The role of eosinophils in physiology and disease: Is complete depletion of eosinophils the goal?

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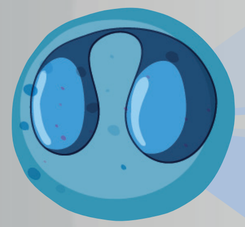
The role of eosinophils in homeostasis and disease

Physiologic roles of eosinophils



Eosinophil

Immune response

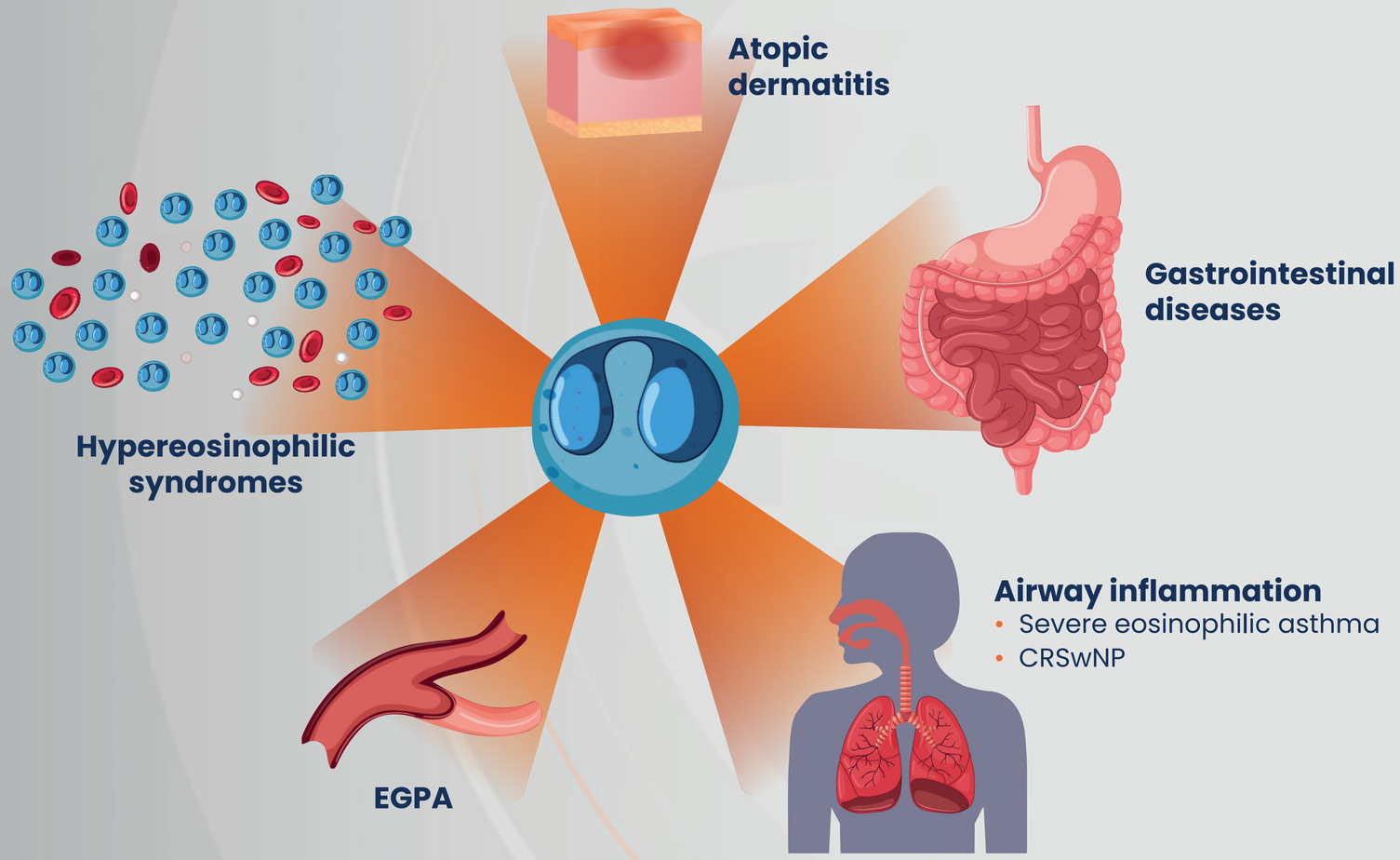
- Production of cytotoxic mediators (MBP, EPO, ECP, EDN)
- Production of pro-inflammatory cytokines and chemokines
- Host defence against parasitic, viral, fungal and bacterial infections

Tissue homeostasis

- Metabolic homeostasis
- Wound healing
- Epithelial remodelling in the respiratory tract
- Homeostasis in the intestinal environment and microbiota

ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; EPO, eosinophil peroxidase; MBP, major basic protein.
Kanda A, et al. *Allergol Int.* 2021;70:9–18.

Pathogenic roles of eosinophils



CRSwNP, chronic rhinosinusitis with nasal polyposis; EGPA, eosinophilic granulomatosis with polyangiitis.
Kanda A, et al. *Allergol Int.* 2021;70:9–18.

The biology of eosinophils and IL-5

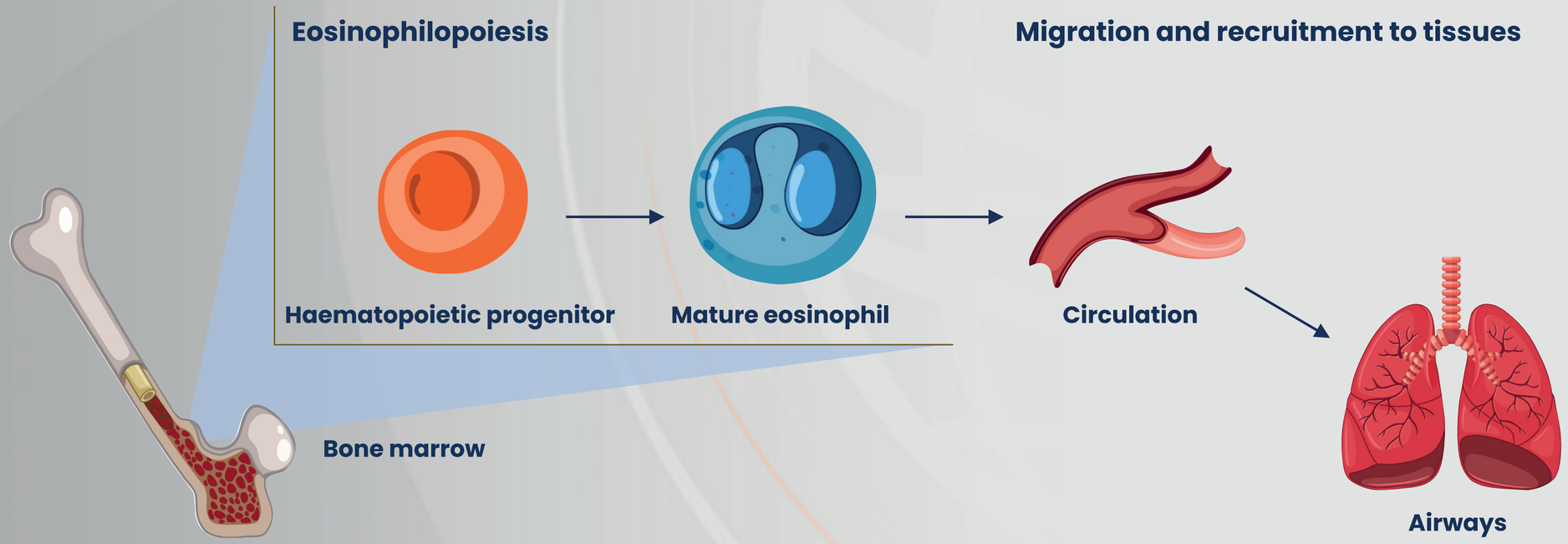
Part 1 of 2

IL-5

- Promotes eosinophil differentiation and maturation from haematopoietic progenitor cells

IL-5

- Synergizes with eotaxins, contributing to eosinophil recruitment to the airways
- Induces eosinophil adhesion to and migration in the extracellular matrix which allows trafficking toward the bronchi



IL, interleukin.
Pelaia C, et al. *Front Physiol.* 2019;10:1514.

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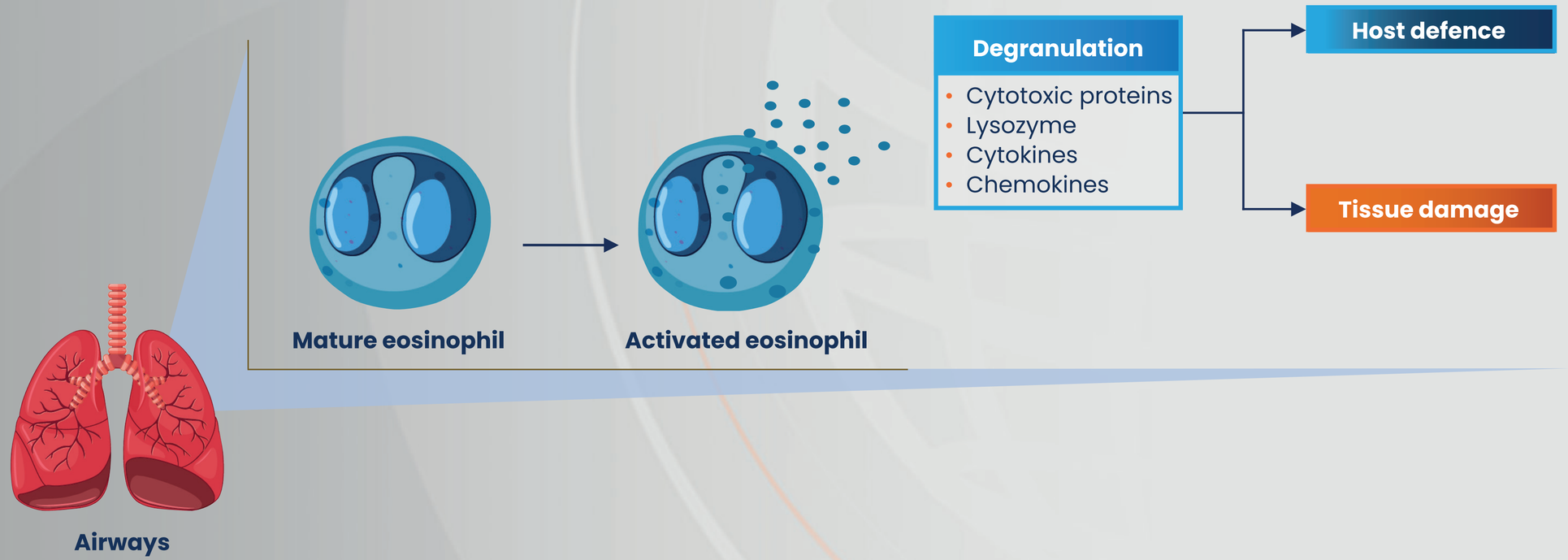
The biology of eosinophils and IL-5

Part 2 of 2

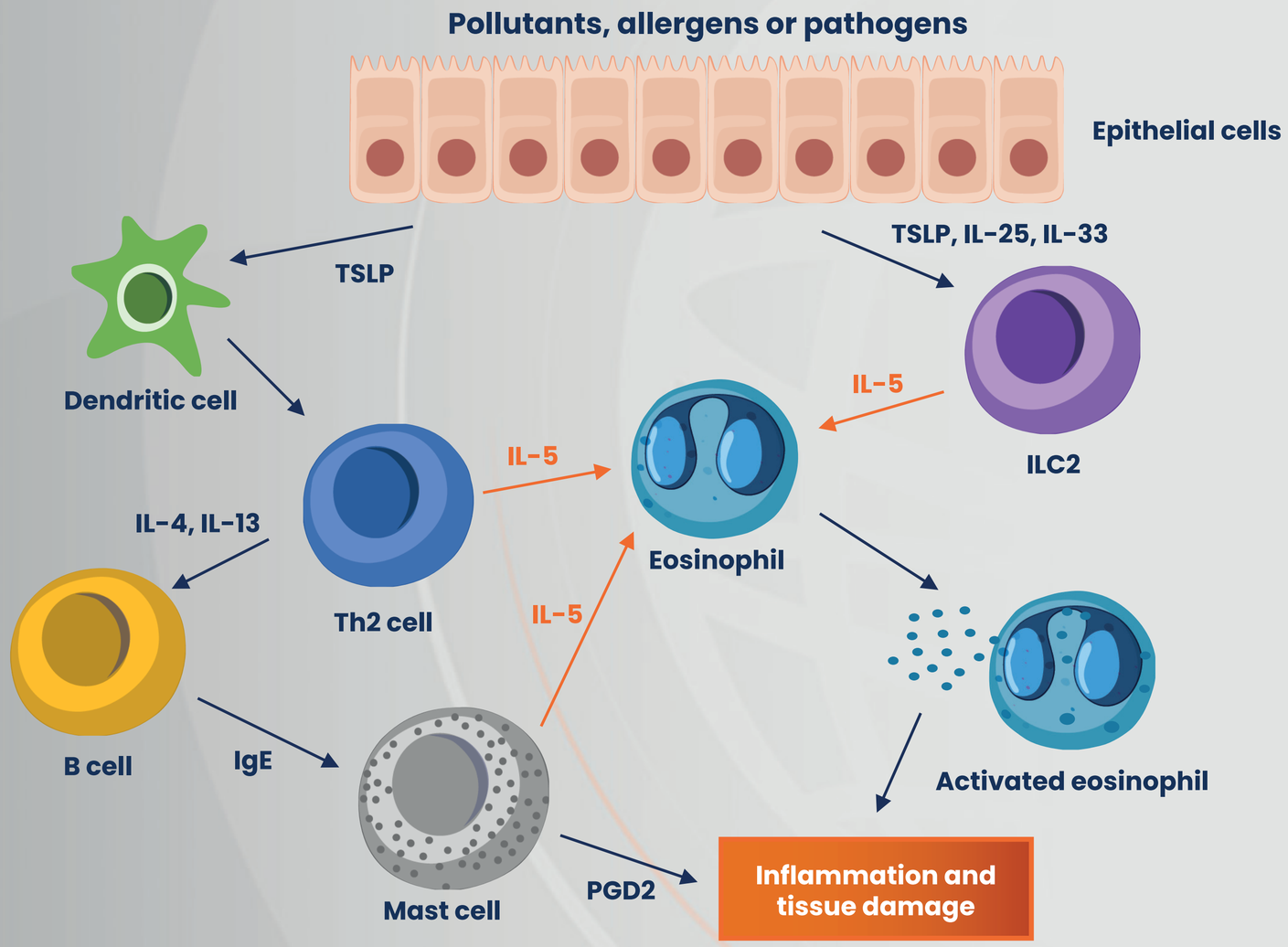
IL-5

- Contributes to eosinophil functional activation
- Inhibits eosinophil apoptosis



IL, interleukin.
Pelaia C, et al. *Front Physiol.* 2019;10:1514.

Physiologic roles of eosinophils



IgE, immunoglobulin E; ILC2, group 2 innate lymphoid cells; PGD2, prostaglandin D2; Th2, T helper 2; TSLP, thymic stromal lymphopoietin.
Pelaia C, et al. *Front Immunol.* 2020;11:603312.

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Eosinophils in homeostasis and disease

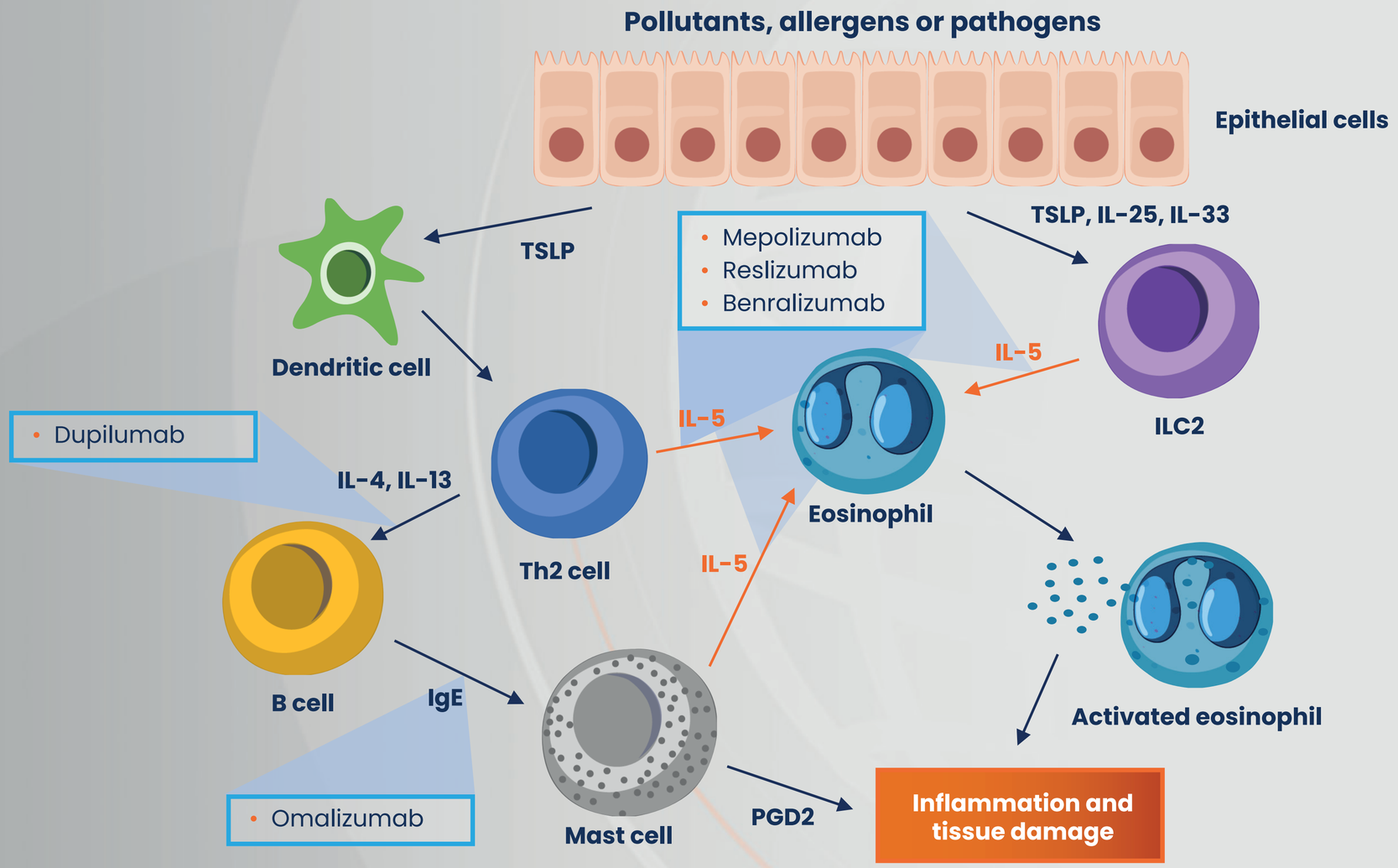
Eosinophils play a central role in physiologic immune response and tissue homeostasis

Excessive or dysregulated eosinophil activation drives the pathogenesis of inflammatory diseases in different tissues and organs, including type 2 asthma

IL-5 is the key cytokine that supports all stages of the life cycle of eosinophils, from eosinophilopoiesis, to migration to tissues and activation

Immunobiology of eosinophilic therapy

Approved biologic agents and molecular targets



IgE, immunoglobulin E; IL, interleukin; ILC2, group 2 innate lymphoid cells; PGD2, prostaglandin D2; Th2, T helper 2; TSLP, thymic stromal lymphopoietin.
Pelaia C, et al. *Front Immunol.* 2020;11:603312.

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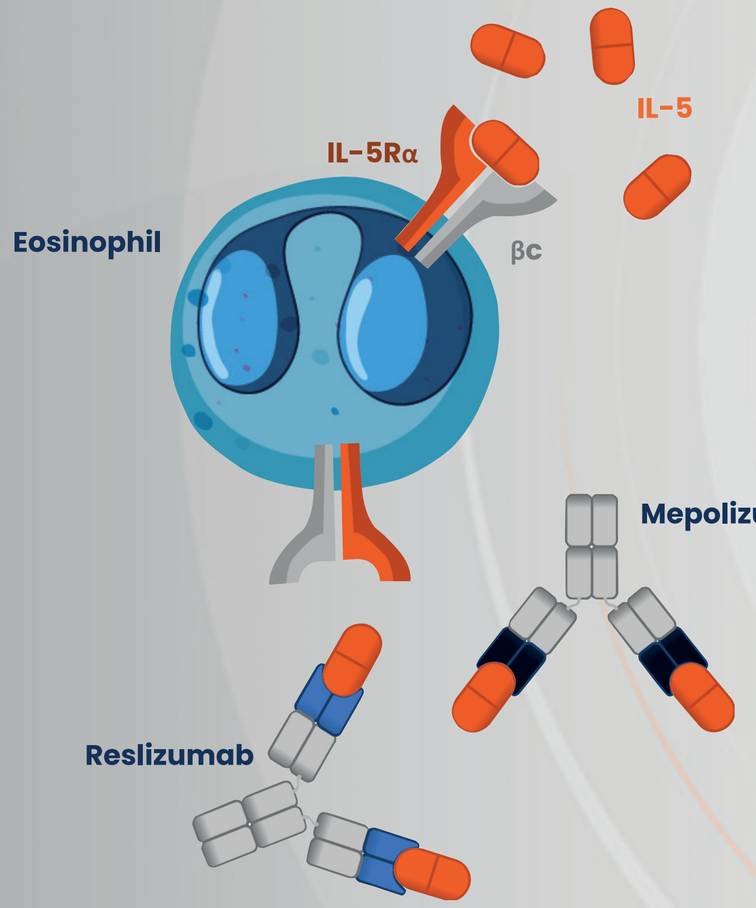
Mepolizumab and reslizumab

Anti-IL-5 monoclonal antibodies



Eosinophil maturation, activation, migration and survival

IL-5 inhibition

- Reduced eosinophilopoiesis
- Reduced migration to tissues
- Inhibition of eosinophil activation
- Reduced survival/increased apoptosis

βc, common beta chain; IL-5Rβ, interleukin-5 receptor beta.
Pelaia C, et al. *Front Immunol.* 2020;11:603312.

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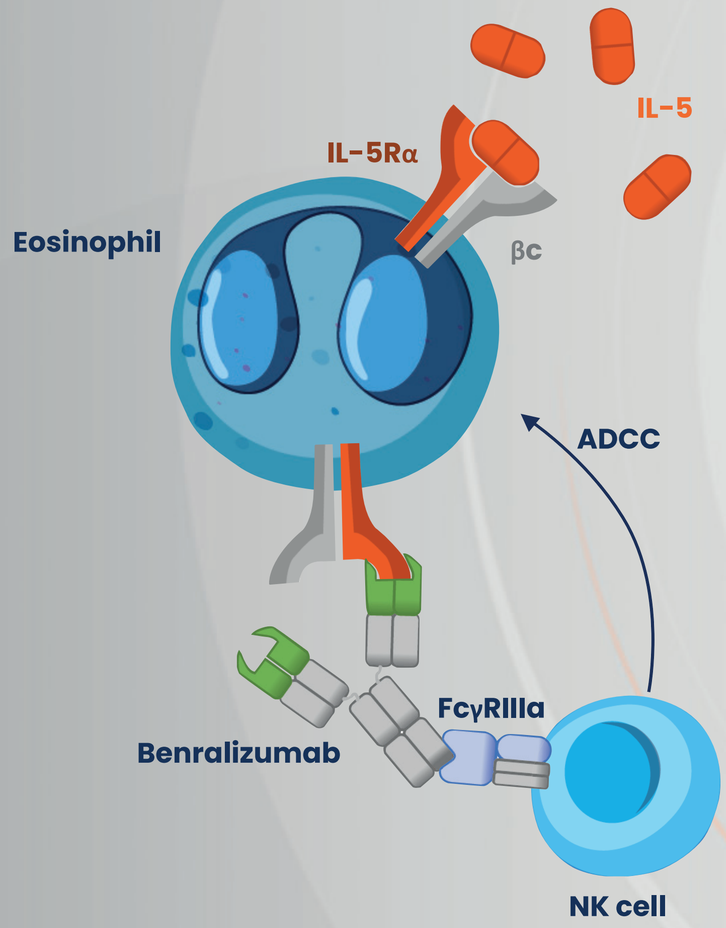
Benralizumab

Anti-IL-5Rα monoclonal antibody



Eosinophil maturation, activation, migration and survival

ADCC

- Induction of apoptosis
- Eosinophil depletion

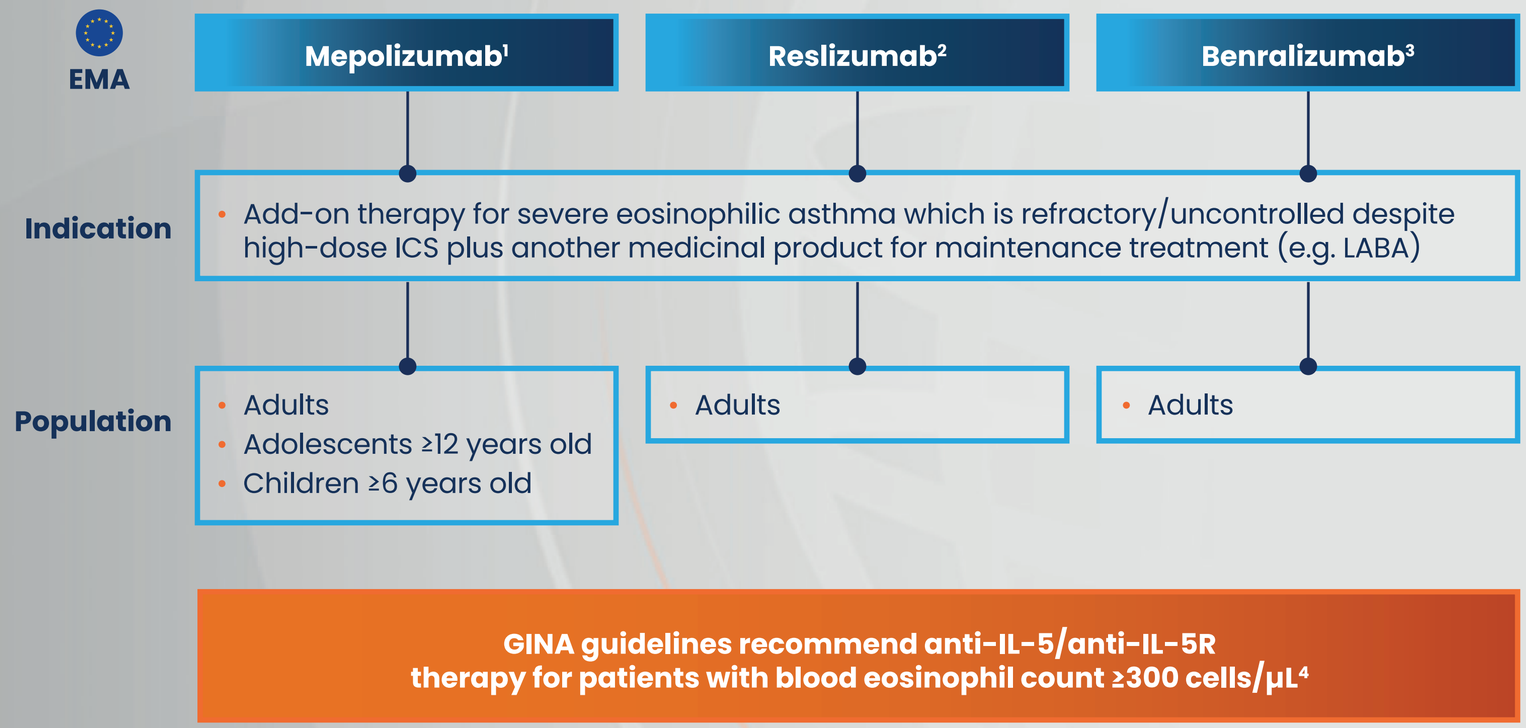
IL-5 inhibition

- Reduced eosinophilopoiesis
- Reduced migration to tissues
- Inhibition of eosinophil activation
- Reduced survival/increased apoptosis

ADCC, antibody-dependent cell-mediated cytotoxicity; FcγRIIIa, fragment crystallizable region gamma receptor IIIa; NK, natural killer.
Pelaia C, et al. *Front Immunol.* 2020;11:603312.

Mepolizumab, reslizumab and benralizumab

EMA approval and recommended use for asthma



EMA, European Medicines Agency; GINA, Global Initiative for Asthma; ICS, intranasal corticosteroids; LABA, long-acting beta-agonists; SPC, summary of product characteristics.

1. EMA. Mepolizumab SPC, 2019. Available at: www.ema.europa.eu/en/documents/product-information/nucala-epar-product-information_en.pdf (accessed 8 February 2021);
2. EMA. Reslizumab SPC, 2019. Available at: www.ema.europa.eu/en/documents/product-information/cinqaero-epar-product-information_en.pdf (accessed 8 February 2021);
3. EMA. Benralizumab SPC, 2020. Available at: www.ema.europa.eu/en/documents/product-information/fasenra-epar-product-information_en.pdf (accessed 8 February 2021);
4. GINA report, 2020. Available at www.ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04-1-wms.pdf (accessed 11 February 2021).

Mepolizumab

Indications for eosinophilic inflammatory diseases other than asthma

Hyper eosinophilic syndrome	
EMA	• Orphan drug designation[1]
FDA	• Approved indication[2]

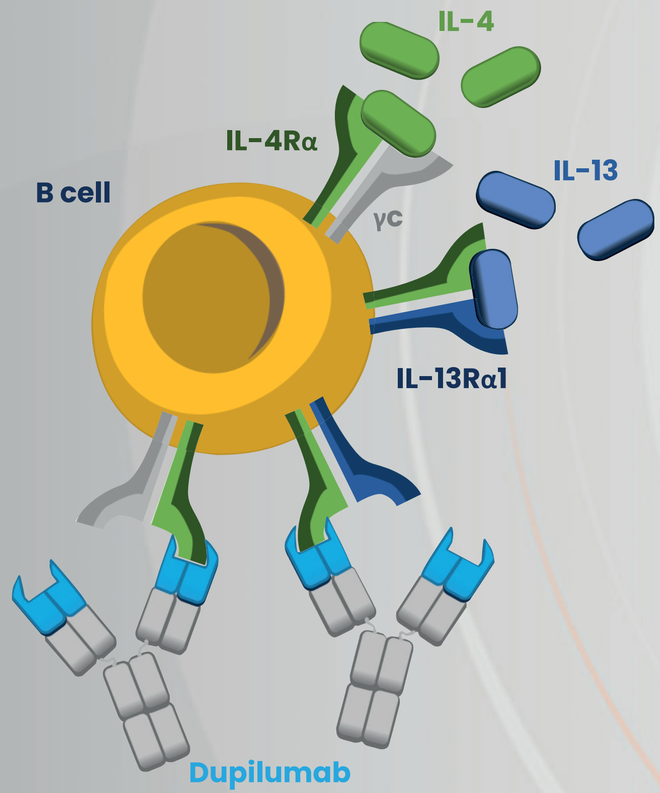
EGPA (Churg Strauss syndrome)	
EMA	• Orphan drug designation[1]
FDA	• Approved indication[2]

EGPA, eosinophilic granulomatosis with polyangiitis; FDA, US Food and Drug Administration; PI, prescribing information.

1. EMA. Mepolizumab, public summary of opinion on orphan designation for hyper eosinophilic syndrome, 2020. Available at: www.ema.europa.eu/en/documents/orphan-designation/eu/3/04/213-public-summary-positive-opinion-orphan-designation-mepolizumab-treatment-hypereosinophilic_en.pdf (accessed 8 February 2021); 2. FDA. Mepolizumab PI, 2020. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/761122s005lbl.pdf (accessed 8 February 2021); 3. EMA. Mepolizumab, public summary of opinion on orphan designation for Churg Strauss syndrome, 2020. Available at: www.ema.europa.eu/en/documents/orphan-designation/eu/3/13/1116-public-summary-opinion-orphan-designationmepolizumab-treatment-churg-strauss-syndrome_en.pdf (accessed 8 February 2021).

Dupilumab

Anti-IL-4Rα monoclonal antibody



IgE class switching and eosinophil chemotaxis

IL-4 and IL-13 signalling inhibition

- Inhibition of IgE class switching
- Prevention of mast cell activation
- Reduced eosinophil chemotaxis

γc, common gamma chain; IL-13Rα1, interleukin-13 receptor alpha 1; IL-4Rα, interleukin-4 receptor alpha.
Pelaia C, et al. *Front Immunol.* 2020;11:603312.

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Dupilumab

EMA approved indications and recommended use for asthma

EMA

Severe asthma (add-on maintenance)[1]

- Adults
- Adolescents ≥12 years old

GINA guidelines recommend anti-IL-4R therapy for patients with FeNO ≥25 ppb or blood eosinophils count ≥150 cells/µL[2]

Atopic dermatitis[1]

- Adults
- Adolescents ≥12 years old
- Children ≥6 years old

Severe CRSwNP (add-on with ICS)[1]

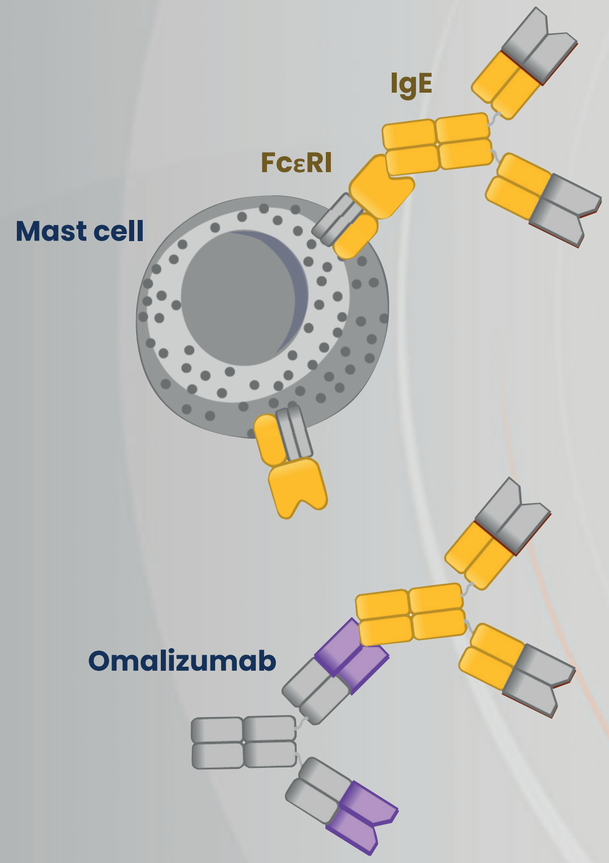
- Adults not responding to ICS or surgery

CRSwNP, chronic rhinosinusitis with nasal polyposis; FeNO, fractional exhaled nitric oxide; ppb, parts per billion.

1. EMA. Dupilumab SPC, 2021. Available at: www.ema.europa.eu/en/documents/product-information/dupixent-epar-product-information_en.pdf (accessed 11 February 2021);
2. GINA report, 2020. Available at www.ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04-1-wms.pdf (accessed 11 February 2021).

Omalizumab

Anti-IgE monoclonal antibody



IgE-mediated allergic inflammatory response

Inhibition of IgE signalling

- Reduced release of proinflammatory mediators
- Reduced inflammatory response

FcεRI, fragment crystallizable region epsilon receptor I.

Pelaia C, et al. *Front Immunol.* 2020;11:603312.

Omalizumab

EMA approved indications and recommended use for asthma

EMA

Allergic asthma[1]

- Adults
- Adolescents ≥12 years old
- Children ≥6 years old

GINA guidelines recommend anti-IgE therapy for patients with sensitization on skin prick test or specific IgE[2]

Chronic spontaneous urticaria (add-on)[1]

- Adults
- Adolescents ≥12 years old
- Not responding to H1-antihistamines

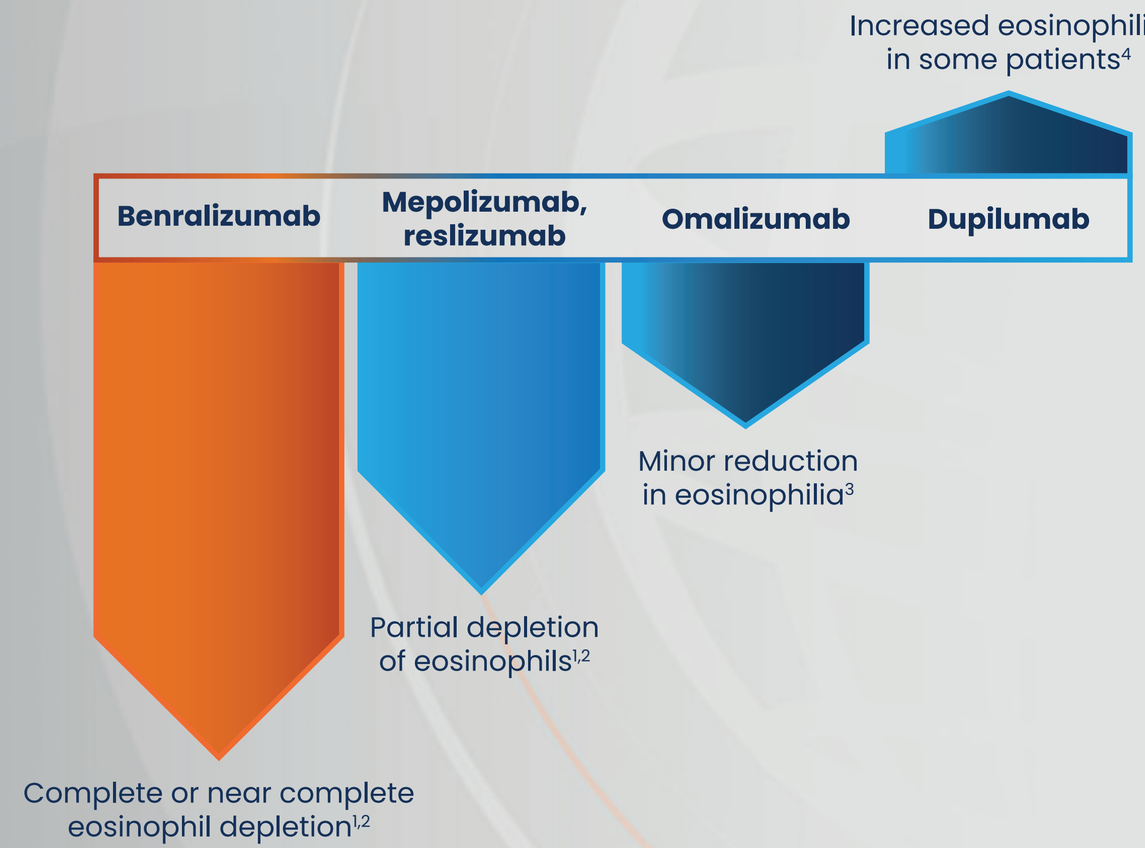
Severe CRSwNP (add-on with ICS)[1]

- Adults not responding to ICS

1. EMA. Omalizumab SPC, 2020. Available at: www.ema.europa.eu/en/documents/product-information/xolair-epar-product-information_en.pdf (accessed 11 February 2021); 2. GINA report, 2020. Available at www.ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04-1-wms.pdf (accessed 11 February 2021).

Complete vs partial eosinophil depletion

Effects of biologics on eosinophil count

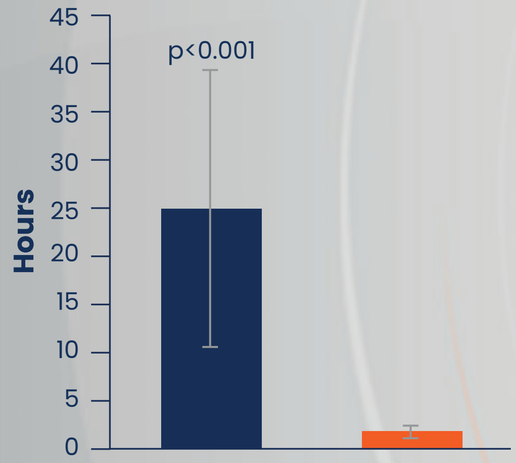


1. Moran AM, et al. *Am J Respir Crit Care Med.* 2020;202:1314–6; 2. Jackson DJ, et al. *Drug Saf.* 2020;43:409–25; 3. Hanania NA, et al. *J Allergy Clin Immunol.* 2019;143:AB95; 4. Castro M, et al. *N Engl J Med.* 2018;378:2486–96.

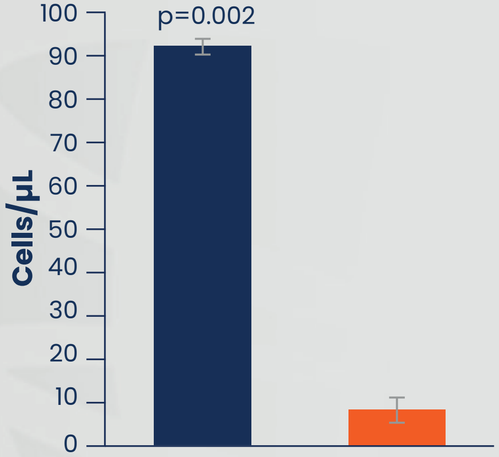
Complete vs partial eosinophil depletion

Data from a substudy of the Oxford Airways Study[1]

Mean time to 50% reduction in blood eosinophil count



Geometric mean eosinophil count 30 days after treatment



Mepolizumab Benralizumab

- Benralizumab causes rapid and near complete depletion of eosinophils compared with mepolizumab[1]
- Eosinophil depletion by benralizumab treatment does not increase risk of infections or malignancies[2]

1. Moran AM, et al. *Am J Respir Crit Care Med.* 2020;202:1314–6; 2. Jackson DJ, et al. *Drug Saf.* 2020;43:409–25.

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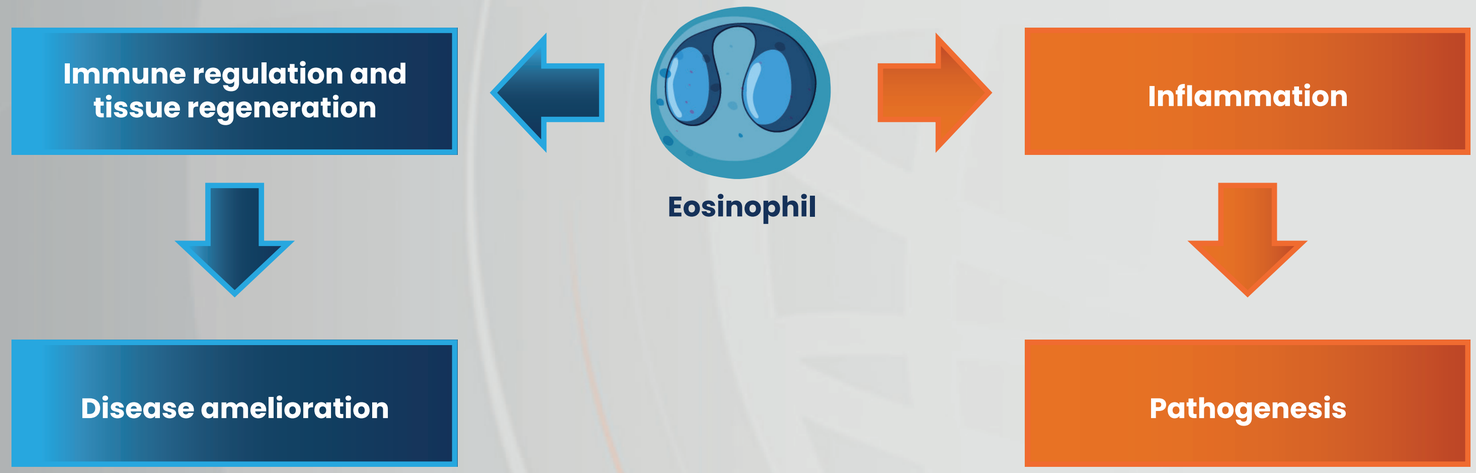
Complete vs partial eosinophil depletion

Distinct eosinophil subgroups exert different functions and may play different roles in inflammatory diseases



1. Simon HU, et al. *Int Arch Allergy Immunol.* 2020;181:11–23.

Eosinophilic therapy

Biologics which target IL-5 signalling or other mechanisms driving type 2 inflammation (IL-4/IL-13, IgE) are effective treatments for patients with moderate-to-severe asthma

Biomarkers such as IgE levels, FeNO and eosinophil count guide the choice of biologic to use and can inform on the chances of positive treatment outcome

It is still debated whether complete eosinophil depletion may be a desirable treatment outcome

Pipeline therapies for eosinophilic immunologic disease

Approved biologics in new disease settings: Mepolizumab

Ongoing phase III trials

Nasal polyps

- MERIT (NCT04607005)

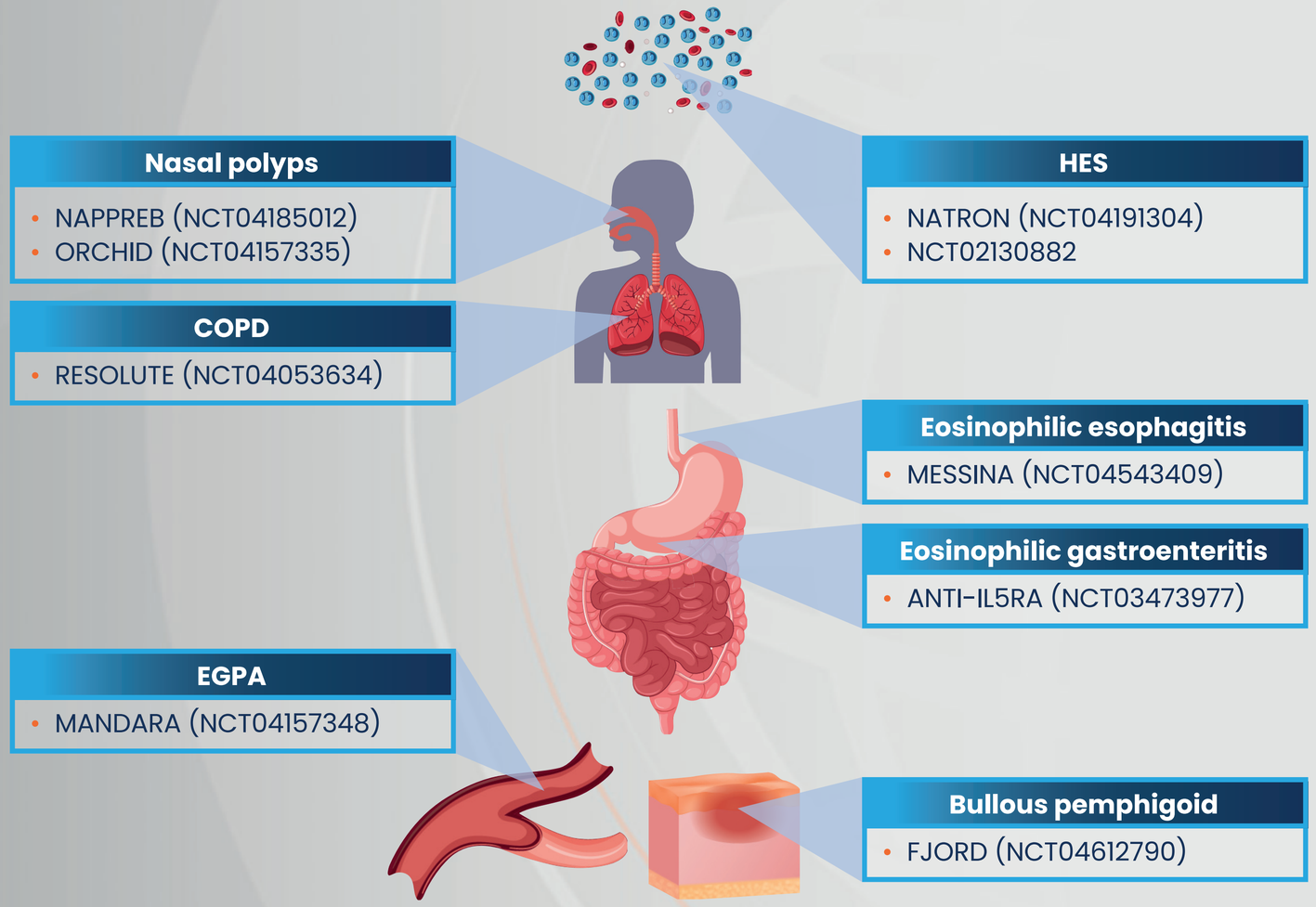
COPD

- MATINEE (NCT04133909)
- COPD-HELP (NCT04075331)

COPD, chronic obstructive pulmonary disease.
Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed 21 February 2021).

Approved biologics in new disease settings: Benralizumab

Ongoing phase III trials



EGPA, eosinophilic granulomatosis with polyangiitis, HES, hypereosinophilic syndrome.
Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed 21 February 2021).

Approved biologics in new disease settings: Dupilumab

Ongoing phase III trials

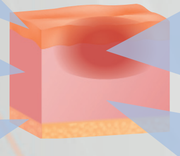
ABPA
- LIBERTY ABPA (NCT04442269)

COPD
- BOREAS (NCT03930732)
- NOTUS (NCT04456673)

Eosinophilic esophagitis
- EoE KIDS (NCT04394351)
- R668-EE-1774 (NCT03633617)

Cold urticaria
- LIBERTY-CINDU (NCT04681729)

CSU
- CUPID (NCT04180488)



Neurodermatitis
- PRIME (NCT04183335)
- PRIME2 (NCT04202679)

Bullous pemphigoid
- LIBERTY-BP (NCT04206553)

Netherton syndrome
- NS-DUPI (NCT04244006)

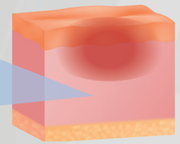
ABPA, allergic bronchopulmonary aspergillosis; CSU, chronic spontaneous urticaria.
Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed 21 February 2021).

Approved biologics in new disease settings: Omalizumab

Ongoing phase III trial

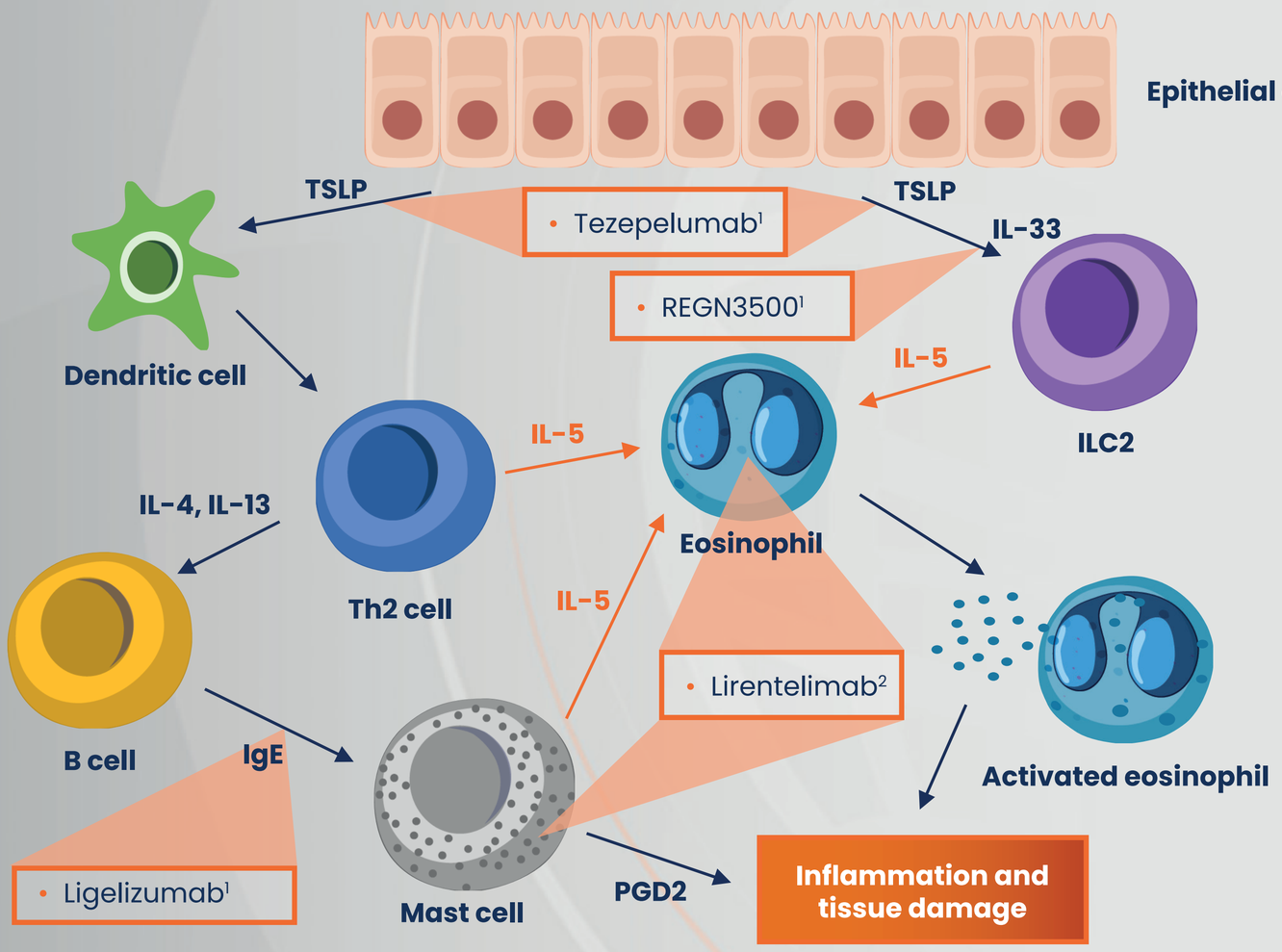
Bullous pemphigoid

- NCT04128176



Clinical trial listed by its identifier at: ClinicalTrials.gov (accessed 21 February 2021).

Emerging biologics for eosinophilic diseases

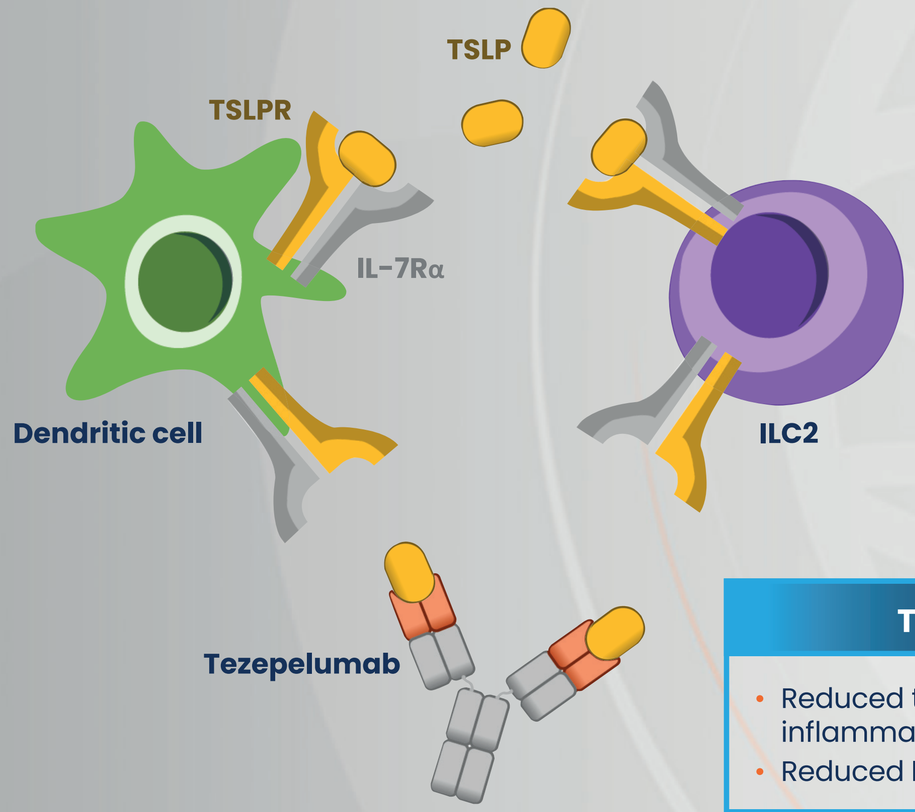


IgE, immunoglobulin E; IL, interleukin; ILC2, group 2 innate lymphoid cells; PGD2, prostaglandin D2; Th2, T helper 2; TSLP, thymic stromal lymphopoietin.

1. Pelaia C, et al. *Front Immunol.* 2020;11:603312; 2. Youngblood BA, et al. Cells. 2020;10:1–14.

Emerging biologics for eosinophilic diseases: Tezepelumab

Anti-TSLP monoclonal antibody



TSLP signalling[1,2]

- Dendritic cell activation leading to Th2 cells differentiation
- Activation of ILC2 cells
- Production of IL-4, IL-5, and IL-13

TSLP inhibition[2]

- Reduced type 2 inflammatory response
- Reduced IL-5 production

IL-7Rα, interleukin-7 receptor alpha; TSLPR, thymic stromal lymphopoietin receptor.

1. Verstraete K, et al. *Nat Commun.* 2017;8:14937; 2. Pelaia C, et al. *Front Immunol.* 2020;11:603312.

Emerging biologics for eosinophilic diseases: Tezepelumab

PATHWAY study (NCT02054130, phase IIb): Study design

- 18–75 years old
- Asthma not controlled by LABA combined with ICS at least 6 months before enrolment
- Within 12 months before enrolment either:
  - Two exacerbations requiring systemic glucocorticoid treatment
  - One severe exacerbation requiring hospitalization

Tezepelumab (subcutaneous)

- 280 mg every 2 weeks (n=137)
- 210 mg every 4 weeks (n=137)
- 70 mg every 4 weeks (n=138)

Placebo (n=138)

Primary endpoint:

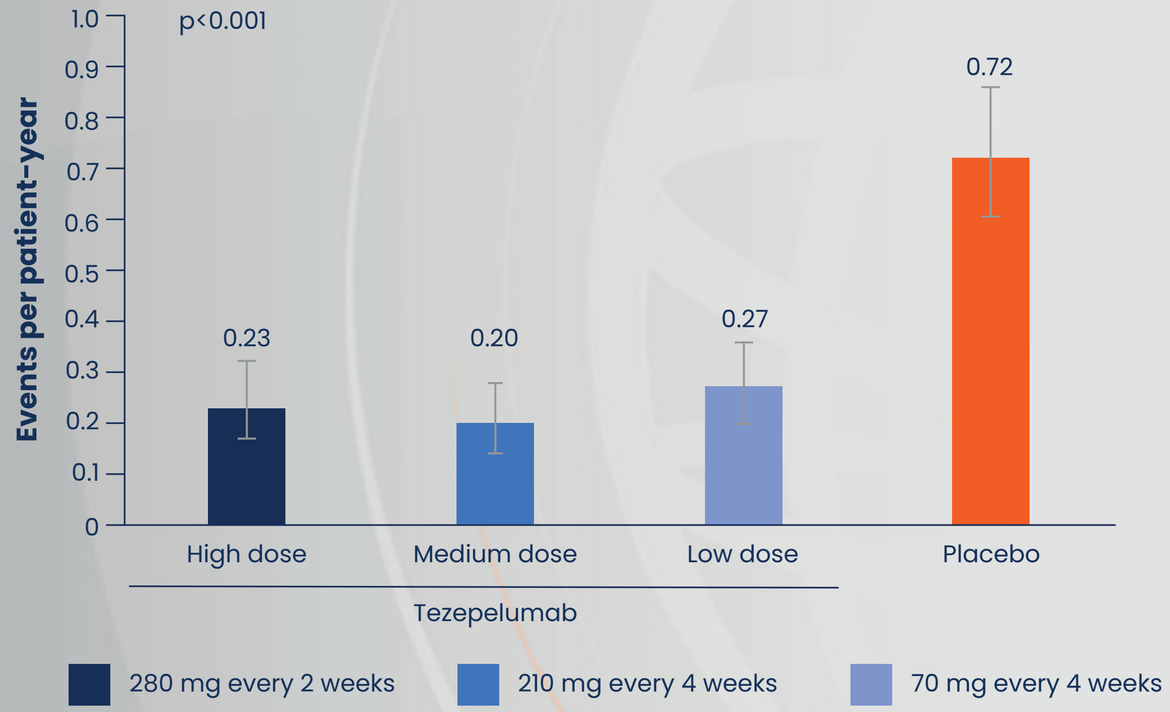
- Annualized rate of asthma exacerbations (events per patient-year) at week 52

ICS, intranasal corticosteroids; LABA, long-acting beta-agonists.

Corren J, et al. *N Engl J Med.* 2017;377:936–46.
Clinical trial listed by its identifier at: ClinicalTrials.gov (accessed 21 February 2021).

Emerging biologics for eosinophilic diseases: Tezepelumab

PATHWAY study (NCT02054130, phase IIb): Outcomes



Treatment with tezepelumab resulted in significantly lower annualized rates of asthma exacerbations at week 52 compared with placebo

Corren J, et al. *N Engl J Med.* 2017;377:936–46.
Clinical trial listed by its identifier at: ClinicalTrials.gov (accessed 21 February 2021).

Emerging biologics for eosinophilic diseases: Tezepelumab

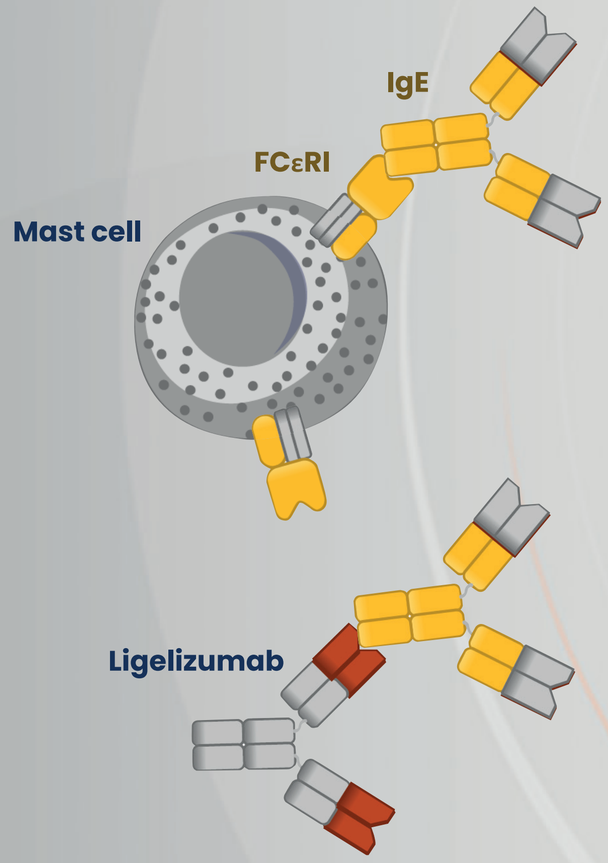
Ongoing phase III trials

Acronym (NCT number)	Conditions	Status
NOZOMI (NCT04048343)	severe asthma	Active, not recruiting
DIRECTION (NCT03927157)	Asthma	Recruiting
DESTINATION (NCT03706079)	Asthma	Active, not recruiting

Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed 21 February 2021).

Emerging biologics for eosinophilic diseases: Ligelizumab

Anti-IgE monoclonal antibody



IgE-mediated allergic inflammatory response

Inhibition of IgE signalling

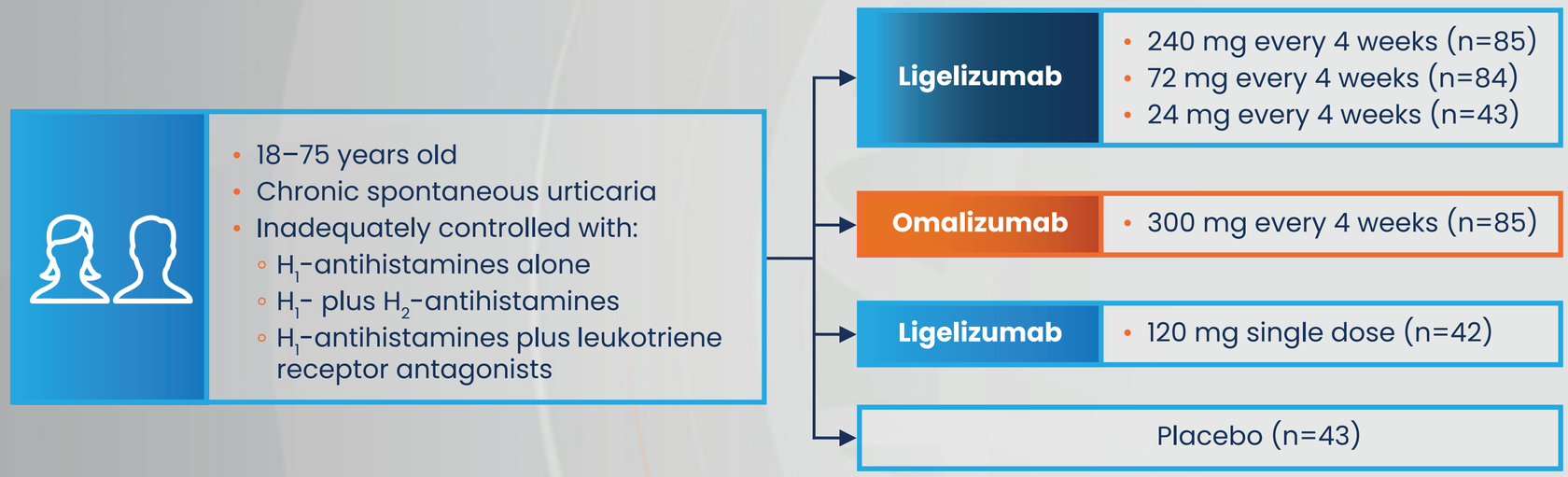
- Reduced release of proinflammatory mediators
- Reduced inflammatory response

FcεRI, fragment crystallizable region epsilon receptor I.

Pelaia C, et al. *Front Immunol.* 2020;11:603312.

Emerging biologics for eosinophilic diseases: Ligelizumab

NCT02477332 (phase IIb): Study design



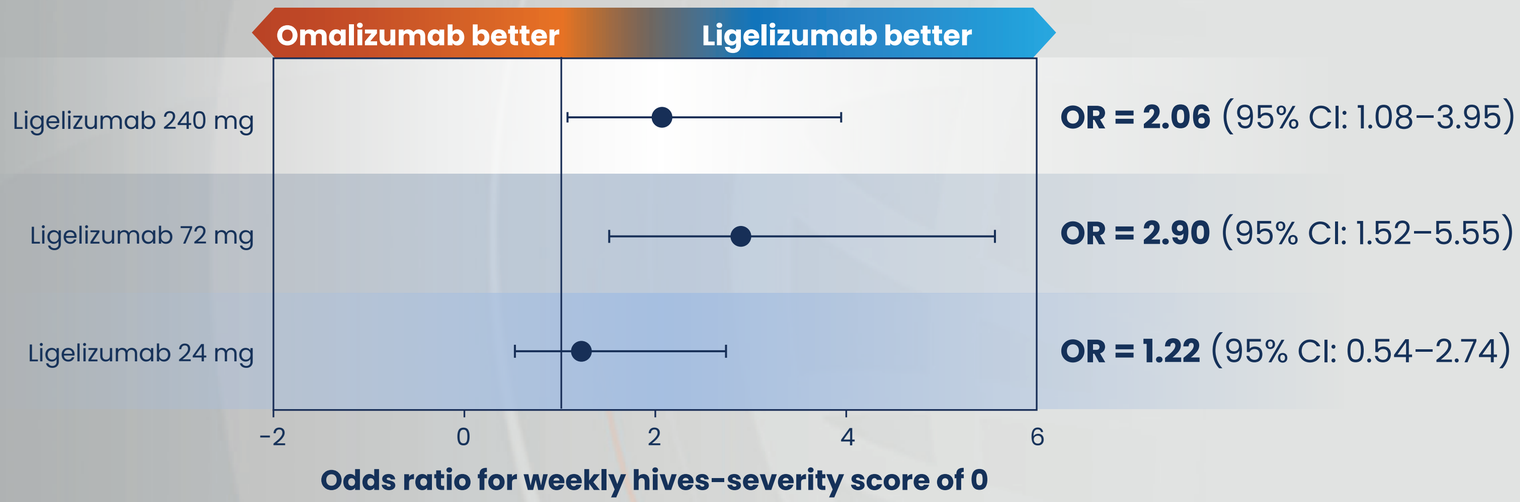
Primary endpoint:

- Dose–response relationship with the achievement of complete hives response (weekly hives-severity score of 0) at week 12

Maurer M, et al. *N Engl J Med.* 2019;381:1321–32.
Clinical trial listed by its identifier at: ClinicalTrials.gov (accessed 21 February 2021).

Emerging biologics for eosinophilic diseases: Ligelizumab

NCT02477332 (phase IIb): Outcomes



A higher percentage of patients had complete control of symptoms with ligelizumab therapy of 72 mg or 240 mg than with omalizumab

CI, confidence interval; OR, odds ratio.
Maurer M, et al. *N Engl J Med.* 2019;381:1321–32.
Clinical trial listed by its identifier at: ClinicalTrials.gov (accessed 21 February 2021).

Emerging biologics for eosinophilic diseases: Ligelizumab

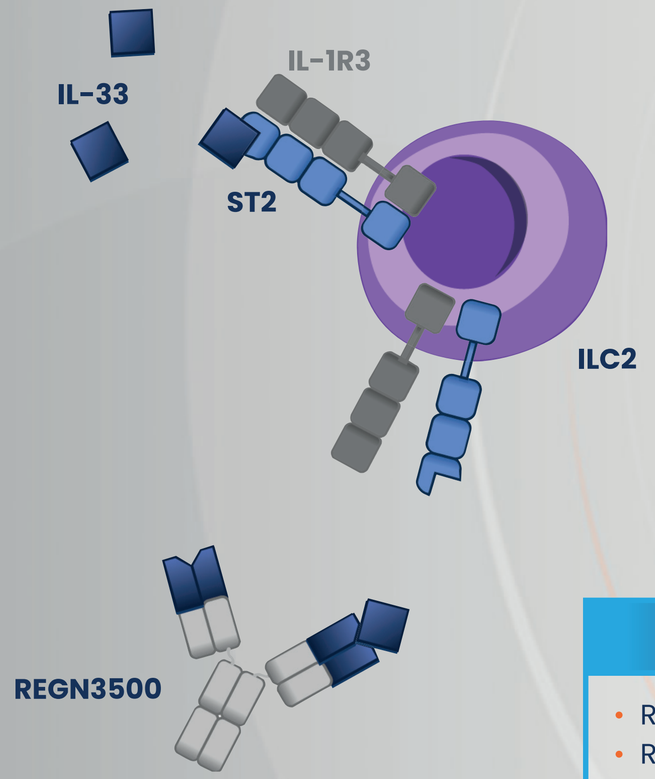
Ongoing phase III trials

NCT number	Conditions	Status
NCT03907878	Chronic spontaneous urticaria	Recruiting
NCT04210843	Chronic spontaneous urticaria	Recruiting
NCT03580369	Chronic spontaneous urticaria	Recruiting
NCT03580356	Chronic spontaneous urticaria	Recruiting

Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed 21 February 2021).

Emerging biologics for eosinophilic diseases: REGN3500

Anti-IL-33 monoclonal antibody



IL-33 signalling[1,2]

- Activation of ILC2 cells
- Induction of IL-13 release

IL-33 inhibition[2]

- Reduced ILC2 activation
- Reduced IL-13 production
- Inhibition of type 2 immune and inflammatory response

IL-1R3, interleukin-1 receptor 3.

1. Dinarello CA. *Immunol Rev.* 2018;281:8–27; 2. Pelaia C, et al. *Front Immunol.* 2020;11:603312.

Emerging biologics for eosinophilic diseases: REGN3500

Top line results of early clinical trial

NCT03387852 (proof of concept, phase II)

- REGN3500 monotherapy improved asthma control compared with placebo
- REGN3500 monotherapy significantly improved lung function compared with placebo
- The greatest improvement was observed in patients with blood eosinophil levels ≥300 cells/μL
- Dupilumab monotherapy showed better outcomes than REGN3500 monotherapy across all endpoints
- REGN3500 plus dupilumab combination did not demonstrate increased benefit compared to dupilumab monotherapy

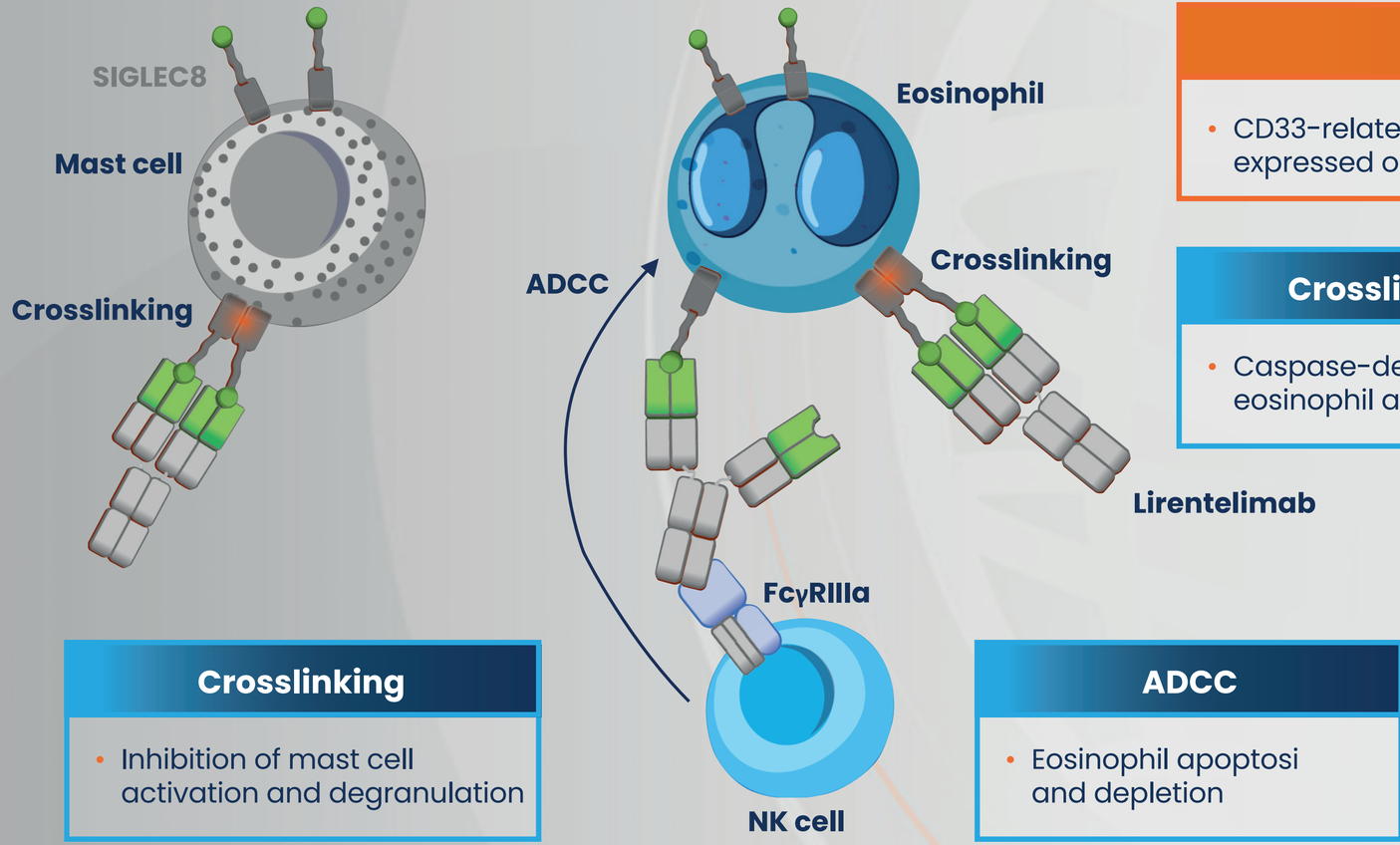
Ongoing phase III trial

Acronym (NCT number)	Conditions	Status
AERIFY-1 (NCT04701938)	COPD	Recruiting

Sanofi, Press release, 21 June 2019. Available at: www.sanofi.com/-/media/Project/One-Sanofi-Web/Websites/Global/Sanofi-COM/Home/media-room/press-releases/2019/2019-06-21-07-00-00-1872229-en.pdf (accessed 21 February 2021). Clinical trial listed by its identifier at: ClinicalTrials.gov (accessed 21 February 2021).

Emerging biologics for eosinophilic diseases: Lirentelimab

Anti-SIGLEC8 monoclonal antibody



SIGLEC8

- CD33-related family member selectively expressed on eosinophils and mast cell

Crosslinking

- Caspase-dependent eosinophil apoptosis

Crosslinking

- Inhibition of mast cell activation and degranulation

ADCC

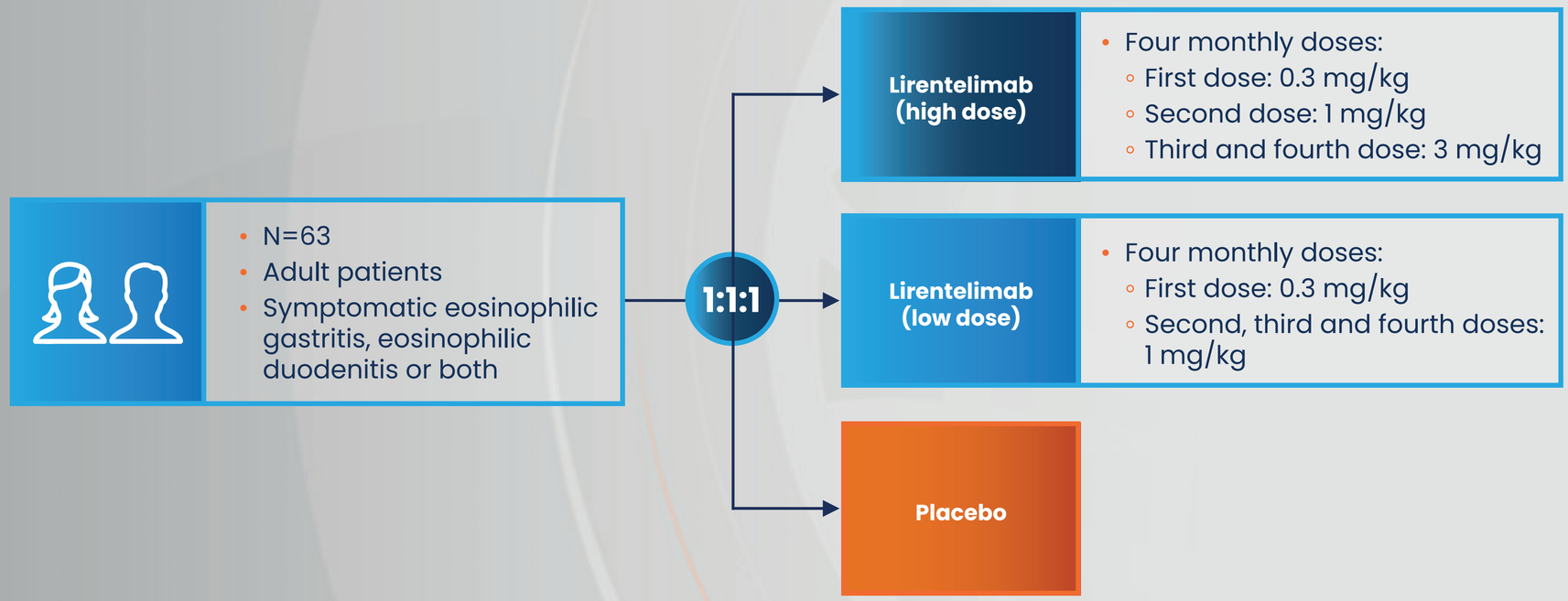
- Eosinophil apoptosi and depletion

ADCC, antibody-dependent cell-mediated cytotoxicity; CD, cluster of differentiation; FcγRIIIa, fragment crystallizable region gamma receptor IIIa; NK, natural killer; SIGLEC8, sialic acid binding Ig like lectin 8.

Youngblood BA, et al. *Cells.* 2020;10:1–14.

Emerging biologics for eosinophilic diseases: Lirentelimab

ENIGMA (NCT03496571 phase II): Study design



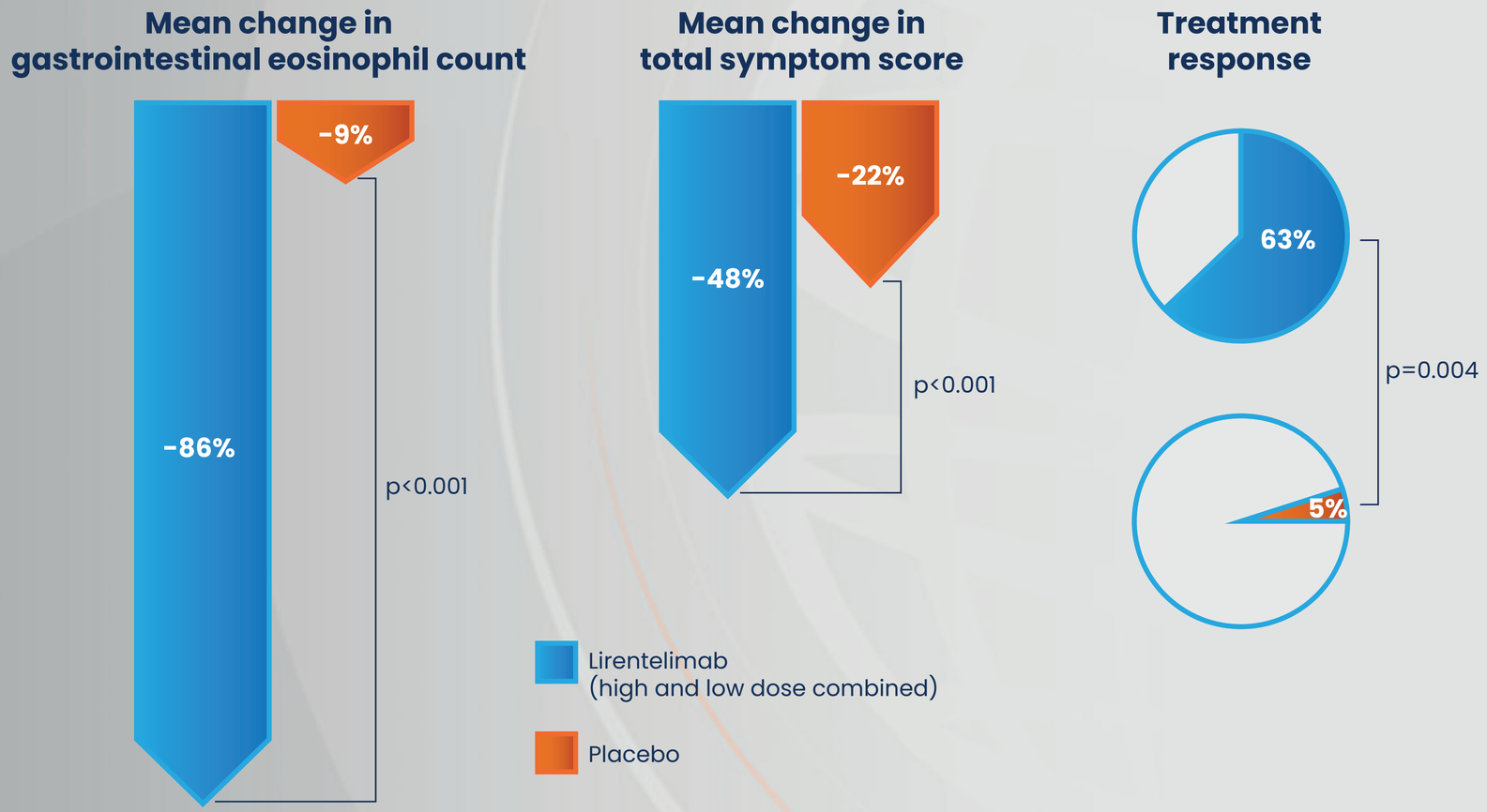
Primary endpoint:

- Change in gastrointestinal eosinophil count from baseline to 2 weeks after the final dose

Dellon ES, et al. *N Engl J Med.* 2020;384:1624–34.
Clinical trial listed by its identifier at: ClinicalTrials.gov (accessed 21 February 2021).

Emerging biologics for eosinophilic diseases: Lirentelimab

ENIGMA (NCT03496571 phase II): Outcomes



Dellon ES, et al. *N Engl J Med.* 2020;384:1624–34.
Clinical trial listed by its identifier at: ClinicalTrials.gov (accessed 21 February 2021).

Emerging biologics for eosinophilic diseases: Lirentelimab

Ongoing phase III trials

Acronym (NCT number)	Conditions	Status
AK002-016X (NCT04620811)	Eosinophilic gastritis/duodenitis	Enrolling by invitation
ENIGMA 2 (NCT04322604)	Eosinophilic gastritis/duodenitis	Recruiting

Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed 21 February 2021).

Emerging therapies for eosinophilic immunologic disease

The panel of approved indications for agents targeting IL-5/IL5R, IL-4Rα and IgE is likely to expand with several phase III clinical trials in a wide range of eosinophilic inflammatory diseases

Novel biologics are under development targeting key molecules in type 2 inflammatory pathways including TSLP, IL-33 and SIGLEC8

It is important to be aware of the evolving landscape of treatment options for type 2 asthma and other eosinophilic inflammatory diseases, with emerging biologics in advanced clinical development