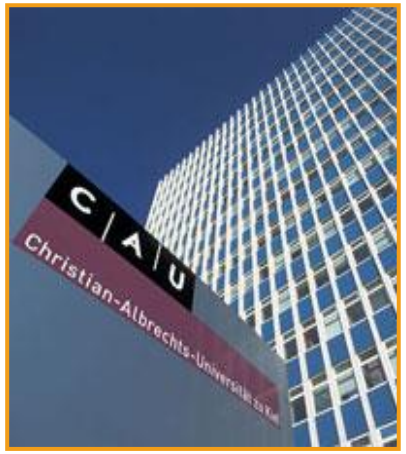
Severe Asthma: An Update

Klaus F. Rabe MD, PhD, FERS

LungenClinic Grosshansdorf & Christian Albrechts Universität Kiel

(ARCN - DEUTSCHES ZENTRUM FÜR LUNGENFORSCHUNG)

www.lungenclinic.de



ARCN | DZL Deutsches Zentrum für Lungenforschung

LungenClinic GROSSHANSDORF

LungenClinic GROSSHANSDORF

ARCN DZL Deutsches Zentrum für Lungenforschung

Severe Asthma: An Update

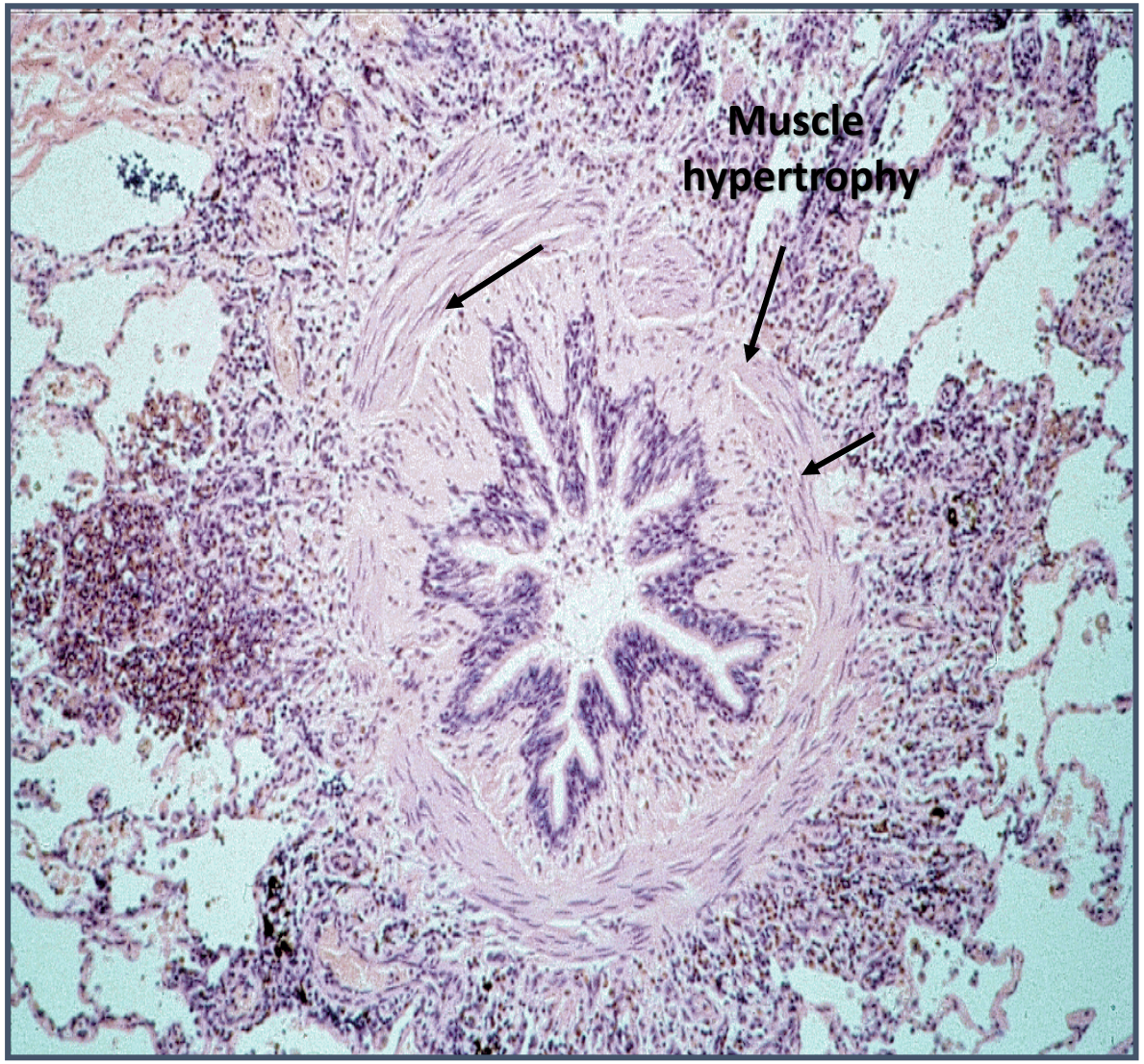
Potential COI: Klaus F. Rabe

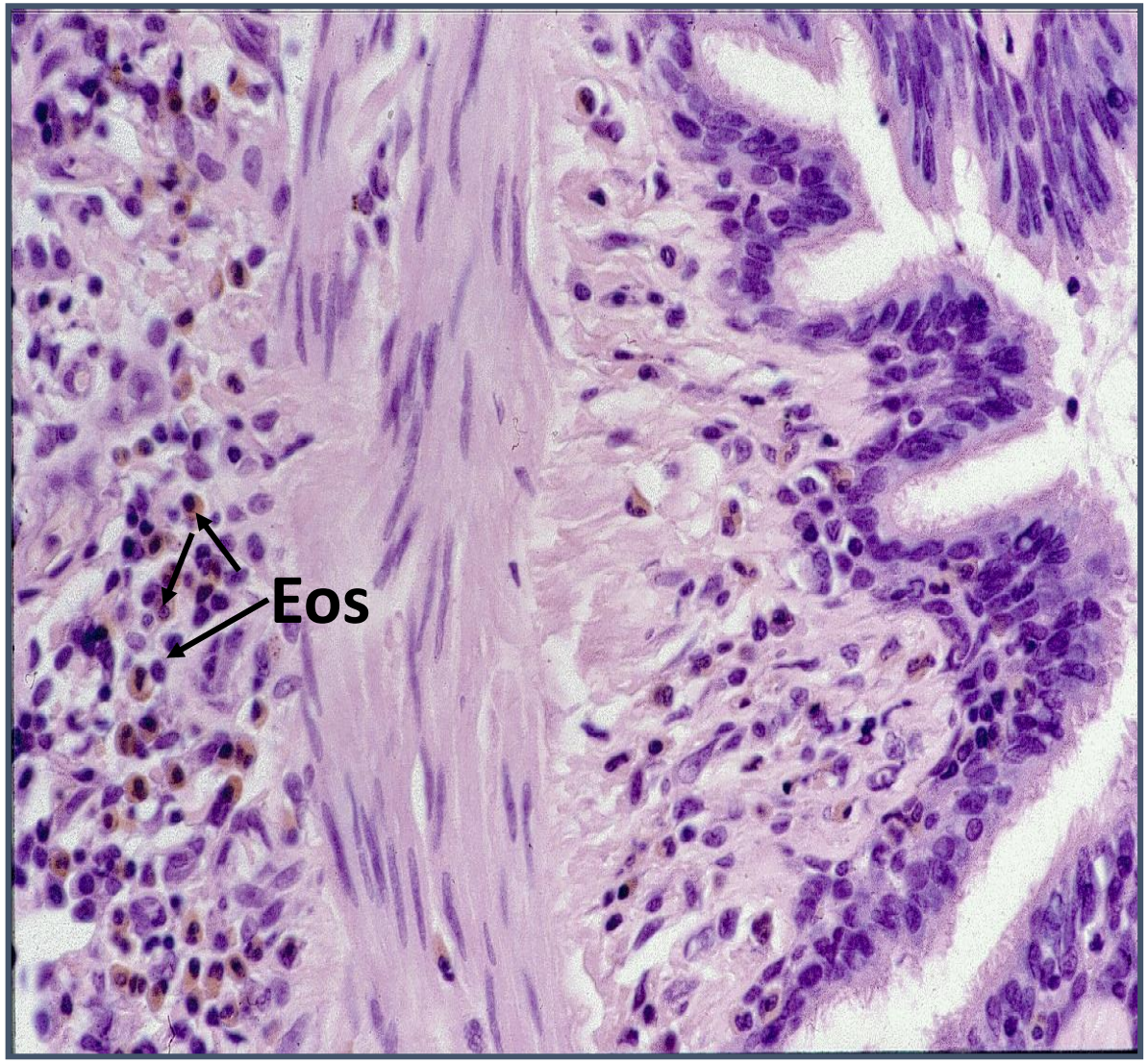
- Has served on FDA and EMA panels for registration of drugs for COPD
- Has served on advisory panels for most pharmaceutical companies making asthma and COPD drugs, and participated in clinical trials
- Has never worked with the tobacco industry (and never will)
- Has no shares or proprietory interests of any kind

LungenClinic GROSSHANSDORF

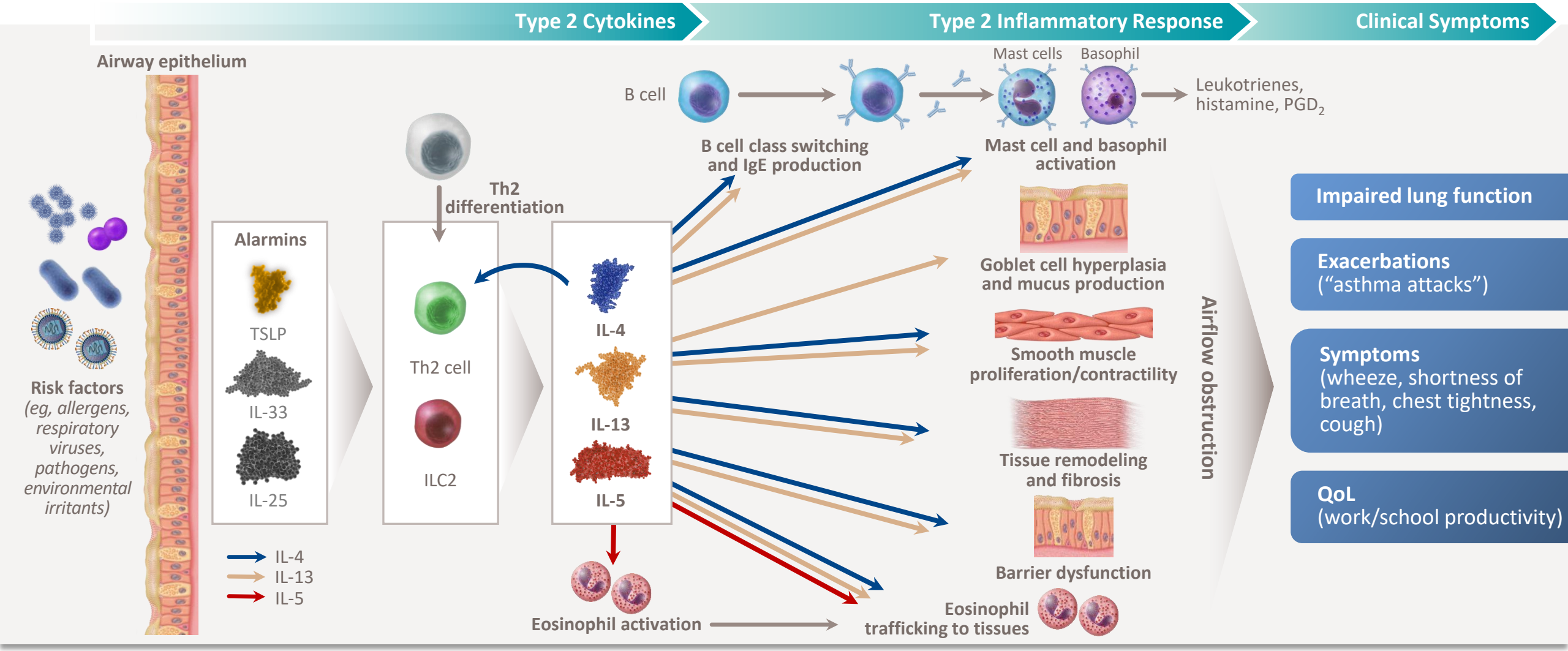
ARCN | DZL Deutsches Zentrum für Lungenforschung

Severe Asthma: General Comments





Severe Asthma: An Update on Inflammation

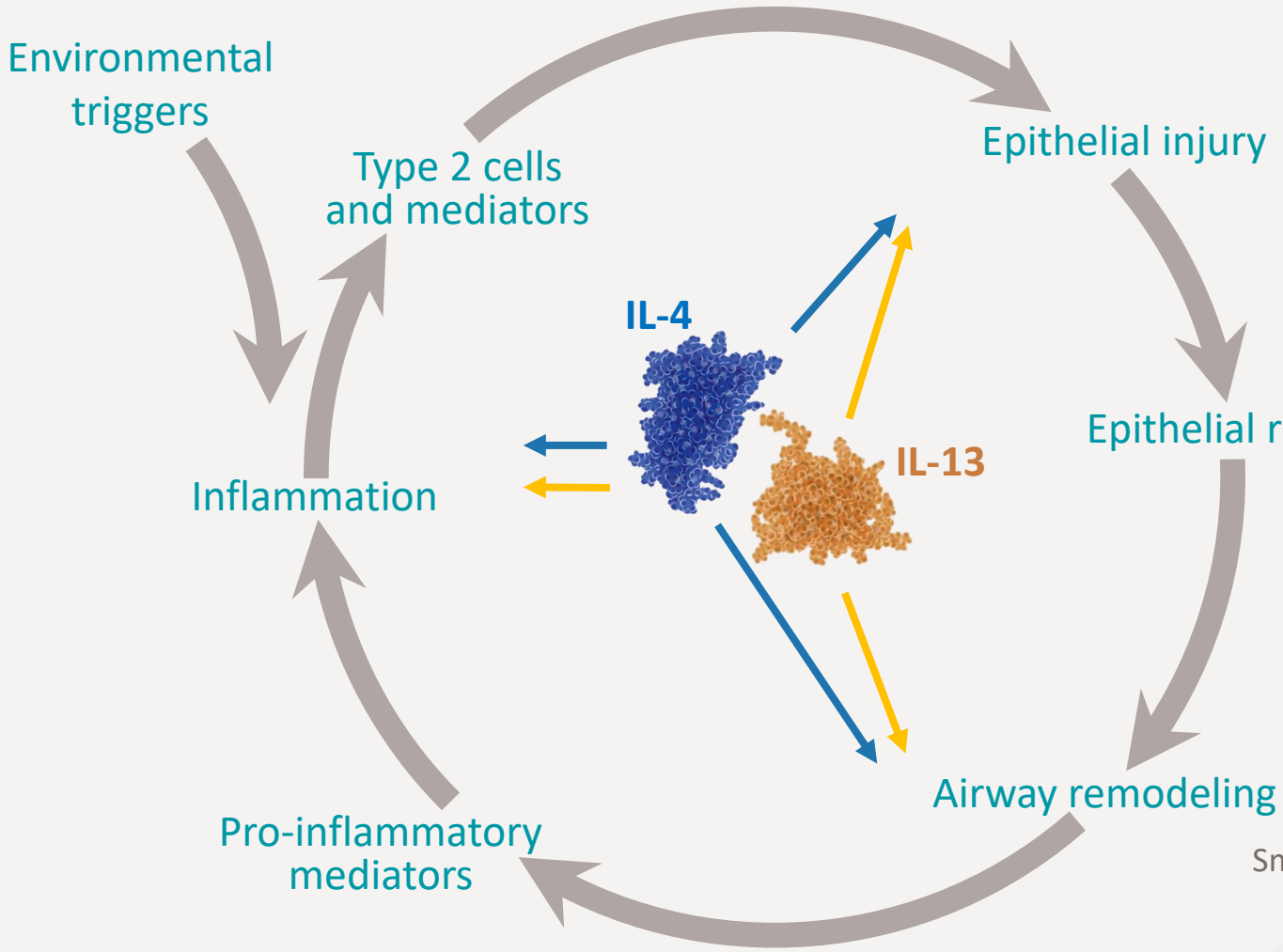


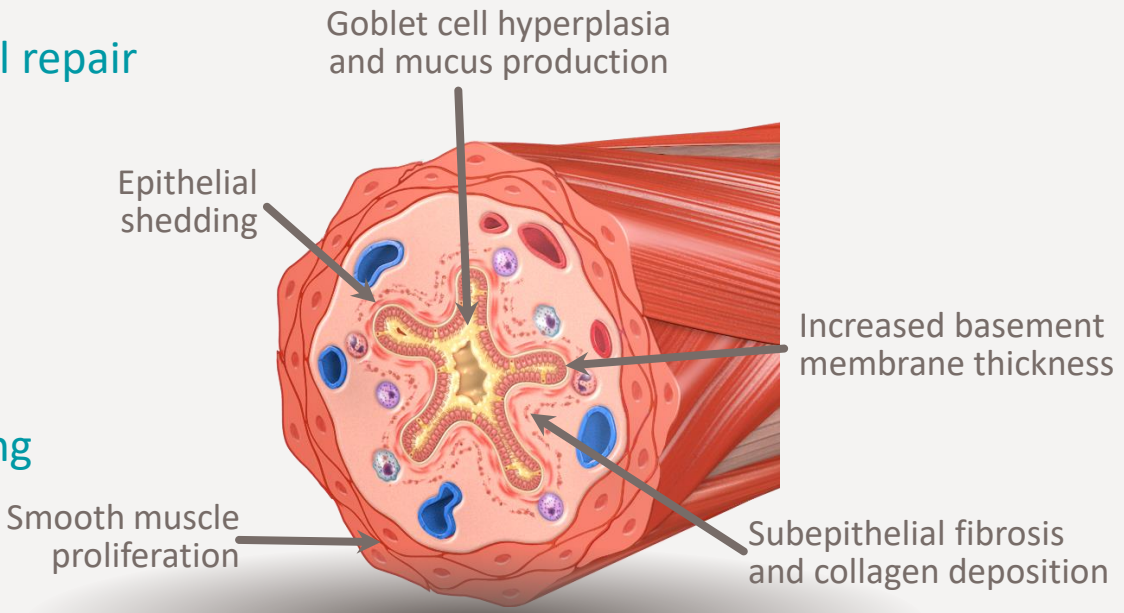
IgE, immunoglobulin E; IL, interleukin; ILC2, innate lymphoid cell type 2; PGD_2, prostaglandin D_2; QoL, quality of life; Th2, T helper 2; TSLP, thymic stromal lymphopoietin.

1. Gandhi NA, et al. *Nat Rev Drug Discov*. 2016;15(1):35-50. 2. Fahy JV. *Nat Rev Immunol*. 2015;15(1):57-65. 3. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Updated 2022. https://ginasthma.org/reports/. Accessed May 18, 2022. 4. Shinkai A, et al. *J Immunol*. 1999;163(3):1602-1610. 5. Borchers MT, et al. *J Leukoc Biol.* 2002;71(6):1033-1041. 6. Kaur D, et al. *Allergy*. 2006;61(9):1047-1053. 7. Le Floc'h A, et al. *Allergy*. 2020;75(5):1188-1204. 8. Manson ML, et al. *J Allergy Clin Immunol*. 2020;145(3):808-817.e2. 9. Chung KF. *Lancet*. 2015;386(9998):1086-1096.

LungenClinic GROSSHANSDORF

Severe Asthma: An Update on Remodelling



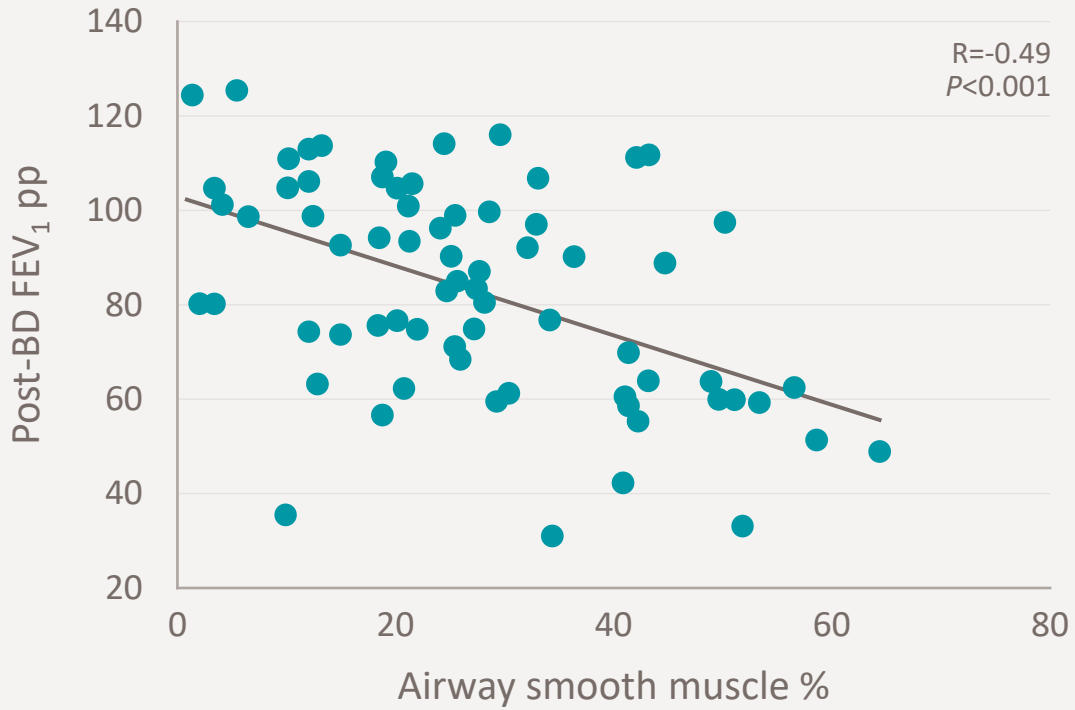


IL, interleukin.

1. Holgate ST, Polosa R. *Lancet*. 2006;368(9537):780-793. 2. Gandhi NA, et al. *Nat Rev Drug Discov*. 2016;15(1):35-50.
3. Schleimer RP, et al. *J Allergy Clin Immunol*. 2017;139(6):1752-1761. 4. Fahy JV. *Nat Rev Immunol*. 2015;15(1):57-65.
5. Fehrenbach H, et al. *Cell Tissue Res*. 2017;367(3):551-569.

Airway Remodeling in Asthma Is Associated With Airflow Obstruction

Airway smooth muscle vs FEV_1 pp



Subjects with persistent airflow limitation had significantly more airway smooth muscle (33.5±15.6% vs 20.1±12.6%; *P*<0.001)

Post-BD FEV_1pp was inversely correlated with airway smooth muscle percent, demonstrating how impaired **lung function may indicate severity of airway remodeling**

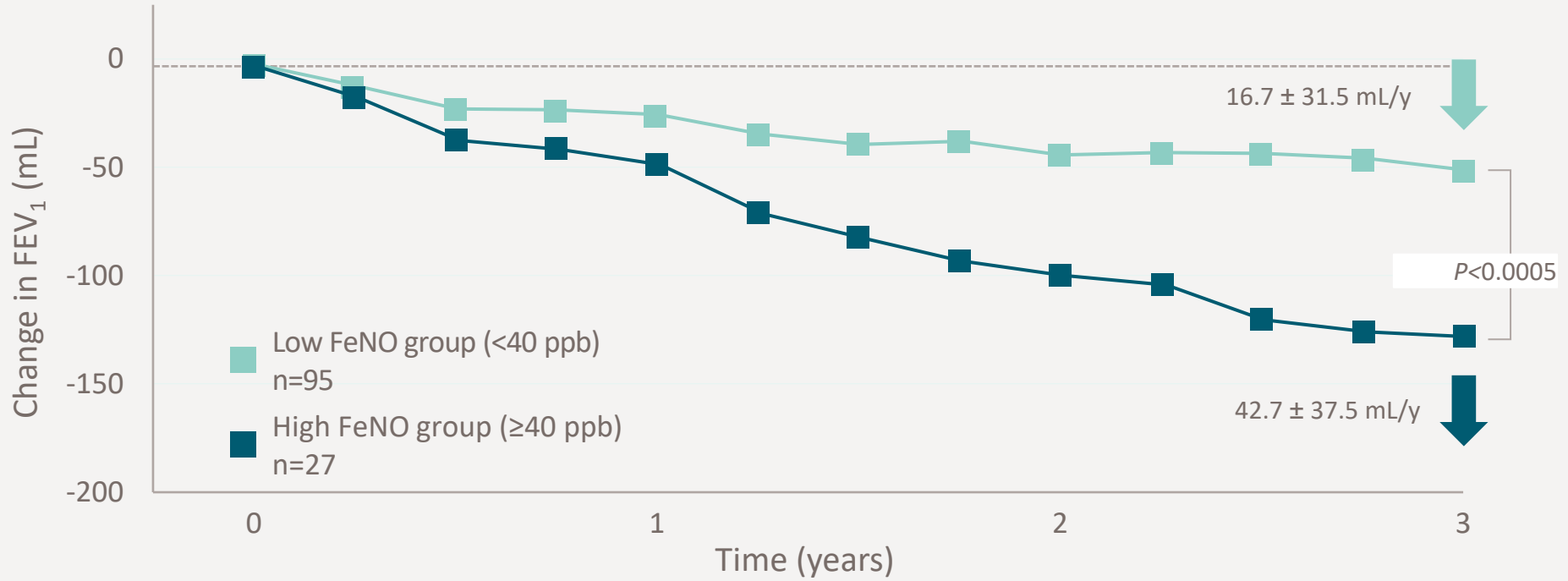
Reprinted from *European Respiratory Journal*, Vol 49/No. 5, Berair R, et al, Associations in asthma between quantitative computed tomography and bronchial biopsy-derived airway remodelling, p1601507, Copyright 2017 with permission from European Respiratory Society.

BD, bronchodilator; FEV_1, forced expiratory volume in 1 second; pp, percent predicted.
Berair R. *Eur Respir J.* 2017;49(5):1601507.

LungenClinic GROSSHANSDORF

Exhaled NO as a Biomarker of Lung Function Decline

3-year prospective cohort study (N=128 patients)



Patients with high FeNO had a significantly higher risk of a rapid decline in FEV_1 compared with those with non-high FeNO (OR, 2.73; 95% CI, 1.44-5.15; *P*<0.01).

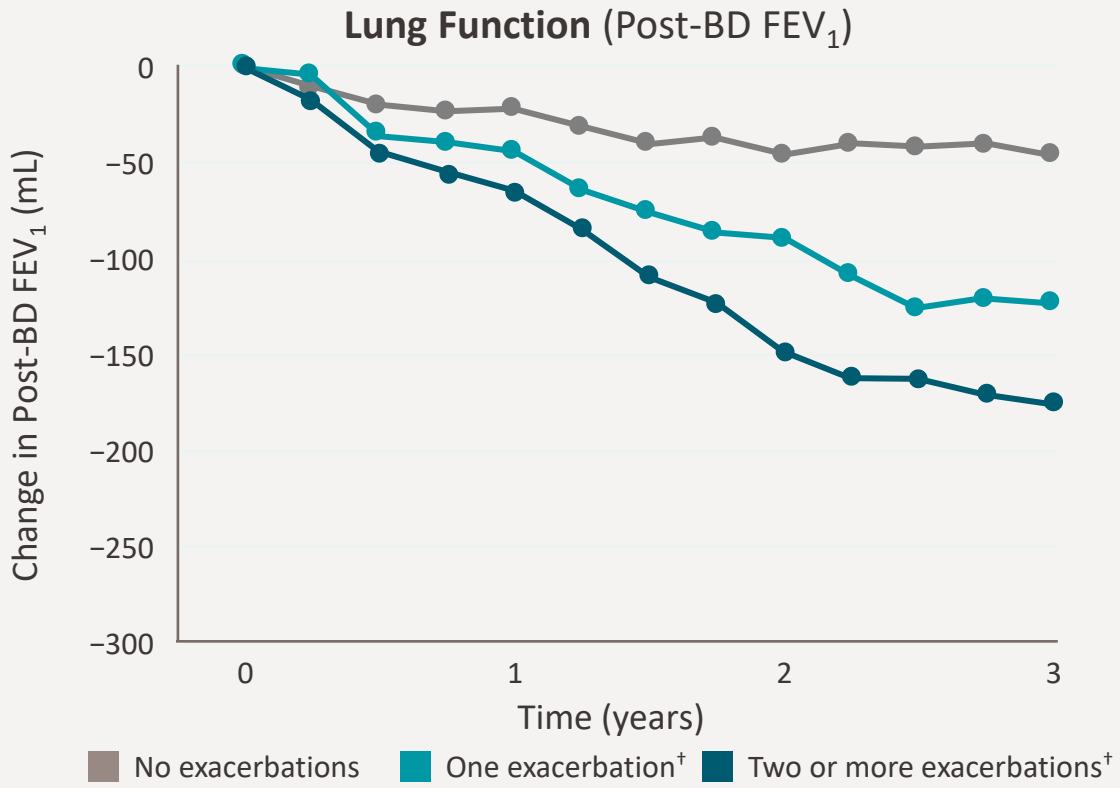
Reprinted from *Allergology International*, Vol 65/No. 3, Matsunaga K, et al, Persistently high exhaled nitric oxide and loss of lung function in controlled asthma, pp266-271, Copyright 2016, with permission from the Japanese Society of Allergology.

CI, confidence interval; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; OR, odds ratio; ppb, parts per billion.
Matsunaga K, et al. *Allergol Int*. 2016;65(3):266-271.

LungenClinic GROSSHANSDORF

Frequent Exacerbations and Airflow Limitation

Patients with well-controlled asthma at baseline followed for 3 years (N=128)[1*]



Post-BD FEV_1 13.6 mL/year

Post-BD FEV_1 41.3 mL/year

Post-BD FEV_1 58.3 mL/year

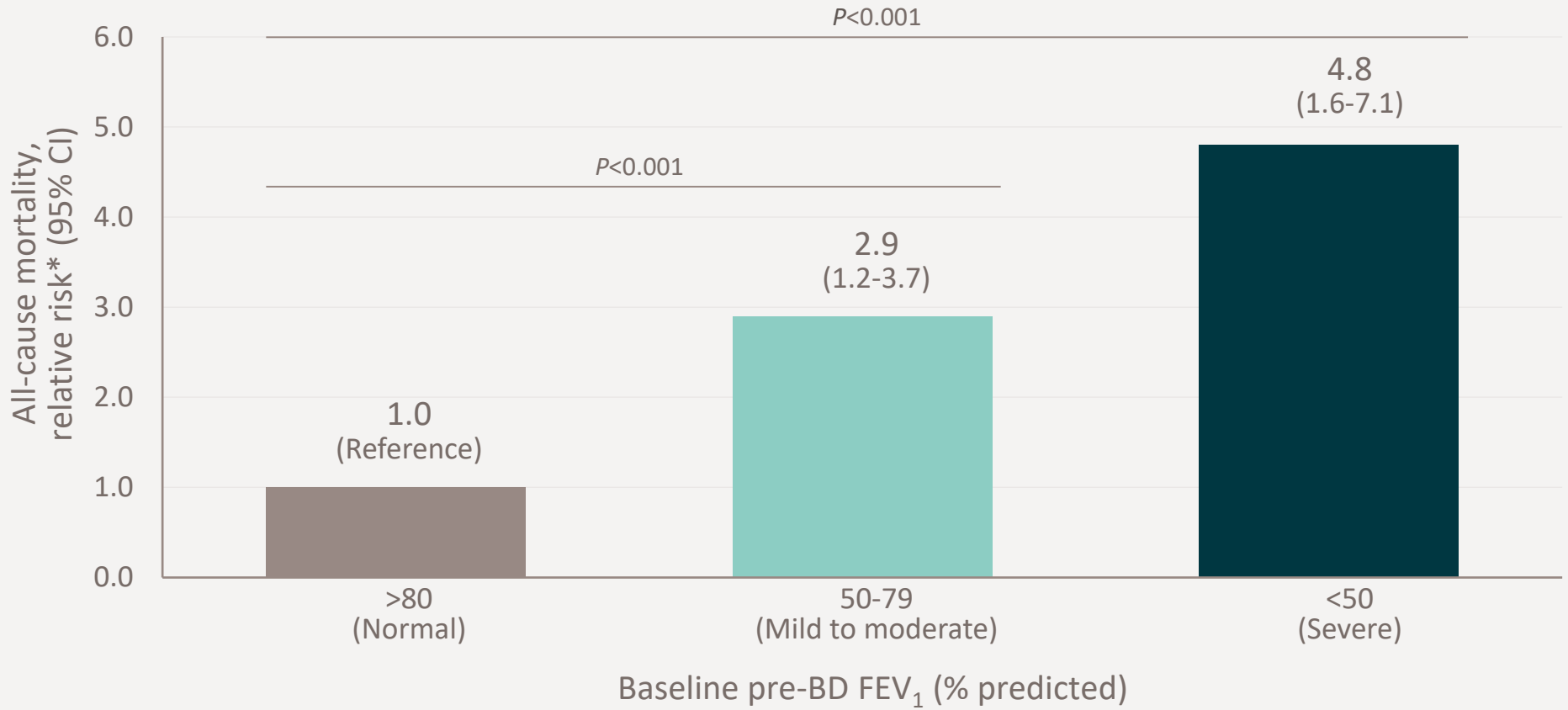
Asthma exacerbations could have long-term adverse consequences on airway structure and function

*No exacerbations (n=100); Exacerbations (n=28). †Severe exacerbation was defined as worsening asthma requiring at least 3 days of treatment with systemic corticosteroids, or a hospitalization due to asthma.
BD, bronchodilator; FEV_1, forced expiratory volume in 1 second.

1. Matsunaga K, et al. *J Allergy Clin Immunol Pract*. 2015;3(5):759-764.

Severe Asthma: An Update on Lung Function and Mortality

25-year follow up in adult patients with asthma (n=1075)

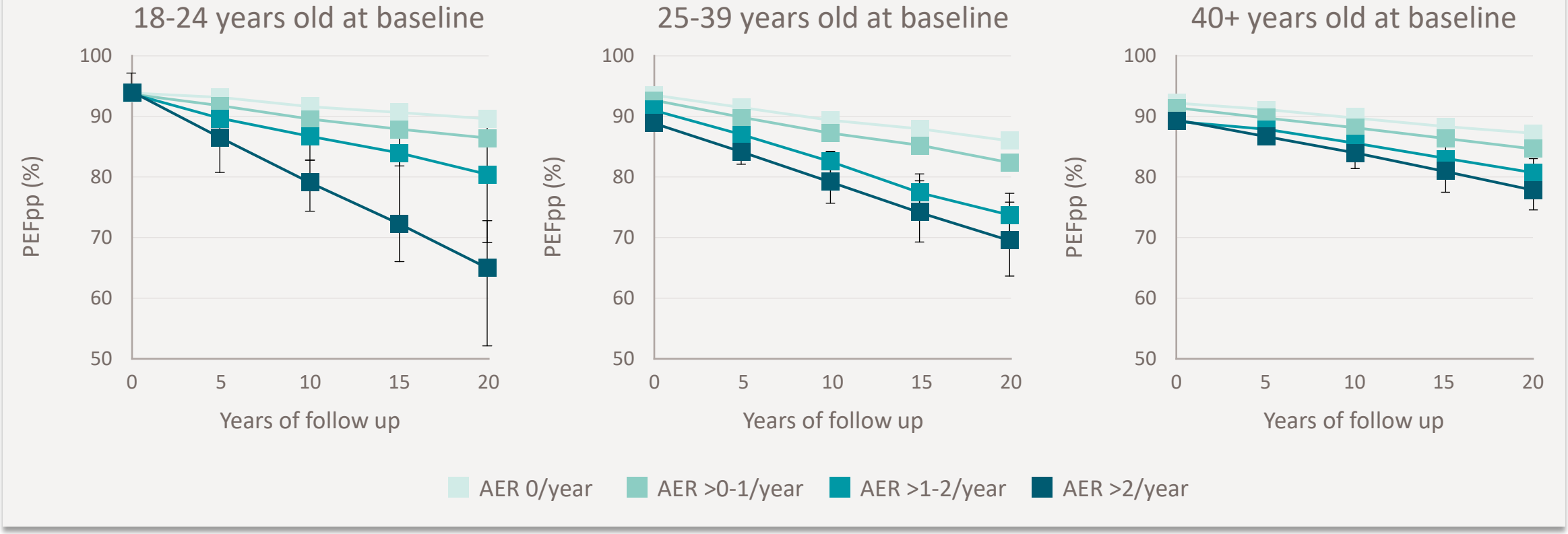


*Relative risk of death from asthma during 25 years of follow up.
BD, bronchodilator; CI, confidence interval; FEV_1, forced expiratory volume in 1 second.
Ali Z, et al. *Chest*. 2013;143:1649-1655.

LungenClinic GROSSHANSDORF

Severe Asthma: Exacerbations and Lung Function Decline

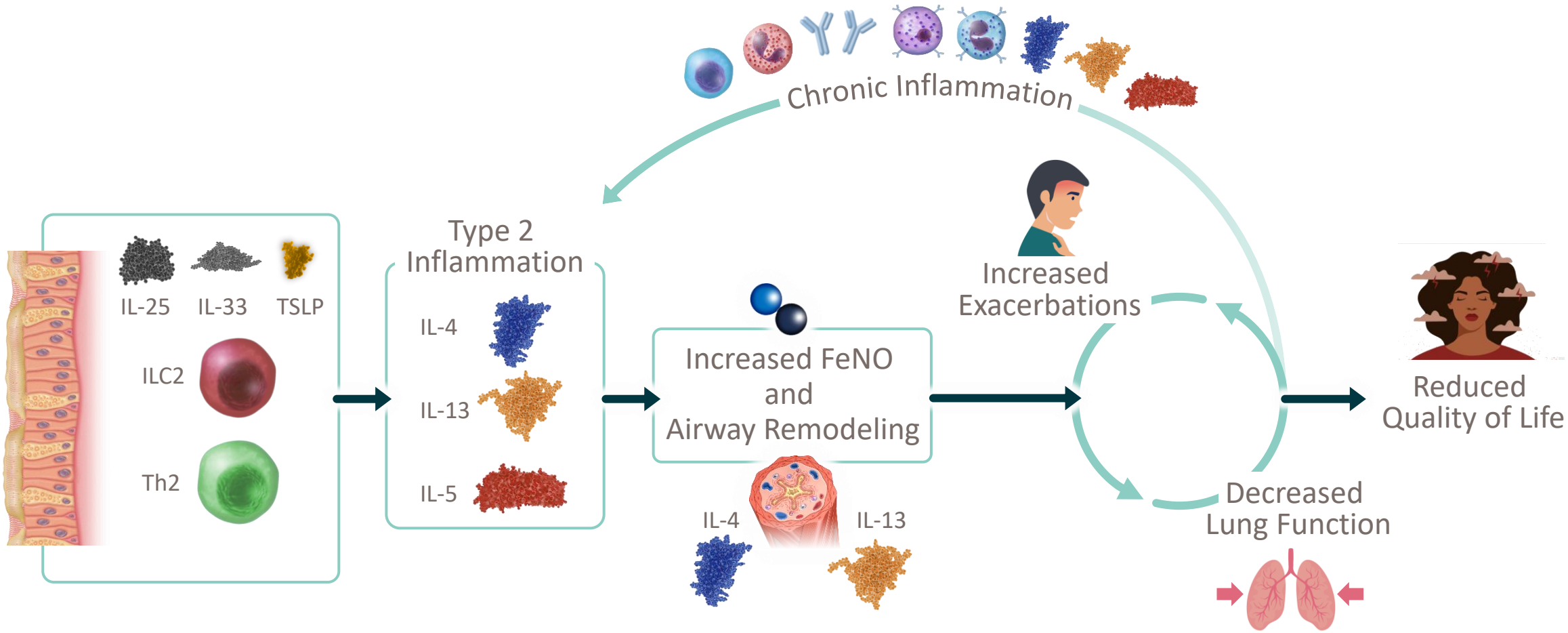
Estimated declines in percent predicted PEF over 20 years according to annual exacerbation rate (OPTIMUM Patient Care Research Database UK)*



*Adjusted for patient age, body mass index, gender, length of follow up, baseline lung function, and smoking status. Exacerbation was defined as asthma-related hospital visit or stay, or acute prescription for ≥3 days of prednisolone.
AER, asthma exacerbation rate; PEFpp, peak expiratory flow percent predicted.
Soremekun S, et al. Poster presented at: 6th Respiratory Effectiveness Group Summit; March 18-20, 2021; Virtual.

LungenClinic GROSSHANSDORF

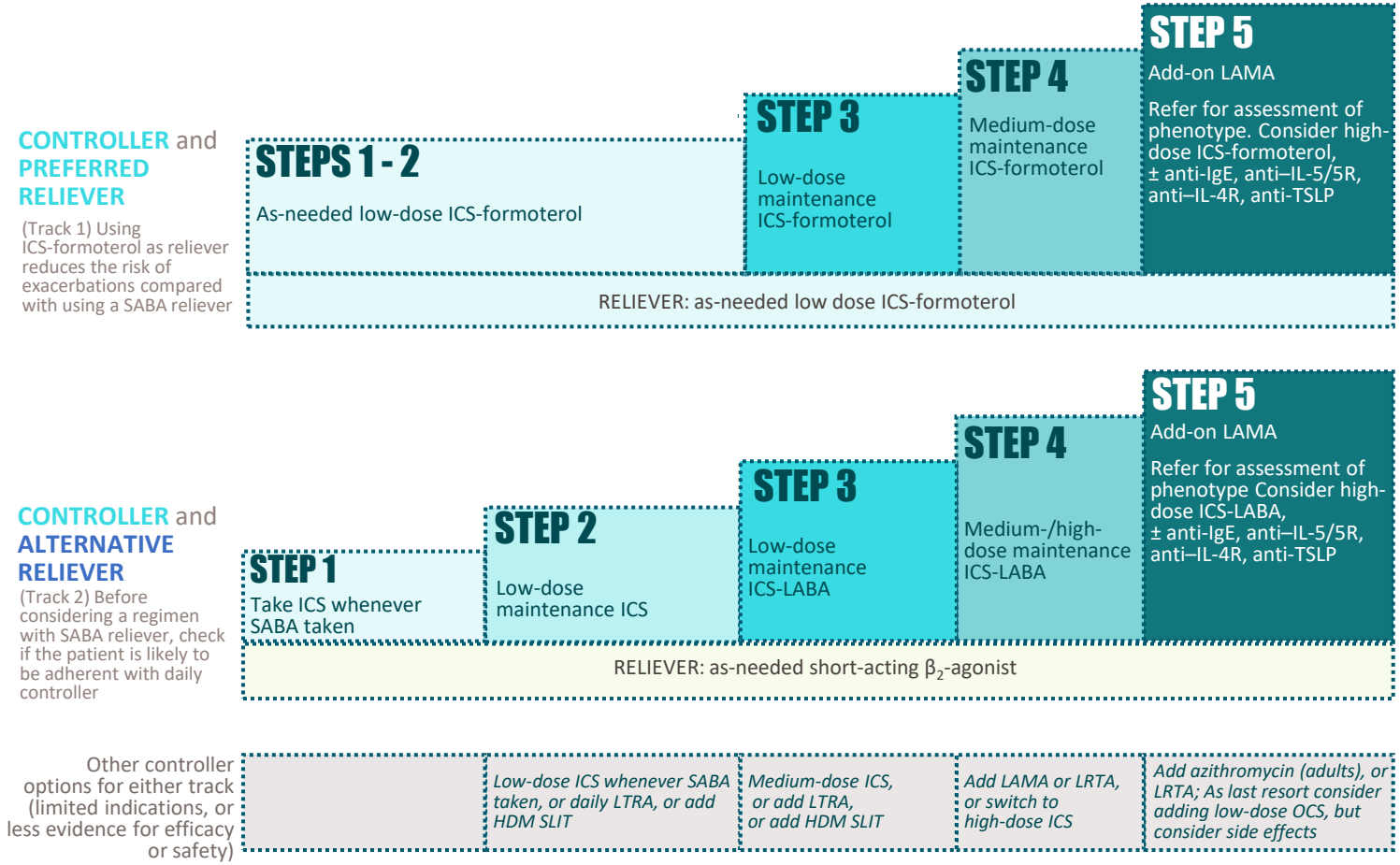
Severe Asthma Driven by Type 2 Inflammation



FeNO, fractional exhaled nitric oxide; IL, interleukin; ILC2, innate lymphoid cell type 2; QoL, quality of life; Th2, T helper 2; TSLP, thymic stromal lymphopoietin.

1. Chung KF. *Lancet*. 2015;386(9998):1086-1096. 2. Gandhi NA, et al. *Nat Rev Drug Discov*. 2016;15(1):35-50. 3. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Updated 2022. https://ginasthma.org/reports/. Accessed May 18, 2022. 4. Bai TR, et al. *Eur Respir J*. 2007;30(3):452-456. 5. Matsunaga K, et al. *J Allergy Clin Immunol*. 2015;3(5):759-764. 6. Dougherty RH, Fahy JV. *Clin Exp Allergy*. 2009;39:193-202. 7. Holgate ST, Polosa R. *Lancet*. 2006;368(9537):780-793. 8. Schleimer RP, et al. *J Allergy Clin Immunol*. 2017;139(6):1752-1761. 9. Alving K, et al. *Eur Respir Mon*. 2010;49:1-31. 10. Foster JM, et al. *Eur Respir J.* 2017;50(3):1700765.

Severe Asthma: GINA Updated



GINA Step 5

Consider **add-on biologic therapy for** patients with **exacerbations or poor symptom control** despite at least high-dose ICS-LABA, and

- Who have **allergic** or **eosinophilic biomarkers**, or
- Who need **maintenance OCS**

Options for stepping down OCS in patients taking high-dose ICS/LABA + OCS	• Continue high-dose ICS/LABA and reduce OCS dose • Use sputum-guided approach to reducing OCS • Alternate-day OCS treatment • Replace OCS with high-dose ICS
Options for stepping down high-dose ICS/LABA + other add-on agents	• Refer for expert advice

*See GINA Main Report for complete guidelines.
GINA, Global Initiative for Asthma; HDM, house dust mite; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL, interleukin; LABA, long-acting beta agonists; LAMA, long-acting muscarinic antagonist; LRTA, leukotriene receptor antagonists; OCS, oral corticosteroids; SABA, short-acting beta agonists; SLIT, sublingual immunotherapy; TSLP, thymic stromal lymphopoietin.
Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Updated 2022. https://ginasthma.org/reports/. Accessed May 18, 2022.

LungenClinic GROSSHANSDORF

Severe Asthma: An Update on Approved Biologics

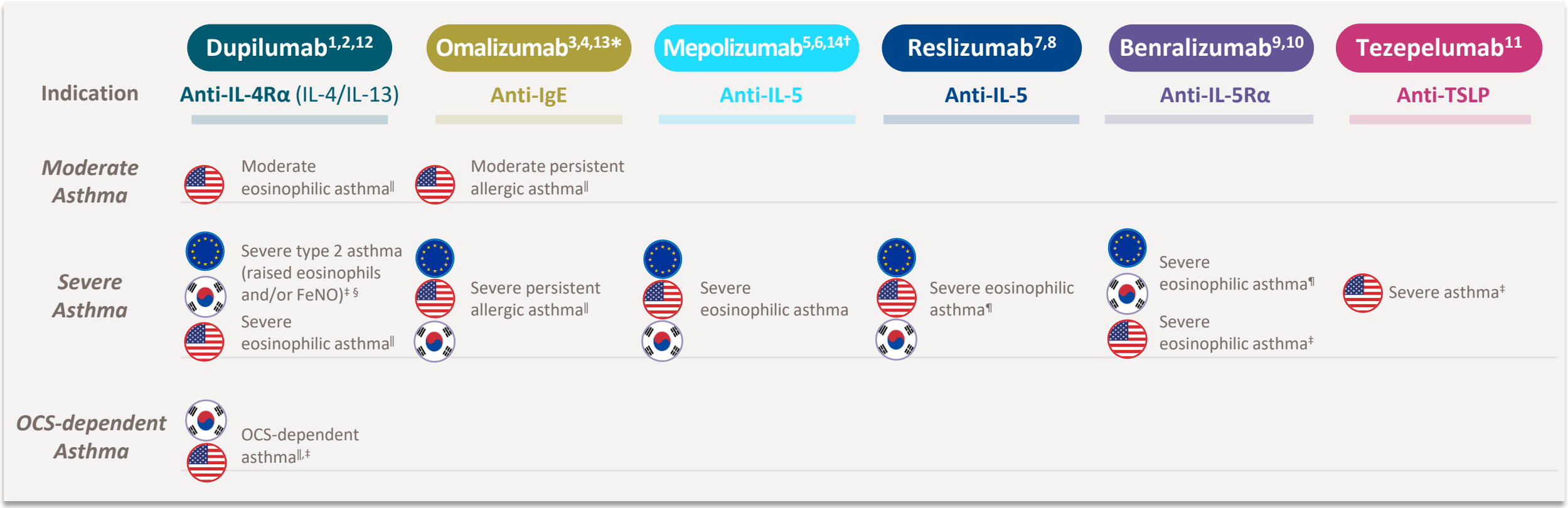


Table updated on Jul 2022. Flags denote approval in the United States, European Union and Korea.
As of Jul 2022, Tezepelumab is not approved for use in patients with severe asthma in Korea.[11]

*Indicated also for patients aged 12 years and older with chronic idiopathic urticaria in the Korea. †Also indicated for adult patients with hypereosinophilic syndrome and patients aged 12 years and older eosinophilic granulomatosis with polyangiitis in the US. ‡Approved for use in adults and adolescents 12 years and older. § Differential dose regimen recommended for OCS-dependent patients. ‖Approved for use in adults, adolescents, and children 6 years and older. ¶Approved for use in adults 18 years and older.

FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin; OCS, oral corticosteroids; TSLP, thymic stromal lymphopoietin.

1. Dupixent (dupilumab) [prescribing information]. Tarrytown, NY: Regeneron Sanofi Genzyme; 2021. 2. Dupixent (dupilumab) [summary of product characteristics]. Paris, France: sanofi-aventis groupe; 2022.
3. Xolair (omalizumab) [prescribing information]. South San Francisco, CA: Genentech, Inc. 2021. 4. Xolair (omalizumab) Summary of Product Characteristics. Camberly, UK: Novartis Europharm Ltd. 2021.
5. Nucala (mepolizumab) SmPC. Cork, Ireland: GlaxoSmithKline. Research Triangle Park, NC. 2021. 6. Nucala (mepolizumab) Prescribing Information. Research Triangle Park, NC: GlaxoSmithKline. 2022.
7. Cinqaero (reslizumab) [SmPC]. Haarlem, The Netherlands: Teva B.V.; 2021. 8. Cinqair Prescribing Information. Updated February 2020. 9. Fasenra (benralizumab) [SmPC]. Södertälje, Sweden: AstraZeneca AB; 2022. 10. Fasenra Prescribing Information. Updated February 2021. 11. Tezspire (tezepelumab) Prescribing Information. Thousand Oaks, CA: Amgen, Inc. 2021. 12. Dupixent (Dupilumab) Korea Prescribing information as of 4Jul2022.
13. Xolair (omalizumab) Korea Prescribing information as of 4Jul2022. 14. Nucala (mepolizumab) Korea Prescrbing information as of 4Jul2022. 15. Cinqaero (reslizumab) Korea Prescribing information as of 4Jul2022. 16. Fasenra (benralizumab) Korea Prescribing information as of 4Jul2022

Severe Asthma: An Update on Approved Biologics

	Omalizumab[1]
Clinical trial	INNOVATE (Week 28)
Population	Total serum IgE ≥30 to ≤700 IU/mL*
Exacerbation history (past 12 months)	≥2, or ≥1 severe
Baseline FEV_1pp	61.0%-61.6%
Change from baseline in pre-BD FEV_1†	**190 mL**
Difference versus placebo in pre-BD FEV_1†	**94 mL**
Annualized exacerbation rate	0.68
Change in ACQ versus placebo‡	—
OCS dose reduction versus placebo	—

Met MCID
Range included MCID
Did not meet MCID
Did not meet primary endpoint

*Intent-to-treat population. **†Minimum clinically important difference (MCID)=0.1-0.2 L.[11] ‡MCID=0.5.[5] §***P*=0.434

Data are not based on head-to-head comparisons of different agents and no comparative conclusions of efficacy should be drawn from this information.
As of March 2, 2022, tezepelumab is not approved for use in patients with severe asthma outside of the United States.

ACQ, Asthma Control Questionnaire; BD, bronchodilator; EOS, eosinophils; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; MCID, minimum clinically important difference; OCS, oral corticosteroid; pp, percent predicted.

1. Humbert M, et al. *Allergy*. 2005;60(3):309-316. 2. Ortega HG, et al. *N Engl J Med*. 2014;371(13):1198-1207. 3. Bleecker ER, et al. *Lancet*. 2016;388(10056):2115-2127. 4. FitzGerald JM, et al. *Lancet*. 2016;388(10056):2128-2141. 5. Castro M, et al. *N Engl J Med*. 2018;378(26):2486-2496. 6. Menzies-Gow A, et al. *N Engl J Med*. 2021;384(19):1800-1809 7. Bel EH, et al. *N Engl J Med*. 2014;371(13):1189-1197. 8. Nair P, et al. *N Engl J Med*. 2017;376(25):2448-2458. 9. Rabe KF, et al. *N Engl J Med*. 2018;378(26):2475-2485. 10. Wechsler ME, et al. Presented at: International Conference of the American Thoracic Society; May 14-19, 2021. 11. Tepper RS, et al. *J Allergy Clin Immunol*. 2012;129(3 suppl):S65-S87.

Severe Asthma: An Update on Approved Biologics

	Mepolizumab[2]
Clinical trial	MENSA (Week 32)
Population	EOS ≥150 cells/µL at baseline or ≥300 cells/µL during previous year*
Exacerbation history (past 12 months)	≥2
Baseline FEV_1pp	59.3%-62.4%
Change from baseline in pre-BD FEV_1†	**183-186 mL**
Difference versus placebo in pre-BD FEV_1†	**98-100 mL**
Annualized exacerbation rate	0.83-0.93
Change in ACQ versus placebo‡	**ACQ-5 -0.44 to -0.42**
OCS dose reduction versus placebo	**SIRIUS[7]** 50%

Met MCID
Range included MCID
Did not meet MCID
Did not meet primary endpoint

*Intent-to-treat population. **†Minimum clinically important difference (MCID)=0.1-0.2 L.[11] ‡MCID=0.5.[5] §***P***=0.434**

Data are not based on head-to-head comparisons of different agents and no comparative conclusions of efficacy should be drawn from this information.

As of March 2, 2022, tezepelumab is not approved for use in patients with severe asthma outside of the United States.

ACQ, Asthma Control Questionnaire; BD, bronchodilator; EOS, eosinophils; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; MCID, minimum clinically important difference; OCS, oral corticosteroid; pp, percent predicted.
1. Humbert M, et al. *Allergy*. 2005;60(3):309-316. 2. Ortega HG, et al. *N Engl J Med*. 2014;371(13):1198-1207. 3. Bleecker ER, et al. *Lancet*. 2016;388(10056):2115-2127. 4. FitzGerald JM, et al. *Lancet*. 2016;388(10056):2128-2141. 5. Castro M, et al. *N Engl J Med*. 2018;378(26):2486-2496. 6. Menzies-Gow A, et al. *N Engl J Med*. 2021;384(19):1800-1809 7. Bel EH, et al. *N Engl J Med*. 2014;371(13):1189-1197. 8. Nair P, et al. *N Engl J Med*. 2017;376(25):2448-2458. 9. Rabe KF, et al. *N Engl J Med*. 2018;378(26):2475-2485. 10. Wechsler ME, et al. Presented at: International Conference of the American Thoracic Society; May 14-19, 2021. 11. Tepper RS, et al. *J Allergy Clin Immunol*. 2012;129(3 suppl):S65-S87.

Severe Asthma: An Update on Approved Biologics

	Benralizumab[3,4]	
Clinical trial	**SIROCCO** (Week 48)	**CALIMA** (Week 56)
Population	EOS ≥300 cells/µL	
Exacerbation history (past 12 months)	≥2	
Baseline FEV_1pp	55.5%-59.4%	57.0%-59.1%
Change from baseline in pre-BD FEV_1†	**345-398 mL**	**330-340 mL**
Difference versus placebo in pre-BD FEV_1†	**106-159 mL**	**116-125 mL**
Annualized exacerbation rate	0.65-0.73	0.60-0.66
Change in ACQ versus placebo‡	**ACQ-6 -0.29 to -0.15**	**ACQ-6 -0.25 to -0.19**
OCS dose reduction versus placebo	**ZONDA[8]** 50%	

Met MCID
Range included MCID
Did not meet MCID
Did not meet primary endpoint

*Intent-to-treat population. **†Minimum clinically important difference (MCID)=0.1-0.2 L.[11] ‡MCID=0.5.[5] §***P*=0.434

Data are not based on head-to-head comparisons of different agents and no comparative conclusions of efficacy should be drawn from this information.

As of March 2, 2022, tezepelumab is not approved for use in patients with severe asthma outside of the United States.

ACQ, Asthma Control Questionnaire; BD, bronchodilator; EOS, eosinophils; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; MCID, minimum clinically important difference; OCS, oral corticosteroid; pp, percent predicted.
1. Humbert M, et al. *Allergy*. 2005;60(3):309-316. 2. Ortega HG, et al. *N Engl J Med*. 2014;371(13):1198-1207. 3. Bleecker ER, et al. *Lancet*. 2016;388(10056):2115-2127. 4. FitzGerald JM, et al. *Lancet*. 2016;388(10056):2128-2141. 5. Castro M, et al. *N Engl J Med*. 2018;378(26):2486-2496. 6. Menzies-Gow A, et al. *N Engl J Med*. 2021;384(19):1800-1809 7. Bel EH, et al. *N Engl J Med*. 2014;371(13):1189-1197. 8. Nair P, et al. *N Engl J Med*. 2017;376(25):2448-2458. 9. Rabe KF, et al. *N Engl J Med*. 2018;378(26):2475-2485. 10. Wechsler ME, et al. Presented at: International Conference of the American Thoracic Society; May 14-19, 2021. 11. Tepper RS, et al. *J Allergy Clin Immunol*. 2012;129(3 suppl):S65-S87.

Severe Asthma: An Update on Approved Biologics

	Dupilumab[5]		
Clinical trial	QUEST (Week 52)		
Population	No minimum inclusion criteria for type 2 biomarker level*	EOS ≥150 to <300 cells/µL	EOS ≥300 cells/µL
Exacerbation history (past 12 months)	≥1		
Baseline FEV_1pp	58.35%-58.51%		
Change from baseline in pre-BD FEV_1†	**320-340 mL**	**250-280 mL**	**430-470 mL**
Difference versus placebo in pre-BD FEV_1†	**130-140 mL**	**0-110 mL**	**210-240 mL**
Annualized exacerbation rate	0.456-0.524	0.471-0.559	0.370-0.403
Change in ACQ versus placebo‡	**ACQ-5 -0.39 to -0.22**	—	—
OCS dose reduction versus placebo	**VENTURE[9]** 50%		

Met MCID
Range included MCID
Did not meet MCID
Did not meet primary endpoint

*Intent-to-treat population. **†Minimum clinically important difference (MCID)=0.1-0.2 L.[11] ‡MCID=0.5.[5] §***P*=0.434
Data are not based on head-to-head comparisons of different agents and no comparative conclusions of efficacy should be drawn from this information.
As of March 2, 2022, tezepelumab is not approved for use in patients with severe asthma outside of the United States.
ACQ, Asthma Control Questionnaire; BD, bronchodilator; EOS, eosinophils; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; MCID, minimum clinically important difference; OCS, oral corticosteroid; pp, percent predicted.
1. Humbert M, et al. *Allergy*. 2005;60(3):309-316. 2. Ortega HG, et al. *N Engl J Med*. 2014;371(13):1198-1207. 3. Bleecker ER, et al. *Lancet*. 2016;388(10056):2115-2127. 4. FitzGerald JM, et al. *Lancet*. 2016;388(10056):2128-2141. 5. Castro M, et al. *N Engl J Med*. 2018;378(26):2486-2496. 6. Menzies-Gow A, et al. *N Engl J Med*. 2021;384(19):1800-1809 7. Bel EH, et al. *N Engl J Med*. 2014;371(13):1189-1197. 8. Nair P, et al. *N Engl J Med*. 2017;376(25):2448-2458. 9. Rabe KF, et al. *N Engl J Med*. 2018;378(26):2475-2485. 10. Wechsler ME, et al. Presented at: International Conference of the American Thoracic Society; May 14-19, 2021. 11. Tepper RS, et al. *J Allergy Clin Immunol*. 2012;129(3 suppl):S65-S87.

Severe Asthma: An Update on Approved Biologics Safety

Omalizumab[1]	Mepolizumab[2]	Benralizumab[3]	Dupilumab[4]
Per EMA SmPC, most common AEs	**Per EMA SmPC, most common AEs**	**Per EMA SmPC, most common AEs**	**Per EMA SmPC, most common AEs**
• Headaches • Injection site reactions – Pain – Swelling – Erythema – Pruritus	• Headache (20%) • Injection site reactions (8%) • Back pain (6%)	• Headache (8%) • Pharyngitis (3%)	• Conjunctivitis • Oral herpes • Eosinophilia • Arthralgia • Injection site reactions

Data are not based on head-to-head comparisons of different agents and no comparative conclusions about safety should be drawn from this information.

As of March 2, 2022, tezepelumab is not approved for use in patients with severe asthma outside of the United States.

AE, adverse event; EMA, European Medicines Agency; SmPC, summary of product characteristics; USPI, United States prescribing information.

1. Xolair (omalizumab) [summary of product characteristics]. Camberly, UK: Novartis Europharm Ltd.; 2020. 2. Nucala (mepolizumab) [summary of product characteristics]. Cork, Ireland: GlaxoSmithKline; 2021. 3. Fasenra (benralizumab) [summary of product characteristics]. Södertälje, Sweden: AstraZeneca AB; 2021.
4. Dupixent (dupilumab) [summary of product characteristics]. Paris, France: sanofi-aventis groupe; 2022. 5. Tezspire (tezepelumab) Prescribing Information. Thousand Oaks, CA: Amgen, Inc. 2021.

Severe Asthma: An Update on OCS Concern

Short-/long-term OCS use is associated with AEs[1-3]


Osteoporosis
Fractures


Obesity


Anxiety
Depression
Sleep disturbances


Type 2 diabetes
Adrenal suppression


Dyslipidemia
Hypertension
Thromboembolism


Increased risk
of infection


Cataracts
Glaucoma


GI bleeds/ulcers

Oral Corticosteroid Stewardship Statement[4]:

"It is time to protect patients with asthma from potential overexposure to OCS—and to recognize OCS overuse for what it often is: *a treatment plan failure*."

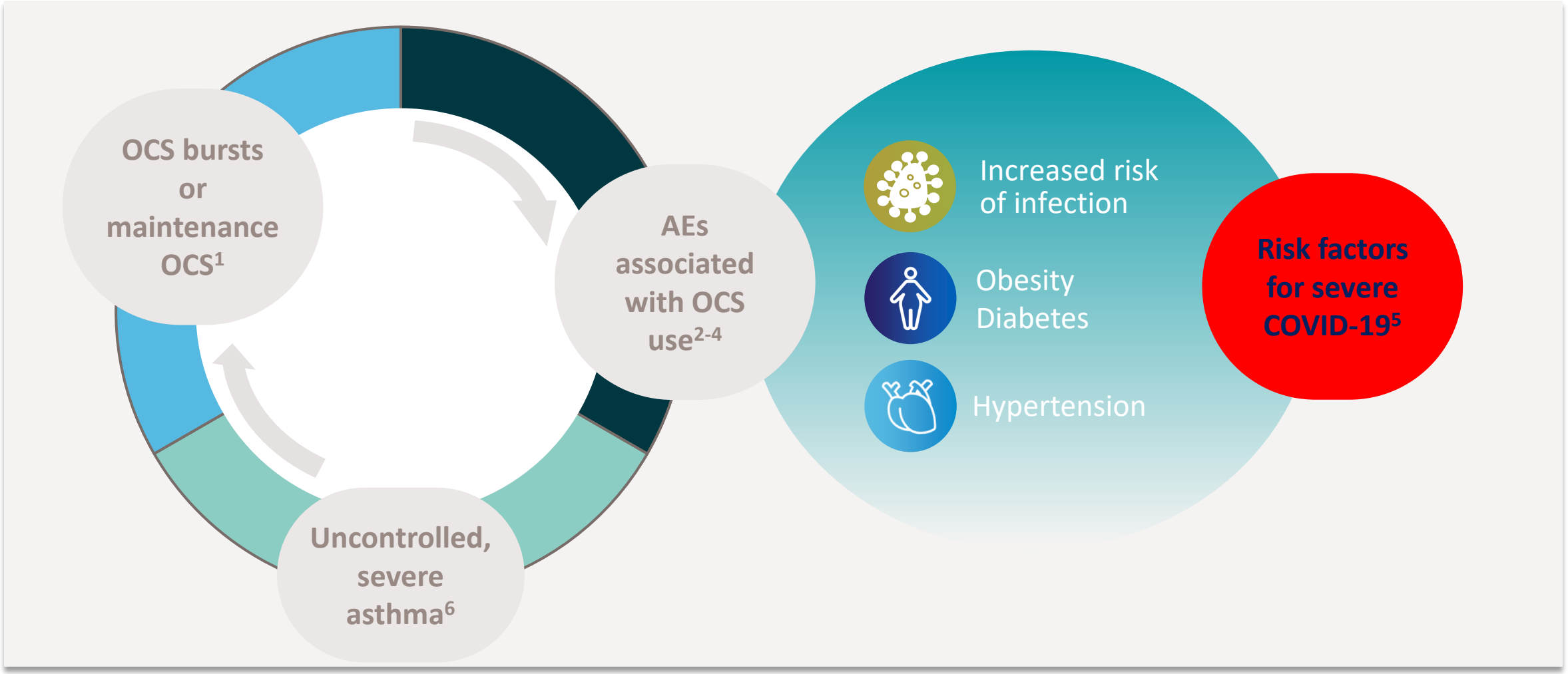
– Allergy & Asthma Network (AAN)*

*In partnership with allergy and asthma patient advocacy groups, professional medical societies, and industry stakeholders.[4]

AE, adverse event; GI, gastrointestinal; GINA, Global Initiative for Asthma; OCS, oral corticosteroids.

1. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Updated 2022. https://ginasthma.org/reports/. Accessed May 18, 2022. 2. Sullivan PW, et al. *J Allergy Clin Immunol*. 2018;141(1):110-116.e7. 3. Bleecker ER, et al. *Am J Respir Crit Care Med*. 2020;201(3):276-293. 4. Asthma and Allergy Foundation of America. Oral corticosteroids stewardship statement 2018. Accessed May 18, 2022. https://www.aafa.org/media/2244/oral-corticosteroid-stewardship-statement-november-2018.pdf

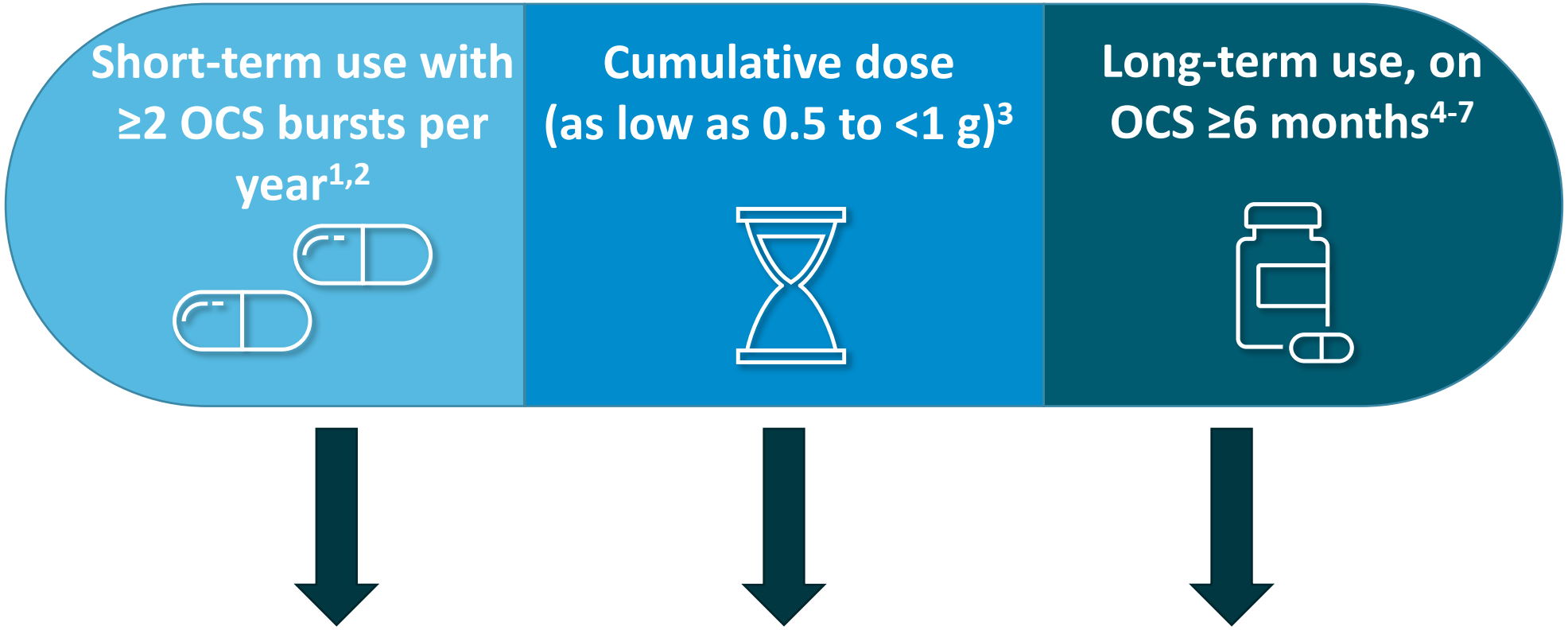
OCS as Risk Factor for Severe Infections



AE, adverse event; COVID-19, coronavirus disease 2019; OCS, oral corticosteroid.

1. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Updated 2022. https://ginasthma.org/reports/. Accessed May 18, 2022. 2. Price DB, et al. *J Asthma Allergy*. 2018;11:193-204. 3. Lefebvre P, et al. *J Allergy Clin Immunol.* 2015;136(6):1488-1495. 4. Walsh LJ, et al. *Thorax*. 2001;56(4):279-284. 5. Gao YD, et al. *Allergy*. 2021;76(2):428-455. 6. Boulet LP, Boulay MÈ. *Expert Rev Respir Med.* 2011;5(3):377-393.

OCS-Dependence in Asthma: Criteria



When assessing patients for step up therapy, consider add-on biologics due to potential for OCS sparing

OCS, oral corticosteroid.

1. Asthma and Allergy Foundation of America. Oral corticosteroids stewardship statement 2018. Accessed May 18, 2022. https://www.aafa.org/media/2244/oral-corticosteroid-stewardship-statement-november-2018.pdf 2. Chung KF, et al. *Eur Respir J*. 2014;43(2):343-373. 3. Price DB, et al. *J Asthma Allergy*. 2018;11:193-204. 4. Rabe KF, et al. *N Engl J Med.* 2018; 378:2475-2485. 5. Bel EH, et al. *N Engl J Med*. 2014;371(13):1189-1197. 6. Nair P, et al. *N Engl J Med*. 2017;376(25):2448-2458. 7. Wechsler ME, et al. *Respir Res*. 2020;21(1):264.

Severe Asthma: Choosing the Right Substance

Characteristic	Anti-IgE	Anti-IL-4Rα	Anti-IL-5/IL-5Rα
Indication	Severe allergic asthma	Severe type 2 asthma	Severe eosinophilic asthma
Age group	Children, adolescents, and young adults	Children, adolescents, and adults	Adults
Onset	Childhood	Childhood or adulthood	Adulthood
Allergy	Prerequisite	Irrespective of allergy	Irrespective of allergy
Dominant biomarker	Serum total IgE	FeNO	Blood eosinophil
Serum total IgE	IgE and weight within dose range	Irrespective of total IgE	Irrespective of total IgE
Blood eosinophil count*	Slightly better response with increased count	>150 to <1500/µL*	Prerequisite: increased counts, >150 to 300/µL*
FeNO*	Slightly better response with increased FeNO	Better response if FeNO >25 ppb	Irrespective of FeNO
Coexisting conditions	AR, CRSwNP, chronic urticaria	AD, CRSwNP	CRSwNP
Exacerbations in the previous year	According to local criteria	According to local criteria	High frequency (≥2)

Data are not based on head-to-head comparisons of different agents and no comparative conclusions of efficacy should be drawn from this information.
In December 2021, the anti-TSLP biologic tezepelumab was approved by the FDA for the add-on maintenance treatment of adult and adolescent patients 12 years of age and older who have severe asthma, with no phenotype or biomarker limitation within its approved label. *Blood eosinophil counts and FeNO values are for patients with severe asthma who are not receiving maintenance OCS therapy.
AD, atopic dermatitis; AR, allergic rhinitis; CRSwNP, chronic rhinosinusitis with nasal polyps; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin; TSLP, thymic stromal lymphopoietin
Brusselle GG, Koppelman GH. *N Engl J Med*. 2022;386(2):157-171.

Severe Asthma: GINA Update Type 2 Inflammation

6 Assess the ***severe asthma phenotype*** → **7** ***Consider other treatments*** → **8** ***Consider add-on biologic type 2–targeted treatments***

Could patient have type 2 airway inflammation?

yes

Type 2 airway inflammation

- Consider adherence tests
- Consider increasing the ICS dose for 3-6 months
- Consider add-on, non-biologic treatment for specific type 2 clinical phenotypes, eg, AERD, ABPA, chronic rhinosinusitis, nasal polyposis, atopic dermatitis

no

Type 2 inflammation

- Blood eosinophils ≥150 µL and/or
- FeNO ≥20 ppb and/or
- Sputum eosinophils ≥2%, and/or
- Asthma is clinically allergen-driven

(Repeat blood eosinophils and FeNO up to 3x, at least 1-2 weeks after OCS or on lowest possible OCS dose)

Note: these are not the criteria for add-on biologic therapy (see 8)

no

No evidence of type 2 airway inflammation

- Review the basics: differential diagnosis, inhaler techniques, adherence, comorbidities, side effects
- Avoid exposures (tobacco smoke, allergens, irritants)
- Consider investigations (if available and not done)
  - Sputum induction
  - High-resolution chest CT
  - Bronchoscopy for alternative/additional diagnosis
- Consider trial of add-on treatments (if available and not already tried)
  - LAMA
  - Low-dose azithromycin
  - Anti-IL-4R* if taking maintenance OCS
  - Anti-TSLP* if not taking maintenance OCS
  - As last resort, consider add-on, low-dose OCS, but implement strategies to minimize side effects
- Consider bronchial thermoplasty (+ registry)
- Stop ineffective add-on therapies

- Consider add-on type 2–targeted biologic therapy for patients with exacerbations or poor symptom control on high-dose ICS-LABA, who have evidence of type 2 inflammation*
- Consider **local payer eligibility criteria,*** **comorbidities,** and **predictors of response** when choosing among available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

Which biologic is appropriate to start first?

Anti-IgE *(omalizumab)*

*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

no / ***no***

Anti-IL-5/Anti-IL-5R *(benralizumab, mepolizumab, reslizumab)*

*Is the patient eligible for **anti-IL-5/IL-5R** for severe eosinophilic asthma?**

- Exacerbations in last year
- Blood eosinophils, eg, ≥150/µL or ≥300/µL

no / ***no***

Anti-IL-4R *(dupilumab)*

*Is the patient eligible for **anti-IL-4R** for severe eosinophilic/type 2 asthma?**

- Exacerbations in last year
- Blood eosinophils ≥150/µL and ≤1500/µL, or FeNO ≥25 ppb, or taking maintenance OCS

no / ***no***

Anti-TSLP *(tezepelumab)*

*Is the patient eligible for **anti-TSLP** for severe asthma?**

- Exacerbations in last year

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

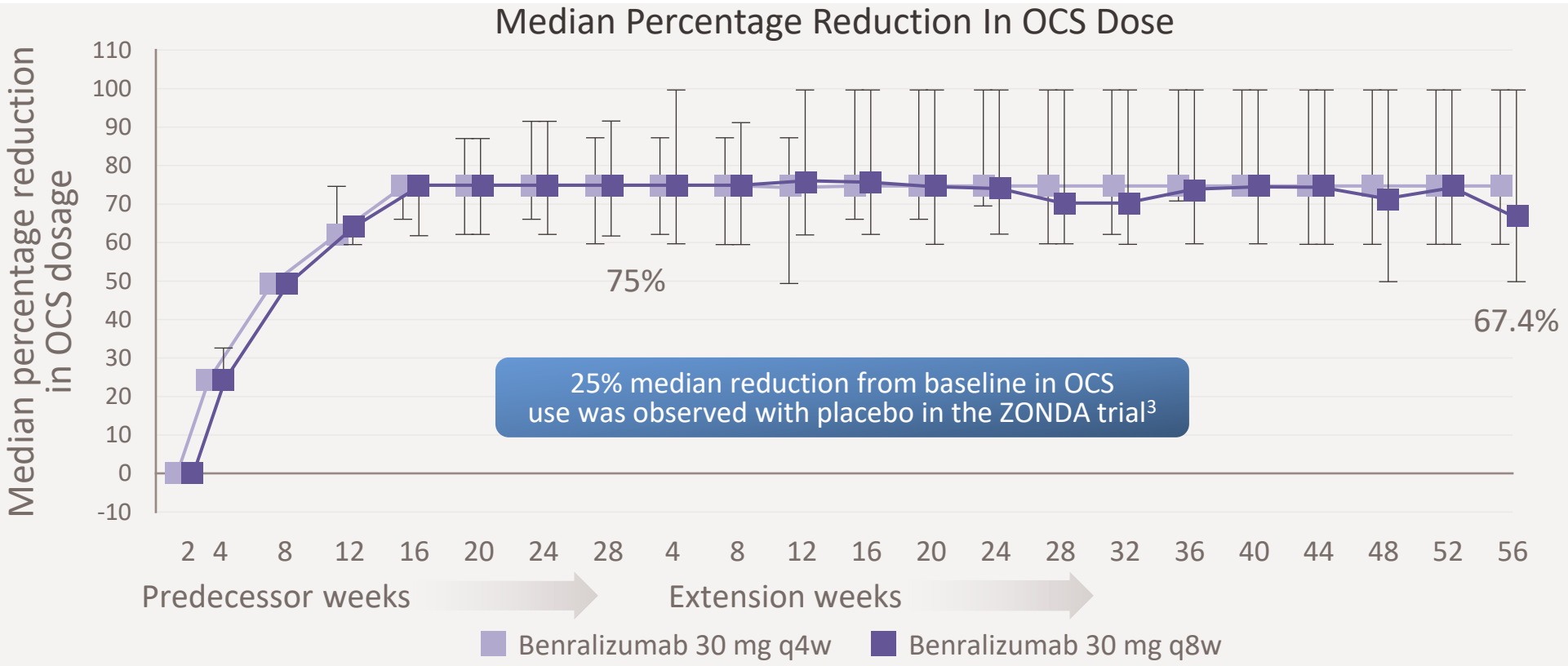
ABPA, allergic bronchopulmonary aspergillosis; AERD, aspirin-exacerbated respiratory disease; CT, computed tomography; FeNO, fractional exhaled nitric oxide; GINA, Global Initiative for Asthma; IL, interleukin; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IV, intravenous; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonists; OCS, oral corticosteroids; ppb, parts per billion; SC, subcutaneous; TSLP, thymic stromal lymphopoietin.

Adapted from: Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Updated 2022. https://ginasthma.org/reports/. Accessed May 18, 2022.

Benralizumab Reduced OCS Dose Regardless of Dosing Regimen

Two-year Integrated Analysis: ZONDA + BORA[1,2]
Blood eosinophil count ≥300 cells/µL*

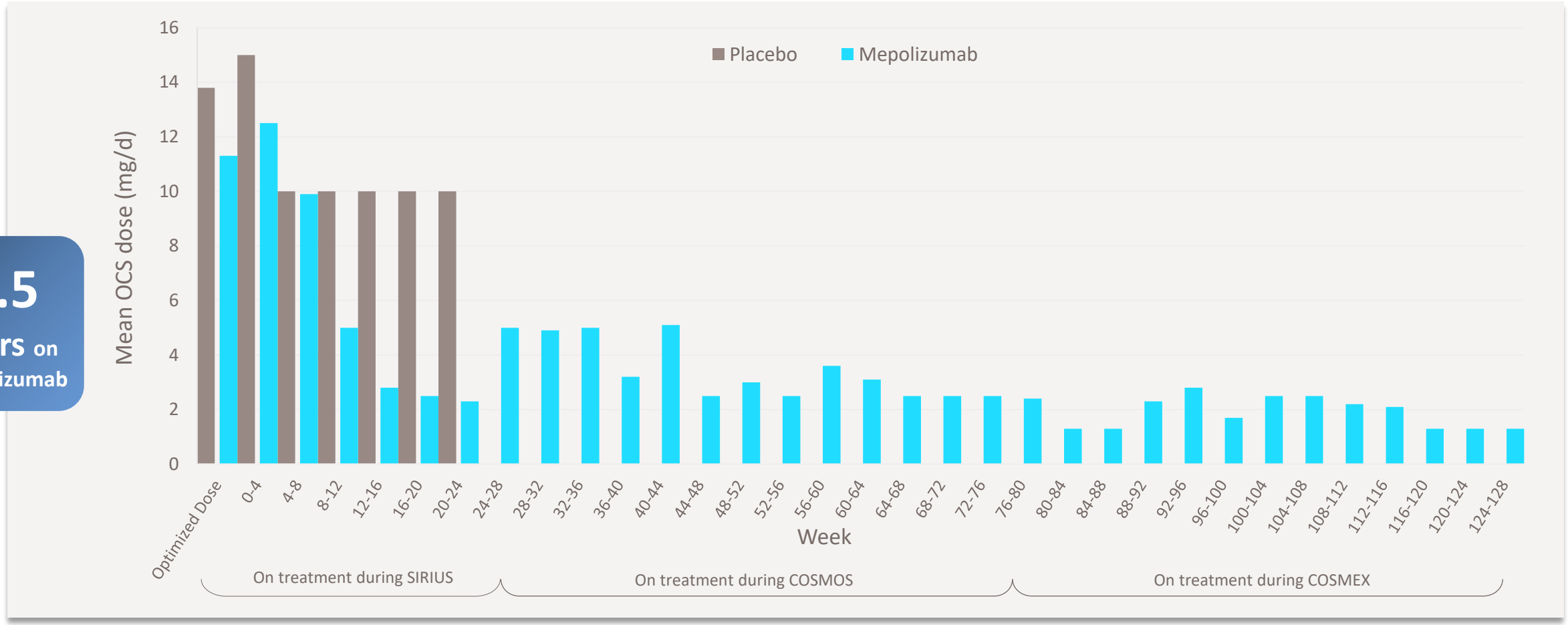
2 years on benralizumab



Reprinted from *Journal of Asthma*, Vol 58/No. 4, Two-year integrated steroid-sparing analysis and safety of benralizumab for severe asthma, pp514-522, Copyright 2021, with permission from Taylor & Francis.
*Eosinophil counts at baseline of preceding pivotal studies.
OCS, oral corticosteroids; q4w, once every 4 weeks; q8w, once every 8 weeks.
1. FitzGerald JM, et al. *J Asthma Allergy*. 2019;12:401-413. 2. Bourdin A, et al. *J Asthma*. 2021 Apr;58(4):514-522. 3. Nair P, et al. *N Engl J Med*. 2017;376(25):2448-2458.

Mepolizumab Provided Sustained Reduction of OCS Dose

2.5 years on mepolizumab



By week 128, 45% of patients no longer required OCS treatment

Reprinted from *Clinical Therapeutics*, Vol 41/No. 10, Khurana S, et al, Long-term Safety and Clinical Benefit of Mepolizumab in Patients With the Most Severe Eosinophilic Asthma: The COSMEX Study, pp2041-2056.e5, Copyright 2019, with permission from Elsevier

mg/d, milligrams per day; OCS, oral corticosteroids.

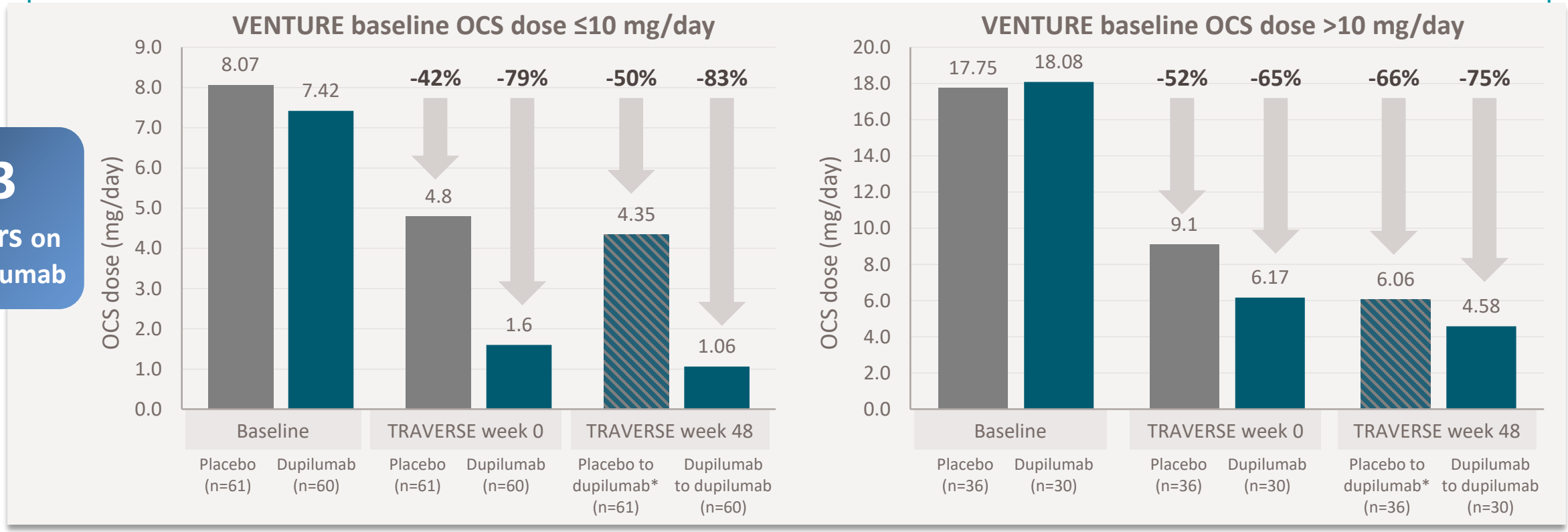
Khurana S, et al. *Clin Ther*. 2019;41(10):2041-2056.e5.

LungenClinic GROSSHANSDORF

Dupilumab Reduced OCS Dose Regardless of Baseline OCS Dose

3 years on dupilumab

Mean OCS use (VENTURE to TRAVERSE)[1]



By TRAVERSE week 96, patients randomized to placebo in VENTURE reduced OCS use by 74% while patients randomized to dupilumab reduced OCS use by 89%[2]

*Placebo to dupilumab group in TRAVERSE was comprised of patients who were randomized to placebo in VENTURE and initiated dupilumab treatment in TRAVERSE.
OCS, oral corticosteroids.

1. Gurnell M, et al. Presented at: International Conference of the American Thoracic Society; May 13-18, 2022. 2. Sher LD, et al. Presented at: International Conference of the American Thoracic Society; May 14-19, 2021.

Severe Asthma: OCS and Approved Biologics

- GINA recommends:
  - Biologics as an add-on controller medication in patients at step 5
  - OCS should only be used as a last resort due to the risk of AEs
- Approved biologics have demonstrated safety and efficacy in phase 3 trials, with variable improvement in lung function and OCS dose

Benralizumab reduced OCS use over 2 years

Mepolizumab reduced OCS use over 2.5 years

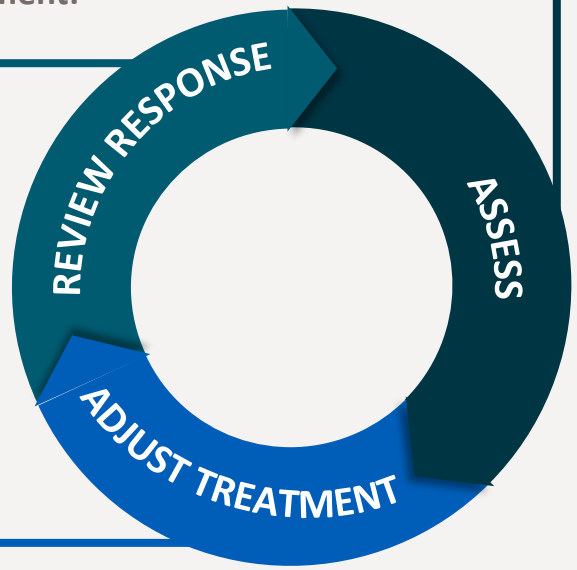
Dupilumab reduced OCS use over 3 years

Note: Long-term extension study data are not available for omalizumab or tezepelumab.
AE, adverse event; GINA, Global Initiative for Asthma; OCS, oral corticosteroid.

GINA: Lung Function is Key Component of Asthma Management

Adults and adolescents 12+ years
Personalized asthma management:
Assess, adjust, review response

- Symptoms
- Exacerbations
- Side effects
- **Lung function**
- Patient satisfaction



- Confirmation of diagnosis if necessary
- Symptom control and modifiable risk factors (**including lung function**)
- Comorbidities
- Inhaler technique and adherence
- Patient goals

- Treatment of modifiable risk factors and comorbidities
- Non-pharmacologic strategies
- Education and skills training
- Asthma medications

Independently of symptom status, a low FEV_1 percent predicted value:

- **Identifies patients at risk for asthma exacerbations**, especially if FEV_1 is <60% predicted
- Is a risk factor for **lung function decline**
- Suggests **limitation of lifestyle**, or poor perception of **airflow limitation**, which **may be due to untreated airway inflammation**

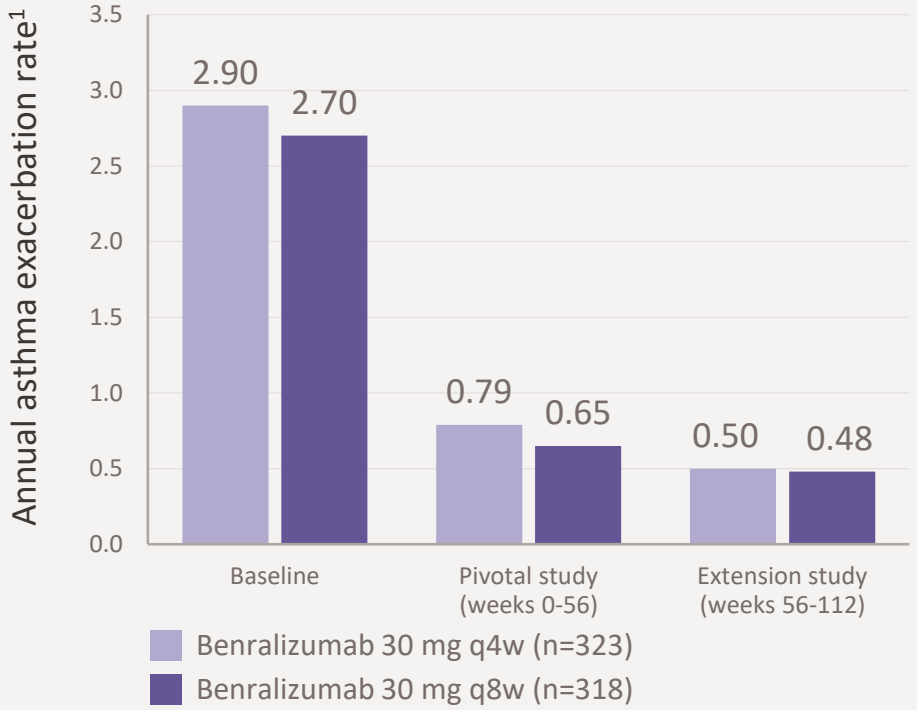
FEV_1, forced expiratory volume in 1 second.
Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Updated 2022. https://ginasthma.org/reports/. Accessed May 18, 2022.

LungenClinic GROSSHANSDORF

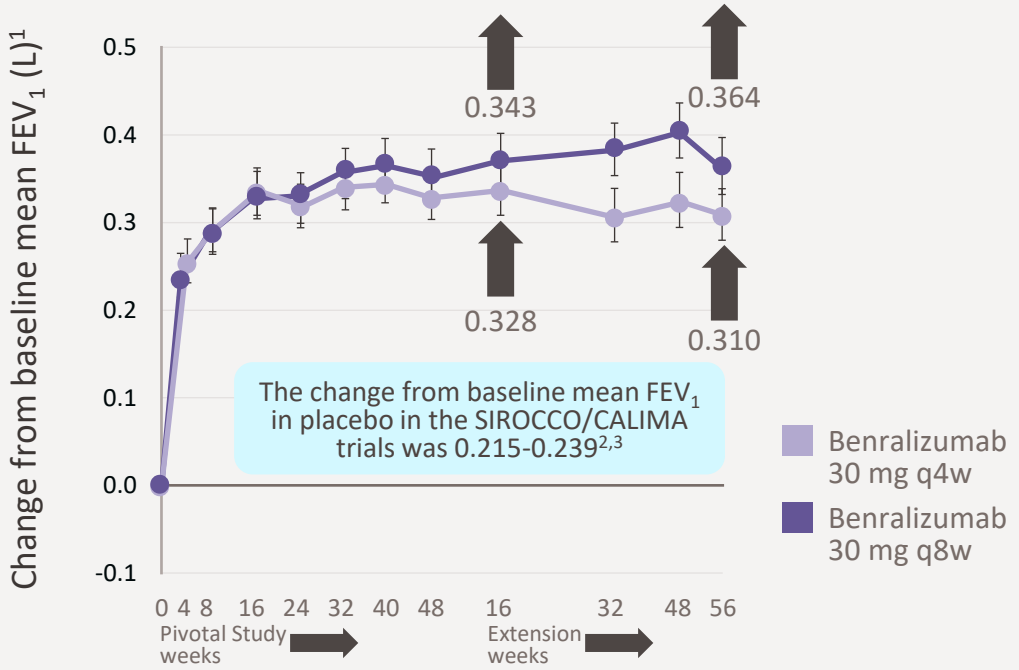
Benralizumab Reduced Exacerbation Rates and Improves Lung Function

2 years on benralizumab

Exacerbations[1]



Lung function[2,3]



Improvements in ACQ-6 at the end of the SIROCCO and CALIMA studies were maintained during extended treatment period[1]

Eosinophil counts at baseline of preceding pivotal studies were ≥300 cells/µL.

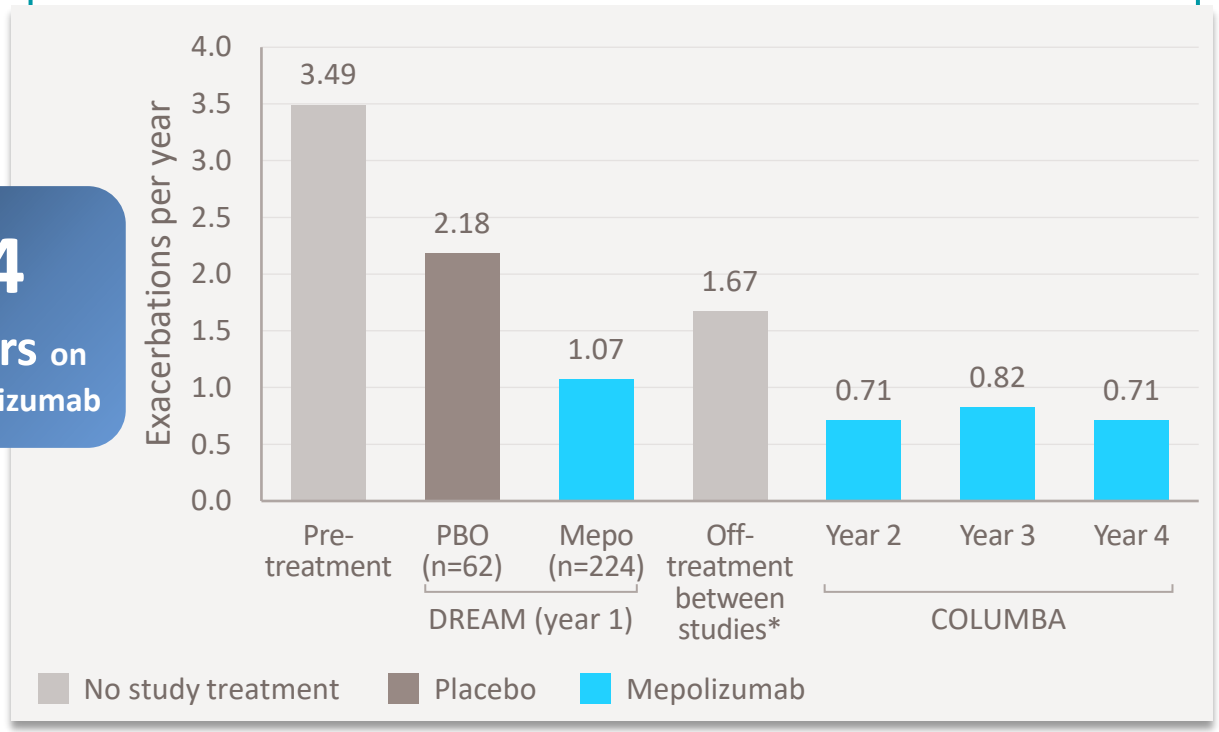
ACQ, Asthma Control Questionnaire; FEV_1, forced expiratory volume in 1 second; q4w, every 4 weeks; q8w, every 8 weeks.

1. FitzGerald JM, et al. *J Asthma Allergy*. 2019;12:401-413. 2. Bleecker ER, et al. *Lancet*. 2016;3889(10056):2115-2127. 3. FitzGerald JM, et al. *Lancet*. 2016;388(10056):2128-2141.

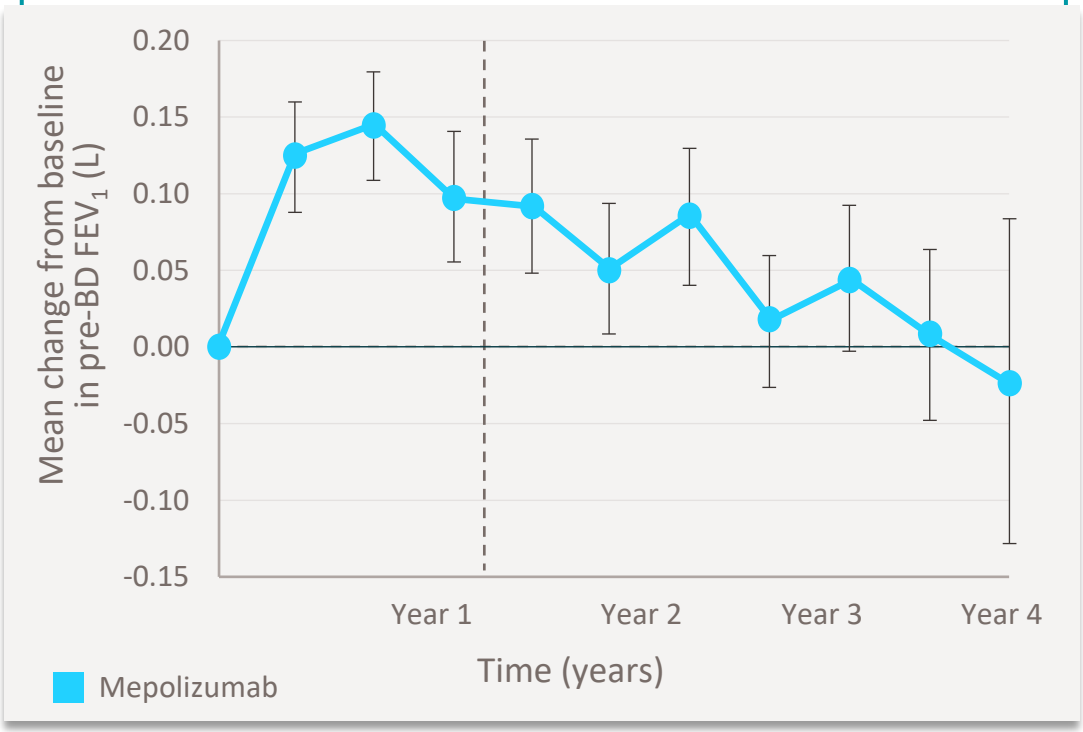
Mepolizumab Reduces Exacerbation Rates - Lung Function Returns to Baseline

4 years on mepolizumab

Exacerbations



Lung function



Mean improvement in ACQ-5 ranged from 0.40 points to 0.66 points throughout the study, with about 50% of patients achieving an improvement of 0.5 or more

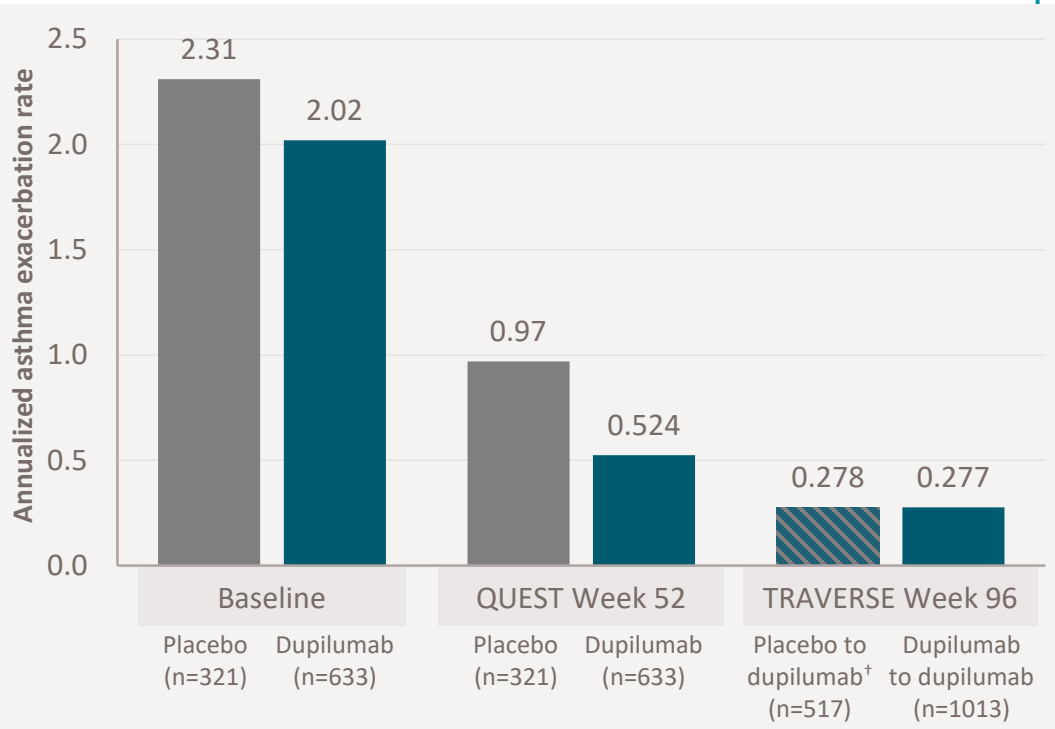
Reprinted from *The Journal of Allergy and Clinical Immunology*, Vol 143/No. 5, Khatri S, et al, Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma, pp1742-1751.e.7, Copyright 2019, with permission from Elsevier.
*12- to 28-month break without clinical trial participation.
Patient population defined as having severe eosinophilic asthma.
ACQ, Asthma Control Questionnaire; BD, bronchodilator; FEV_1, forced expiratory volume in 1 second; Mepo, mepolizumab; PBO, placebo.
Khatri S, et al. *J Allergy Clin Immunol*. 2019;143(5):1742-1751.e7.

LungenClinic GROSSHANSDORF

Dupilumab Reduces Exacerbation Rate and Improves Lung Function

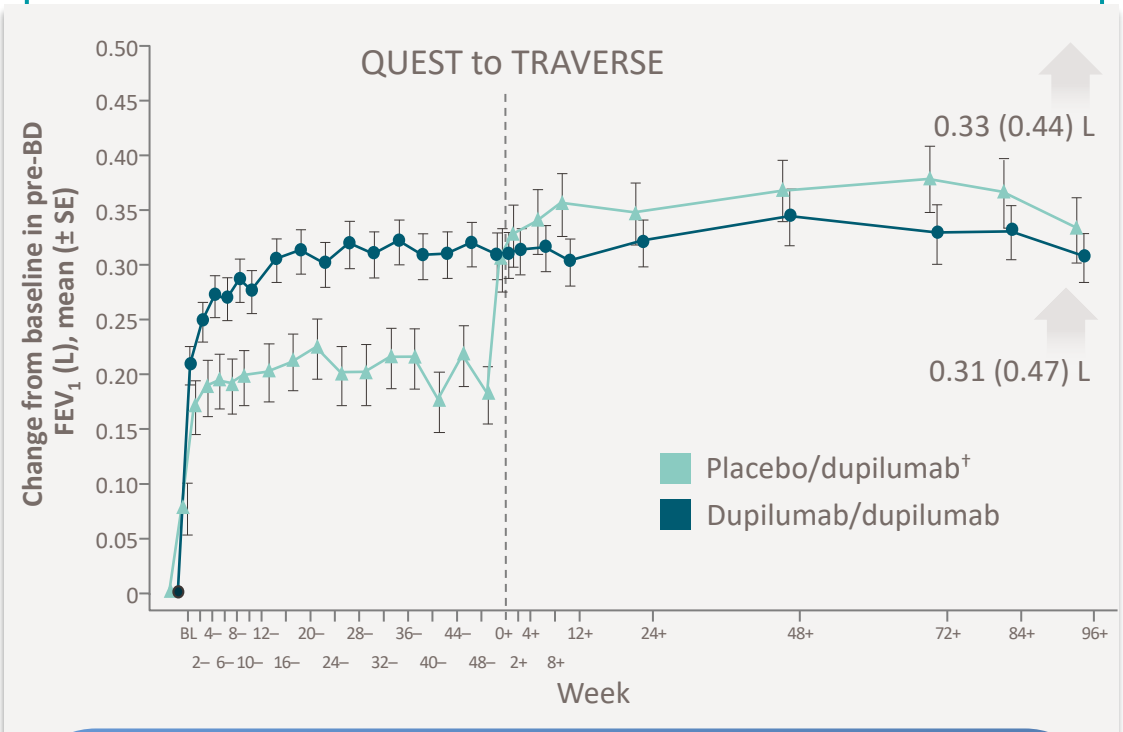
3 years on dupilumab

Exacerbations[1,2*]



Asthma control improvements from QUEST were sustained during TRAVERSE[2]

Lung function[2]

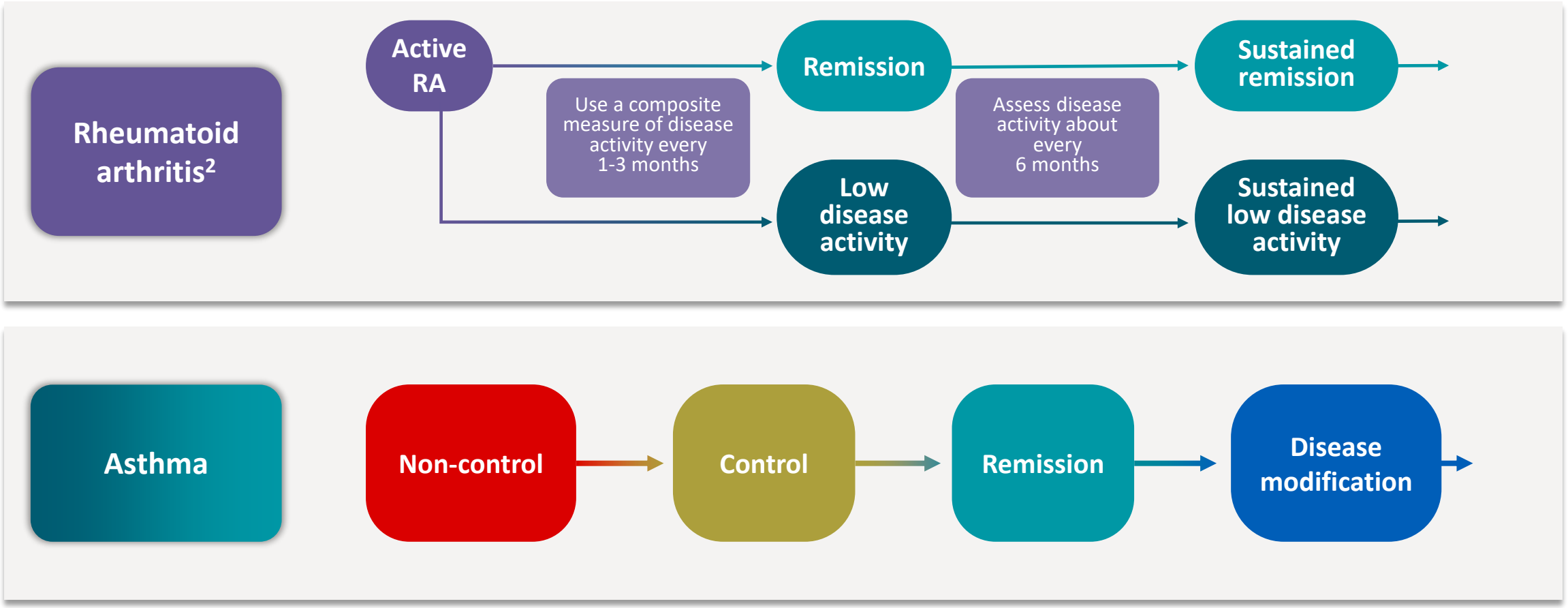


Similar results were obtained in patients with OCS-dependent asthma, regardless of OCS dose[2,3]

BD, bronchodilator; FEV_1, forced expiratory volume in 1 second; SE, standard error.
*Teal bars represent data for 300-mg dupilumab. Similar results were obtained for the 200-mg dose. All TRAVERSE participants were on the 300-mg dupilumab dose.
†Placebo to dupilumab group in TRAVERSE was comprised of patients who were randomized to placebo in QUEST and initiated dupilumab treatment in TRAVERSE.
1. Castro M, et al. *N Engl J Med*. 2018;378(26):2486-2496. 2. Wechsler ME, et al. *Lancet Respir Med*. 2022;10(1):11-25. 3. Gurnell M, et al. ATS 2022. Abstract. A2365.

Severe Asthma: ReMission Impossible…?

Disease remission can be defined as "a state or period with low to no disease activity that can be spontaneous or a result of therapy"[1]



RA, rheumatoid arthritis.

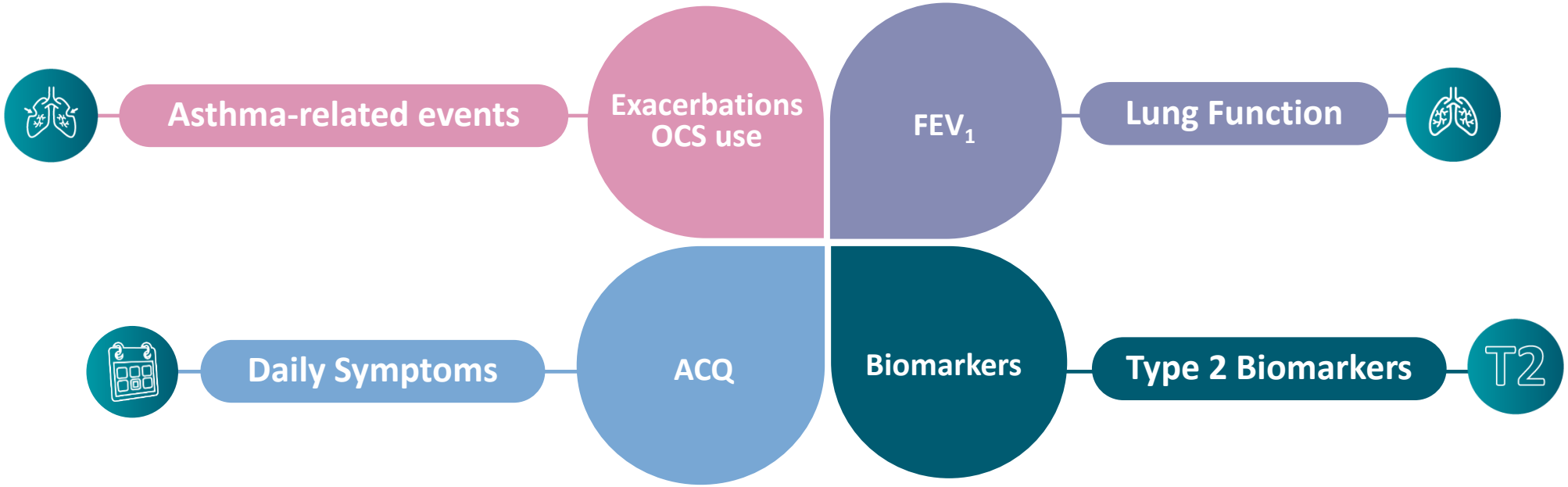
1. Menzies-Gow A, et al. *J Allergy Clin Immunol.* 2020;145(3):757-765. 2. Smolen JS, et al. *Ann Rheum Dis*. 2016;75(1):3-15.

LungenClinic GROSSHANSDORF

Severe Asthma: Thoughts on Remission

Remission Treatment Target must be[1]:

- ✓ Measurable in clinical practice
- ✓ Meaningful for patients
- ✓ Associated with disease progression



Clinical remission in severe asthma can be achieved by using targeted treatments, such as biologics, to address the underlying inflammation[2]

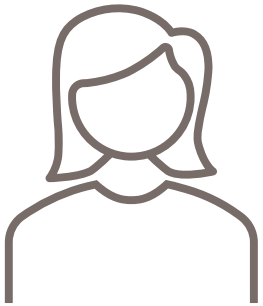
ACQ, Asthma Control Questionnaire; FEV_1, forced expiratory volume in 1 second; OCS, oral corticosteroid.

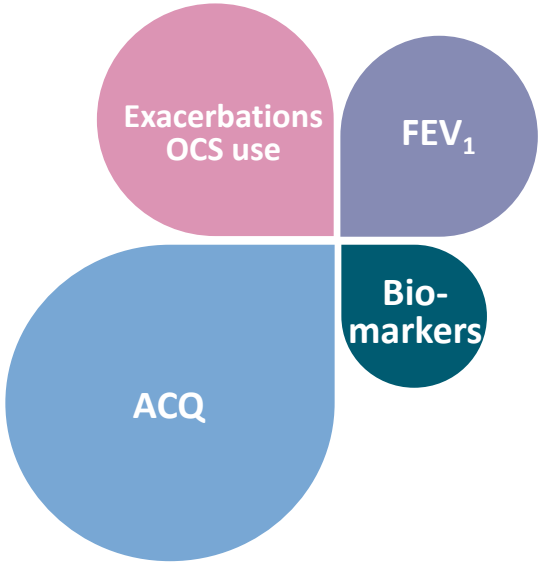
1. Menzies-Gow A, et al. *J Allergy Clin Immunol.* 2020;145(3):757-765. 2. Menzies-Gow A, et al. *Adv Ther*. 2022;39(5):2065-2084.

LungenClinic GROSSHANSDORF

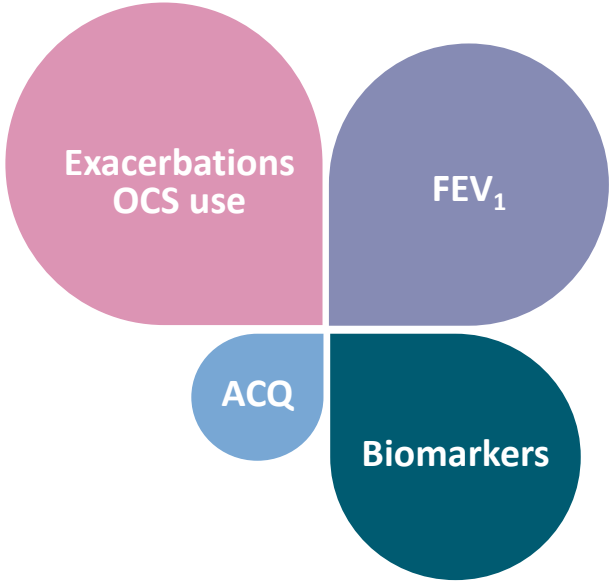
Severe Asthma: Variable Thoughts on Remission

Patient





Healthcare Provider

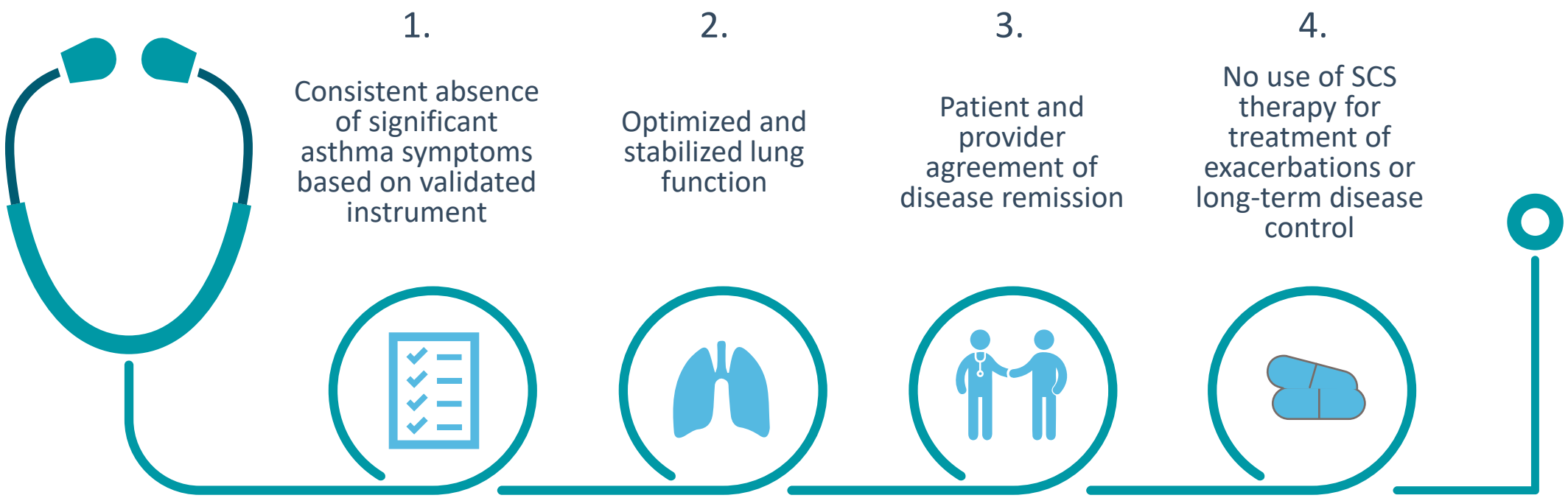


ACQ, Asthma Control Questionnaire; FEV_1, forced expiratory volume in 1 second; HCP, healthcare provider; OCS, oral corticosteroid.

1. Matsunaga K, et al. *J Allergy Clin Immunol Pract*. 2019;7(8):2634-2641. 2. Price D, Fletcher M, van der Molen T. *NPJ Prim Care Respir Med*. 2014;24:14009. 3. Gruffydd-Jones K, Hansen K. *Adv Ther*. 2020;37(1):1-9.

Severe Asthma Remission: Attempted Consensus

At least 12 months of the following, with or without treatment[1]:



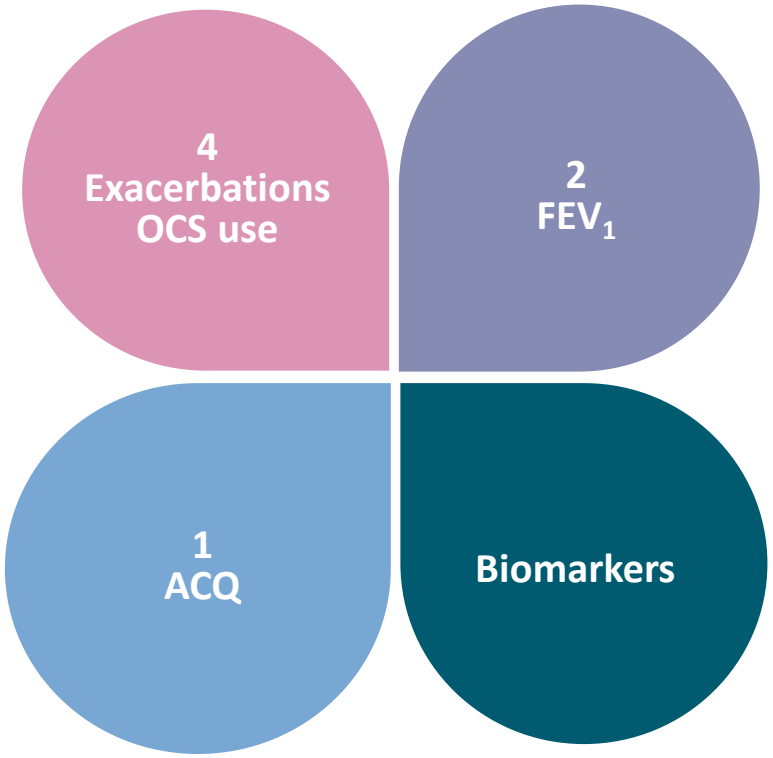
There have thus far been limited real-world data establishing the proportion of patients with asthma who achieve clinical remission[2]

SCS, systemic corticosteroids.

1. Menzies-Gow, A, et al. *J Allergy Clin Immunol.* 2020;145(3):757-765. 2. Chipps, B. et al. Presentation 442. Presented at AAAAI February 25-28, 2022; Phoenix, AZ.

LungenClinic GROSSHANSDORF

Clinical Remission and Composite Endpoints



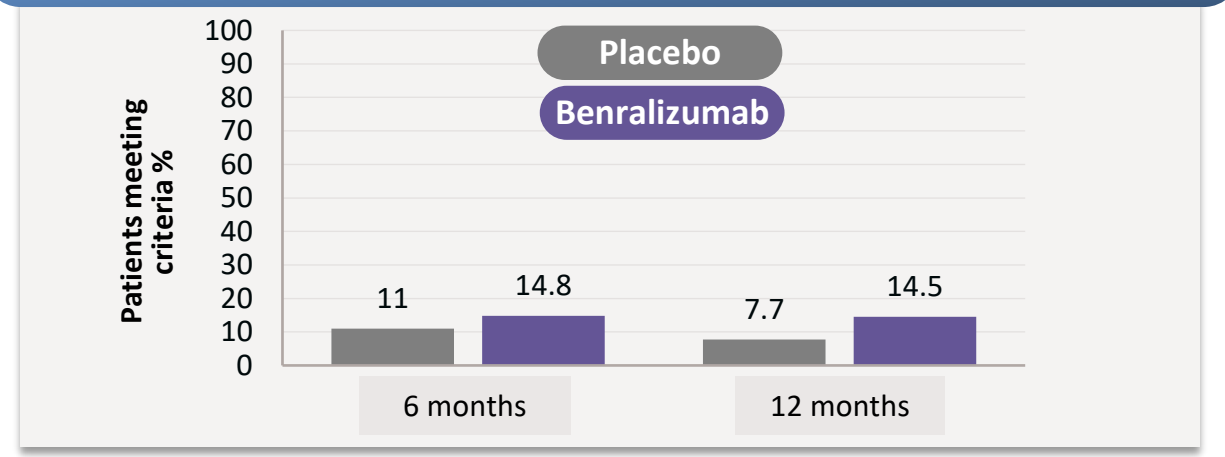
		Dupilumab 2021, Pavord ID, et al.[2]	Benralizumab 2022, Menzies-Gow A, et al.[3]
Clinical Remission			
For ≥12 months:			
1.	Sustained absence of significant asthma symptoms based on validated instrument **and**	ACQ-5 <1.5	ACQ-6 <1.5 or ≤0.75
2.	Optimization and stabilization of lung function **and**	Post-BD FEV_1 ≥80% predicted	Pre-BD FEV_1 increase ≥100 mL
3.	Patient and HCP agreement regarding disease remission **and**	Not assessed	
4.	No use of systemic corticosteroid therapy for exacerbation treatment or long-term disease control	No exacerbations; No OCS use	No exacerbations; No OCS use

ACQ-5/ACQ-6, 5-item/6-item Asthma Control Questionnaire; BD, bronchodilator; FEV_1, forced expiratory volume in 1 second; HCP, healthcare professional; OCS, oral corticosteroid.

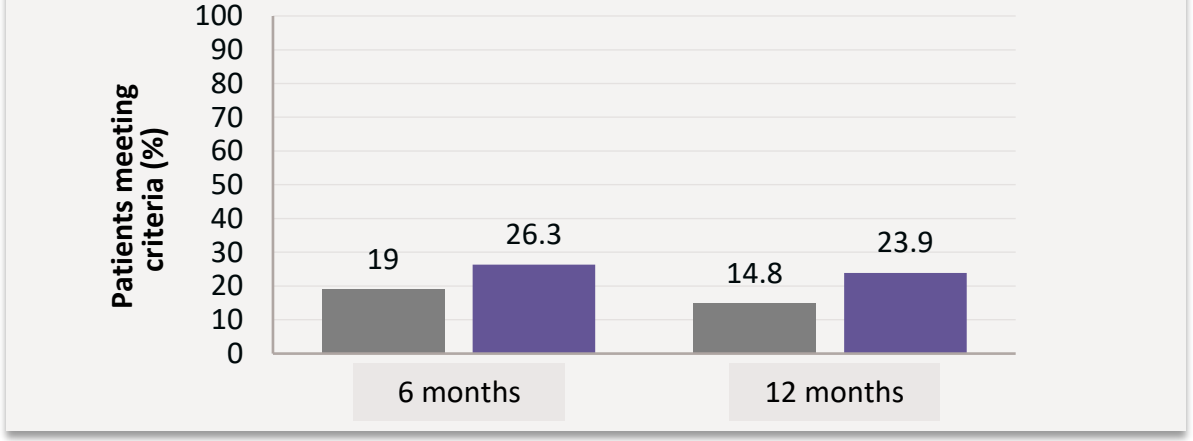
1. Menzies-Gow A, et al. *J Allergy Clin Immunol.* 2020;145(3):757-765. 2. Pavord ID, et al. Poster presented at: American College of Allergy, Asthma, and Immunology (ACAAI); November 4-8, 2021; New Orleans, LA.
3. Menzies-Gow A, et al. *Adv Ther*. 2022;39(5):2065-2084.

Benralizumab Shows Benefits in Achieving Various Definitions of Remission

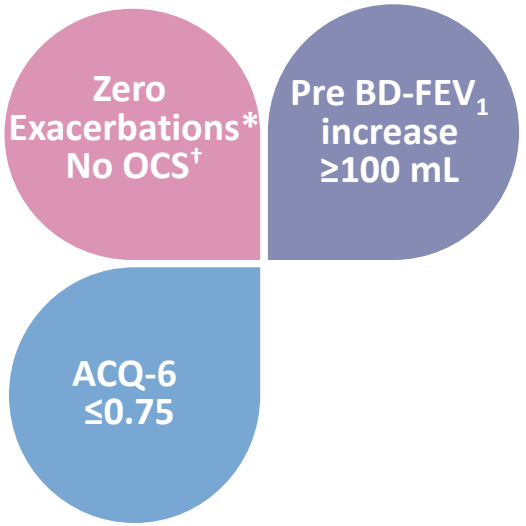
SIROCCO/CALIMA patients achieving clinical remission

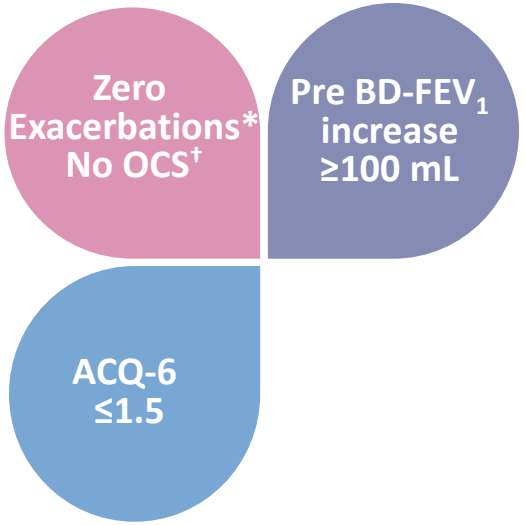


SIROCCO/CALIMA patients achieving remission



Clinical remission



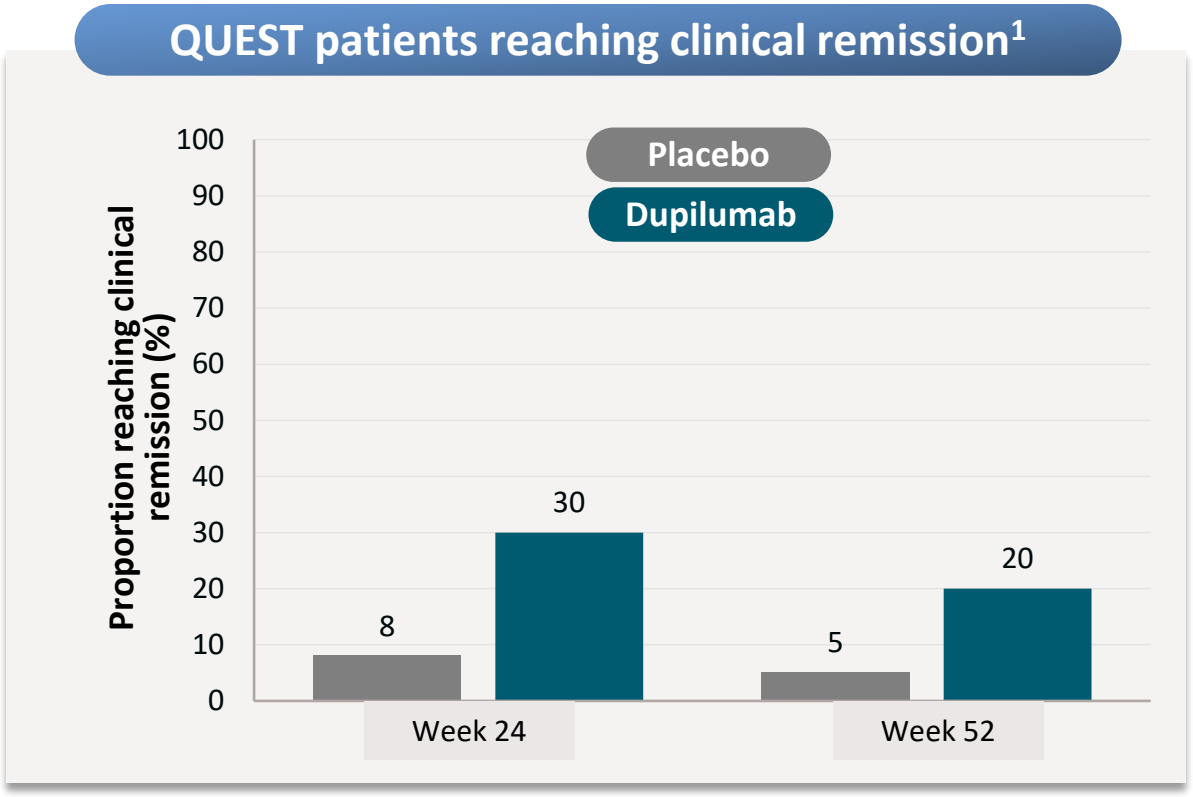


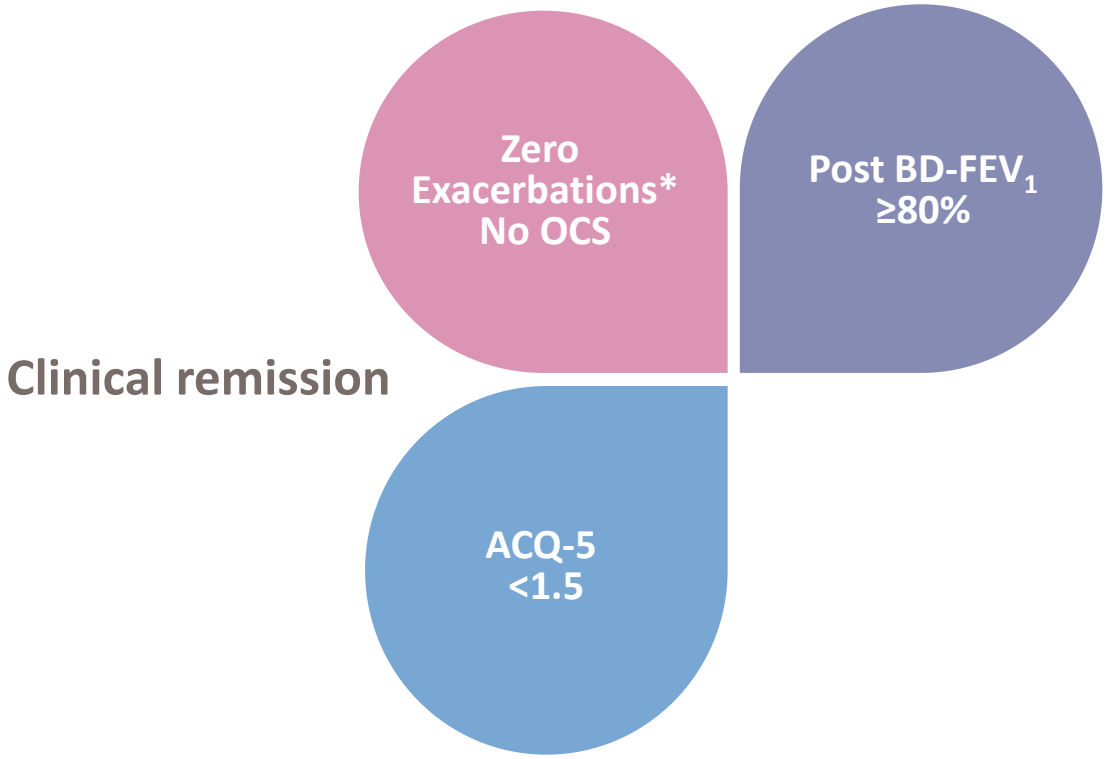
*An exacerbation was defined as a worsening of asthma resulting in use of systemic corticosteroids, temporary increase in OCS dose for ≥3 days, a dose of injected corticosteroid, emergency department visit, or hospital admission. †Patients from SIROCCO and CALIMA trials on oral corticosteroids at baseline were excluded from analysis.

ACQ-6, 6-item Asthma Control Questionnaire; pre/post-BD, pre/post-bronchodilator; FEV_1, forced expiratory volume in 1 second; OCS, oral corticosteroids.

Menzies-Gow A, et al. *Adv Ther*. 2022;39(5):2065-2084.

Dupilumab Shows Benefits in Achieving Remission





*A severe asthma exacerbation was defined as a deterioration of asthma leading to treatment for 3 days or more with systemic glucocorticoids or hospitalization or an emergency department visit leading to treatment with systemic glucocorticoids.[2]

ACQ-5, 5-item Asthma Control Questionnaire; post-BD, post-bronchodilator; FEV_1, forced expiratory volume in 1 second; OCS, oral corticosteroids.

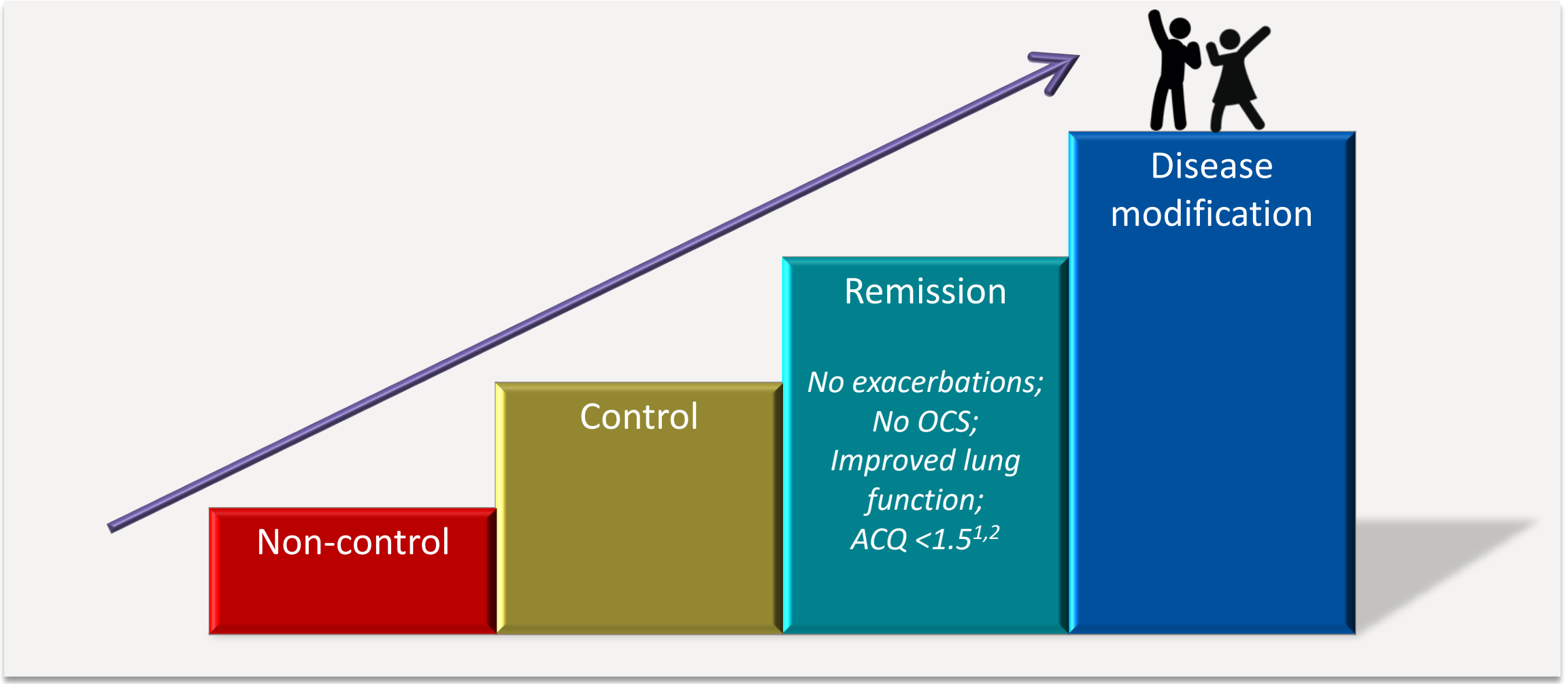
1. Pavord ID, et al. Poster presented at: American College of Allergy, Asthma, and Immunology (ACAAI); November 4-8, 2021; New Orleans, LA. 2. Castro M, et al. *N Engl J Med*. 2018;378(26):2486-2496.

LungenClinic GROSSHANSDORF

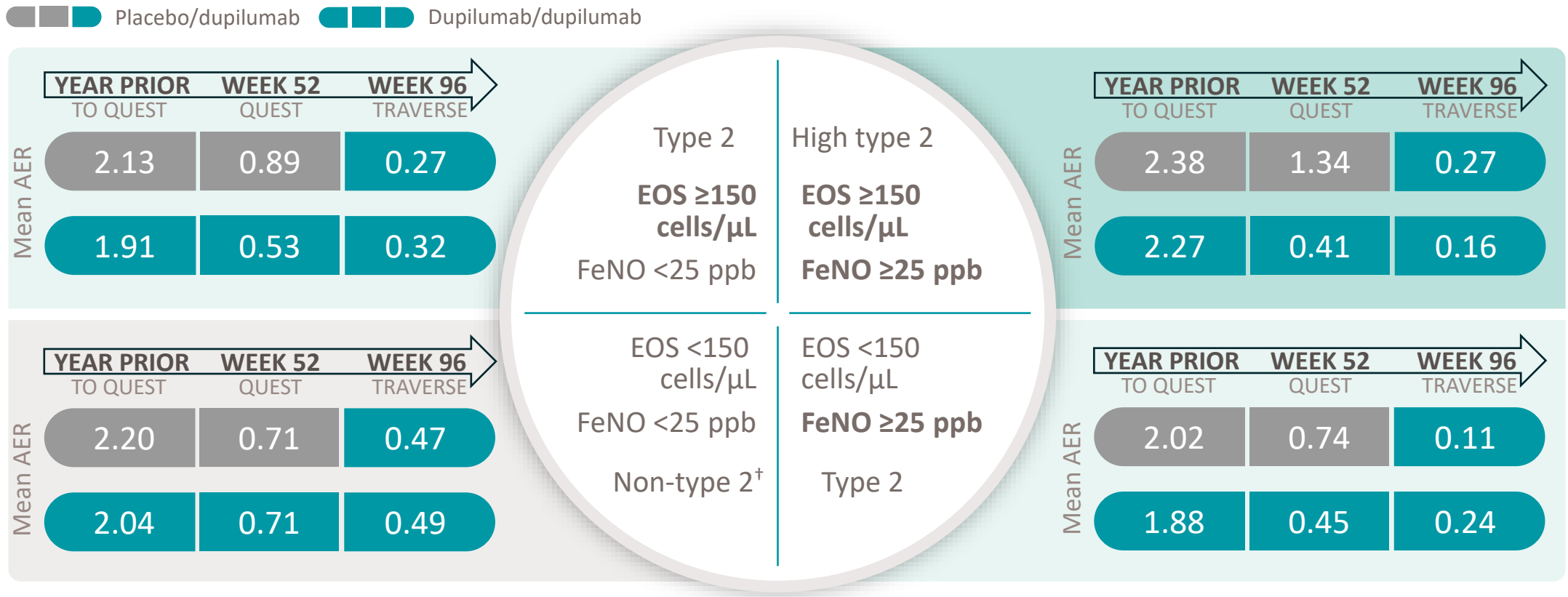
Severe Asthma: Summary of an Update

ARCN DZL Deutsches Zentrum für Lungenforschung

From Biologic Targeted Therapy to Remission and Disease Modification



TRAVERSE: Dupilumab Treatment Resulted in Sustained Reduction of Exacerbation Rate* Across Baseline Biomarker Populations



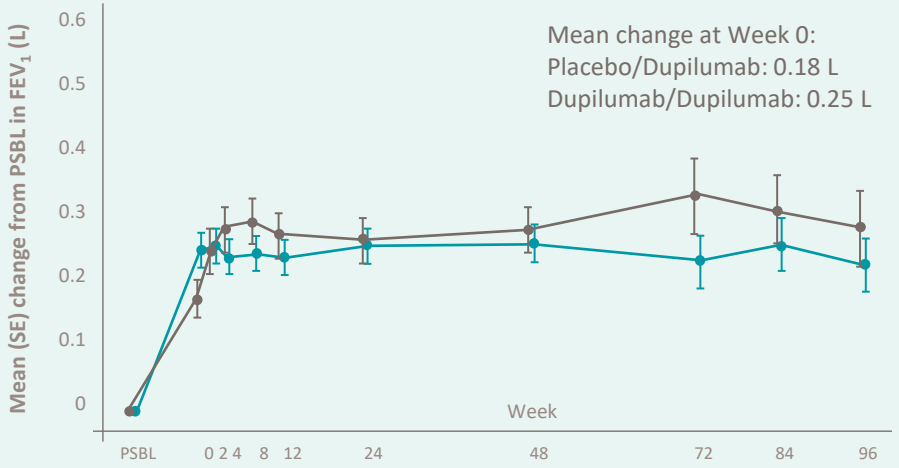
Dupilumab showed greatest efficacy in populations with elevated FeNO ≥25 ppb

*The total number of events that occurred during the observational period divided by the total patient-years that followed in the observational period. †Dupilumab is not indicated for this population.
AER, annualized exacerbation rate; EOS, eosinophils; FeNO, fractional exhaled nitric oxide; ppb, parts per billion.
Wechsler ME, et al. Presented at the 2022 Annual Meeting of the American Academy of Allergy, Asthma and Immunology (AAAAI 2022); Phoenix, AZ, USA; February 25-28, 2022.

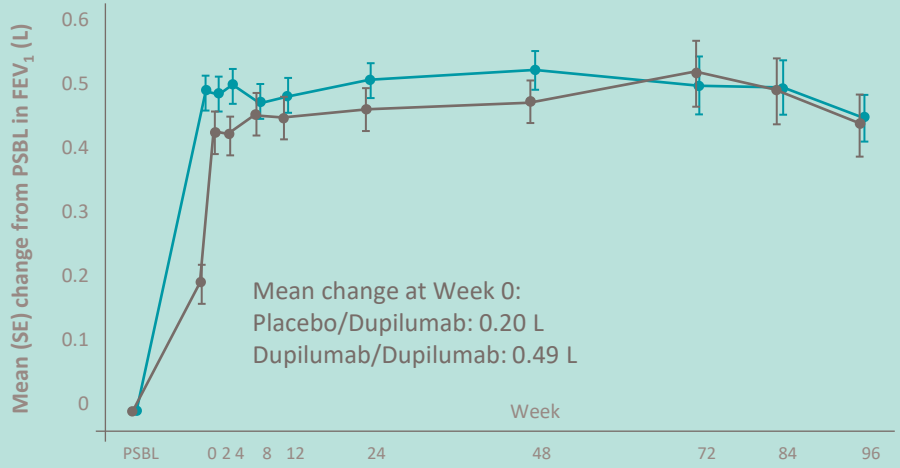
TRAVERSE: Dupilumab Treatment Resulted in Rapid and Sustained Improvement in Lung Function Across All Type 2 Baseline Biomarker Populations

3 years on dupilumab

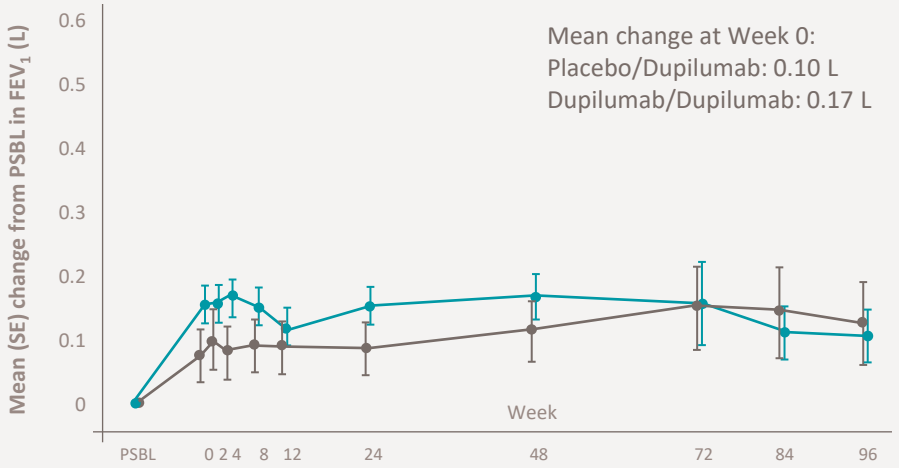
Type 2 (EOS ≥150 cells/µL, FeNO <25 ppb)



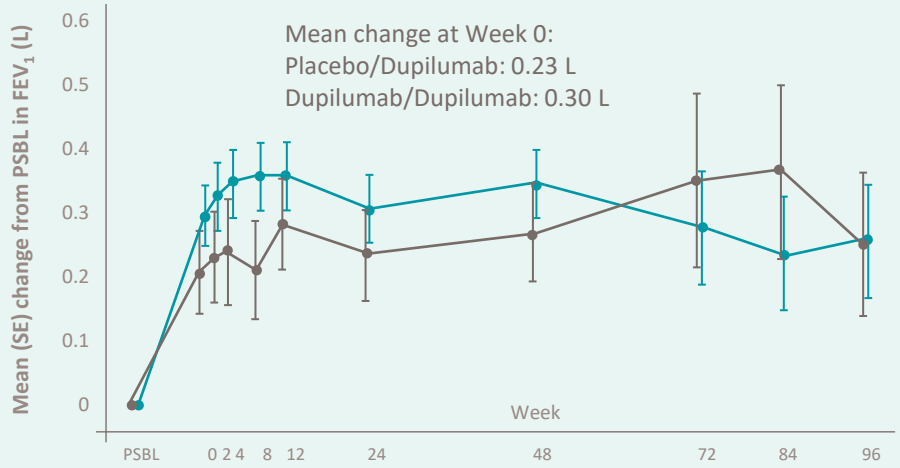
High Type 2 (EOS ≥150 cells/µL **and** FeNO ≥25 ppb)



Non-type 2 (EOS <150 cells/µL **and** FeNO <25 ppb)*



Type 2 (EOS <150 cells/µL, FeNO ≥25 ppb)



*Dupilumab is not indicated for this population. EOS, eosinophils; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in one second; ppb, parts per billion; PSBL, parent study baseline.

Wechsler ME, et al. Presented at the 2022 Annual Meeting of the American Academy of Allergy, Asthma and Immunology (AAAAI 2022); Phoenix, AZ, USA; February 25–28, 2022.

Can Remission Help in the Quest Towards Disease Modification?

Remission → *Disease modification*

CHINOOK Study

ATLAS TRIAL

VESTIGE TRIAL

Approved Asthma Biologics Can Provide Long-Term Improvement

Dupilumab reduced exacerbations and improved lung function over **3 years** in all populations

Current data suggest that disease remission may be achievable in asthma patients with biologics

Note: Long-term extension study data are not available for omalizumab or tezepelumab.