Clinical Remission in Asthma: Is it Achievable?

Rohit Katial, MD, FAAAAI, FACAAI, FACP
Professor of Medicine
Associate Vice President of Education
Director, Center for Clinical Immunology
Irene J. & Dr. Abraham E. Goldminz,
Chair in Immunology and Respiratory Medicine
National Jewish Health &
University of Colorado, Denver

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Breathing Science is Life.®

Objectives

- Describe clinical remission in asthma
  - the evolution of the concept
  - disease remission approaches in other disease states
  - definitions of clinical remission in asthma
  - supporting evidence
  - advantages and disadvantages
- Discuss unmet needs and next steps for clinical remission in asthma
  - activities that that may be necessary to support this anticipated paradigm shift in asthma care
  - understand the value of forwarding the concept

Remission of asthma

- Remission from childhood wheezing or asthma, off treatment
  - Parents/caregivers often ask if their child will 'grow out of their asthma'
  - Rates vary depending on population and age, e.g. 59% at age 6, 15% at age 26
  - Asthma often recurs: remission is not cure, and patients may develop persistent airflow limitation
  - Say to parent/caregiver 'Their asthma has gone quiet for a while'
- Remission in adults, on treatment
  - Current reports are mostly for patients with severe asthma treated with biologic therapy
  - Remission also seen in non-severe asthma with ICS-containing treatment, and sometimes spontaneously
  - Research needed to identify pathways in patients who have ongoing respiratory symptoms, e.g. multimorbidity, anxiety and/or depression, moderate or severe persistent airflow limitation
- Evidence about goal-setting tells us that treatment goals for patients should be personalized and achievable
- Avoid encouraging automatic step-up of therapy
  - Treat comorbidities and modifiable risk factors first (including poor inhaler technique and poor adherence); use non-pharmacologic strategies; if high-dose ICS or ICS-LABA is used, limit to 3–6 months whenever possible
  - Use GINA Track 1 regimen to reduce exacerbations using *lower* ICS doses

GINA goal of asthma management

The goal is to achieve the **best possible long-term asthma outcomes** for each patient:

- Long-term symptom control, which may include:
  - Few/no asthma symptoms, quickly relieved
  - No sleep disturbance
  - Unimpaired physical activity
- Long-term asthma risk minimization, which may include:
  - No exacerbations
  - Improved or stable personal best lung function
  - No requirement for maintenance oral corticosteroids
  - No medication side-effects

When discussing best possible long-term outcomes with a patient, consider:

- Their asthma phenotype
- Clinical features
- Multimorbidity
- Risk factors (e.g. poor adherence, smoking, persistent airflow limitation)
- Availability, cost and adverse effects of medications
- The patient's goals (these may be different from medical goals)

- Assessing symptom control is not enough! Patients with few asthma symptoms can still have severe or fatal exacerbations related to individual risk factors or external triggers (viruses, allergen, pollution)
- Encourage referral for expert advice for patients with difficult-to-treat or severe asthma

Control Symptoms and Minimize Risk
Relegate Treat-to-Failure, Elevate Treat-to-Target

The current pharmacologic treatment paradigm is a *step-wise* approach with maximizing of doses and addition of treatments when patients are uncontrolled (ie, 'treat to failure')

Asthma treatment goals do not aim for remission and focus on:

- Symptom control and maintenance of normal activity levels
- Reducing risk of exacerbations, airflow limitations, and side effects

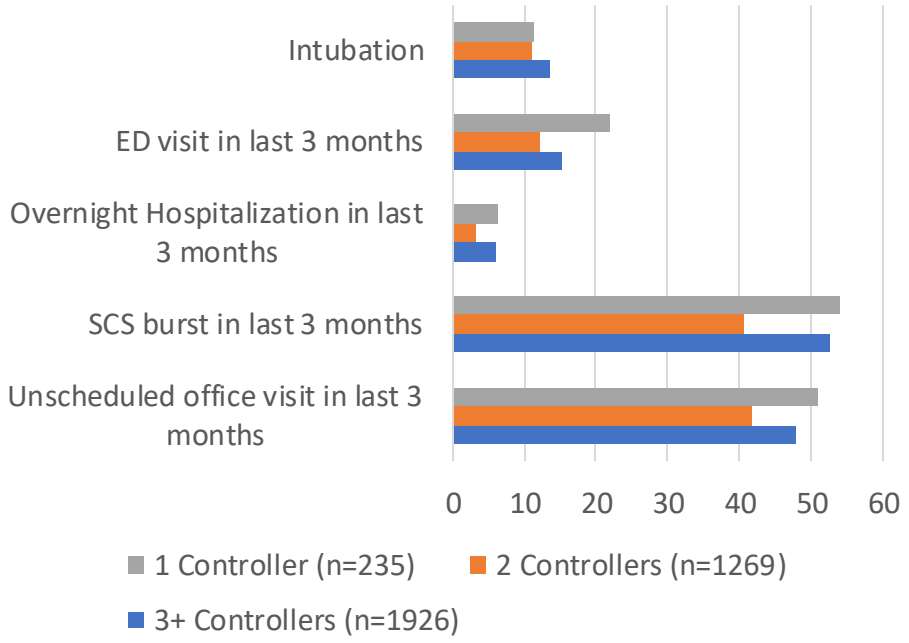
Patients with severe asthma are typically on multiple asthma controller-medications and still can be uncontrolled

What if patients were treated to target, with goal of *NO* exacerbations and stabilized lung function?

With the availability of precision medicines (i.e. biologics):

- HCPs: can target underlying inflammation with precision, more aggressively treat for better outcomes, and raise expectations to achieve clinical remission
- Patients: can realize freedom from a daily disease burden with a quicker timeline to achieving sustained improvement in outcomes, avoidance of OCS exposure, and greater quality of life

TENOR Study: Rates of Healthcare Utilization by Long-term Asthma Controllers (Patients 18+ Years)[5]



The TENOR study showed that despite receiving multiple long-term asthma controllers, there was limited improvement in outcomes in patients with severe, difficult-to-treat asthma[5]

1. Global Initiative for Asthma. 2021. Available from: www.ginasthma.org. 2. Suehs CM, Menzies-Gow A, Price D, et al, on behalf of the Oral Corticosteroids Tapering Delphi Expert Panel. *Am J Respir Crit Care*. 2021;203:871-881. 3. Song HJ, Blake KV, Wilson DL, et al. *J Asthma Allergy.* 2020;13:545-555. 4. Suruki RY, Daugherty JB, Boudiaf N, et al. *MBC Pulmonary Mediciane.* 2017:17:74. 5. Chipps BE, Zeiger RS, Borish L, et al for the TENOR Study Group. *J Allergy Clin Immunol.* 2012;130:332-42.

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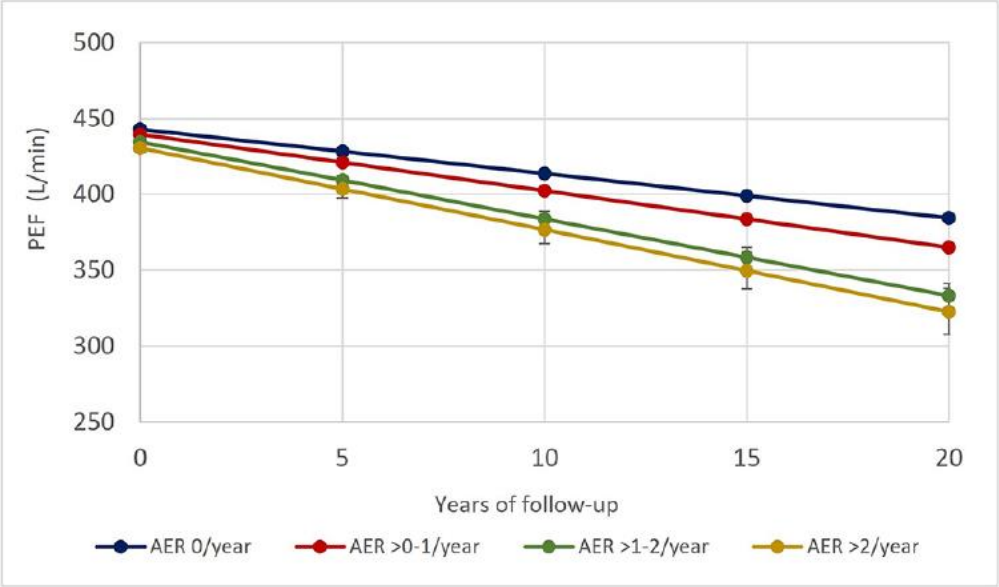
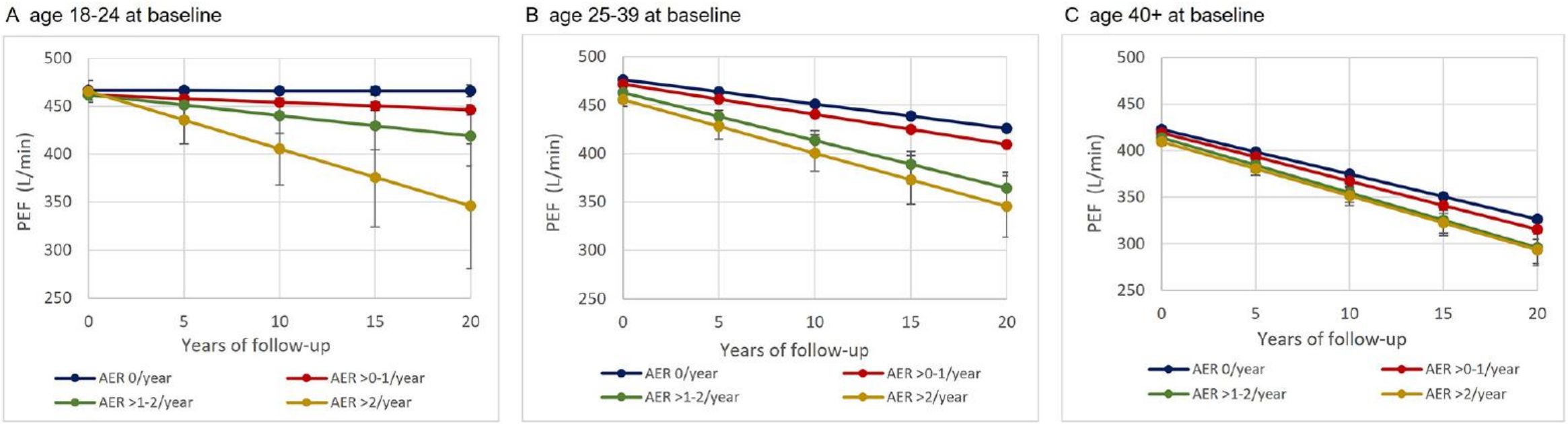
OPCRD Effect of Repeat Exacerbations on Lung Function



Annual exacerbation rate	Decline in PEF L/min/yr (95% CI)	Average difference in PEF L/min/yr decline between AER categories (95% CI; p)
0/yr	**-2.93 L**/min/yr (-3.04, -2.82)	
>0-1/yr	**-3.74 L**/ min/yr (-3.84, -3.64)	-0.81 L (-0.93, -0.70) p ≤0.001
>1-2/yr	**-5.05 L**/ min/yr (-5.38, -4.73)	-2.13 L (-2.46, -1.80) p ≤0.001
>2/yr	**-5.38 L**/ min/yr (-5.98, -4.78)	-2.46 L (-3.06, -1.85) p ≤0.001

Soremekun S, et al. Thorax 2022:1-10

OPCRD Effect of Repeat Exacerbations on Lung Function



Soremekun S, et al. Thorax 2022:1-10

Why Is It Time For More Ambitious Composite Outcome Measures?

- Better reflect broad impact of treatment
- Helps to ‘market’ severe asthma as a treatable problem to payers
- Reflects an ambitious goal and a state that might be associated with disease modification
- Provides a rationale for earlier biomarker assessment and intervention

Defining Remission

Clinical Remission[1]

The state of no disease activity in patients on or off treatment

Cure[1]

Absence of symptoms and reversal to the normal pathological state of the airways, off treatment

Disease Modification[2]

A process that can affect the underlying pathophysiology of the disease, prevent structural or clinical progression, or cause a sustained reduction in disease activity beyond the temporal effects of other interventions

1. Thomas D et al. In Press. *Eur Respir J*. 2022; 2. Busse WW et al. Eur Respir Rev. 2022; 31:210183.

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Clinical Remission ≠ Response to Treatment

Clinical status (a point in time)

Clinical remission

Example clinical proxies

- No exacerbations
- No long-term OCS use
- Well controlled asthma

≠

Clinical response (change over time)

Response

Example clinical proxies

- Fewer exacerbations
- Less long-term OCS use
- Increased asthma control

OCS, oral corticosteroids

1. Menzies-Gow A *et al. J Allergy Clin Immunol*. 2020; **145:** 757–65 2. Upham JW *et al. J Allergy Clin Immunol Pract.* 2021; **9:** 3997–4004

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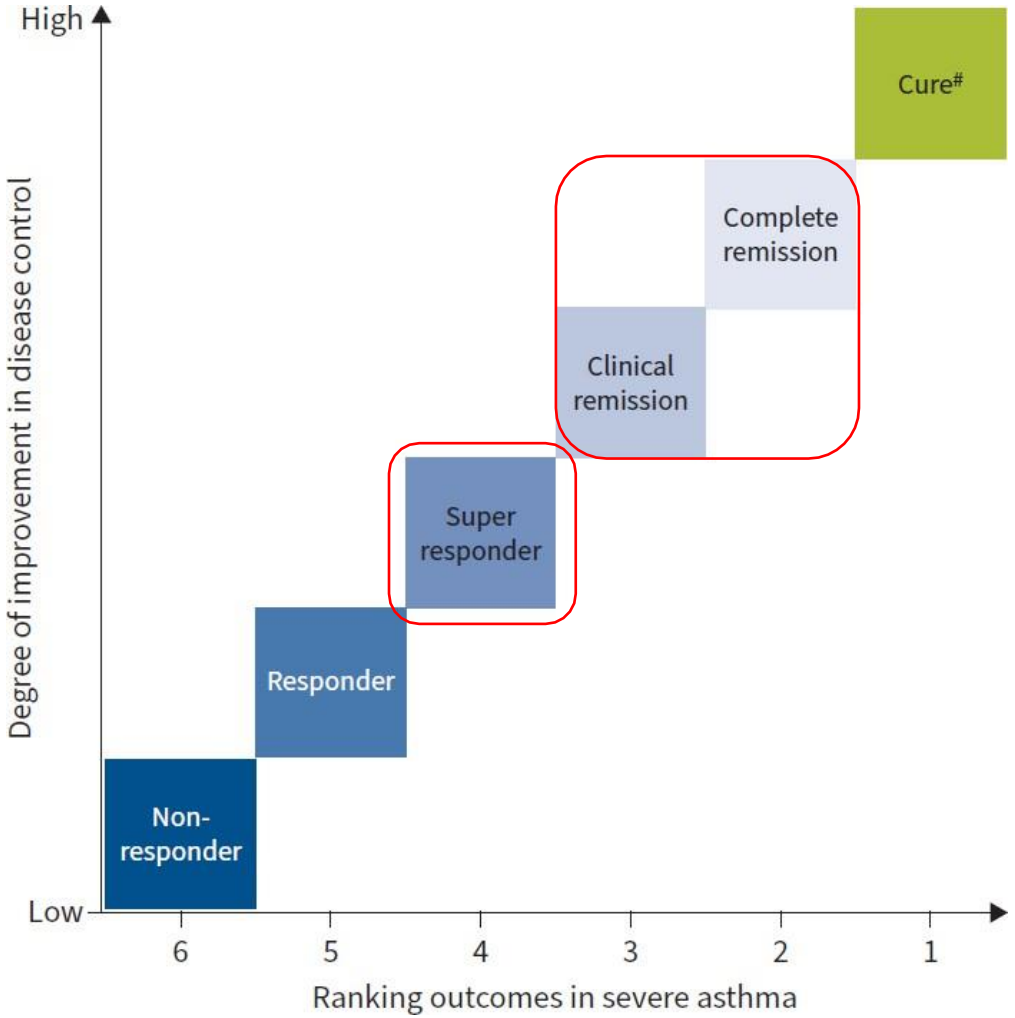
The Hierarchy Of Possible Outcomes



Beasley R, et al. Eur Respir J 2023; 62: 2301844

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What can we learn about clinical remission from other inflammatory diseases?

Rheumatoid arthritis

- State of **absent** or **low disease activity**[1]
  - Few patients could achieve a complete absence of disease activity[1]
- Thresholds for tender and swollen joint counts, CRP, PRO, and SDAI[1]

Ulcerative colitis

- Endoscopic assessment could confirm remission[2]
  - Histopathology (mucosal healing) may have **prognostic value**[2]
- Remission could involve **ongoing treatment**[2]
  - Corticosteroid-free remission is of interest[3]

Crohn's disease

- Concept of '**treat to target**':
  - Remission defined using **clinical and inflammatory parameters**[4]
  - Treatment chosen based on patient's **clinical features and prognosis**[4]
- Early-stage Crohn's disease:
  - Complete mucosal healing predicts steroid-free remission[4]

SLE

- Duration of remission is controversial as SLE is **relapsing and remitting**[5]
- Remission could involve **ongoing treatment**[5]
  - Patients receiving low-dose long-term prednisone (≤5 mg/day) are considered to be in remission[5]

In each of these diseases, biologics target the inflammatory process[6–9]

Establishing Consensus Definitions for Remission: Definitions in Other Chronic Inflammatory Conditions

Condition	Descriptor	On Treatment	Duration of Disease Activity
RA	Clinical remission	✓	Current
UC[a]	Clinical remission	✓	Current
	Corticosteroid-free remission	✓	Current
CD[a]	Clinical remission	✓	Past 7 days
SLE	On therapy remission	✓	'Durable' (unspecified)

•RA: rheumatoid arthritis; UC: ulcerative colitis, CD: Crohn's disease; CS: corticosteroids; HCP, health care provider; RA, rheumatoid arthritis; SLE: systemic lupus erythematosus; UC, ulcerative colitis;
[a]Chronic CS not allowed on treatment.
•Menzies-Gow A, et al. *J Allergy Clin Immunol.* 2020;145(3):757-765.

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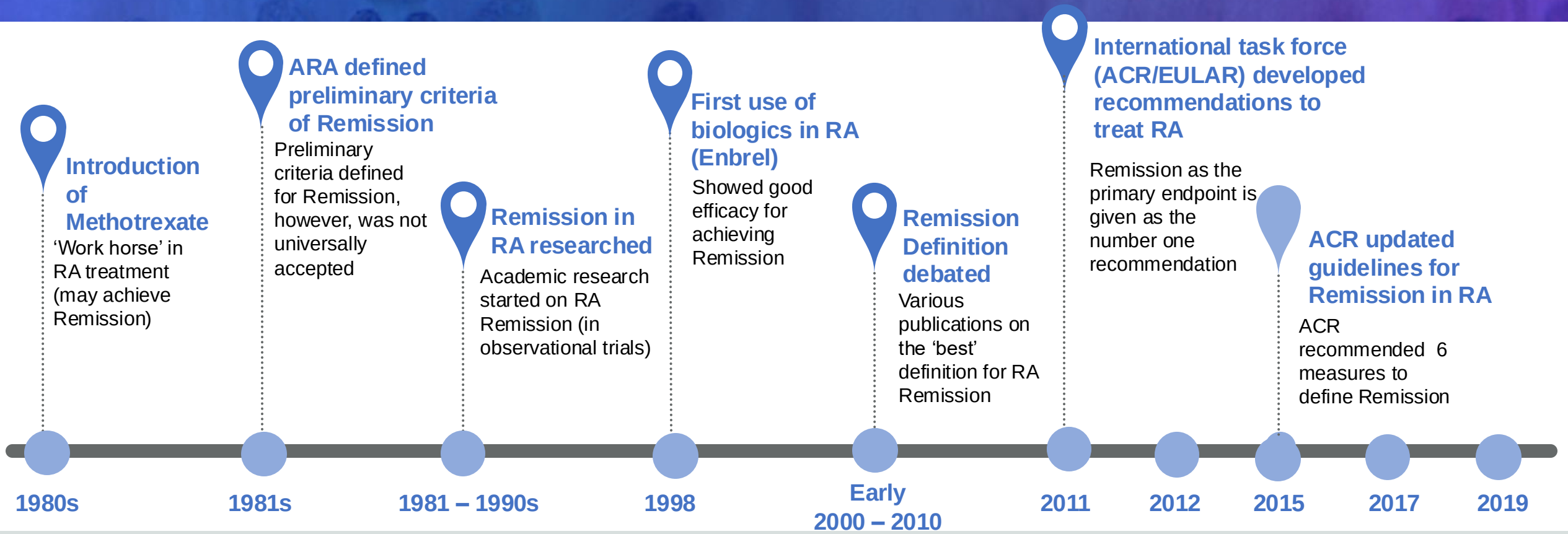
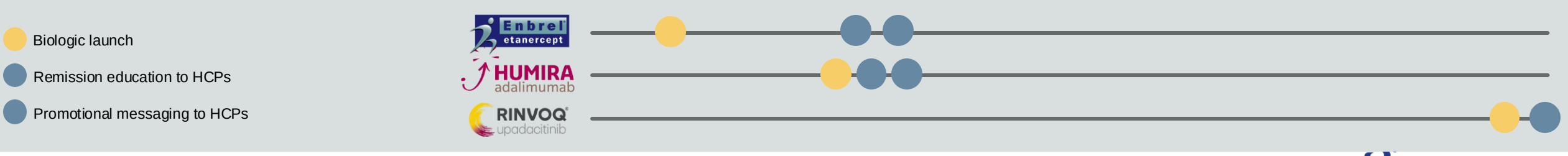
RA Remission Journey





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Source for data: BMJ Journals, 2004 ;BMJ Journals, 2011; NCBI 2013; American college of Rheumatology, 2015

Can RA Be A Model For How To Achieve Remission In SA

Rheumatoid arthritis	Severe asthma
Incurable inflammatory condition[1]	✓ Incurable inflammatory condition[4]
Disease progression results in irreversible joint damage and visible disability[2]	✓ Disease progression results in irreversible lung function decline[5] and disability that is not visibly perceived; underestimated disease burden contributes to worse outcomes[6]
Multiple targeted treatments, including DMARDs available with a realistic goal of clinical remission[1,3]	? Multiple targeted treatments available[7]; whether remission can be achieved is currently being explored[8]

DMARD = disease modifying anti-rheumatic drug.

1. Girdler SJ, et al. *J Orthop.* 2019;17:17-21; 2. Brown PM, et al. *Clin Med (Lond).* 2014;14(Suppl 6):s50-55; 3. Felson DT, et al. *Arthritis Rheum.* 2011;63:573–586; 4. Busse WW, et al. *Eur Respir Rev.* 2022;31(163):210183; 5. Pascual, RM, Peters SP. *J Allergy Clin Immunol.* 2009;124(5):883-892; 6. Crespo-Lessmann A, et al. *BMJ Open Respir Res.* 2017;4:e000189; 7. Pelaia C, et al. *Front Immunol.* 2020;11:603312; 8. Menzies-Gow A, et al. *J Allergy Clin Immunol.* 2020;145(3):757-765.

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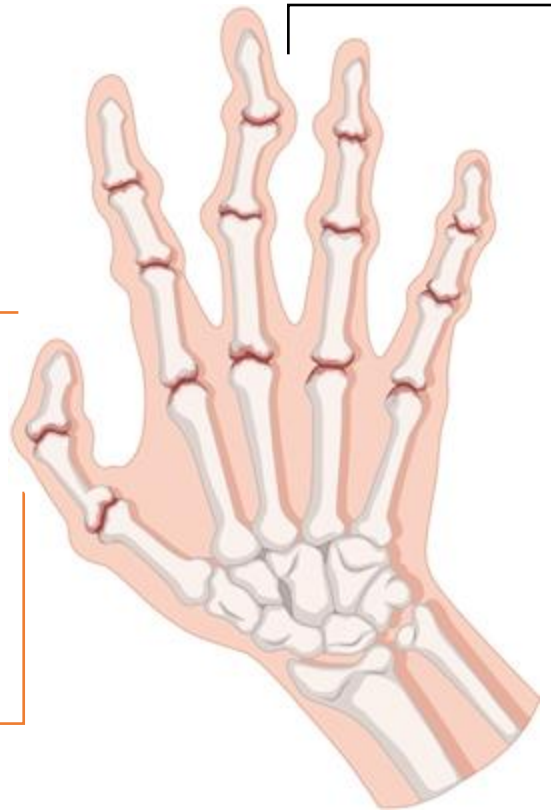
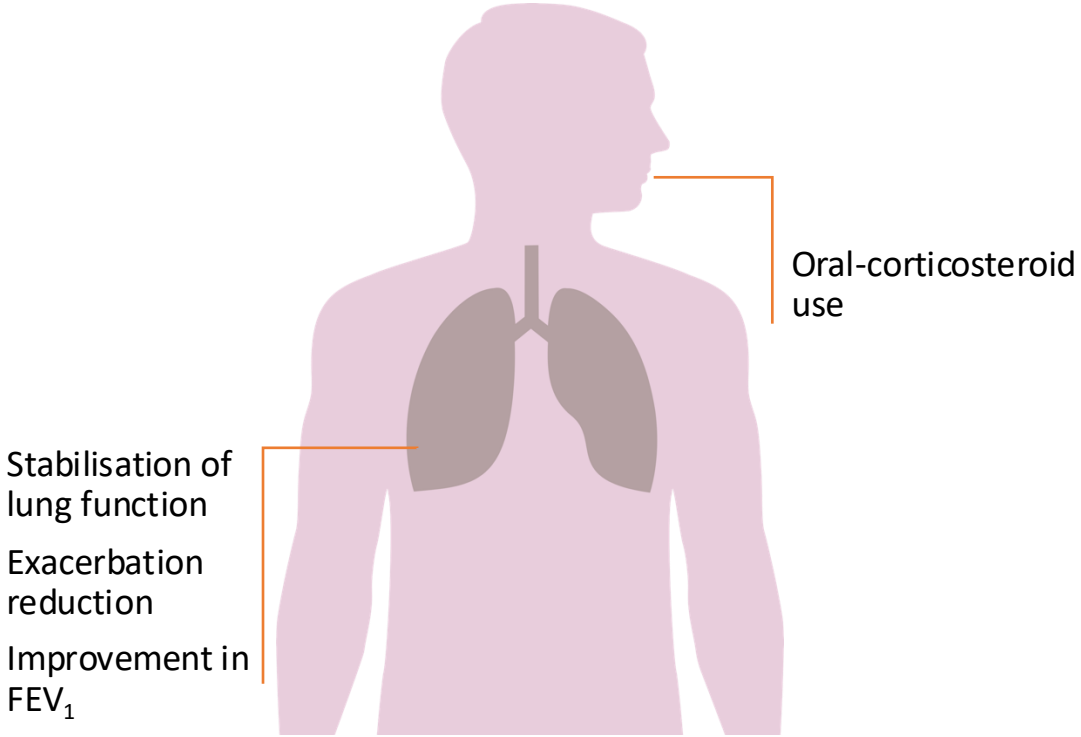
Defining Clinical Remission: How Is Asthma Different From Rheumatoid Arthritis?

- In rheumatoid arthritis, it is easy to look at joints[1]



- In asthma, we need to use clinical correlates[2]



1. Mount Sinai. Rheumatoid arthritis. https://www.mountsinai.org/health-library/diseases-conditions/rheumatoid-arthritis [Accessed 18 July 2022]
2. Menzies-Gow A *et al. Adv Ther.* 2022; **39:** 2065–84.

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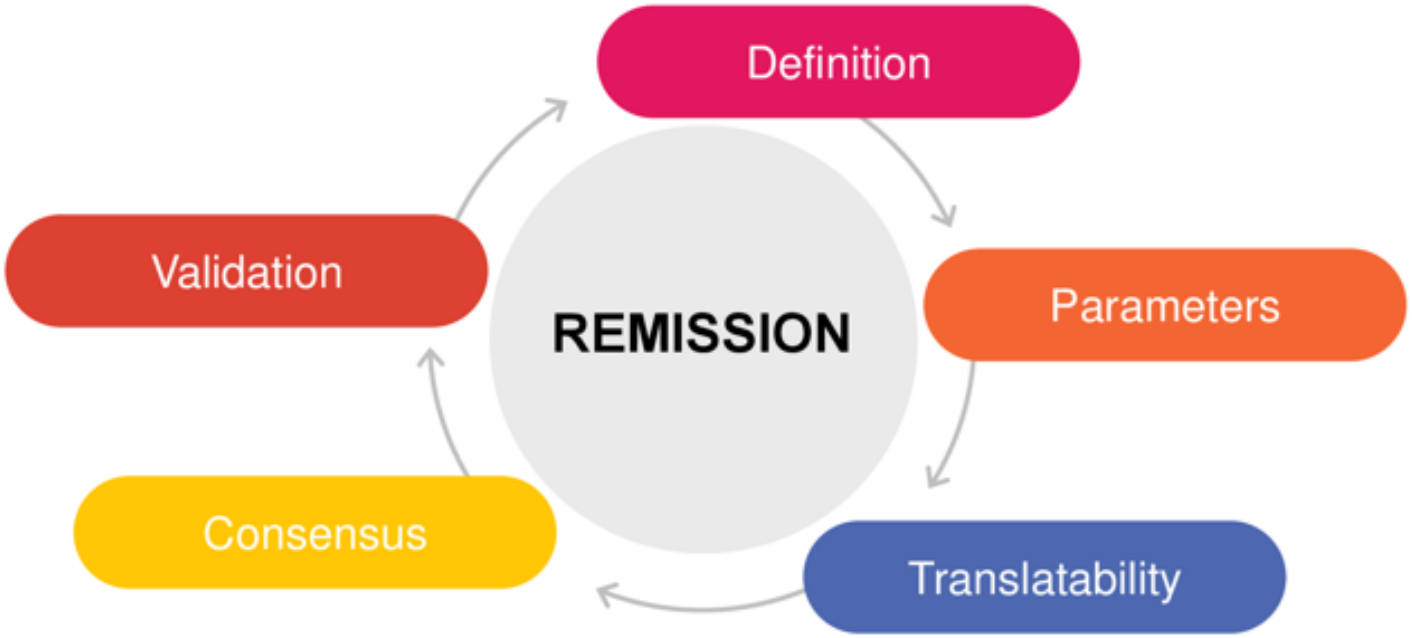
Pathway to Remission for RA an Iterative Process to Strive for Better

Iterative Process of Building, Refining and Improving



HCP = health care practitioner; QOL = quality of life.

1. Singh JA, et al. *Arthritis Care Res (Hoboken)*; 2016;68:1-25; 2. Menzies-Gow A, et al. *J Allergy Clin Immunol*. 2020;145:757-765.

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Defining Asthma Remission In The Pre-Biologic Era

7/8 absence of symptoms

Study	Criteria for asthma remission	Time frame
Bronnimann & Burrows, 1986	No asthma attacks, symptoms or medications	1 year
Boulet et al., 1994	No symptoms or medication requirement	2 years
Ronmark et al., 1999	No wheeze, dyspnoea or medications	1 year
Horak et al., 2003	No wheeze	3 years
Sears et al., 2003	No wheeze	1 year
Vonk et al., 2004	No active symptoms, no inhaled steroids	3 years
de Marco et al., 2006	No asthma attack	2 years
	No asthma medications	1 year
Holm et al., 2007	No asthma symptoms, no medications	2 years

Upham JW, James AL. Pharmacol Ther. 2011 Apr;130(1):38-45

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Defining Asthma Remission In The Pre-Biologic Era

7/8
absence of
symptoms

2/8
absence of
asthma
attacks

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7/8
absence of symptoms

2/8
absence of asthma attacks

6/8
no medications

1/8
Specific mention of ICS

0/8
Specific mention of OCS

0/8
lung function

0/8
Airways Inflammation or AHR

Upham JW, James AL. Pharmacol Ther. 2011 Apr;130(1):38-45

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4/8
1 year

4/8
2-3 years

Upham JW, James AL. Pharmacol Ther. 2011 Apr;130(1):38-45

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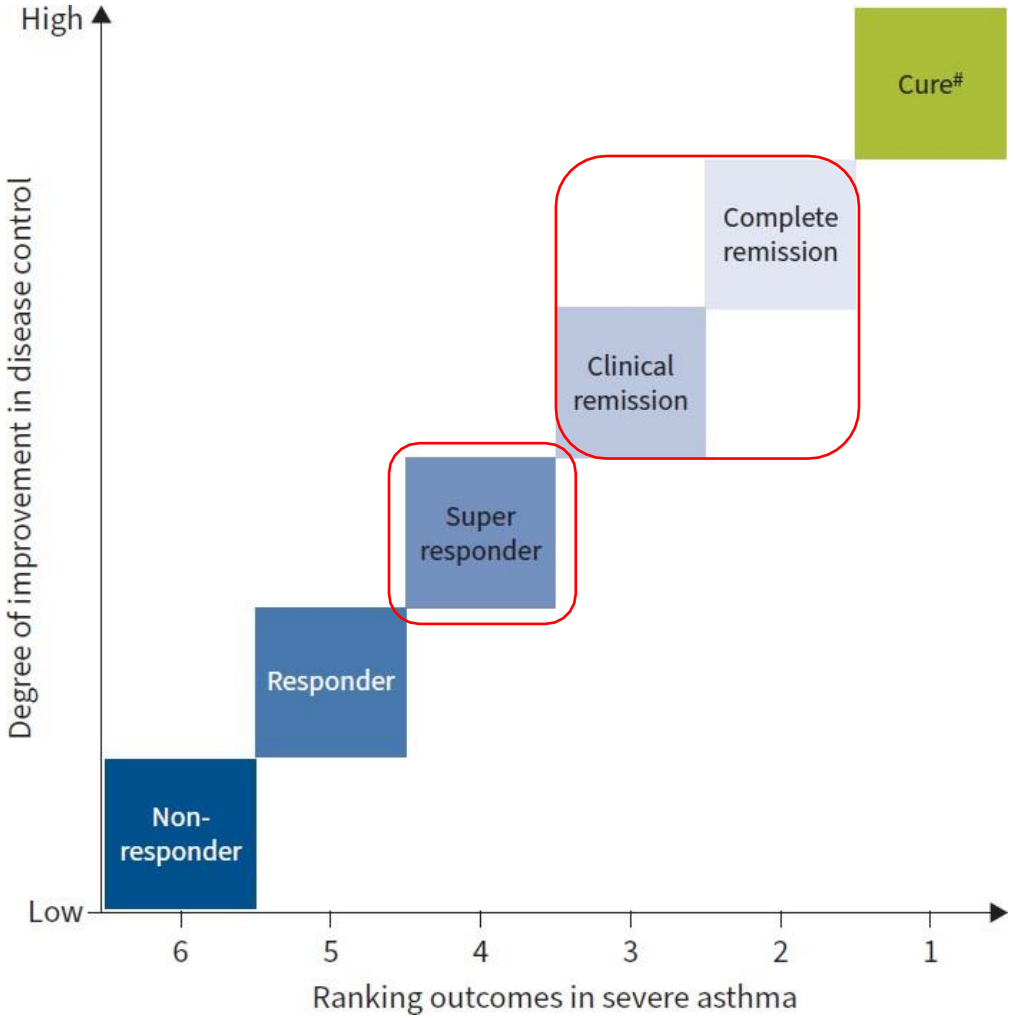
The Hierarchy Of Possible Outcomes



Beasley R, et al. Eur Respir J 2023; 62: 2301844

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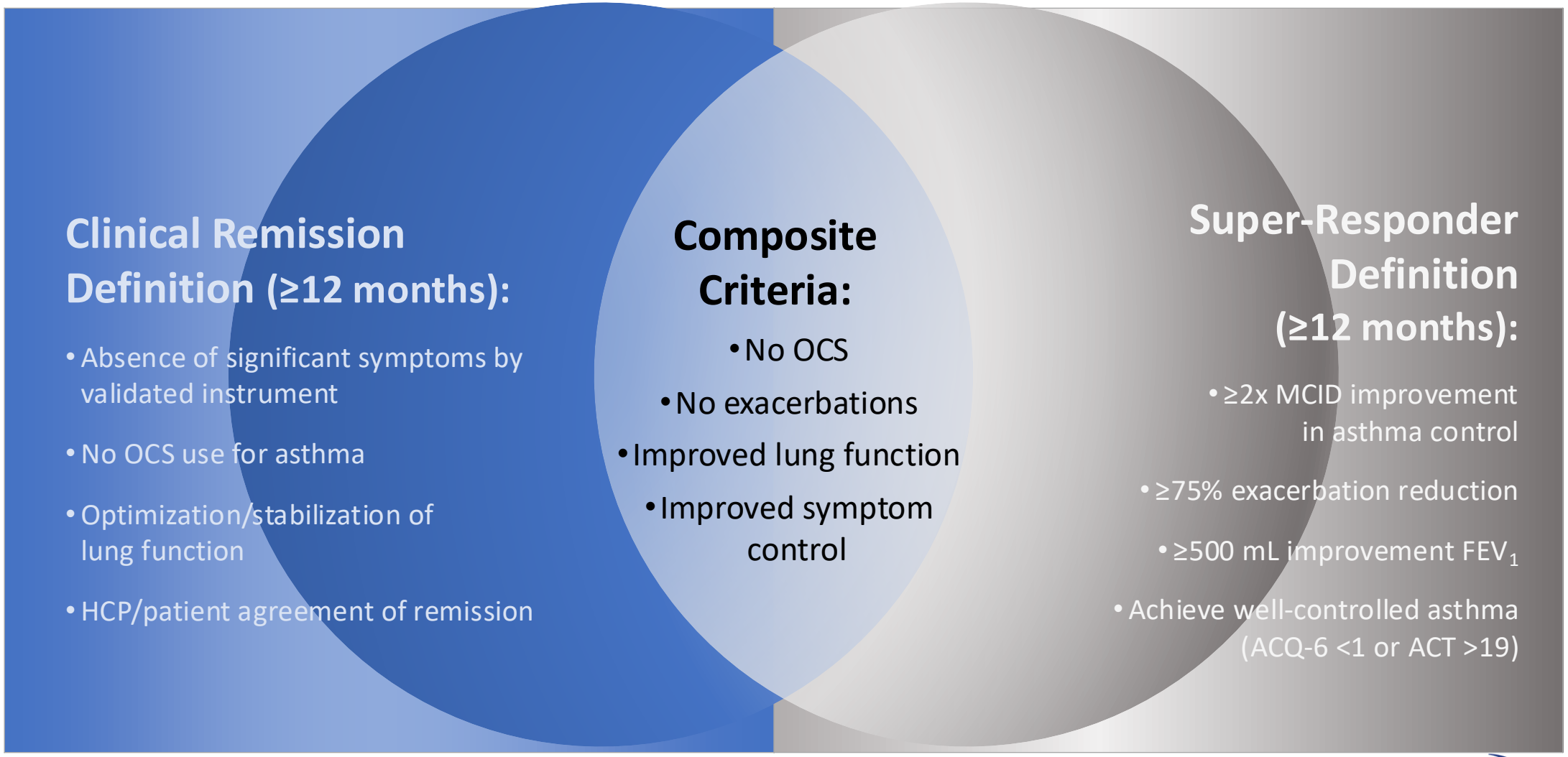
Clinical Remission vs Super-Responders[1,2]



1. Menzies-Gow A, et al. *J Allergy Clin Immunol*. 2020;145(3):757-765.
2. Upham JW, et al. *J Allergy Clin Immunol Pract.* 2021;9(11):3997-4004.

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Asthma Remission Could be Considered As a Spectrum Consisting of Different States that Can Vary Over Time

Lexicon

- A clear lexicon to **differentiate remission from asthma control, treatment response,** and **cure** is important
- Clarity around **expectations** when discussing remission (eg on/off treatment or with/without OCS) is required
- The remission concept should highlight an **absence of disease activity** to differentiate it from existing terms (partial, total, or super response)

Defining remission

Types of remission

- **Remission could be considered in two ways**:

1. **Clinical/symptomatic remission**:
   - No exacerbations
   - Optimal symptom control,
   - Optimal pulmonary function
   - No background OCS (unless presence of adrenal insufficiency with OCS ≤5 mg)
2. **Complete/inflammatory remission**:
   - Same as above **plus no inflammation** (as indicated by biomarkers) or **airway hyperresponsiveness**

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Delphi: Expert Consensus Framework for Clinical Remission in Asthma

Clinical remission on treatment

For ≥12 months:

- Sustained absence of significant asthma symptoms based on validated instrument, **and**
- Optimization and stabilization of lung function, **and**
- Patient and HCP agreement regarding disease remission, **and**
- No use of systemic corticosteroid therapy for exacerbation treatment or long-term disease control

Clinical remission off treatment

Same criteria maintained without asthma treatment for ≥12 months

Complete remission on treatment

Clinical remission plus the following:

- Current, objective evidence of the resolution of previously documented asthma-related inflammation (e.g. reduced blood or sputum eosinophil counts, FeNO and/or other relevant measures), **and**
- In appropriate research settings: current negative bronchial hyper-responsiveness

Complete remission off treatment

Same criteria maintained without asthma treatment for ≥12 months

FeNO, fractional exhaled nitric oxide; HCP, healthcare professional

Menzies-Gow A *et al. J Allergy Clin Immunol*. 2020; **145:** 757–65

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German Respiratory Society S2k Guidelines Include Clinical Remission

The general therapy concept no longer focuses on reacting to symptoms, but on sustainable prevention of their occurrence – S2k Guidelines

Criteria for asthma remission—all criteria must be met
Sustained (≥12 months) absence of asthma symptoms
Sustained (≥12 months) absence of exacerbations
Stable lung function
No need for systemic glucocorticoids for the treatment of asthma

Lommatzsch M, et al. S2k-Leitlinie zur fachärztlichen Diagnostik und Therapie von Asthma 2023 [S2k guidelines for specialist diagnostics and treatment of asthma 2023]. Published by the German Respiratory Society (DGP) March 6, 2023. Accessed May 11, 2023. https://register.awmf.org/assets/guidelines/020-009l_S2k_Fachaerztliche-Diagnostik-Therapie-von-Asthma_2023-03.pdf

SANI Definition of Partial vs. Complete Clinical Remission in Severe Asthma

	Partial Clinical Remission
Definition	Obtained when there is no further need for using OCS, and **2 out of the 3** following criteria are met:
Criteria	• Absence of asthma symptoms • Absence of asthma exacerbations/attacks • Stability of lung function
Time	For at least 12 months
Scores	ACT score of 20-25 ACQ score of <1.5

	Complete Clinical Remission
Definition	Obtained when there is no further need for using OCS, and **all of the 3** following criteria are met:
Criteria	• Absence of asthma symptoms • Absence of asthma exacerbations/attacks • Stability of lung function
Time	For at least 12 months
Scores	ACT score of 20-25 ACQ score of <1.5

Definitions of partial and complete clinical remission obtained from this Delphi Analysis will be used to test the efficacy of different treatments in >2200 patients enrolled into the SANI registry

ACQ, asthma control questionnaire; ACT, asthma control test; OCS, oral corticosteroids; SANI, Severe Asthma Network Italy.

Canonica GW, et al. J Allergy Clin Immunol Pract. 2023;S2213-2198(23)00816-4.

The 2023 Japan Asthma Society Guidelines Provide a Definition of Clinical Remission

Clinical Remission
ACT score ≥ 23 over 1 year
No exacerbations over 1 year
No use of OCS as regular medication over 1 year

*Assess lung function if clinical remission can be achieved

Japan Asthma Society (JAS). Practical Guidelines for Asthma Management (PGAM). Updated July 2023. Accessed August 30, 2023. https://jasweb.or.jp/guideline.html

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The Spanish GEMA 5.3 Guidelines Explore the Concept of Remission

"The concept of 'remission'…should encompass the absence of clinical manifestations, hyperresponsiveness, and bronchial inflammation for a prolonged period of time."

Clinical Remission
The absence, for at least 12 months, of symptoms and exacerbations without the use of systemic steroids
Optimization and stabilization of lung function

GEMA, Spanish Asthma Management Guidelines.

GEMA 5.3: Guía Española para el manejo del asma [GEMA 5.3: Spanish asthma management guidelines]. Accessed May 11, 2023. https://www.separ.es/node/1827

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An ACAAI/ATS/AAAAI/EUFOREA Workgroup Has Proposed a Clinical Remission Definition

"While the attainment of a state of remission in asthma is laudable, the workgroup consensus is that this should be a high bar to achieve"

Asthma Clinical Remission On-Treatment Criteria
NO exacerbations requiring a physician visit, emergency care, hospitalization, and/or systemic corticosteroid for asthma (ie, oral, injectable)
NO missed work or school over a 12-month period due to asthma-related symptoms
Stable and optimized pulmonary function results on all occasions, when measured over a 12-month period, with ≥2 measurements per year
Continued use of controller therapies (ICS, ICS/LABA, leukotriene receptor antagonist) **ONLY at low-medium dose of ICS or less**, as defined by most recent GINA strategy
An ACT >20, AirQ <2, ACQ <0.75 on all occasions measured over the previous 12-month period, with ≥2 measurements per year
Symptoms requiring one-time reliever therapy (SABA, ICS-SABA, ICS-LABA) no more than once a month

AAAAI, American Academy of Asthma, Allergy, and Immunology; ACAAI, American College of Asthma, Allergy, and Immunology; ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AirQ, Asthma Impairment and Risk Questionnaire; ATS, American Thoracic Society; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; SABA, short-acting beta agonist.

Blaiss M, et al. Ann Allergy Asthma Immunol. Published online September 7, 2023. doi: 10.1016/j.anai.2023.08.609.

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Conclusion from NJH Consensus Panel 2024

- Remission is the best outcome for patients with RA
  - No progression of damage
  - Maximization of physical function, quality of life and working capacity
  - Minimization of comorbidities

- Respiratory Feedback
  - Determination of clinical remission is sufficient – remission by imaging does not lead to better outcomes but to more adverse events and costs → counterproductive
  - However, it should be stringent clinical remission, not a definiton of remission with residual activity to just increase the number of patients defined as in remission
  - Low disease activity is a very important alternative target, since patients with chronic disease have irreversible damage and will not be able to reach remission

- While the availability of targeted therapies over the last two decades has lead to improved outcomes, The development of therapeutic targets and strategic treatment concepts has added dramatically to this improvement

- →The path to the target is also a target!

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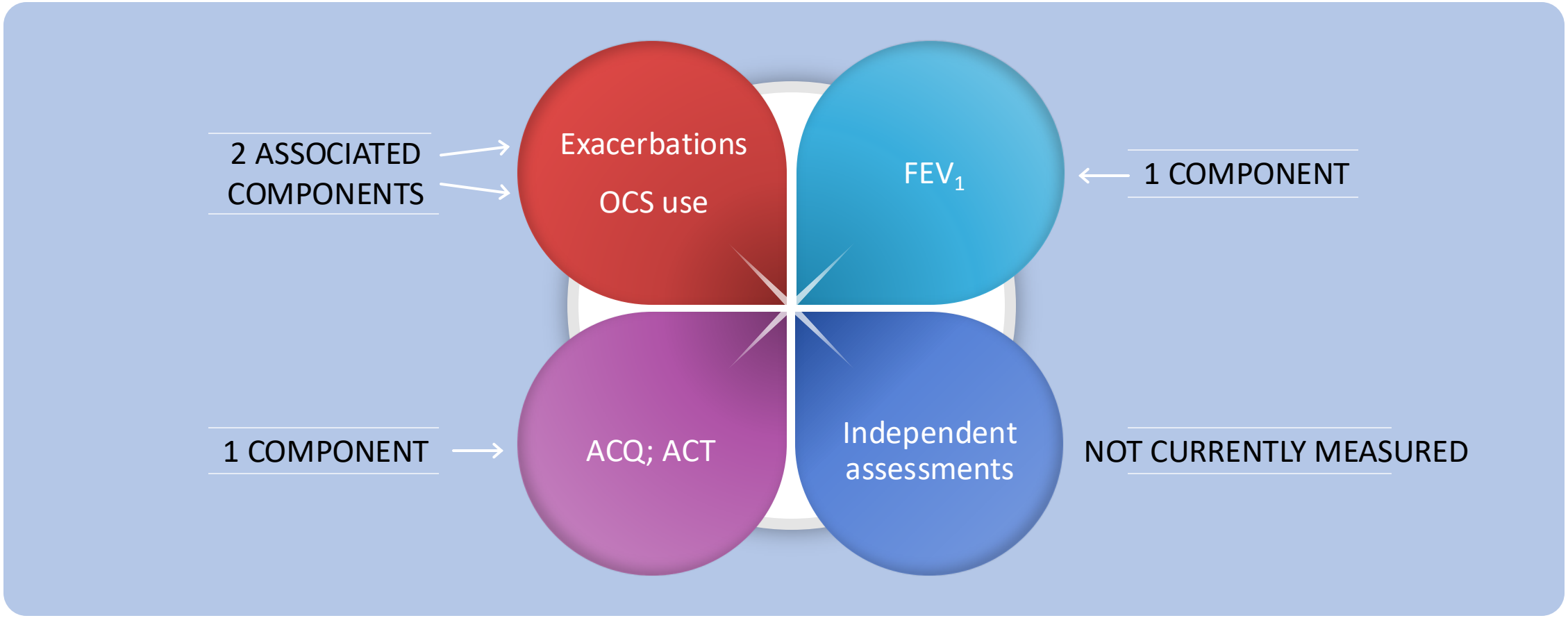
Current Data!!!!

Most Biologic Publications Use a 4-Component Clinical Remission Definition[1-5]



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

1. Pavord I, et al. *Front Immunol*. 2023;14:1150162. 2. Brusselle G, et al. Presented at the American Thoracic Society International Conference; May 19-24, 2023; Washington, DC. Poster 203.
3. Menzies-Gow A, et al. *Adv Ther*. 2022;39(5):2065-2084. 4. Pavord ID, et al. Presented at the American Thoracic Society International Conference; May 19-24, 2023; Washington, DC. Poster 9747.
5. Castro M, et al. Presented at the European Respiratory Society International Congress (hybrid); September 4-6, 2022; Barcelona, Spain.

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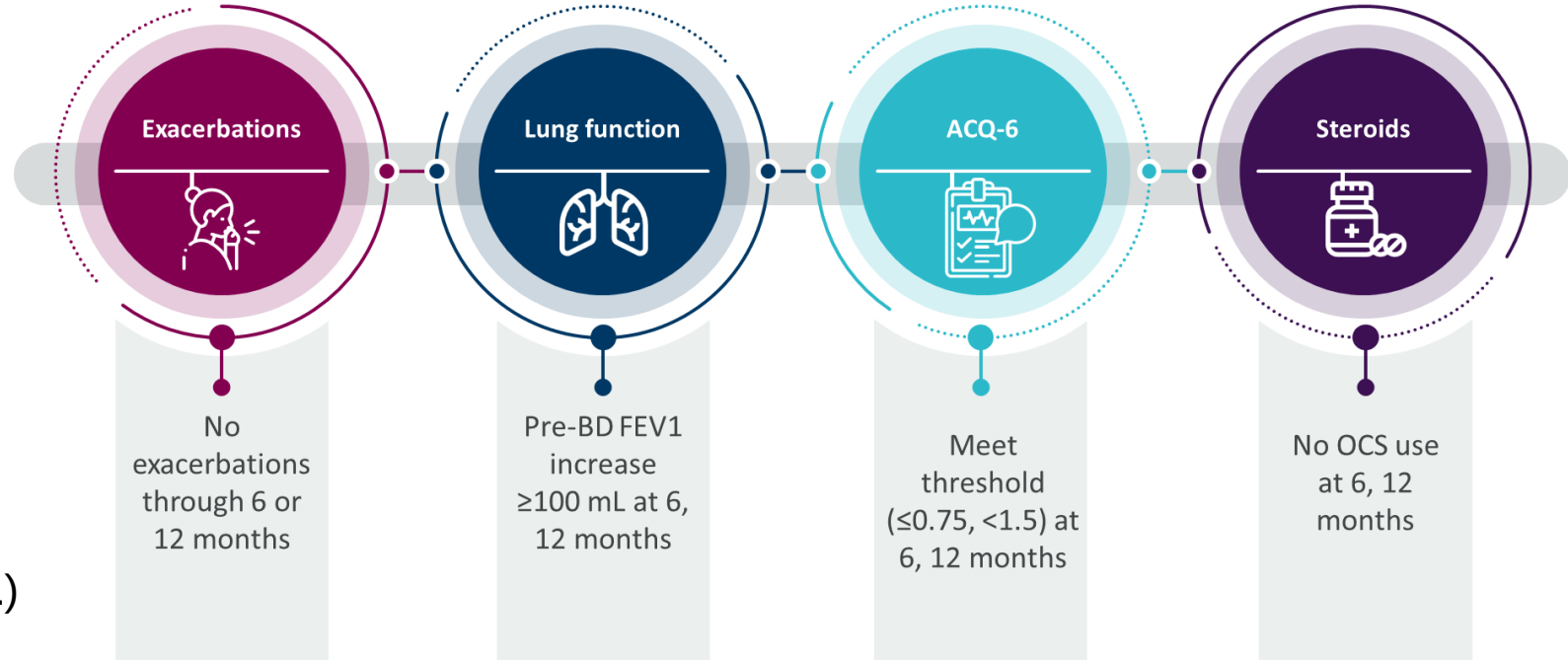
Remission Components

The **four core components** to define clinical remission in this post-hoc analysis are aligned to a recently published expert consensus definition[1], which include:

- **No exacerbations**
- **No use of OCS** for exacerbations or long-term disease control
- Sustained absence of symptoms (**ACQ ≤0.75 or <1.5**)
- Improvement in lung function (**increase ≥100mL pre-BD FEV1**)



Menzies-Gow A, …Katial RK. *Adv Ther*. 2022;39(5):2065-2084

Consistent with previous definitions from the phase 3 trials, an exacerbation was defined as a worsening of asthma that resulted in one of the following: use of systemic corticosteroids, a temporary increase in OCS dosage (by any amount) for at least 3 days, or a dose of injectable corticosteroids; a visit to the emergency department or an urgent care centre; or an inpatient hospital stay. (b) The ≥100 mL threshold for improvement in post-BD FEV_1 was selected as a clinically relevant change, although it is noteworthy that a consensus definition of FEV_1 improvement has not been established and nor has the optimal way to assess lung function changes over time.

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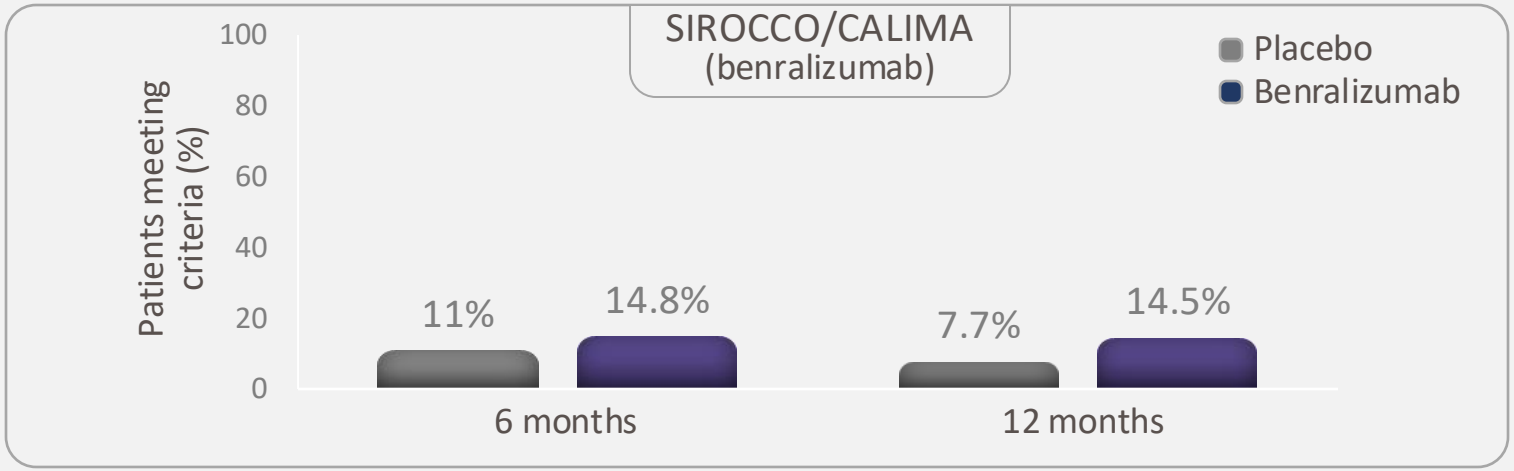
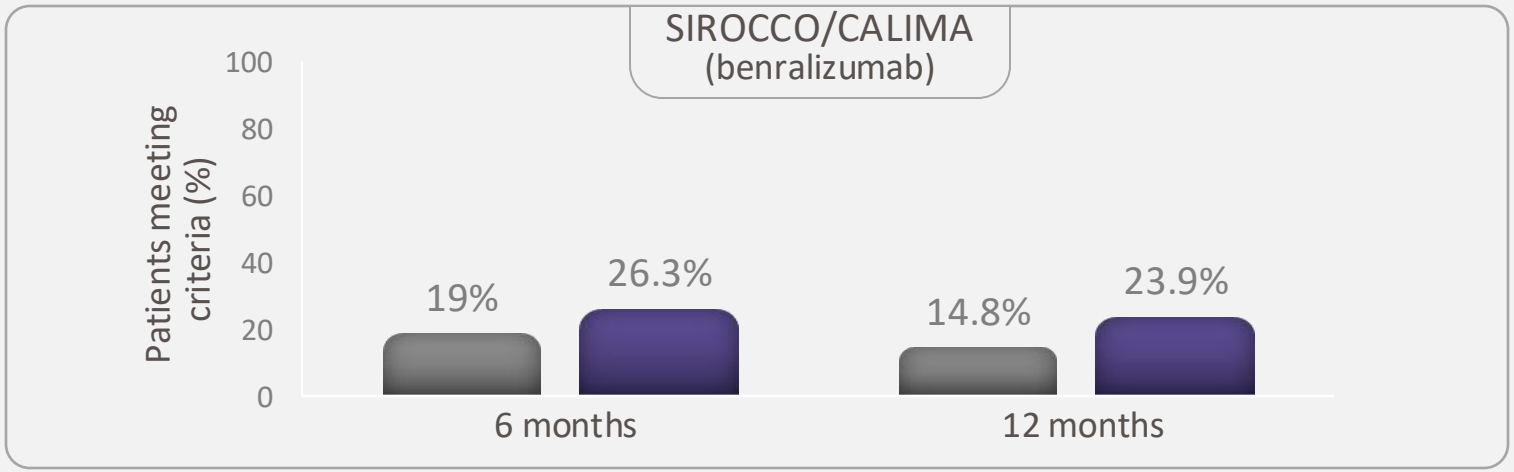
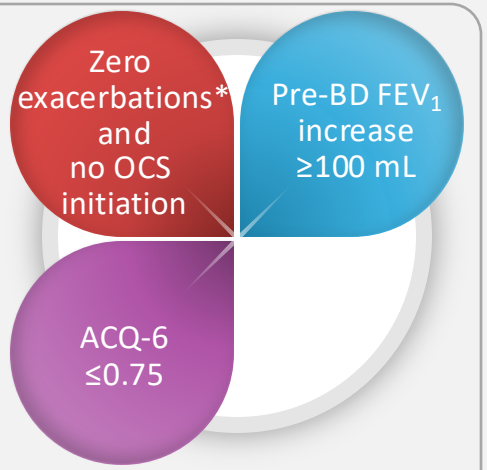
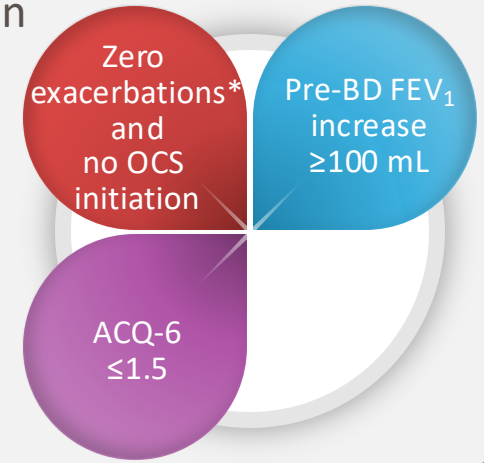
Benralizumab Showed Benefits in Achieving On-Treatment Clinical Remission





On-treatment clinical remission at 6 and 12 months





*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 corticosteroids, or an emergency department visit or inpatient hospital admission.

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

Menzies-Gow A, …Katial RK. *Adv Ther*. 2022;39(5):2065-2084.

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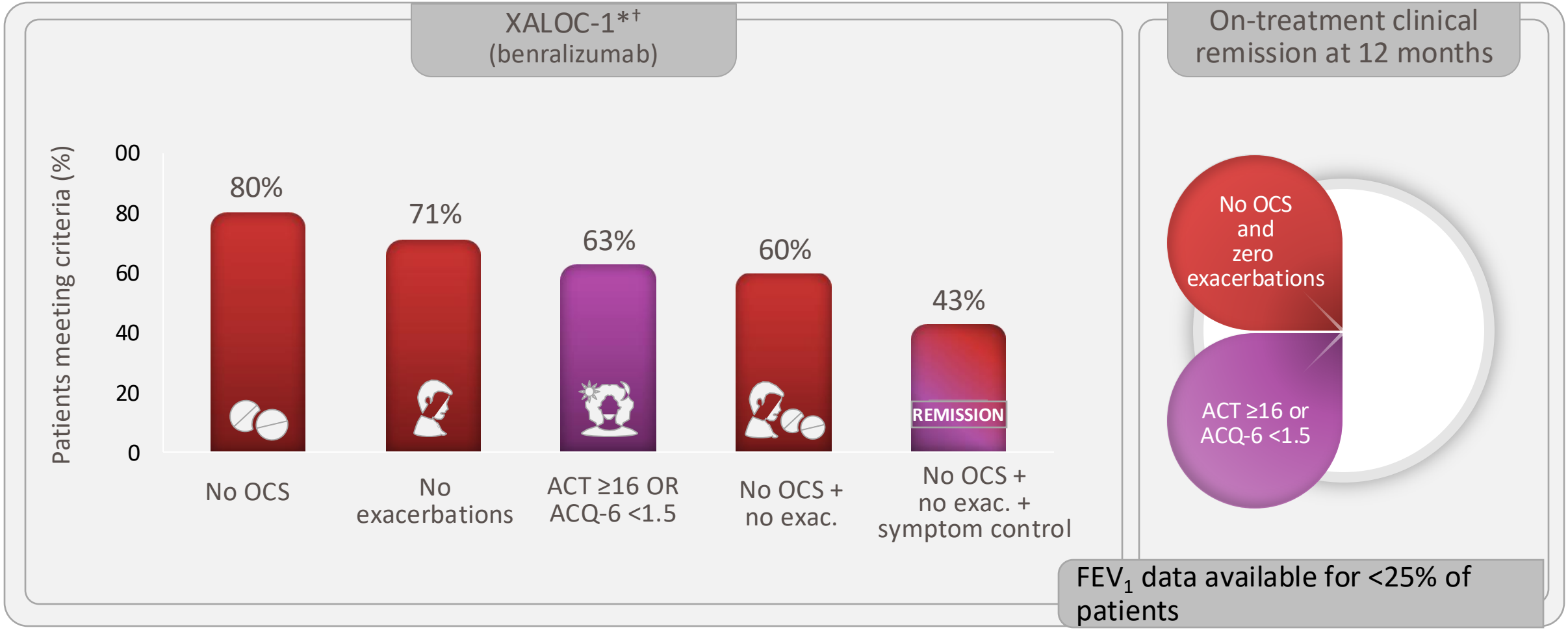
RWE: Severe Asthma Patients Achieved Clinical Remission With Benralizumab



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*XALOC-1 was an international retrospective study in patients with severe eosinophilic asthma treated with benralizumab in Canada, Italy, Spain, and the United Kingdom.

ACQ-6, 6-Item Asthma Control Questionnaire; ACT, Asthma Control Test; exac., exacerbations; FEV_1, forced expiratory volume in 1 second; OCS, oral corticosteroids; RWE, real-world evidence.

Jackson DJ, et al. Poster presented at the American Academy of Allergy, Asthma, & Immunology Annual Meeting; February 24-27, 2023; San Antonio, TX. Poster 39;
Eur Respir J 2024;64: 2301521

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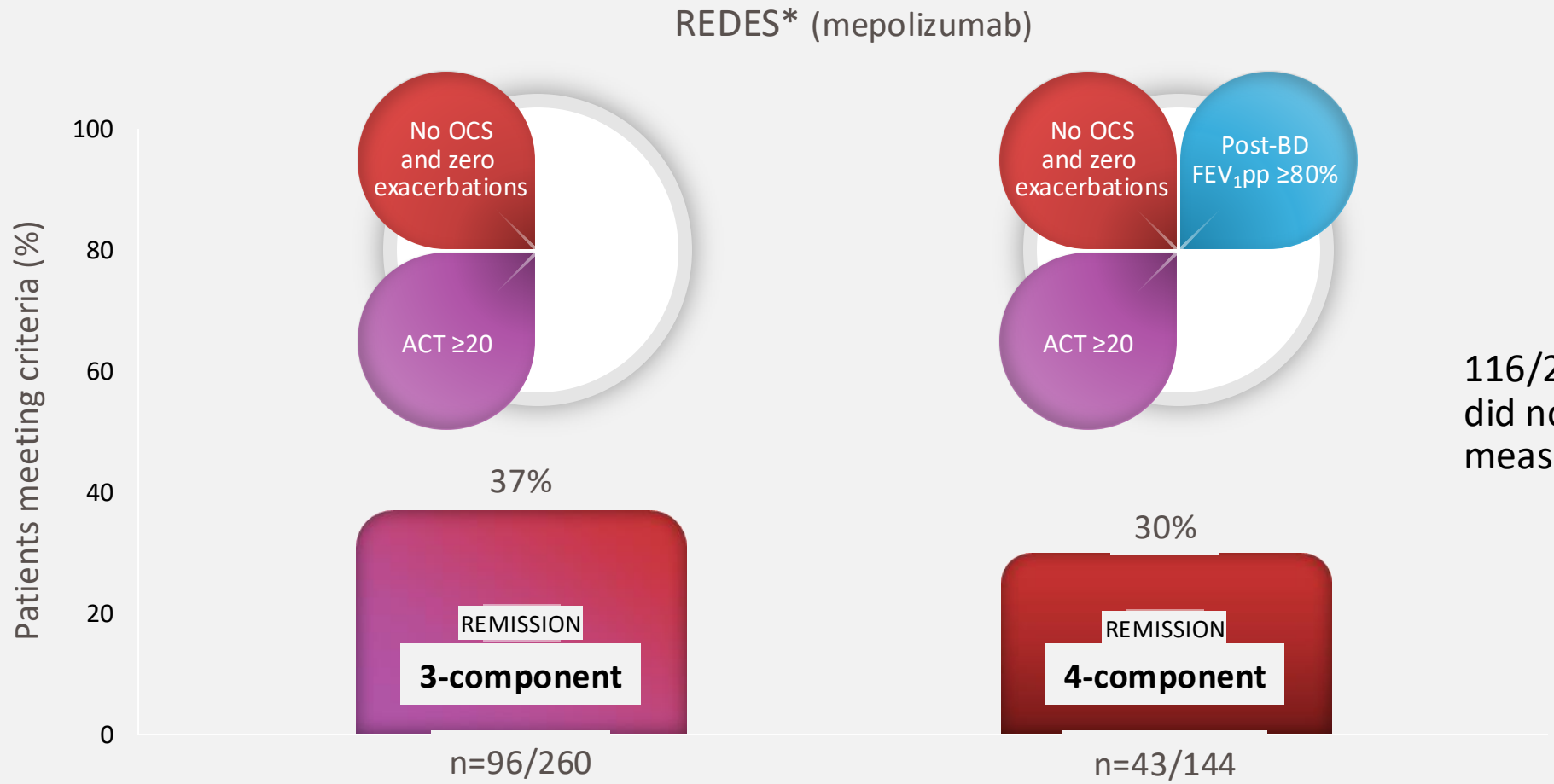
RWE: Mepolizumab Showed On-Treatment Clinical Remission in Severe Asthma Patients



116/260 of patients did not have FEV_1 measurements

*The REDES study was a retrospective, observational cohort study in patients with severe eosinophilic asthma treated with mepolizumab across 24 specialized hospital asthma units in Spain.
ACT, Asthma Control Test; BD, bronchodilator; FEV_1, forced expiratory volume in 1 second; FEV_1pp, FEV_1 percent predicted; OCS, oral corticosteroid; RWE: real-world evidence.
Pavord I, et al. *Front Immunol*. 2023;14:1150162.

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REDES post-hoc analysis suggests that we need to intervene earlier in order to achieve better patient outcomes

Patient baseline characteristics	Patients who achieved clinical remission (n=96)	Patients who did not achieve clinical remission (n=164)
Age, years (mean)	56.9	57.0
Age at asthma diagnosis, years (mean)	32.2	35.5 [n=155]
Annual exacerbations,[†] n (mean)	4.1	4.9
BEC, cells/µL (geometric mean)	675.9	433.2
ACT score, mean	**15.2** [n=90]	**13.6** [n=154]
Post-BD FEV_1%pred, mean	**82.2** [n=70]	**73.6** [n=102]
OCS dependent,[‡] n	**20** [21%]	**85** [52%]
OCS dose, mg/day (median)	**5.0** [n=13]	**10.0** [n=67]

Patients with the potential to achieve remission had less severe disease[1]

[†]Exacerbations in the 12 months pre-Nucala treatment; [‡]OCS dependent in the 12 months pre-Nucala treatment.

ACT, Asthma Control Test; BD, bronchodilator; BEC, blood-eosinophil count; FEV_1, forced expiratory volume in the first second; OCS, oral corticosteroid.

1. Domingo-Ribas C et al. Presented at: ERS 2022; Poster PA1344.

Pavord et al. Frontiers Immunol 2023

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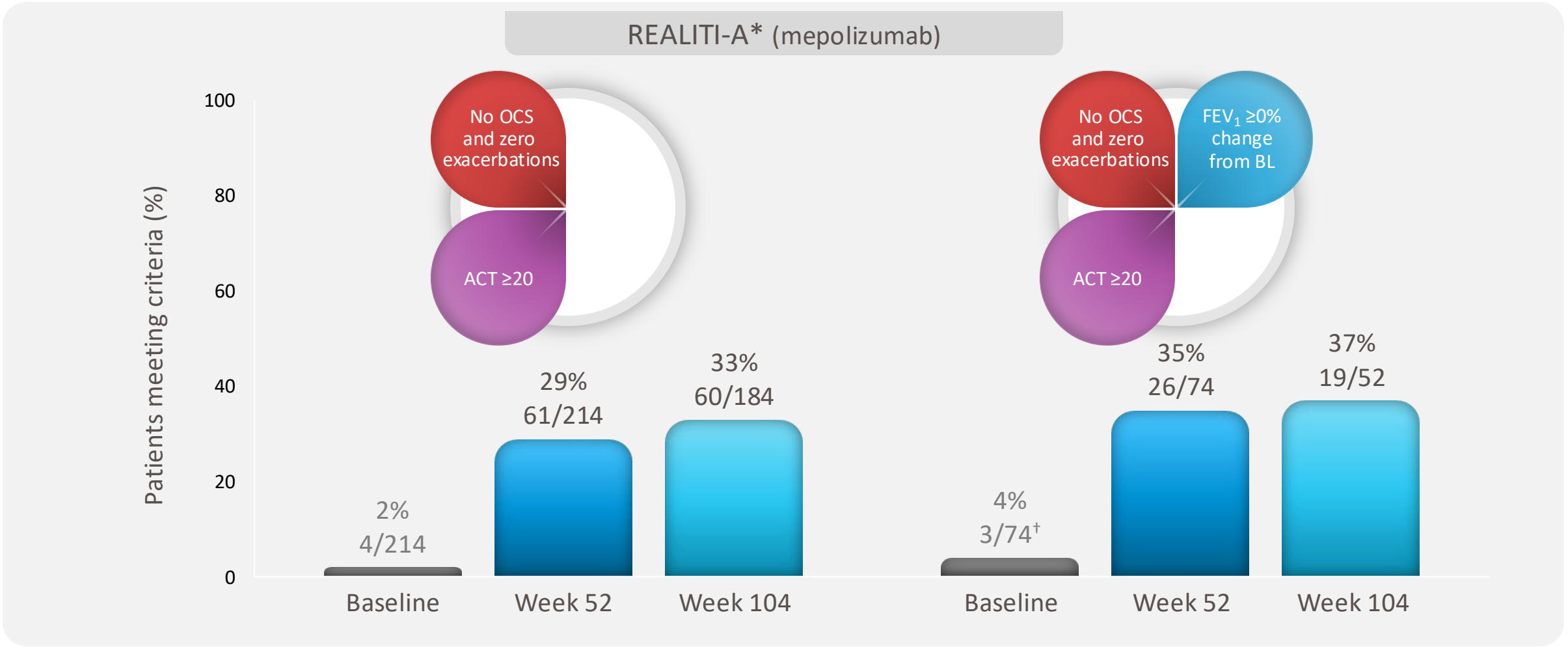
RWE: Patients Achieved Clinical Remission on Mepolizumab Over Two Years



*Post hoc analysis of the real-world REALITI-A study in asthma patients ≥18 yeas of age who were newly prescribed mepolizumab with a 24-month follow-up period. †Out of the total population, 74 patients had both ACQ-5 and FEV_1 change from baseline measurements.

ACT, Asthma Control Test; BD, bronchodilator; BL, baseline; FEV_1, forced expiratory volume in 1 second; OCS, oral corticosteroid; RWE: real-world evidence.

Brusselle G, et al. Poster presented at the American Thoracic Society International Conference; May 19-24, 2023; Washington, DC. Poster 203.

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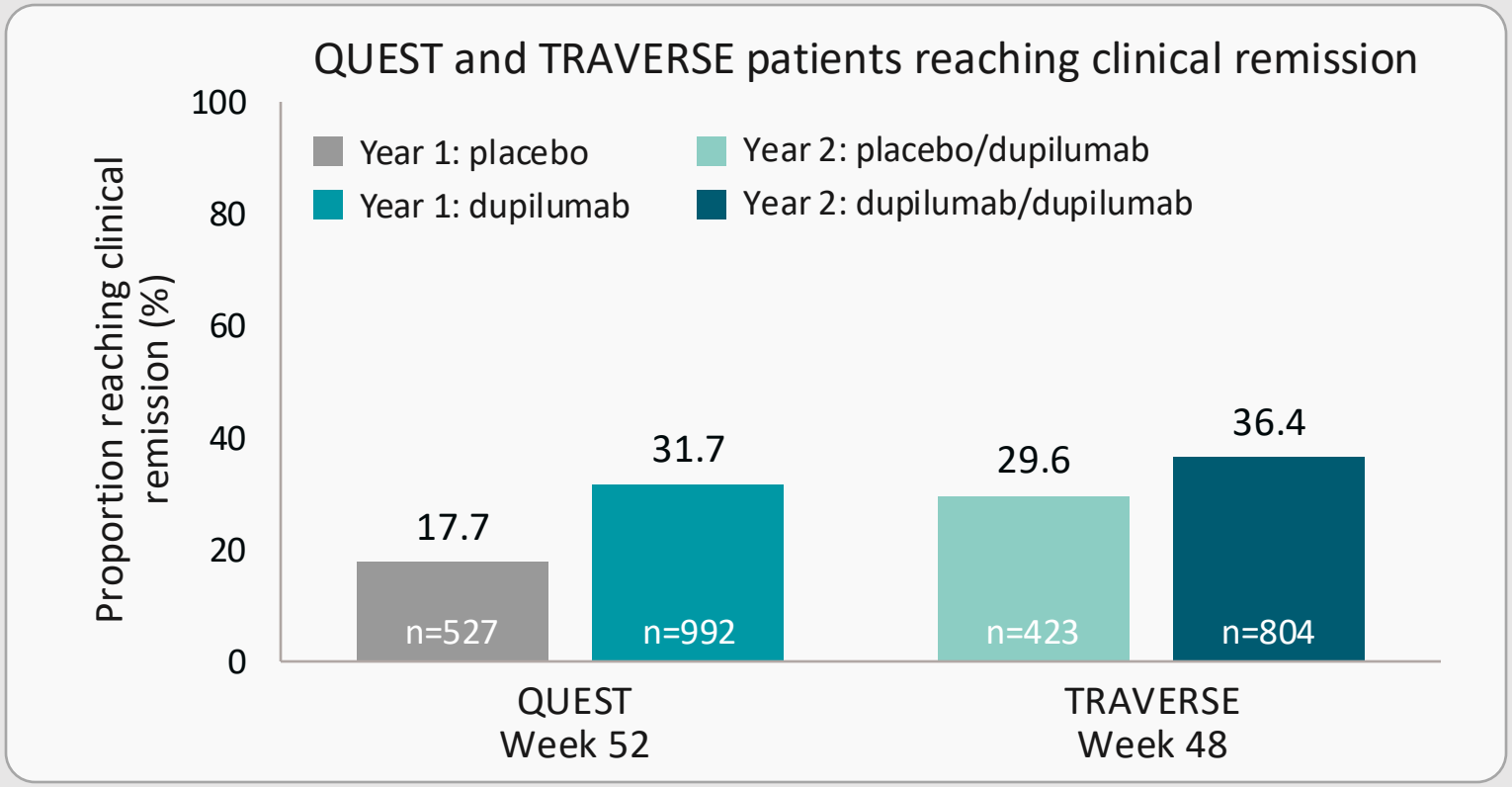
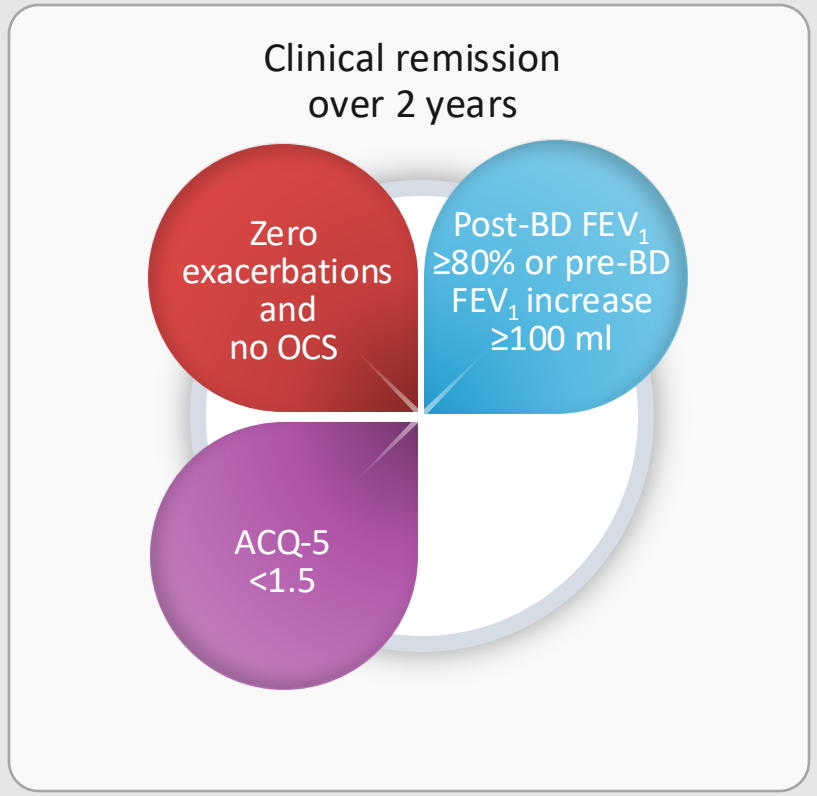
Dupilumab Led to Clinical Remission Over 2 Years*





*Clinical remission was defined as patients having no exacerbations and no OCS use, ACQ-5 <1.5, and either percent predicted post-BD FEV_1 ≥80% or improvement over PSBL in pre-BD FEV_1 ≥100 ml.

ACQ-5, 5-Item Asthma Control Questionnaire; FEV_1, forced expiratory volume in 1 second; OCS, oral corticosteroids; post-BD, post-bronchodilator; PSBL, parent study baseline.

Pavord ID, et al. Poster presented at the American Thoracic Society International Conference; May 19-24, 2023; Washington, DC.

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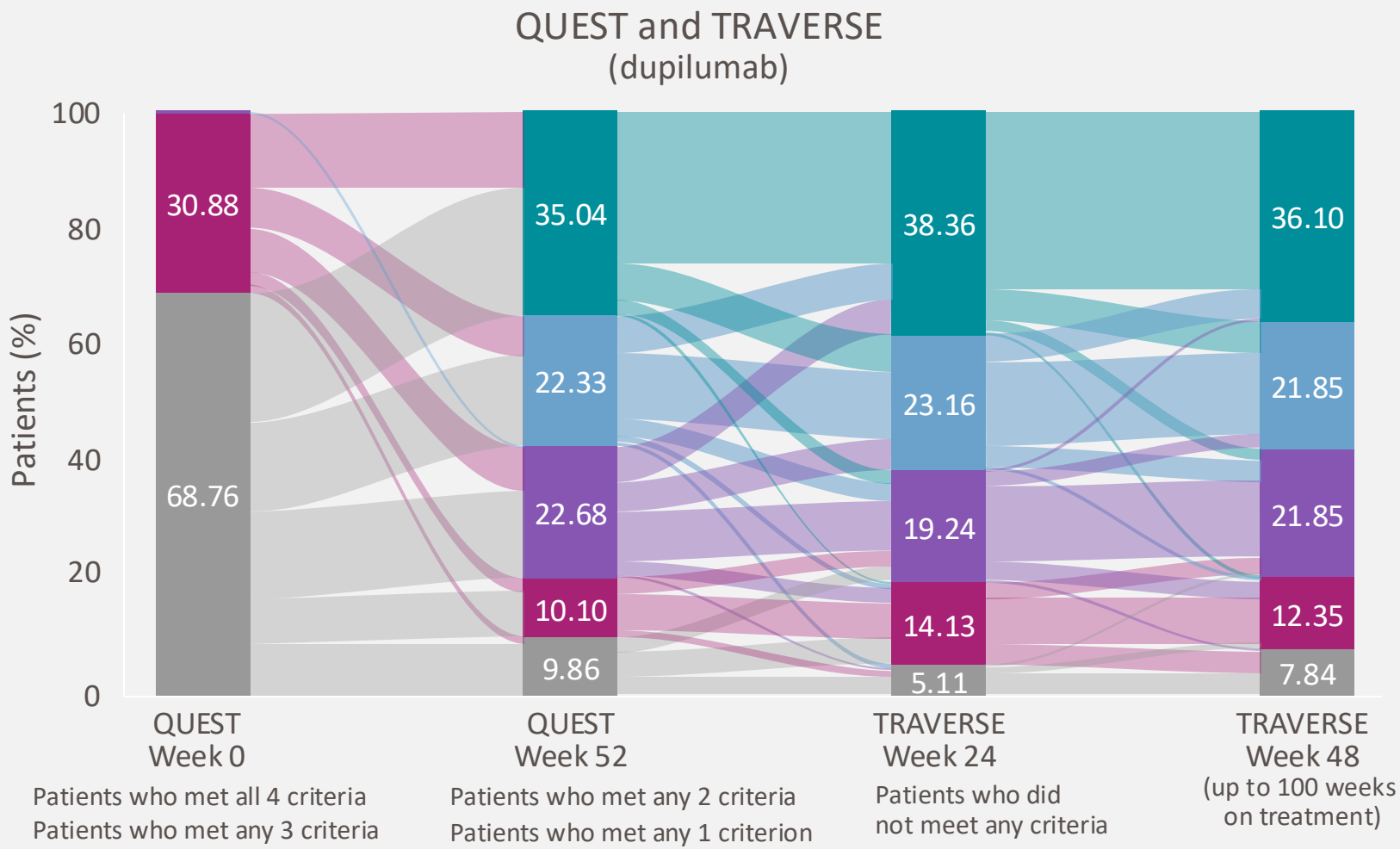
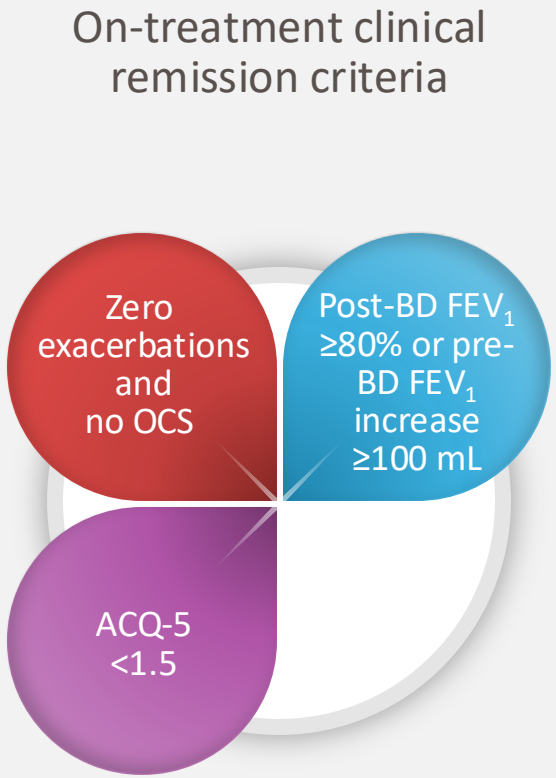
Many Dupilumab Patients Maintained On-Treatment Clinical Remission Over 2 Years*





Of the 35% of patients who achieved remission at QUEST Week 52, 70% maintained remission through TRAVERSE Week 48

*Clinical remission was defined as patients having no exacerbations and no OCS use, ACQ-5 <1.5, and either percent predicted post-BD FEV_1 ≥80% or improvement over PSBL in pre-BD FEV_1 ≥100 mL.
ACQ-5, 5-Item Asthma Control Questionnaire; FEV_1, forced expiratory volume in 1 second; OCS, oral corticosteroids; post-BD, post-bronchodilator; PSBL, parent study baseline.
Pavord ID, et al. Poster presented at the American Thoracic Society International Conference; May 19-24, 2023; Washington, DC.

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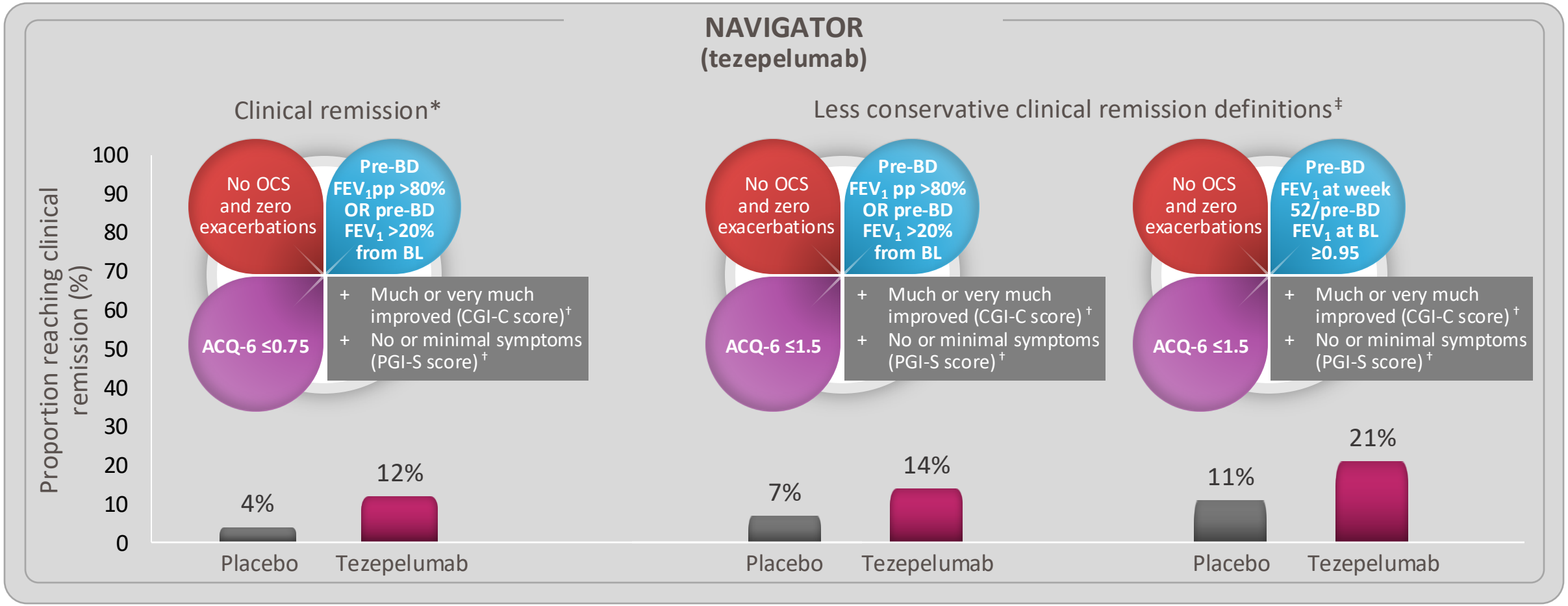
Tezepelumab Patients Achieved On-Treatment Clinical Remission by Week 52*



*Clinical remission at Week 52 was defined as improvement from baseline in ACQ-6 score to ≤0.75, improvement from baseline in pre-BD FEV_1 of >20% or pre-BD FEV_1 value of >80%, no use of OCS, no exacerbations, improvement based on physician's assessment (CGI-C score), and no or minimal symptoms based on patient's assessment (PGI-S score). †CGI-C and PGI-S scores not validated to define patient/HCP agreement. ‡Sensitivity analysis.

ACQ-6, 6-item Asthma Control Questionnaire; BD, bronchodilator; BL, baseline; CGI-C, Clinical Global Impression of Change; FEV_1, forced expiratory volume in 1 second; FEV_1pp, FEV_1 percent predicted; HCP, healthcare provider; OCS, oral corticosteroids; PGI-S, Patient Global Impression of Severity.

Castro M, et al. Poster presented at the European Respiratory Society International Congress (hybrid); September 4-6, 2022; Barcelona, Spain.

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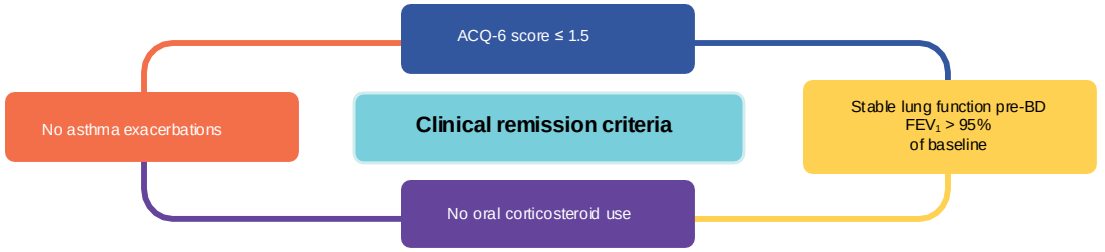
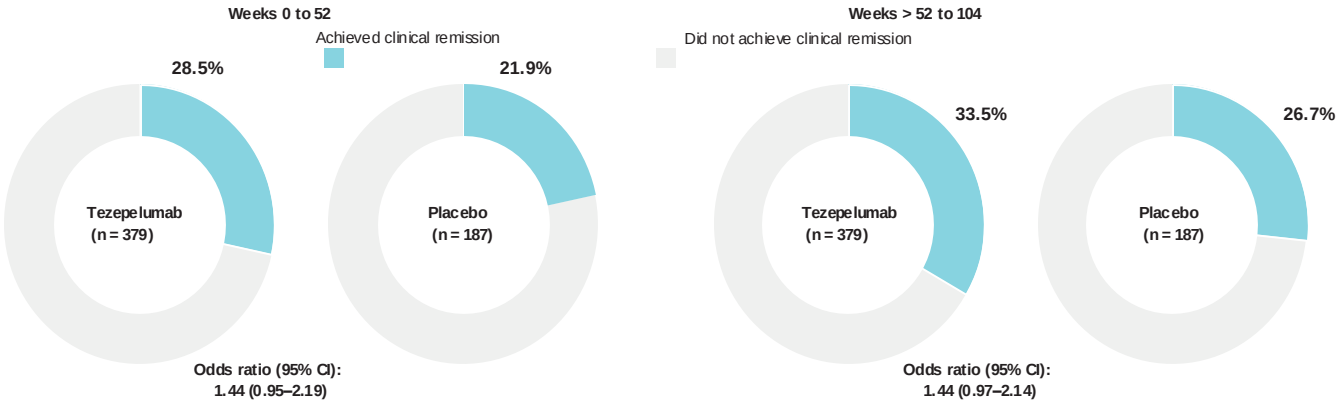
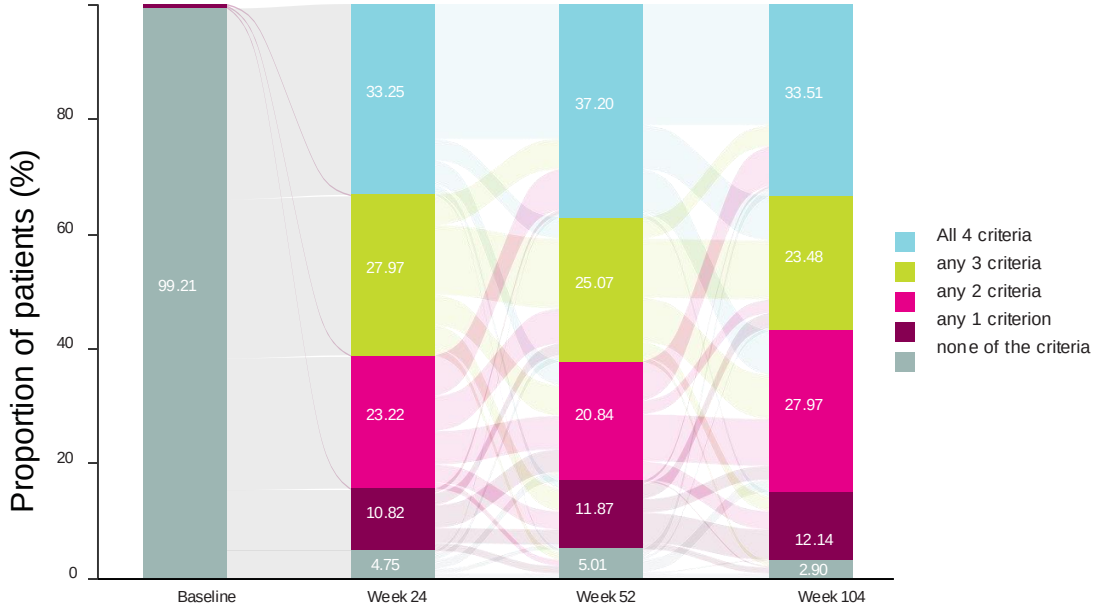
On-treatment clinical remission with tezepelumab in patients with severe, uncontrolled asthma in the phase 3 DESTINATION study







In this analysis, for patients who completed treatment with data missing at week 104, the next available off-treatment measurement was input at week 104.
Blue shading indicates the proportion of patients at weeks 24, 52 and 104 who met all four remission criteria since the previous period (i.e. with on-treatment clinical remission). At baseline, the purple shading represents patients who met both the study inclusion criterion and the remission criterion for ACQ-6 score (i.e. 1.5).
At week 52, remission was assessed from week 24 to week 52. At week 104, remission was assessed from week 52 to week 104.

Wechsler ME et al. European Respiratory Journal 2023 62: PA4722; DOI: 10.1183/13993003.congress-2023.PA4722

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Systematic Review and Meta-analysis

- 25 studies included after 1812 screened
- 8- 3 component definition, 38%
- 25 four component 30%

- Results impacted by worse Fev1 and sx, longer asthma duration and use of maintenance OCS
- Co-morbidities: depression and obesity

Shackleford A, Heaney L, et al. Online Nov 13, 2024. Lancet 2024. https://doi.org/10.1016/ S2213-2600(24)00293-5

Reduction of daily maintenance inhaled corticosteroids in patients with severe eosinophilic asthma treated with benralizumab (SHAMAL): a randomised, multicentre, open-label, phase 4 study

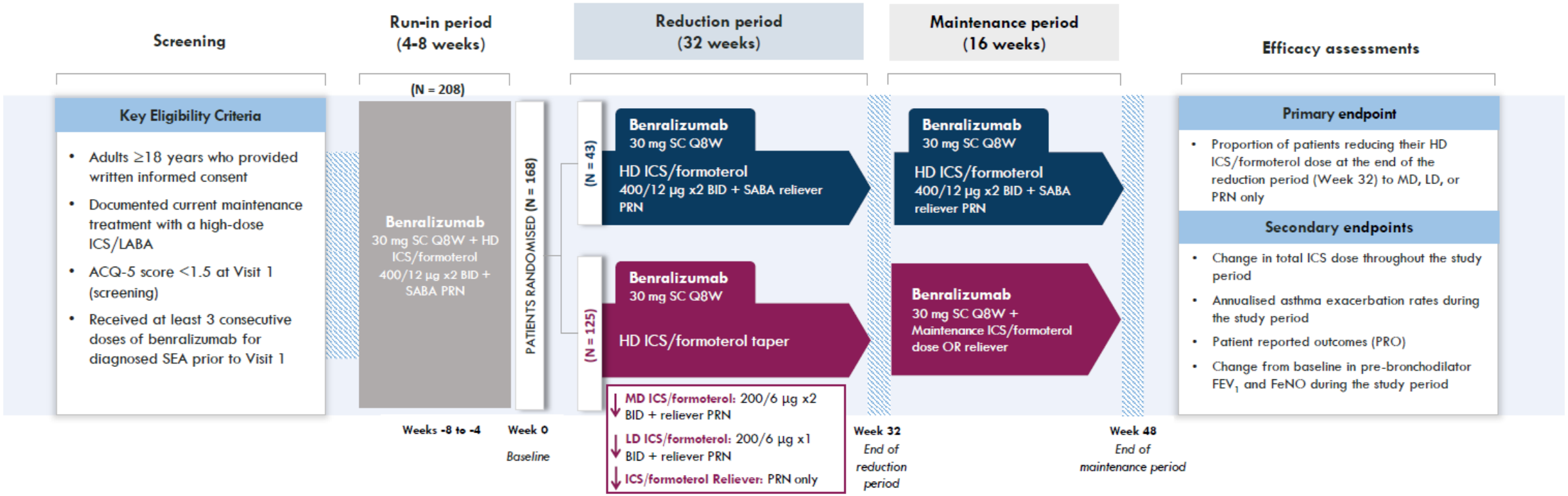
*David J Jackson, Liam G Heaney, Marc Humbert, Brian D Kent, Anat Shavit, Lina Hiljemark, Lynda Olinger, David Cohen, Andrew Menzies-Gow, Stephanie Korn, on behalf of the SHAMAL Investigators**

THE LANCET

Jackson DJ, et al. *Lancet* 2023

SHAMAL: Reduction of ICS dose on benralizumab

SHAMAL (NCT04159519) was a randomised, open-label, parallel-group, active-controlled, multicentre, phase 4 study in adults with SEA.



Note: Patients were randomly assigned to either the reduction or the reference arm in a 3:1 ratio.

ACQ-5, 5-Item Asthma Control Questionnaire; BID, twice daily; FEV_1, forced expiratory volume in 1 second; FeNO, fractional exhaled nitric oxide; HD, high-dose; ICS/LABA, inhaled corticosteroid/long-acting β_2 agonist; LD, low-dose; MD, medium-dose; PRN, as needed; PRO, patient reported outcomes; Q8W, every 8 weeks; SABA, short-acting β_2 agonist; SC, subcutaneous; SEA, severe eosinophilic asthma.

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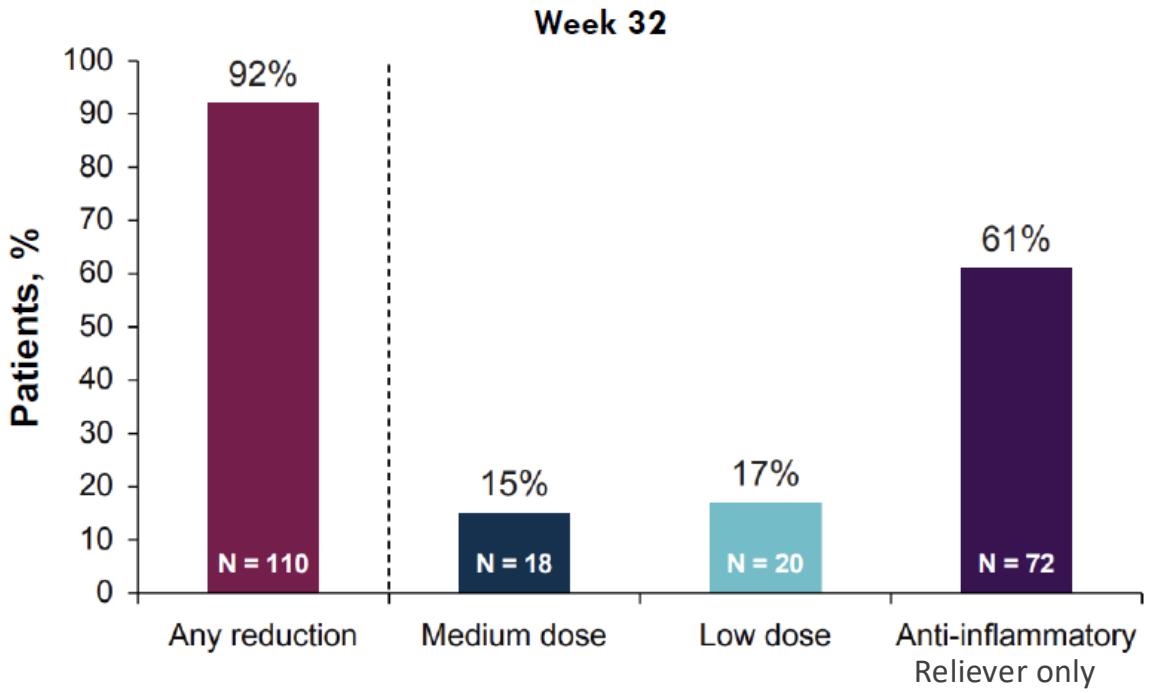
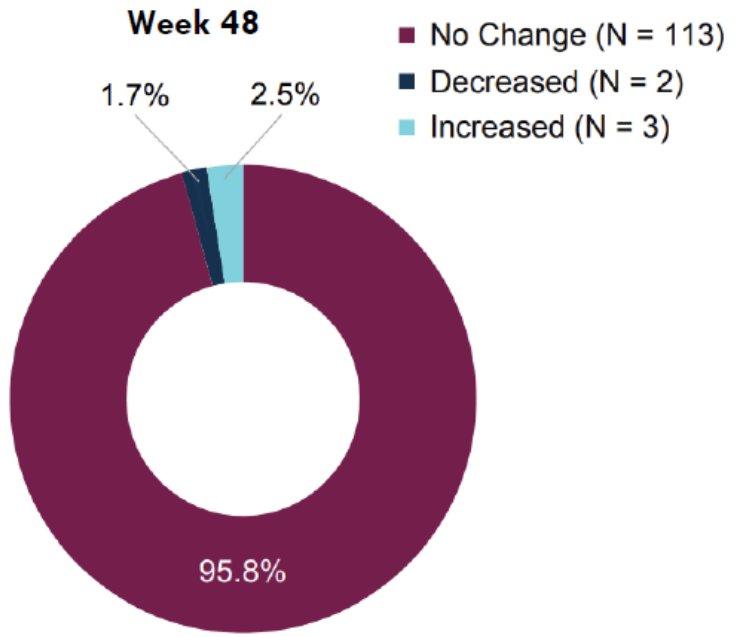
Primary endpoint:
Reduction of HD ICS/formoterol dose by week 32

Overall, 92% of patients well-controlled on benralizumab were able to reduce their ICS/formoterol dose by Week 32: 15% to a medium-dose, 17% to a low-dose, and 61% to a reliever as needed. Most patients (≈96%) maintained their reduced ICS/formoterol dose through week 48[a].





[a]Secondary endpoint.
ICS, inhaled corticosteroid.

- Jackson DJ, et al. *Lancet* 2023

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What Can Be Achieved With Biologics?

	Dupilumab	Dupilumab	Benralizumab	Benralizumab	Tezepelumab	Mepolizumab	Multiple Biologics	
	2021[1] QUEST Phase 3	2022[2] TRAVERSE OLE	2022[3] SIROCCO/CALIMA Phase 3	2022[4] ANDHI Phase 3b	2022[5] NAVIGATOR Phase 3	2022[6] REDES	2022[7] CHRONICLE	2022[8] Danish Registry
 Absence of symptoms[a,b] and	ACQ-5 <1.5	ACQ-5 <1.5	ACQ-6 <1.5 or ≤0.75	ACQ-6 <1.5 or ≤0.75	ACQ-6 ≤0.75[a,b]	ACT ≥ 20	Majority≥ (50%) ACT ≥ 20	ACQ ≤ 1.5
 Optimized/ stabilized lung function and	Post-BD FEV_1pp ≥80%	Post-BD FEV_1 ≥80% *OR* pre-BD FEV_1 ≥100 mL	Pre-BD FEV_1 increase ≥100 mL	Pre-BD FEV_1 increase ≥100 mL	Pre-BD FEV_1pp >80% *OR* Pre-BD FEV_1 >20% from baseline	Not included	Not included	Post-BD FEV_1pp ≥80%
 No exacerbations; no OCS[c]	✓	✓	✓	✓	✓[d]	✓	✓	✓
 Prevalence of clinical remission	31.7%	36.4%	14.5%	28.7%	12.7%	37%	35%	19%

[a]Sustained absence of significant asthma symptoms based on validated instrument; [b]There should be agreement between the HCP and patient regarding symptom improvement and remission; [c]No OCS use for exacerbations *OR* long-term disease control; [d]In this analysis, exacerbations and OCS use were individually evaluated· ACQ:Asthma Control Questionnaire; ACT, Asthma Control Test; BD, bronchodilator; FEV_1, forced expiratory volume in 1 second; HCP, healthcare provider; OCS, oral corticosteroid; OLE, open-label extension; pp, percent predicted

1. Pavord ID, et al. Poster presented at ACAAI, November 4–8, 2021, New Orleans, LA, USA; 2. Pavord ID, et al. Poster presented at ASCIA, August 30–September 2, 2022, Melbourne, Australia; 3. Menzies-Gow A, et al. Adv Ther 2022;39:2065–2084; 4. Harrison T, et al. Presented at ATS International Conference, May 13–18, 2022, San Francisco, CA, USA. Poster 625; 5. Castro M, et al. Poster presented at ERS, September 4–6, 2022, Barcelona, Spain; 6. Ribas DC et al. Drugs 2021;81(15):1763-1774. 7. Chipps, B et al. JACI 2022;149:Suppl AB147 8. Hansen S et al ERJ 2022;60:3553

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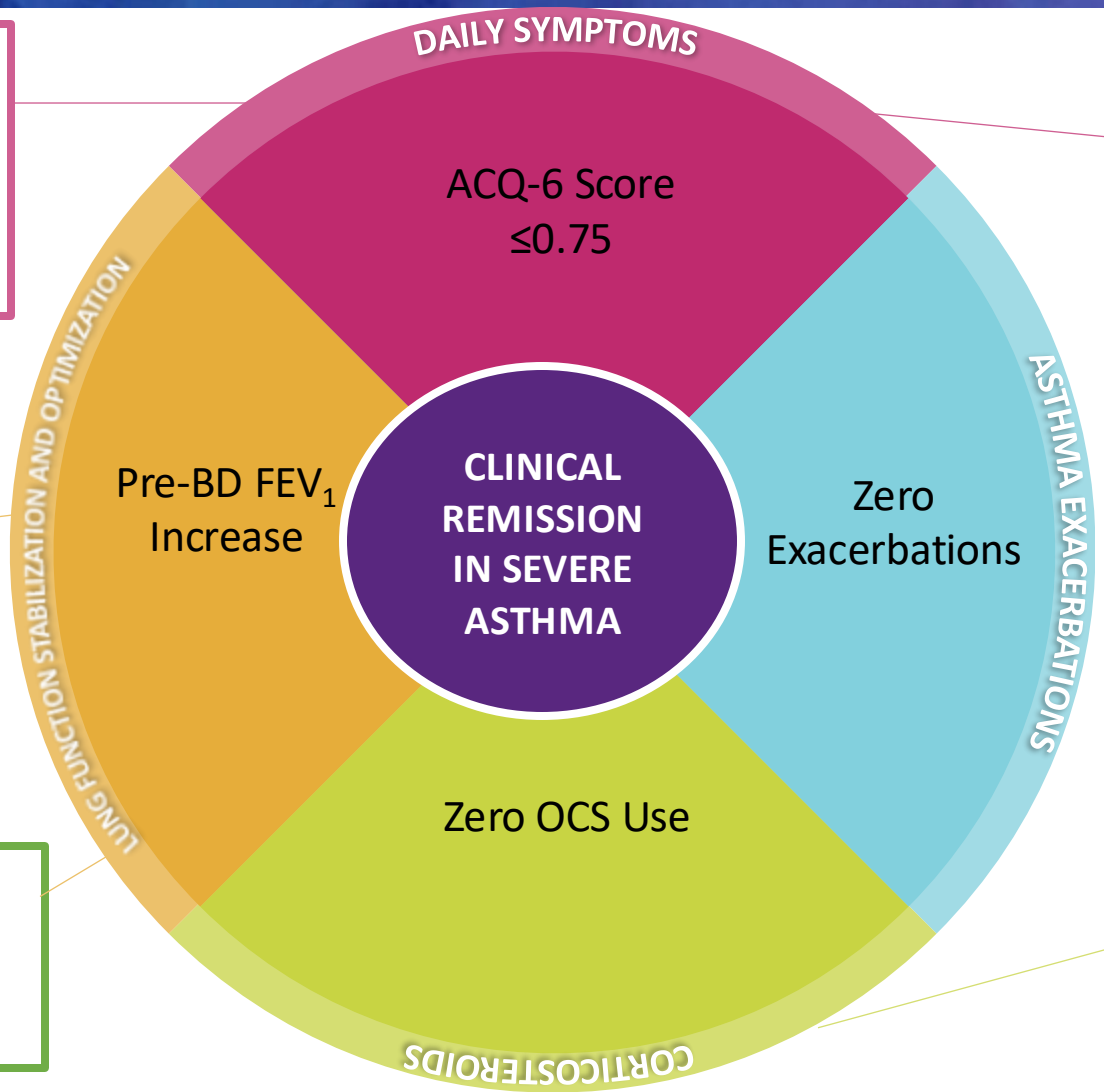
Limitations of Theoretical Framework

Many PRO tools other than ACQ-6 are available to measure improvements in symptom control

Type of Lung Function measurements captured in randomized trials differed

Consensus definition of FEV_1 improvement has not been established



Cutoffs in severe asthma daily symptoms are not established

Zero OCS use may not be feasible for patients who use OCS for reasons other than asthma

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

Menzies-Gow A, …Katial RK. *Adv Ther*. 2022;39(5):2065-2084.

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Unmet Needs & Next Steps for Clinical Remission in Severe Asthma

	Additional studies are necessary to understand how achieving clinical remission criteria correlates clinically to underlying disease pathology or progression
	An expert consensus is necessary to address the question of whether time/duration of disease remission should be a factor in the definition of asthma remission
	An **expert group** of primary and secondary care **physicians**, with **diverse clinical expertise** from across different regions, should **begin working** on **Clinical Guidelines** for **Remission**
	**Clinical Guidelines** should be **developed** according to the **GRADE methodology**

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Why Asthma Remission is Within Reach

	Rates of response to various individual remission criteria reflect the heterogeneous clinical presentation of severe asthma
	There are limitations of the theoretical framework definition published to date, but it informs a data-driven evolution of the definition of clinical remission in severe asthma
	Future studies should apply remission definitions to patients in RWE settings in longer time frames for evaluation and in patient populations from other completed clinical trials
	Precision medicine represents a promising way to strive for clinical remission as the ultimate goal for patients with severe asthma which may inform future guideline-directed care and improve asthma-related health outcomes in patients with severe asthma

ACQ-6: Asthma Control Questionnaire, 6-item; OCS: oral corticosteroids; RWE: real-world evidence.

Menzies-Gow A, …Katial RK. *Adv Ther*. 2022;39(5):2065-2084

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