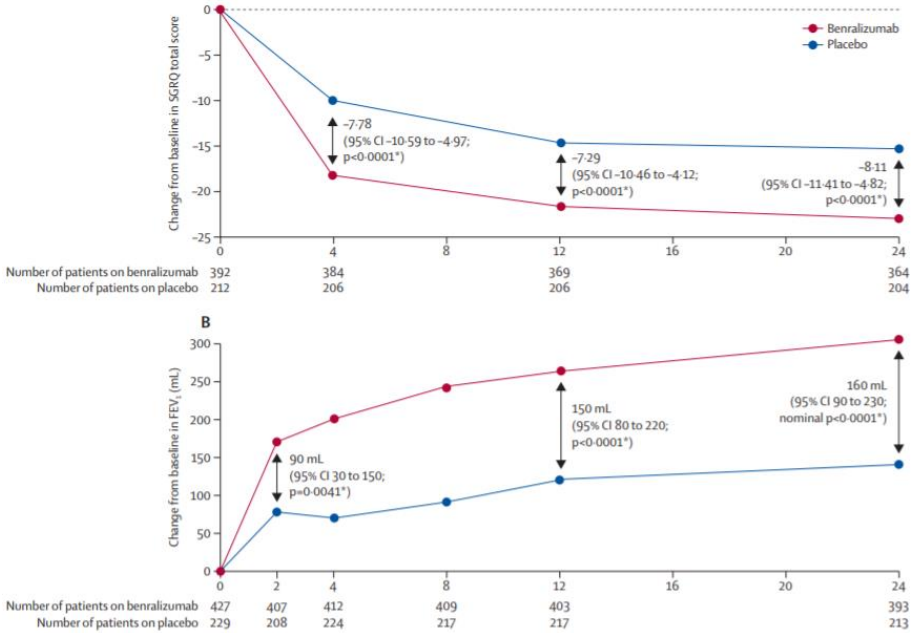
These results suggest that mepolizumab may directly affect upper airway type 2 inflammatory conditions.

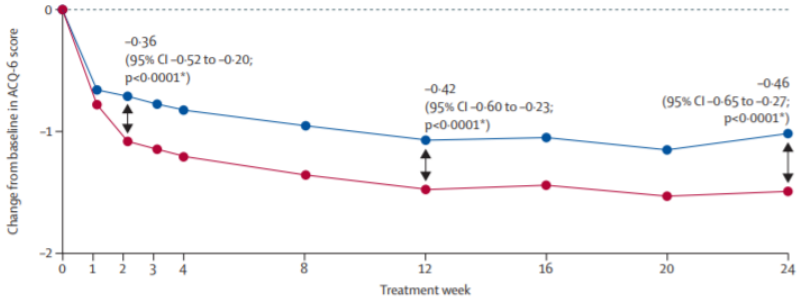
Bradford ES et al., J ALLERGY CLIN IMMUNOL 2020 Feb 19

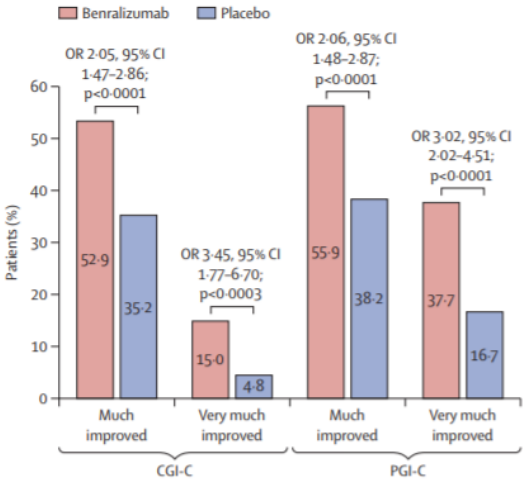


Onset of effect and impact on health-related quality of life, exacerbation rate, lung function, and nasal polyposis symptoms for patients with severe eosinophilic asthma treated with benralizumab (ANDHI): a randomised, controlled, phase 3b trial

(Harrison TW et al., Lancet Respiratory Medicine 2021 Mar;9(3):260-274)

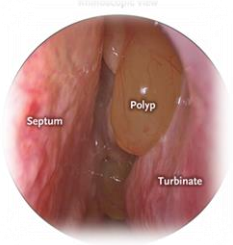




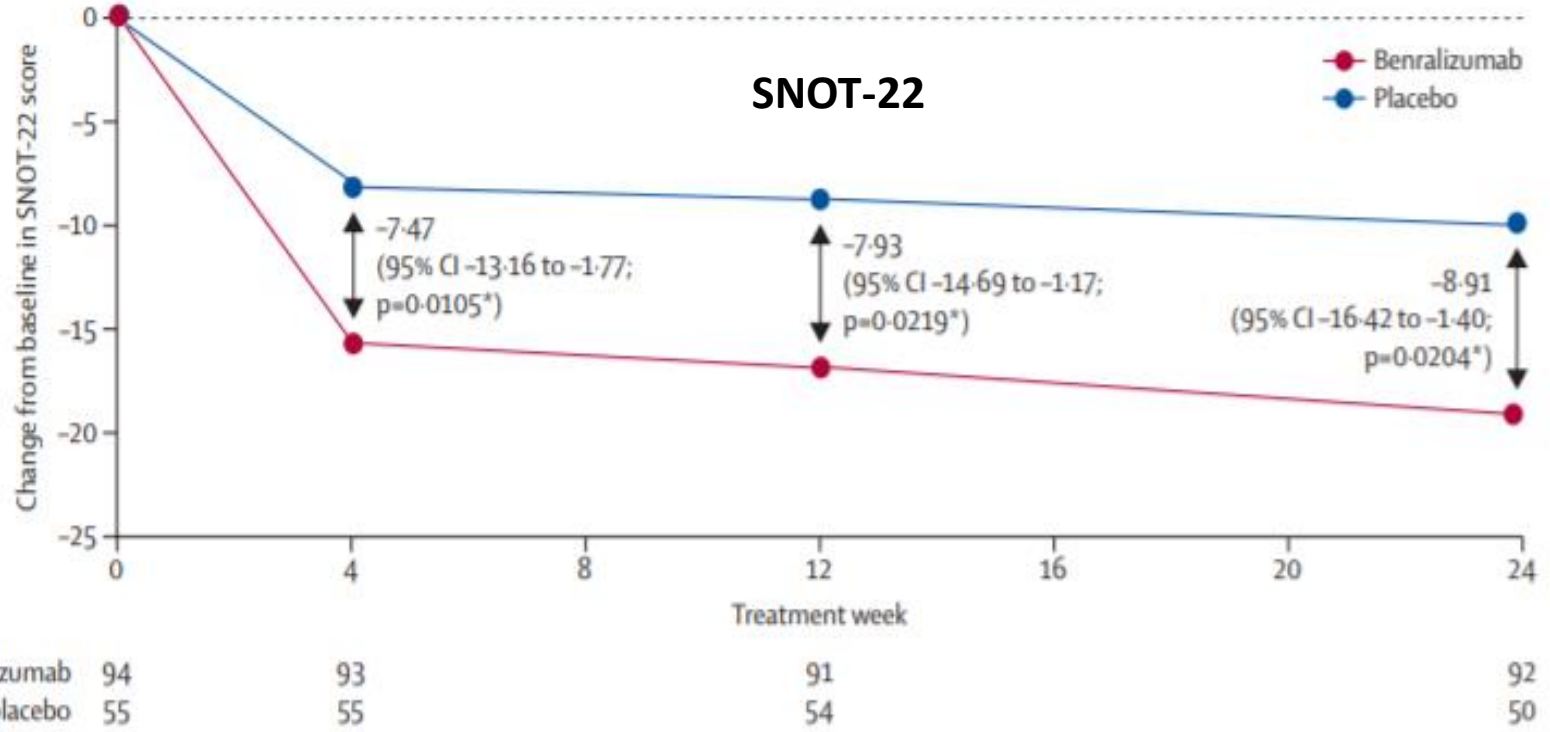


CGI-C=Clinician Global Impression of Change.

PGI-C=Patient Global Impression of Change.



SNOT-22



The results extend the efficacy profile of benralizumab for patients with severe eosinophilic asthma, showing early clinical benefits in patient-reported outcomes, HRQOL, lung function, and nasal polyposis symptoms.

(Harrison TW et al., Lancet Respiratory Medicine 2021 Mar; 9 (3) : 260-274)

Efficacy of Benralizumab in severe asthma in real life and focus on nasal polyposis

Respiratory Medicine 171 (2020)

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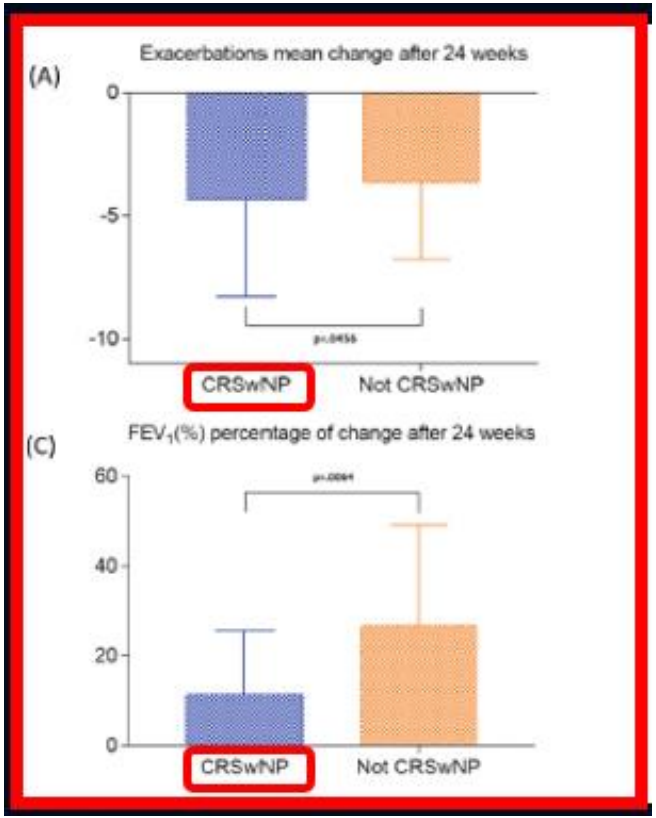
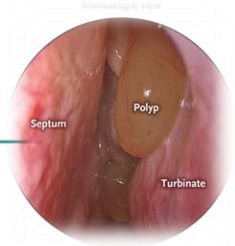
59 patients with severe uncontrolled asthma (21 males, age range 32–78) and treated with benralizumab for at least 24 weeks

- CRSwNP is a common comorbidity in severe asthmatic people.
- Benralizumab proved to be effective both in patients with or without CRSwNP.
- Benralizumab proved to be effective in reducing nasal symptoms in CRSwNP patients.



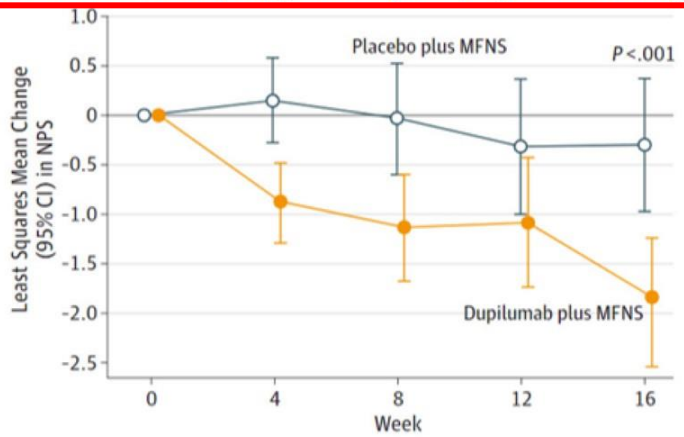
Dupilumab
Treatment of CRSwNP



- Randomized, double-blind, placebo-controlled parallel group study

- **60 pts**
- **45 pts had comorbid asthma**

Endoscopic nasal polyp score (NPS) by treatment group



No. of patients					
Placebo plus MFNS	30	29	26	25	23
Dupilumab plus MFNS	30	30	27	26	29

Adults resistant to corticosteroid treatment, addition of dupilumab to MFNS
↓ endoscopic nasal polyp burden in 16 weeks

Bachert C, et al. *JAMA*. 2016 2;315:469-479.

Table 1 Efficacy of subcutaneous add-on dupilumab in adults with severe chronic rhinosinusitis with nasal polyps

Endpoint [LSM change from BL (LSM BGD vs PL; 95% CI)]	SINUS-24		SINUS-52	
	DUP ($n=143$)	PL ($n=133$)	DUP ($n=295$)[a]	PL ($n=153$)
Bilateral endoscopic nasal polyp score[b]	−1.89 (−2.06; −2.43, −1.69)*	+0.17	−1.71 (−1.80; −2.10, −1.51)*	+0.10
Nasal congestion or obstruction score[b]	−1.34 (−0.89; −1.07, −0.71)*	−0.45	−1.25 (−0.87; −1.03, −0.71)*	−0.38
Lund-Mackay CT score[c]	−8.18 (−7.44; −8.35, −6.53)*	−0.74	−5.21 (−5.13; −5.80, −4.46)*	−0.09
Total symptom score[d]	−3.77 (−2.61; −3.04, −2.17)*	−1.17	−3.45 (−2.44; −2.87, −2.02)*	−1.00
Smell test score	+11.26 (+10.56; +8.79, +12.34)*	+0.70	+9.71 (+10.52; +8.98, +12.07)*	−0.81
Loss of smell score	−1.41 (−1.12; −1.31, −0.93)*	−0.29	−1.21 (−0.98; −1.15, −0.81)*	−0.23
SNOT-22 total score	−30.43 (−21.12; −25.17, −17.06)*	−9.31	−27.77 (−17.36; −20.87, −13.85)*	−10.40

Results at week 24 from two multinational, phase III studies [10]. Endpoints were assessed in a hierarchical manner (as per the table order)

BGD between-group difference, *BL* baseline, *DUP* dupilumab, *LSM* least-squares mean, *PL* placebo, *qxw* every x weeks, *SNOT* Sino-Nasal Outcome Test

*$p=0.0001$ vs PL

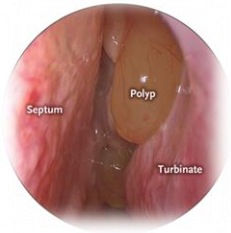
[a]Pooled data at 24 weeks from the DUP 300 mg q2w for 52 weeks ($n=150$) and DUP 300 mg q2w for 24 weeks followed by DUP 300 mg q4w for 24 weeks ($n=145$) arms

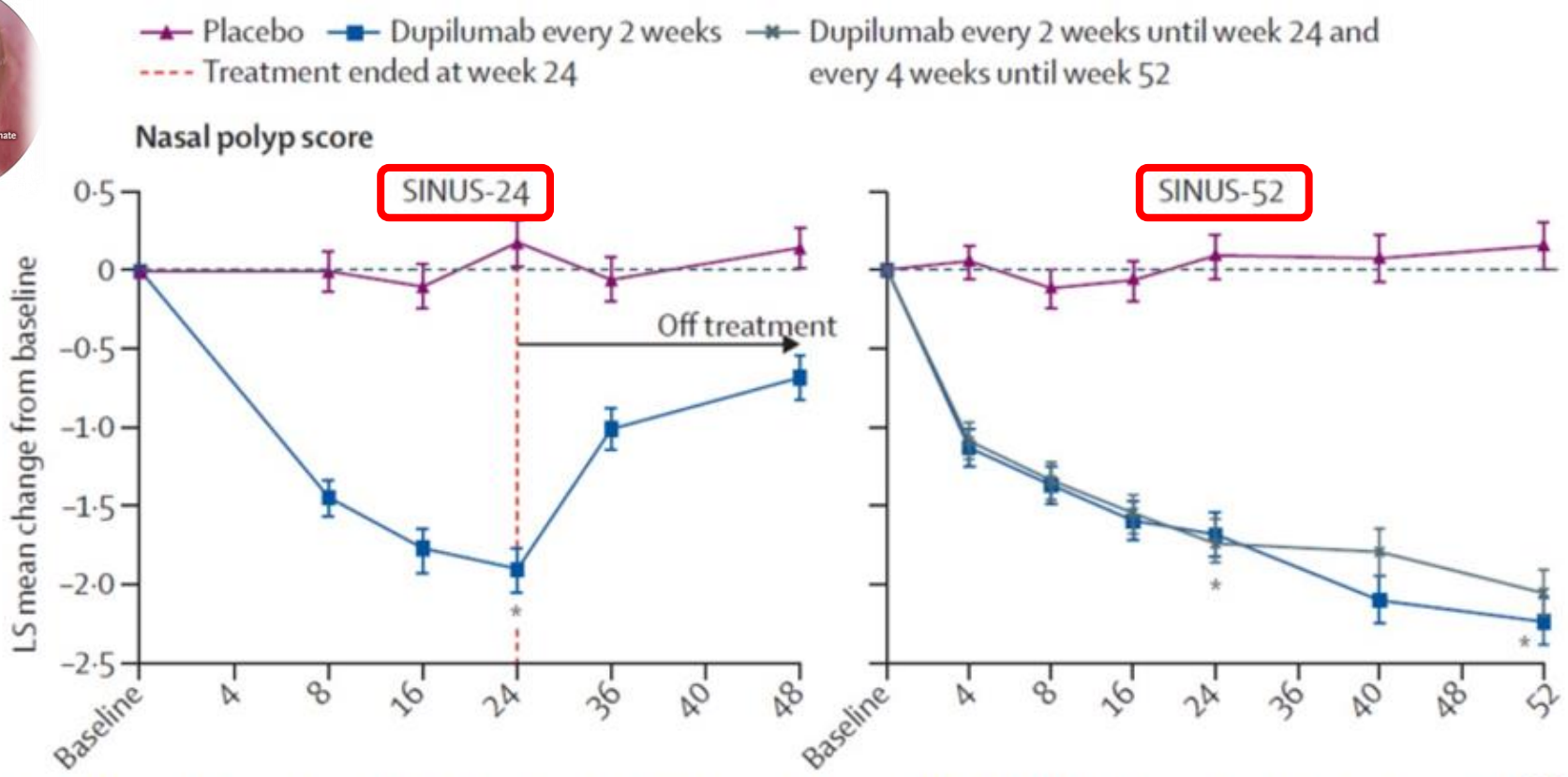
[b]Co-primary endpoint

[c]Co-primary endpoint in Japan

[d]Composite severity score comprising the sum of daily symptoms of nasal congestion, loss of smell, and anterior or posterior rhinorrhoea; scores range from 0–9, with higher scores indicating greater disease severity

(Hoy SM, Drugs (2020) 80:711–717)

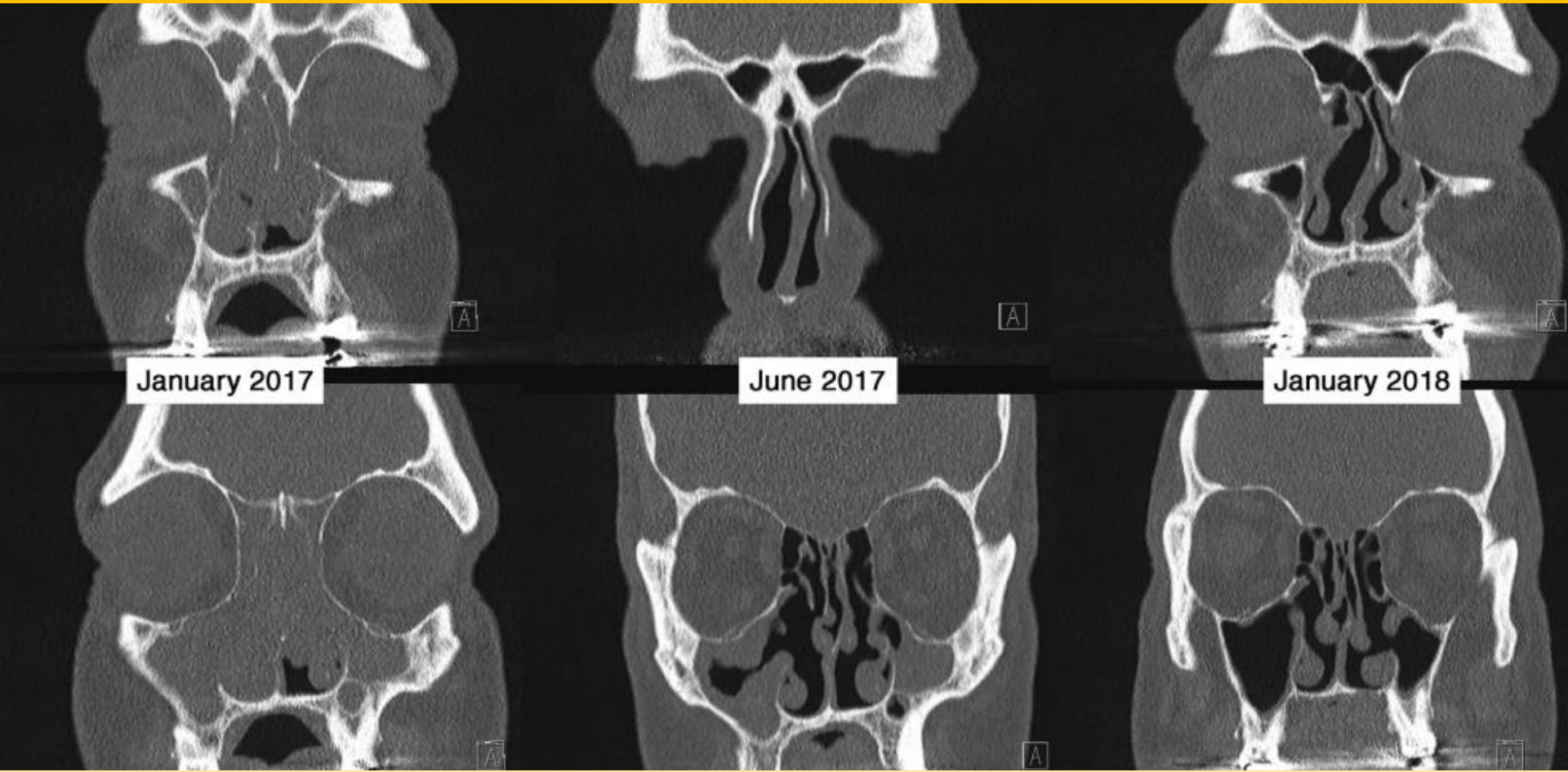




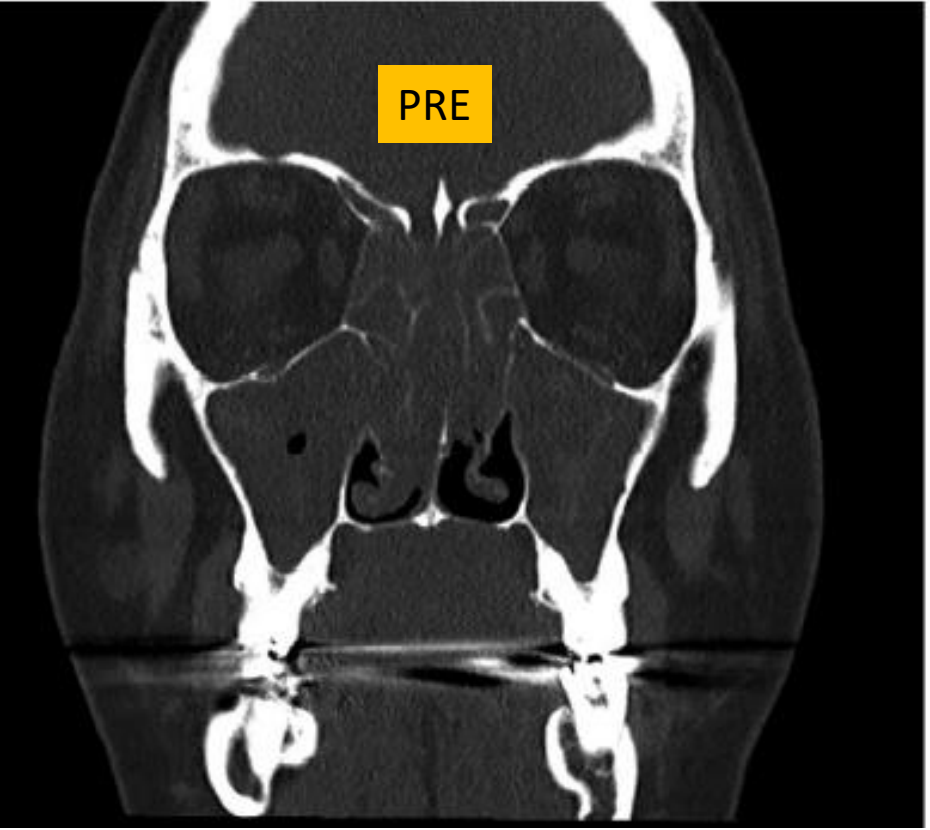
Dupilumab Reduced Polyp Size in Patients (n > 700) With Chronic Rhinosinusitis[a]

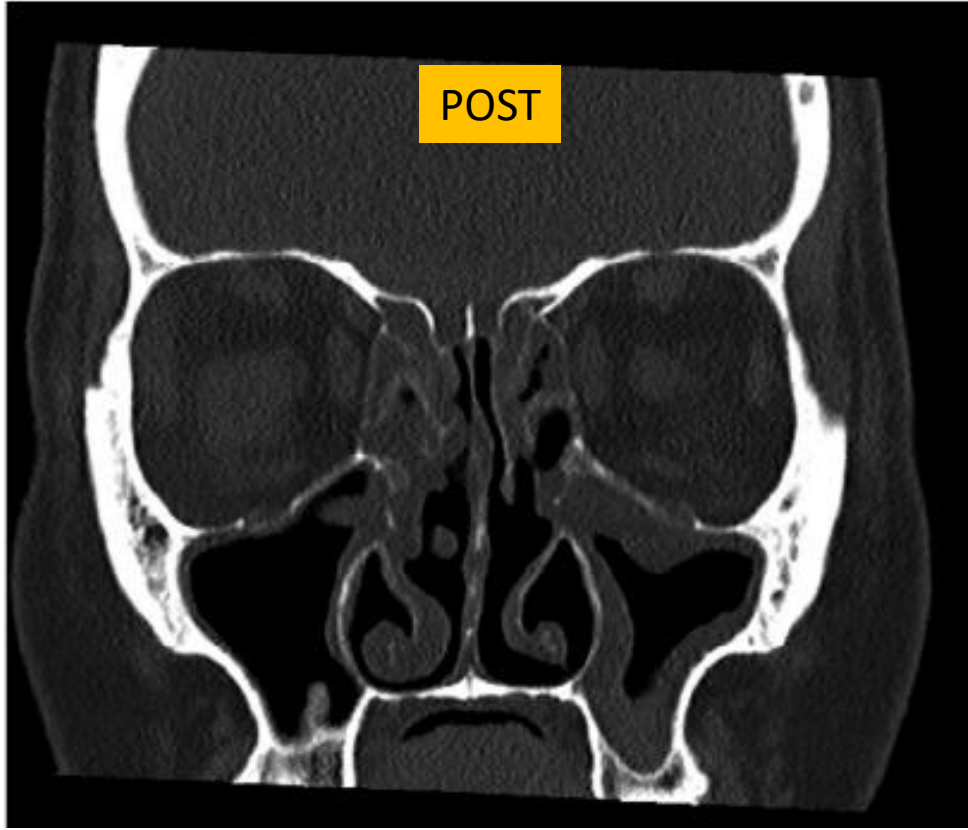
Bachert C, et al. *Lancet.* 2019;394;1638-1650;

CT scans over 1 year in a patient with CRSwNP under dupilumab



(Bachert C et al., J Allergy Clin Immunol 2020; 145:725-39)



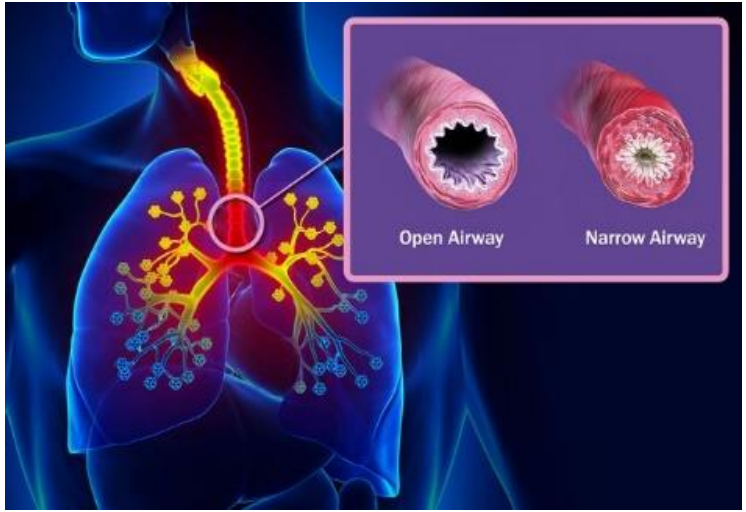


Response to dupilumab in a patient with AERD before starting treatment with dupilumab (left) and again after 4 months of every-other-week dupilumab treatment (right).

Legenda : AERD aspirin-exacerbated respiratory disease

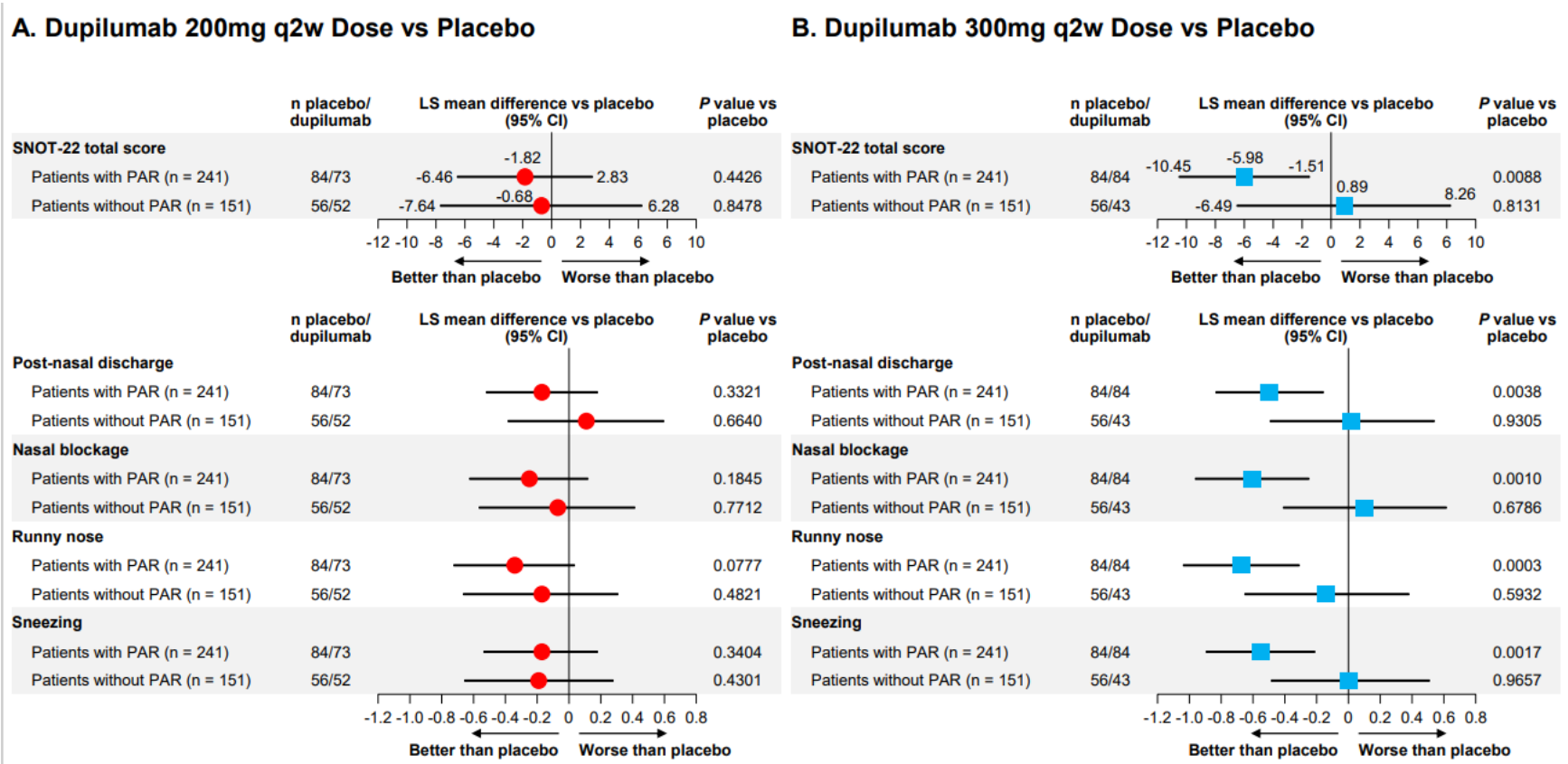
(Laidlaw T et al., Ann Allergy Asthma Immunol 124 (2020) 326-332)

Efficacy and safety of dupilumab in perennial allergic rhinitis and comorbid asthma



Post-hoc analysis
465 patients with asthma, 241 (61%) patients had PAR.

(Weinstein SF, et al., Journal of Allergy and Clinical Immunology, 2018)



CONCLUSION: Dupilumab 300 mg q2w significantly improved AR-associated nasal symptoms in patients with uncontrolled persistent asthma and comorbid AR.

(Weinstein SF, et al., Journal of Allergy and Clinical Immunology, 2018)

Efficacy of dupilumab on clinical outcomes in patients with asthma and perennial allergic rhinitis

Objective:

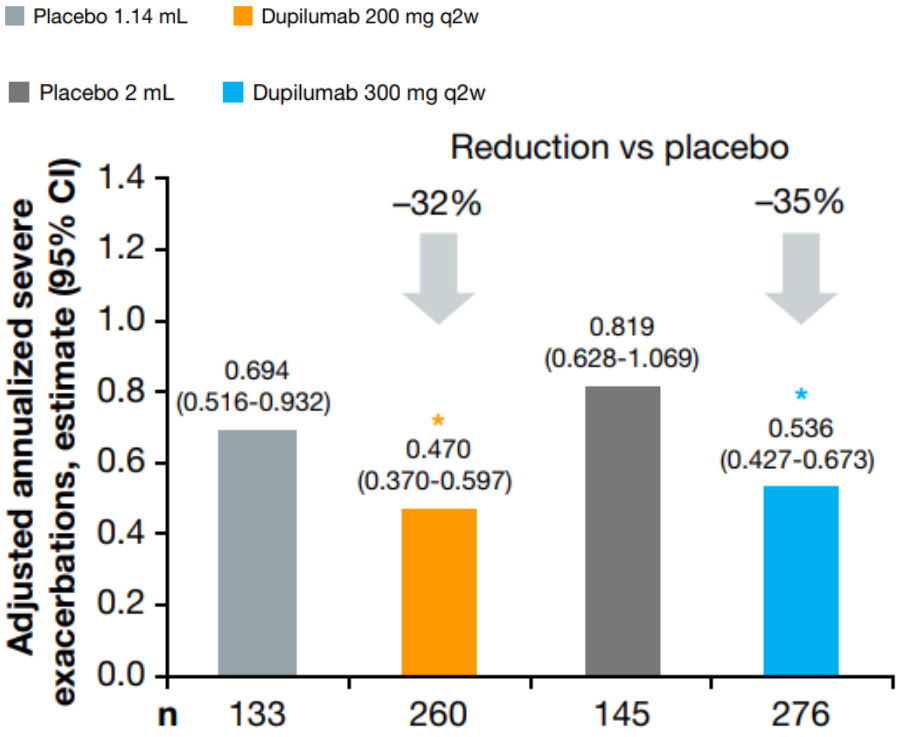
To assess dupilumab efficacy in LIBERTY ASTHMA QUEST patients with comorbid PAR;

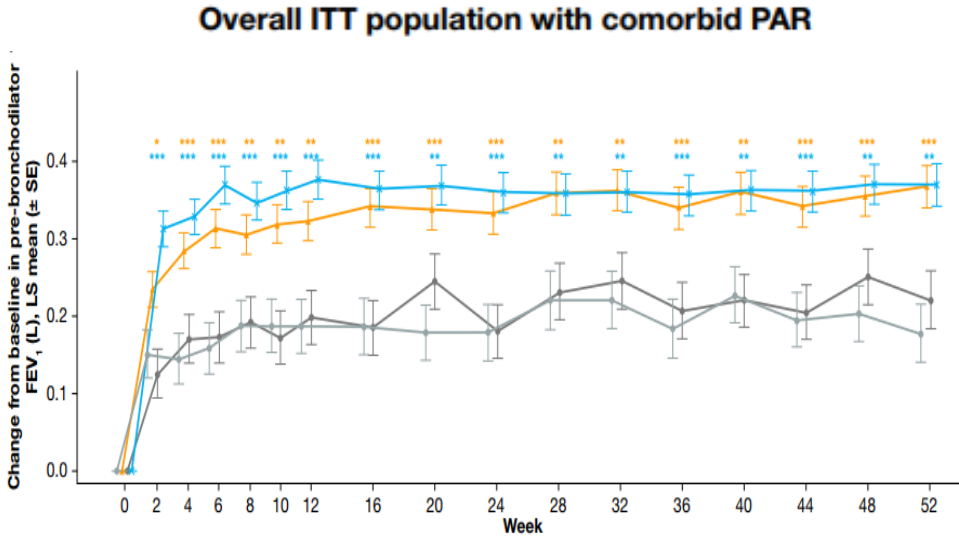
A total of 814 of the 1902 patients (42.8%) had comorbid PAR

Results: A total of 814 of the 1902 patients (42.8%) had comorbid PAR (defined as an allergic rhinitis history and ≥1 perennial aeroallergen specific immunoglobulin E (IgE) level ≥0.35 kU/L at baseline). Dupilumab, 200 and 300 mg every 2 weeks, vs placebo reduced severe exacerbations rates by 32.2% and 34.6% ($P < .05$ for both) and improved FEV_1 at week 12 by 0.14 L and 0.18 L ($P < .01$ for both); greater efficacy was observed in patients with elevated baseline blood eosinophil counts (≥300 cells/μL) and fractional exhaled nitric oxide. Dupilumab treatment also numerically improved the 5-item Asthma Control Questionnaire and Standardized Rhinoconjunctivitis Quality of Life Questionnaire +12 scores and suppressed type 2 inflammatory biomarkers.

(Busse W et al., Ann Allergy Asthma Immunol 2020)

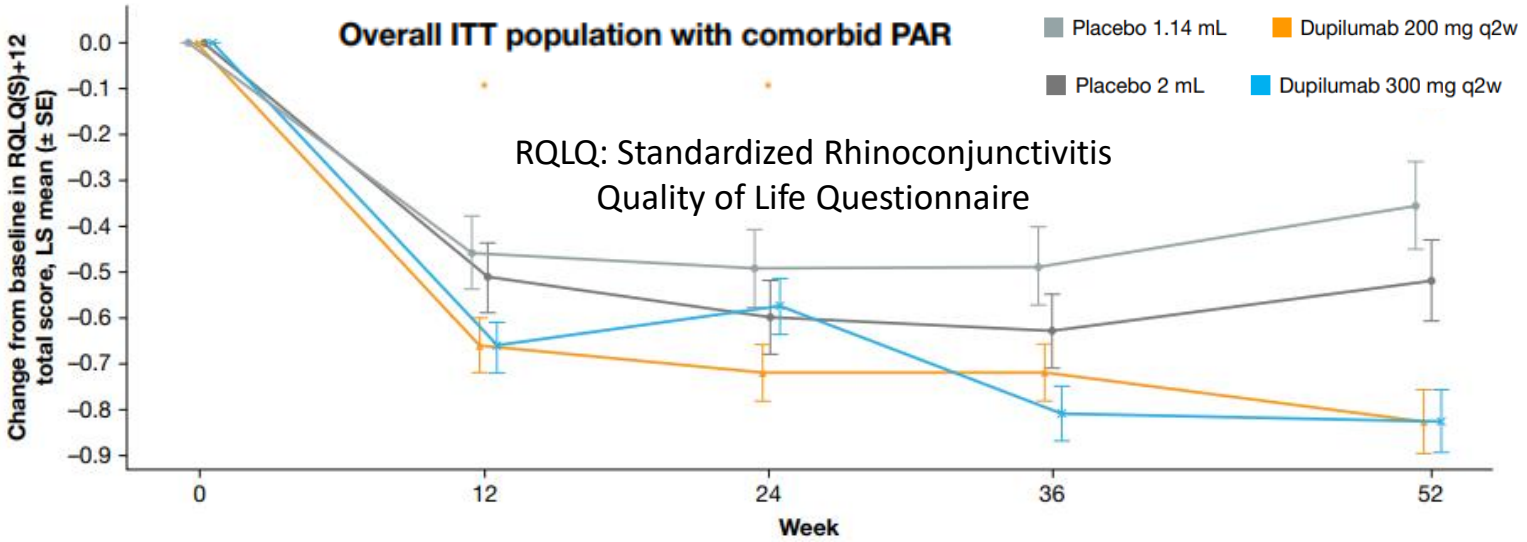
Efficacy of dupilumab on clinical outcomes in patients with asthma and perennial allergic rhinitis





(Busse W et al., Ann Allergy Asthma Immunol 2020)

Efficacy of dupilumab on clinical outcomes in patients with asthma and perennial allergic rhinitis

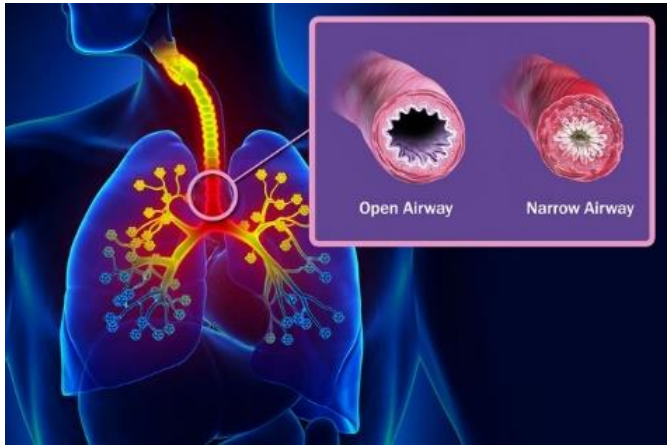


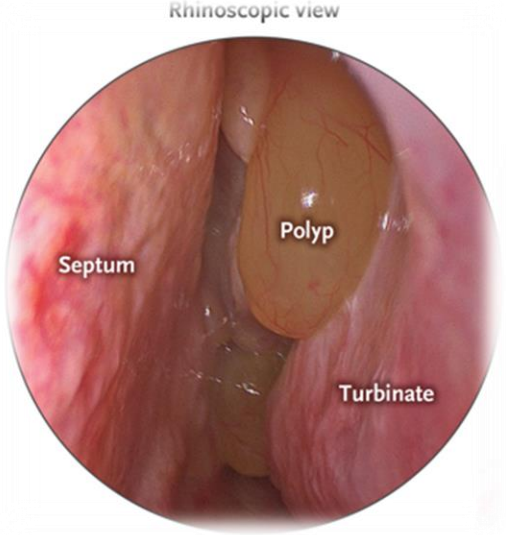
RQLQ: Standardized Rhinoconjunctivitis Quality of Life Questionnaire

No. of patients					
Placebo 1.14 mL q2w	118	116	113	112	92
Dupilumab 200 mg q2w	228	220	217	215	178
Placebo 2 mL q2w	134	131	124	126	104
Dupilumab 300 mg q2w	242	237	232	226	185

(Busse W et al., Ann Allergy Asthma Immunol 2020)

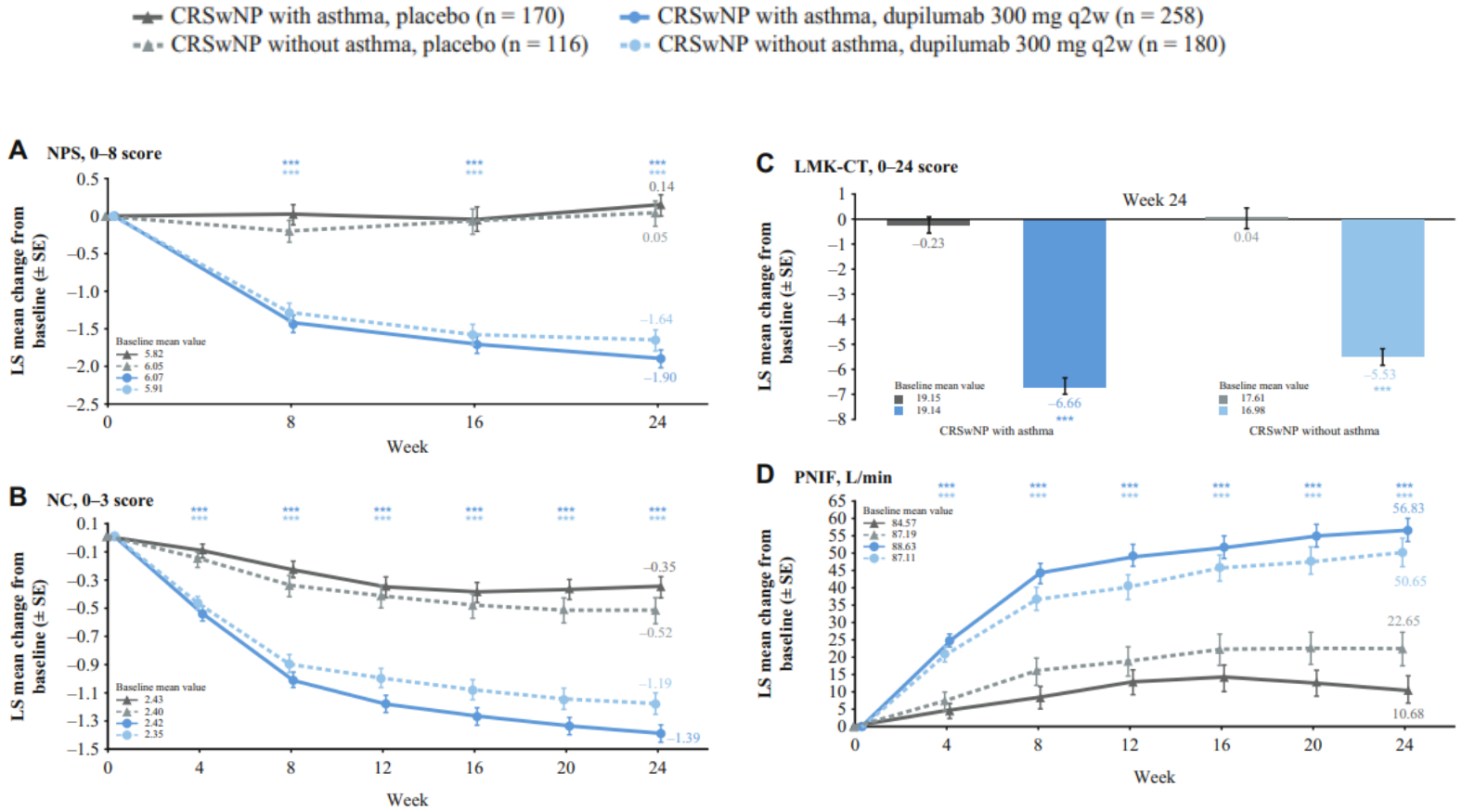
Dupilumab improves upper and lower airway disease control in chronic rhinosinusitis with nasal polyps and asthma





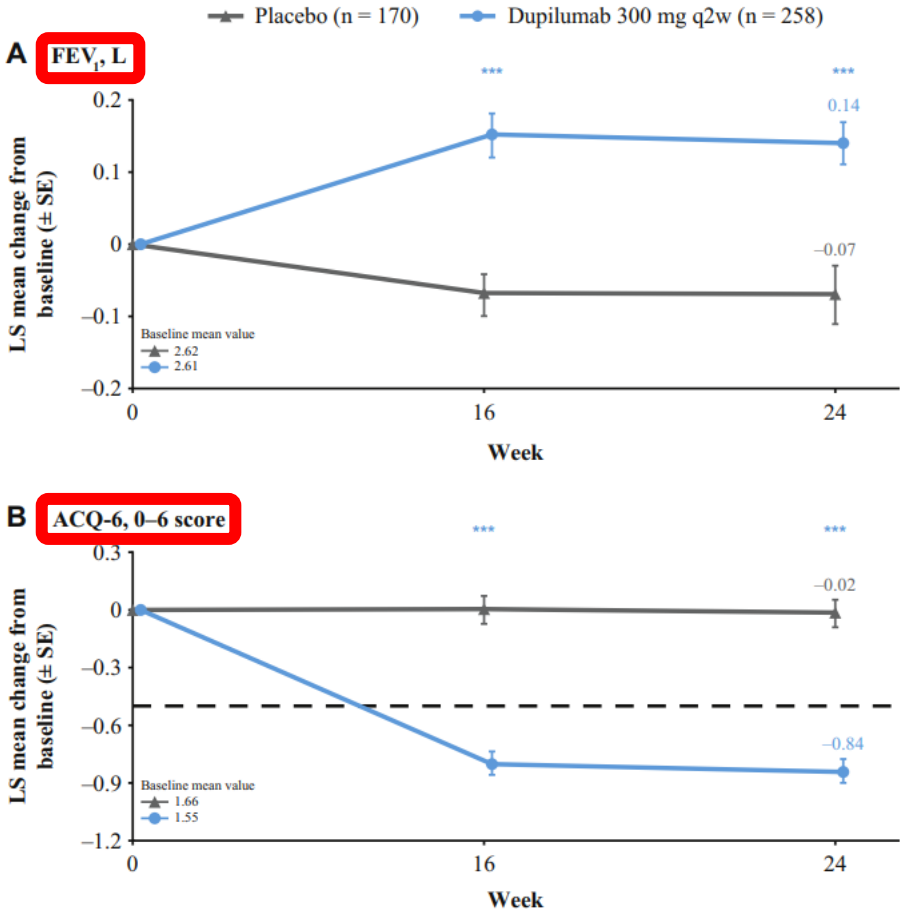
Of the 724 patients with CRSwNP randomized, 428 (59.1%) had comorbid asthma

(Laidlaw M. et al., Ann Allergy Asthma Immunol 126 (2021) 584-592)



LMK-CT, Lund-Mackay computed tomography; LS, least squares; NC, nasal congestion; NPS, nasal polyp score; PNIF, peak nasal inspiratory flow

(Laidlaw M. et al., Ann Allergy Asthma Immunol 126 (2021) 584-592)

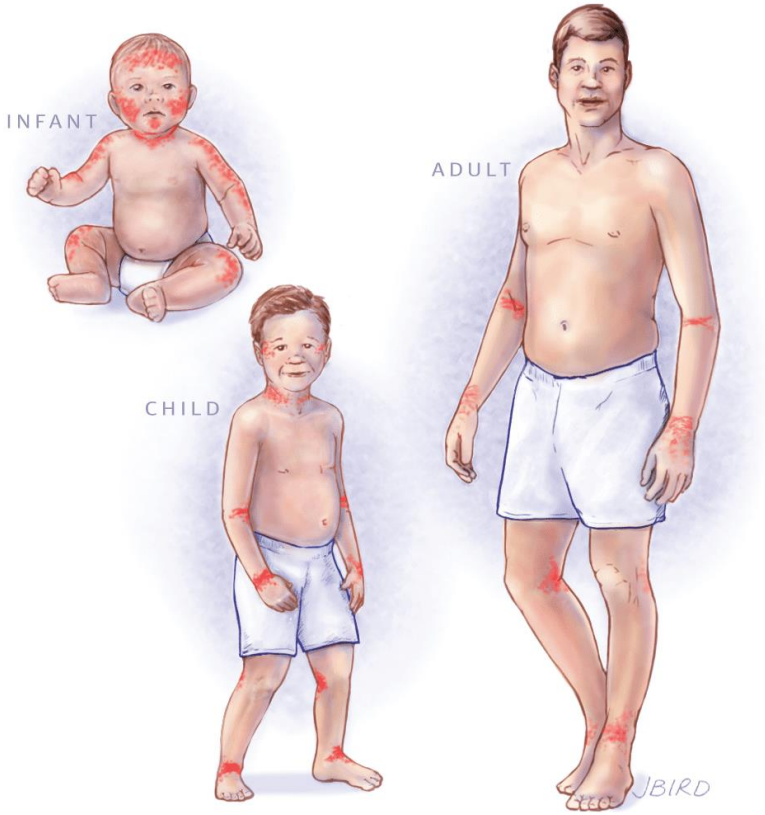


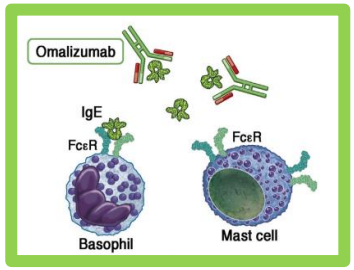
Conclusion :

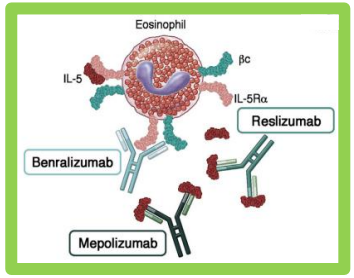
Dupilumab improved upper and lower airway outcome measures and HRQoL in patients with severe CRSwNP and comorbid asthma and was well tolerated.

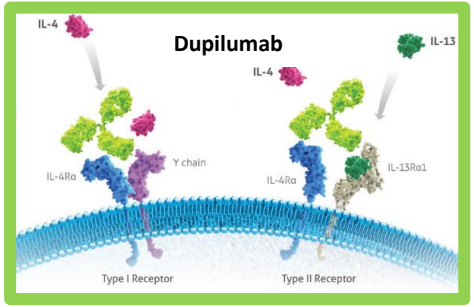
(Laidlaw M. et al., Ann Allergy Asthma Immunol 126 (2021) 584-592)

ATOPIC DERMATITIS & BIOLOGICAL AGENTS







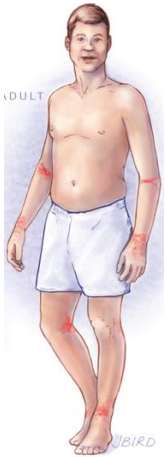


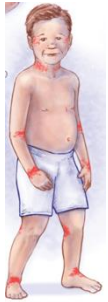
Clinical trials for T2-targeted therapies in atopic dermatitis

Target	Agent	Mechanism	Phase status	Clinical trials	Patients enrolled
Th2	Dupilumab	Anti-IL-4Rα mAb	IV ongoing	NCT03411837	500
	Lebrikizumab	Anti-IL-13 mAb	IIb completed	NCT03443024	280
			III ongoing	NCT04178967	400
			III ongoing	NCT04146363	400
	Tralokinumab	Anti-IL-13 mAb	III completed	NCT03131648	802
			III recruiting	NCT03587805	1123
			III completed	NCT03160885	794
			III ongoing	NCT03526861	294
	Nemolizumab	Anti-IL-31RA mAb	II completed	NCT03181503	70
			III ongoing	NCT03985943	750
			III ongoing	NCT03989349	750
	Mepolizumab	Anti-IL-5 mAb	II terminated	NCT03055195	34
	Tezepelumab	Anti-TSLP mAb	IIa completed	NCT02525094	113
			IIb ongoing	NCT03809663	300
	MK-8226	Anti-TSLPR mAb	I terminated	NCT01732510	65
	GBR 830	Anti-TSLP mAb	II completed	NCT02683928	64
			IIb ongoing	NCT03568162	468
	KHK4083	Anti-OX40 mAb	I completed	NCT03096223	26
			II ongoing	NCT03703102	250

(Baghoomian W et al.: "New and Emerging Biologics for Atopic Dermatitis", Am. J. of Clin. Dermatol. April 2020)

Summary of recently published dupilumab clinical trials in adults, adolescents and children with atopic dermatitis





Summary of recently published clinical trials and retrospective review of new biologics in atopic dermatitis

Biologic agents	Target	Phase	Region	Study population	Administration	Study duration	Efficacy	Safety
In adults and adolescents								
Dupilumab	IL4 receptor alpha chain	Real-life multicenter retrospective cohort study	France	241 adults (>18 years) with moderate-to-severe AD	Subcutaneous injection	3.8 ± 3.7 months	Significant improvement in disease severity at 3 months of treatment	High frequency of conjunctivitis and eosinophilia
Dupilumab	IL4 receptor alpha chain	Phase 3, RCT (3-arm trial)	USA, Canada	251 adolescents (12-17 years) with moderate-to-severe AD	Subcutaneous injections with dulipumab 200 mg (baseline weight <60 kg) or 300 mg (baseline weight ≥ 60 kg) every 2 weeks, 300 mg every 4 weeks, or placebo	16 weeks	Significant improvement in AD signs, symptoms and quality of life; efficacy of the every-2-week regimen was generally superior to the every-4-week regimen	No significant difference between dupilumab and placebo groups; safety is acceptable
In children								
Dupilumab	IL4 receptor alpha chain	Multi-center retrospective review of off-label use	USA	111 children with the age of 13.0 ± 3.9 years (range 3.1 to 18.0) with moderate-to-severe AD	Subcutaneous injections of a mean of 8.7 mg/kg (range, 4–15.5; SD 2.2) loading dose followed by a mean of 5.1 mg/kg (range, 2.0-15.3; SD 2.2) maintenance dose every other week	9 weeks	64.3% experienced ≥ 2-point IGA improvement; 22.1% reported a 1-point improvement, and 12.6% experienced no improvement.	AEs are comparable to previous adolescent and adult trials.

Faiz S, Giovannelli J, Podevin C, Jachiet M, Bouaziz JD, Reguiai Z, Nosbaum A, Lasek A, Ferrier le Bouedec MC, Du Thanh A *et al.*: **Effectiveness and safety of dupilumab for the treatment of atopic dermatitis in a real-life French multicenter adult cohort.** *J Am Acad Dermatol* 2019, **81**:143-151.

Simpson EL, Paller AS, Siegfried EC, Boguniewicz M, Sher L, Gooderham MJ, Beck LA, Guttman-Yassky E, Pariser D, Blauvelt A *et al.*: **Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial.** *JAMA Dermatol* 2020, **156**:44-56.

Igelman S, Kurta AO, Sheikh U, McWilliams A, Armbrecht E, Jackson Cullison SR, Kress DW, Smith A, Castelo-Soccio L, Treat J *et al.*: **Off-label use of dupilumab for pediatric patients with atopic dermatitis: a multicenter retrospective review.** *J Am Acad Dermatol* 2020, **82**:407-411.

Dupilumab Trials

Open Label Extensions in Adults and Adolescents

- LIBERTY AD OLE: Adults ≥ 18[a]
- LIBERTY AD PED-OLE: ≥ 12 to < 18 years[b]

Pediatric Trials

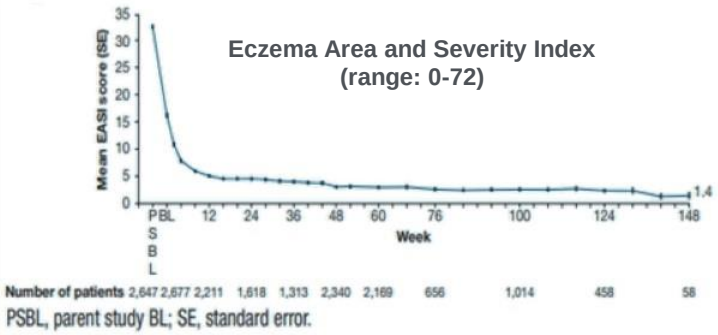
- LIBERTY AD PED: Children ≥ 6 to < 12 years[c]
- LIBERTY AD PRE-SCHOOL: ≥ 2 to < 6 years[d]

a. Thaci D, et al. RAD 2020. Poster 125; b. Blauvelt A, et al. RAD 2020. Poster 129; c. Paller A, et al. AAD 2020. Presentation F053; d. Simpson EL, et al. RAD 2020. Poster 128.

LIBERTY AD OLE Trial

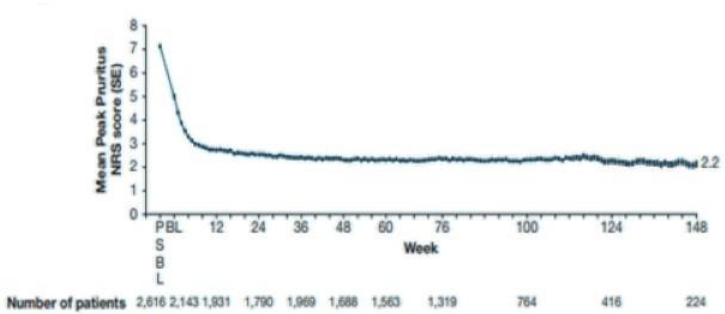
Long-Term Efficacy in Adults: 3-Year Follow-Up

Mean EASI Scores Over Time



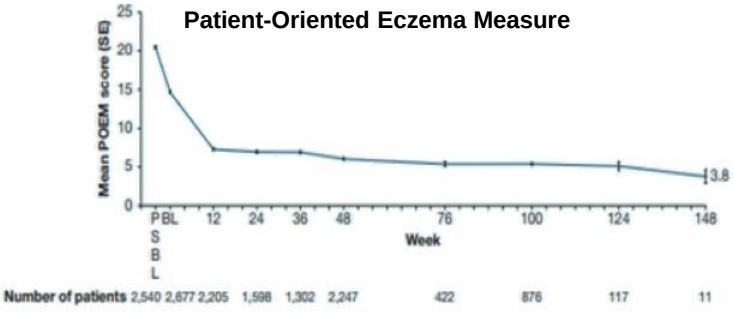
PSBL, parent study BL; SE, standard error.

Mean Peak Pruritus NRS Scores Over Time

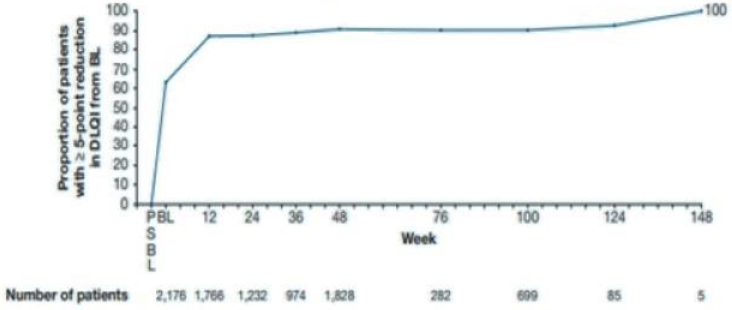


Mean POEM Scores Over Time

Patient-Oriented Eczema Measure



Proportion of Patients With ≥ 5-Point Reduction in DLQI from PSBL (Patients With PSBL DLQI Score ≥ 5)



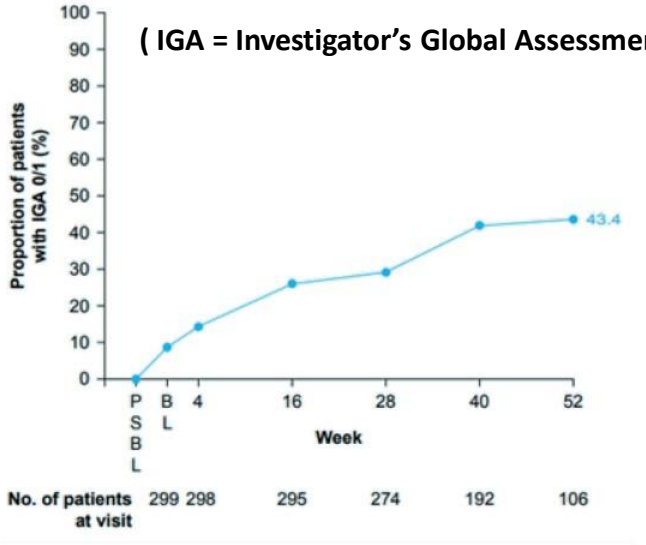
Thaci, et al. RAD 2020. Poster 125.

LIBERTY AD PED-OLE

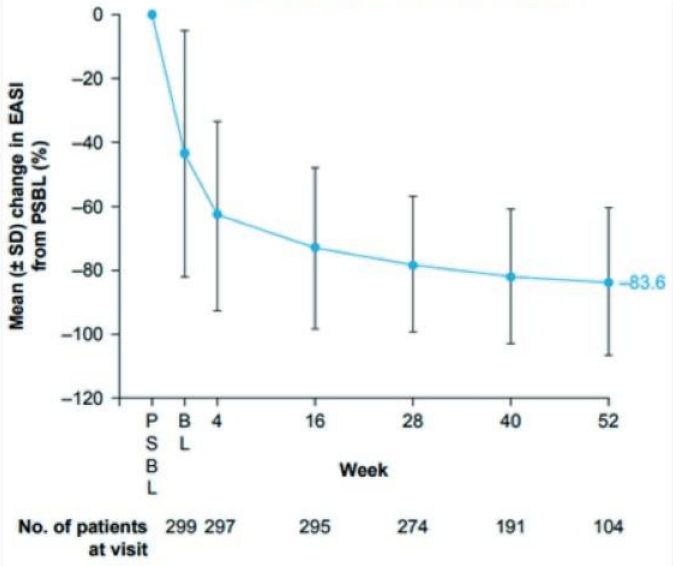
Long-Term Efficacy in Adolescents: 1-Year Follow-Up

Proportion of Patients With IGA 0 or 1 Over Time

(IGA = Investigator's Global Assessment)



Percent Change in EASI from PSBL Over Time



It is important to use medication for an adequate amount of time before discontinuing to see if truly ineffective

Blauvelt A, et al. RAD 2020. Poster 129.

LIBERTY AD OLE Trial

Safety

Comparison Between OLE Trial and Results From the CHRONOS Trial

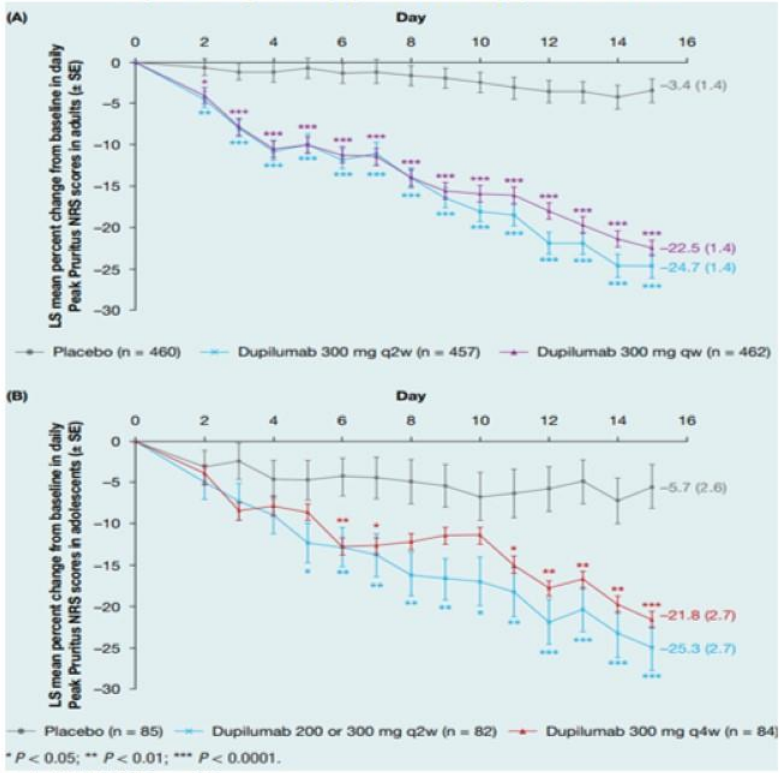
	OLE (AD-1225)			CHRONOS (AD-1224) Week 52, Final Data Set					
	Dupilimub 300 mg qw N = 2677			Placebo + TCS n = 315			Dupilumab 300 mg qw + TCS n = 315		
	Events	n (%)	nP/100PY	Events	n (%)	nP/100PY	Events	n (%)	nP/100PY
TEAE	13,826	2264 (84.6)	173.74	1520	268 (85.1)	325.08	1500	263 (83.5)	322.43
Severe TEAE	355	246 (9.2)	5.08	46	28 (8.9)	10.31	24	17 (5.4)	5.88
SAE	354	256 (9.6)	5.28	24	16 (5.1)	5.75	11	10 (3.2)	3.40
SAE Related to Study Drug	36	31 (1.2)	0.61	3	3 (1.0)	1.06	2	2 (0.6)	0.68
TEAE Leading to Study Discontinuation	116	95 (3.5)	1.87	30	25 (7.9)	8.31	10	9 (2.9)	2.58

Safety profile consistent with former safety studies, no new AEs observed

Thaci D, et al. RAD 2020. Poster 125.

Post Hoc Analysis — LIBERTY AD SOLO 1 and 2 and ADOL Trials
Results

LS mean percent change from baseline in daily Peak Pruritus NRS from Day 2 to Day 15 in (A) adults and (B) adolescents



- Improvement in itch as early as day 2 in adults and day 5 in adolescents was seen with dupilumab treatment
- Clinical improvement after the first dose in adults and adolescents
- Acceptable safety profile

Yosipovitch G, et al. AAAAI 2020. Poster 609.

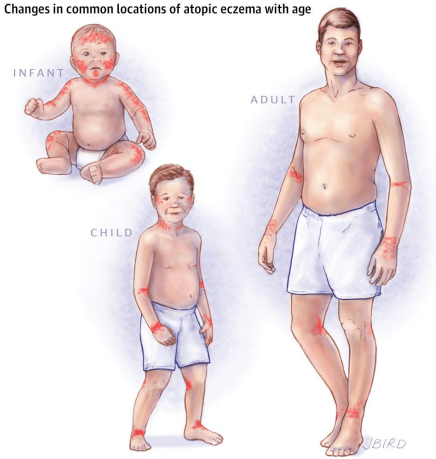
Dupilumab
AE: Conjunctivitis

- Conjunctivitis is an AE seen in patients who have AD and are taking dupilumab
- This AE has not been seen in patients with asthma or nasal polyposis taking dupilumab

Ocular exams are very important for patients with AD treated with dupilumab

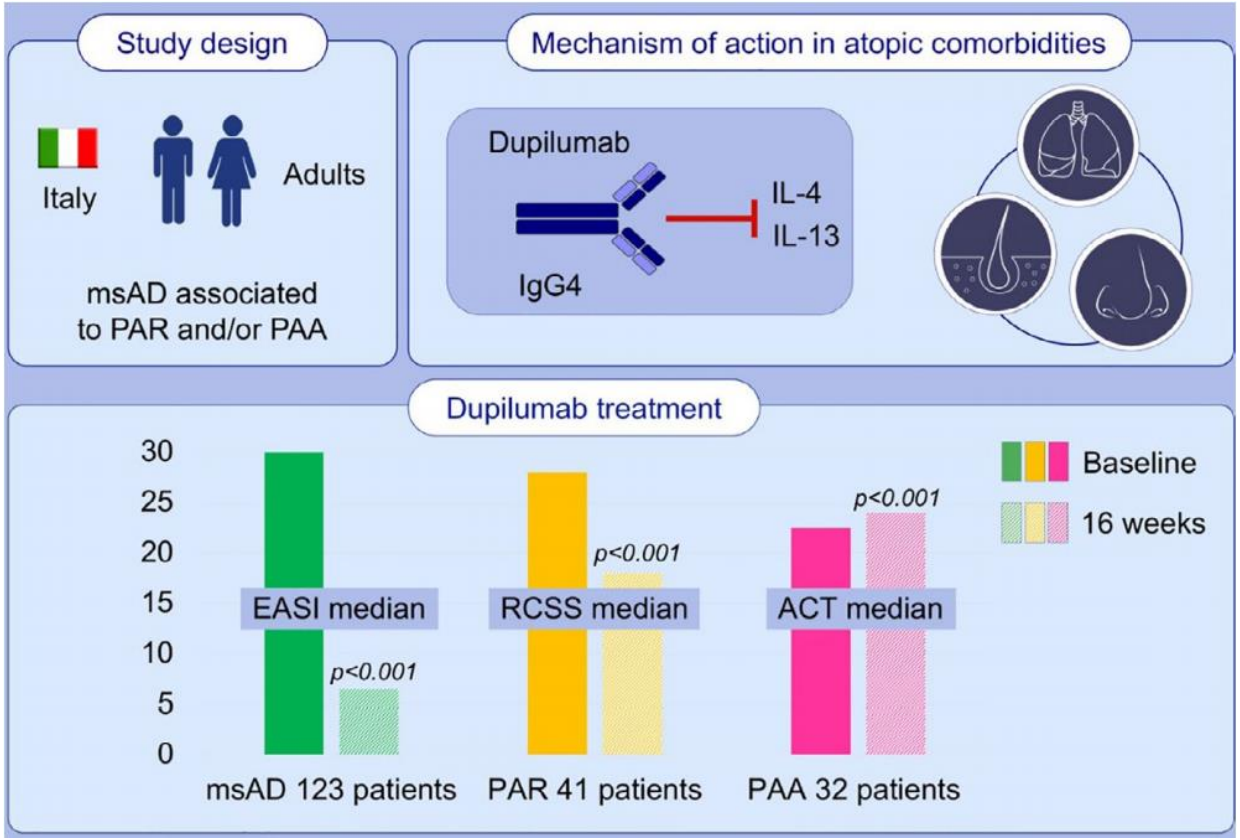
Maudinet A, et al. *Ophthalmol Ther.* 2019;8:485-490.

Efficacy of dupilumab in atopic comorbidities associated with moderate-to-severe adult atopic dermatitis



(Nettis E, et al., Allergy. 2020)

Efficacy of dupilumab in atopic comorbidities associated with moderate-to-severe adult atopic dermatitis



EASI = Eczema Area and Severity Index
RCSS= Rhinitis Control Scoring System

multicentric, prospective, observational, real-life study.

- **123 adult pts with moderate-to-severe AD.**
- **41 pts with comorbid PAR**
- **32 pts with comorbid PAA**

Conclusion:
The results support the benefits of dupilumab for adult patients with PAR and/or PAA associated with msAD.

(Nettis E, et al., Allergy. 2020)

Dupilumab è indicato in Europa e in Italia per dermatite atopica, asma grave e poliposi nasale

DERMATITE ATOPICA	Dupilumab è indicato per il trattamento della dermatite atopica da moderata a grave, negli **adulti e negli adolescenti** di età pari o superiore ai 12 anni eligibili per la terapia sistemica.	**27 SETTEMBRE 2017** Pazienti adulti (≥18 anni **6 AGOSTO 2019** Pazienti adolescenti
ASMA GRAVE	Dupilumab è indicato negli **adulti e negli adolescenti** di età pari o superiore ai 12 anni come trattamento aggiuntivo di mantenimento per l'asma grave con **infiammazione di tipo 2**, caratterizzata da un aumento degli **eosinofili ematici e/o del FeNO**, non adeguatamente controllati con ICS (corticosteroidi per via inalatoria) a dosaggio alto e un altro prodotto medicinale per il trattamento di mantenimento.	**7 MAGGIO 2019** Pazienti adulti e adolescenti (≥12 anni) con **Asma Grave**
POLIPOSI NASALE	Dupilumab è indicato come terapia aggiuntiva a corticosteroidi intranasali per il trattamento di **adulti con CRSwNP grave** per i quali la terapia con corticosteroidi sistemici e/o la chirurgia non fornisce un controllo adeguato della malattia.	**29 OTTOBRE 2019** Pazienti adulti (≥18 anni) con **Rinosinusite Cronica** con **Poliposi Nasale (CRSwNP)**

Pubblicate in Gazzetta ufficiale il 9 dicembre 2020 le determine che ammettono la rimborsabilità da parte del Servizio sanitario nazionale di dupilumab in tre nuove indicazioni che succedono alla rimborsabilità già ottenuta nei pazienti adulti affetti da dermatite atopica. Valide quindi quelle relative agli adulti e adolescenti con asma grave con infiammazione di tipo 2, negli adulti con rinosinusite cronica con poliposi nasale grave, negli adolescenti dai 12 ai 17 anni con dermatite atopica grave.

Comorbidities and Type 2 Inflammation

- The presence of comorbidities linked to type 2 inflammation may influence the biologic agent selected
- Non-allergic eosinophilic asthma is often associated with chronic rhinosinusitis and nasal polyps
  - Both are responsive to anti-IL-4/IL-13 agents, eg, dupilumab
- Atopic dermatitis is an important comorbidity in severe asthma.



Grazie per l'attenzione!

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