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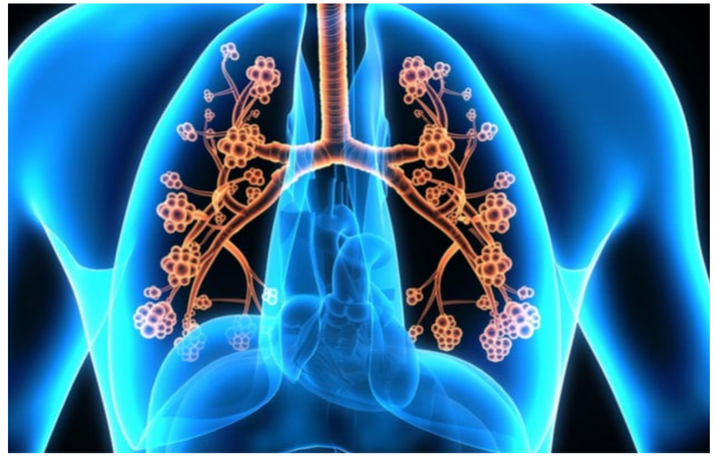
società italiana per le malattie respiratorie infantili

XXVIII CONGRESSO NAZIONALE SIMRI

Il respiro: scienza e terapia per la salute del bambino




Asma Grave: le terapie biologiche



Meyer

Grazia Fenu
Broncopneumologia, AOU, IRCCS, Meyer
grazia.fenu@meyer.it

Ai sensi dell’Accordo Stato-Regione in materia di formazione continua nel settore “Salute” (Formazione ECM) vigente,

Dichiarazione sul Conflitto di Interessi

Il sottoscritto Grazia Fenu

in qualità di relatore

nell’ambito dell’evento XXVIII Congresso Nazionale SIMRI
Torino 10-12 Ottobre 2024

ai sensi dell’Accordo Stato-Regione in materia di formazione continua nel settore “Salute” (Formazione ECM) vigente,

Dichiara

che negli ultimi due anni ha avuto rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

Boehringer-Ingelheim, Novartis, Sanofi

Asma Grave: le terapie biologiche

Summary

- Asthma: heterogeneous disease
- Stepping down
- Stepping up
- Focus Step 4-5 (6-11 years and adolescents and adults)
- Pit-stop: we phenotype! Remember: size of the problem
- Difficult to treat asthma? Severe asthma?
- Biologic therapy
- Conclusions

- About 300 million people worldwide have asthma

- Chronic Inflammatory Disease of the Airways with Reversible Airway Obstruction, Bronchial Hypersensitivity, and varying degrees of symptoms

- The different asthma subtypes result from the complex interaction among several genetic and environmental factors and present as multiple phenotypes.

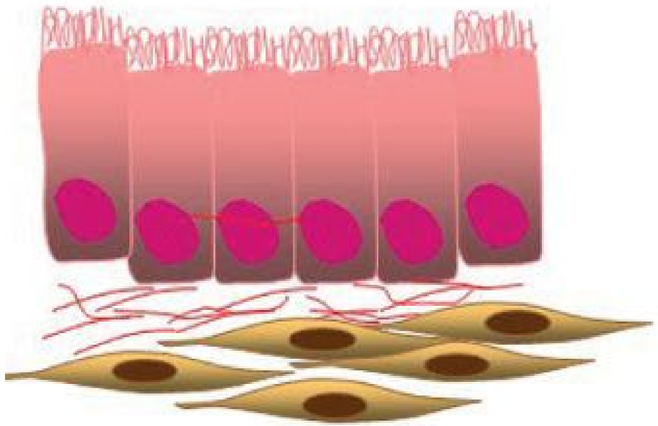
- Asthma is heterogeneous disease…..different pathophysiological mechanisms …….” Asthma Syndrome”

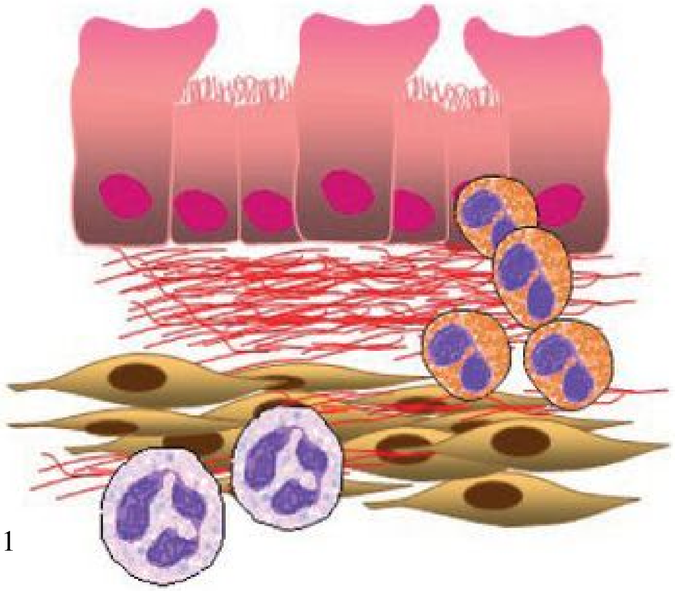
Early-life factors that increase or decrease the risk of asthma

Health
Rural
Term birth
Normal weight gain
Farmyard (animal exposure)
Protective airway/gut microbiome

Genetic susceptibility
Viral infection (RSV/HRV)
Environment
Atopic sensitisation

Asthma
Urban
Smoke exposure
Pollution
Excess early weight gain
Prematurity
Pathologic airway/gut microbiome



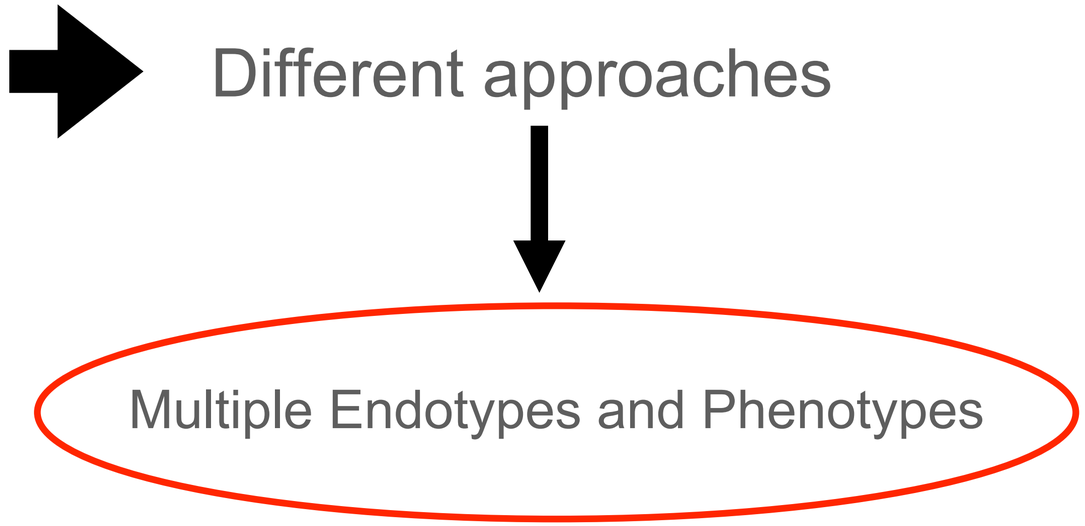


Pijnenburg MW, Frey U, De Jongste JC, Saglani S (2022) Childhood asthma: pathogenesis and phenotypes. Eur Respir J 59(6):2100731

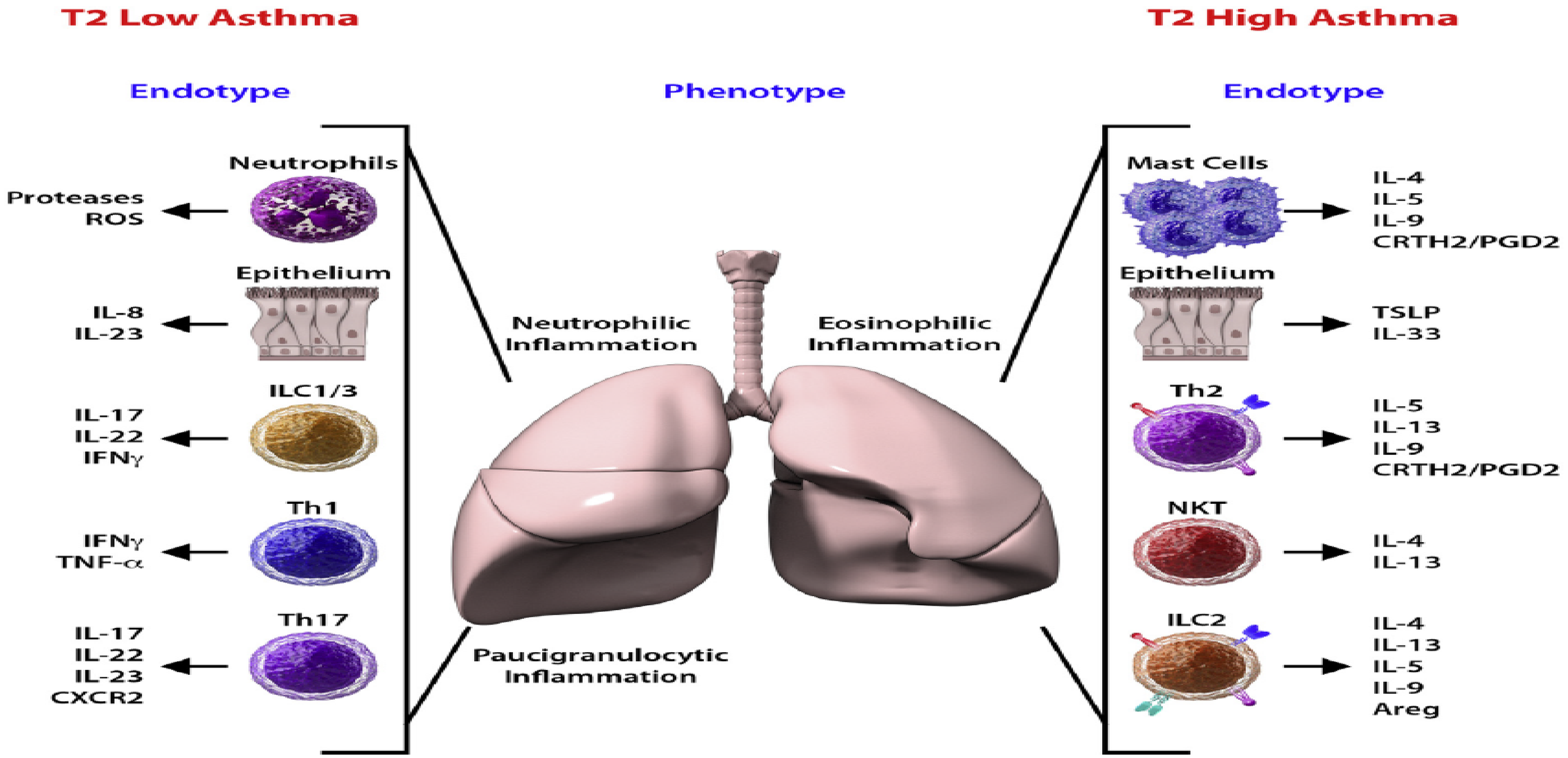
Heterogeneity in Childhood Asthma, why?

differences in:

- the **onset** of the disease
- the **progression** of the disease,
- the **severity** of symptoms,
- the **frequency** of exacerbations,
- **inflammatory profiles**,
- and **response to therapy**



Pijnenburg MW, Fleming L (2020). Lancet Respir Med 8(10):1032–1044.



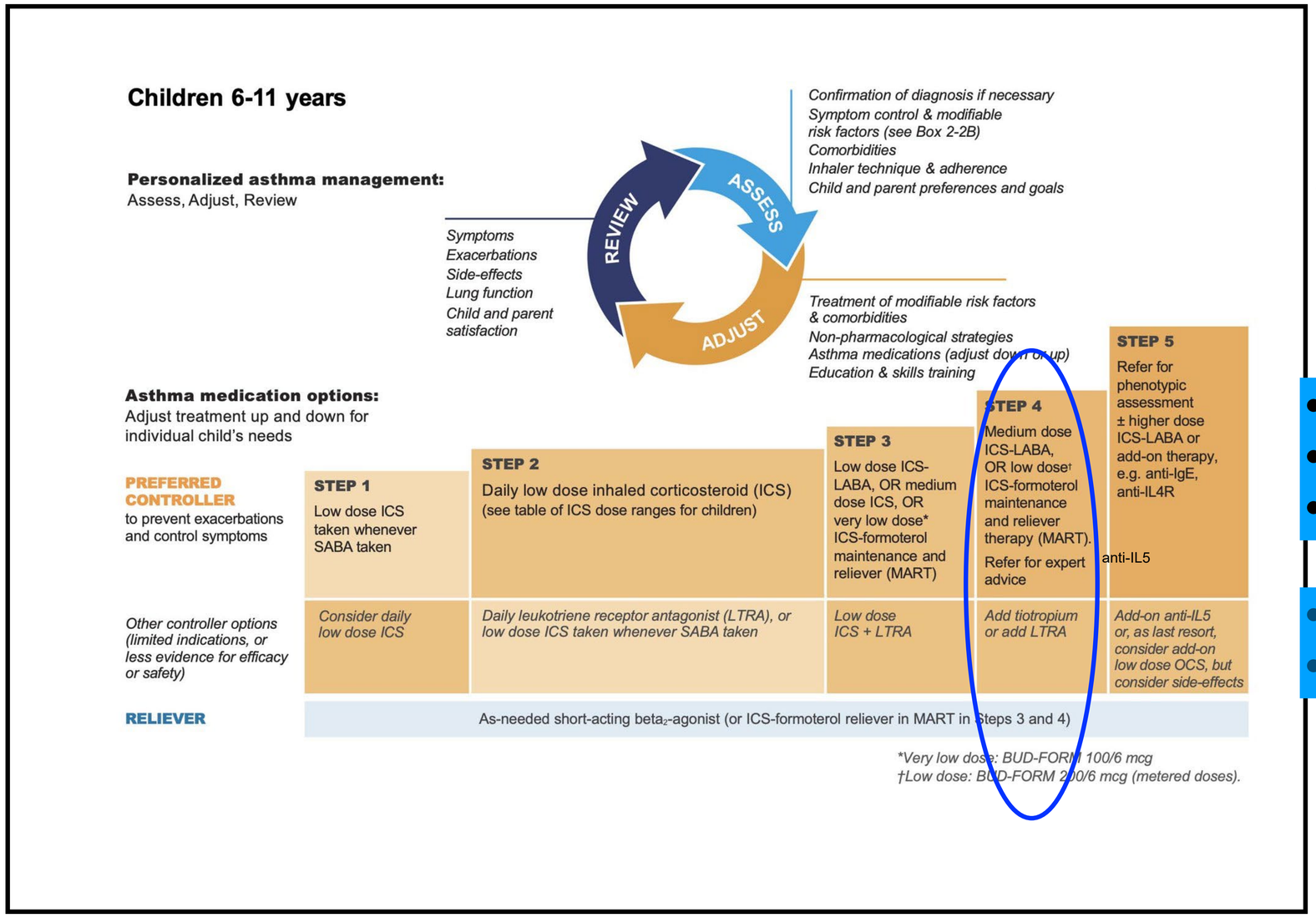
Viswanathan RK, et al. *Ann Allergy Asthma Immunol*. 2020;125(2):137-149.

Infiammatory profile ➡️ ICS

- 1970 introduction ICS: enormous step forward in controlling the disease in pediatric patients with asthma

Brown HM et al. Beclomethasone dipropionate steroid aerosol in treatment of perennial allergic asthma in children. Br Med J. 1973;3(5872):161-4

Asthma therapy: 6-11 years



2024 Global Strategy for Asthma Management and Prevention

Updated 2023

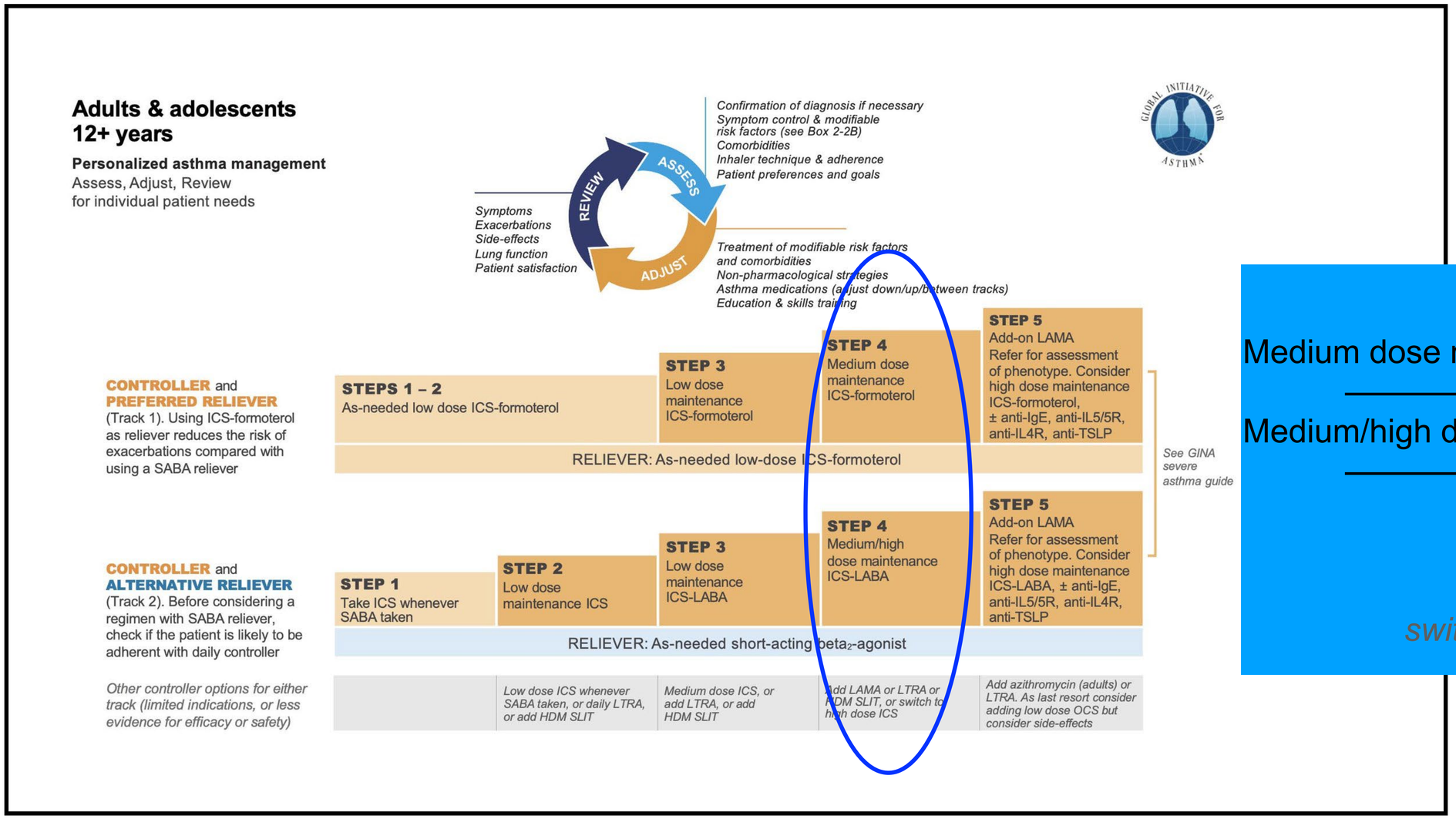
Symptoms most days or waking with asthma once a week or more, and low lung function

STEP 4

- Medium dose ICS-LABA or
- Low dose ICS-formoterol (MART)
- Refer for expert advice

- *Add tiotropium* or
- *Add LTRA*

Asthma therapy: adolescents & adults



STEP 4

Medium dose maintenance ICS-formoterol

Medium/high dose maintenance ICS-LABA

Add LAMA or LTRA or HDM SLIT or switch to high dose ICS

Stepping down

- When Asthma Symptoms have been **well controlled** and **lung function** has been stable for **3 or more months** (Evidence D);

- Step down only with close supervision: if the patient has **risk factors for exacerbations** (history of exacerbations in the past years, or persistent airflow limitations)

- **Appropriate time**: no respiratory infection, patient not traveling, *not pregnant*

- **Approach each step as a therapeutic trial**:
  - engage the patient in the process;
  - document asthma status (asthma control questionnaire, lung function);
  - provide clear informations;
  - written action plan;
  - ensure the patient has sufficient medication to resume their previous dose if necessary, schedule follow-up visit (Evidence D)

- Stepping down I**CS doses by 25-50%** at 3 months intervals is feasible and safe for most patient (Evidence A)

GINA 2023 Full report BOX 3-16, p.83

Stepping up

1. Incorrect inhaler technique
2. Poor adherence
3. Persistent exposure at home/work to agents such as allergens, tobacco smoke, indoor or outdoor air pollution, or to medications such as beta-blockers or (in some patients) non steroidal anti-infiammatory drugs (NSAIDs)
4. Comorbidities
5. Incorrect diagnosis

Expert Rev. Respir. Med. 5(3), 377–393 (2011)

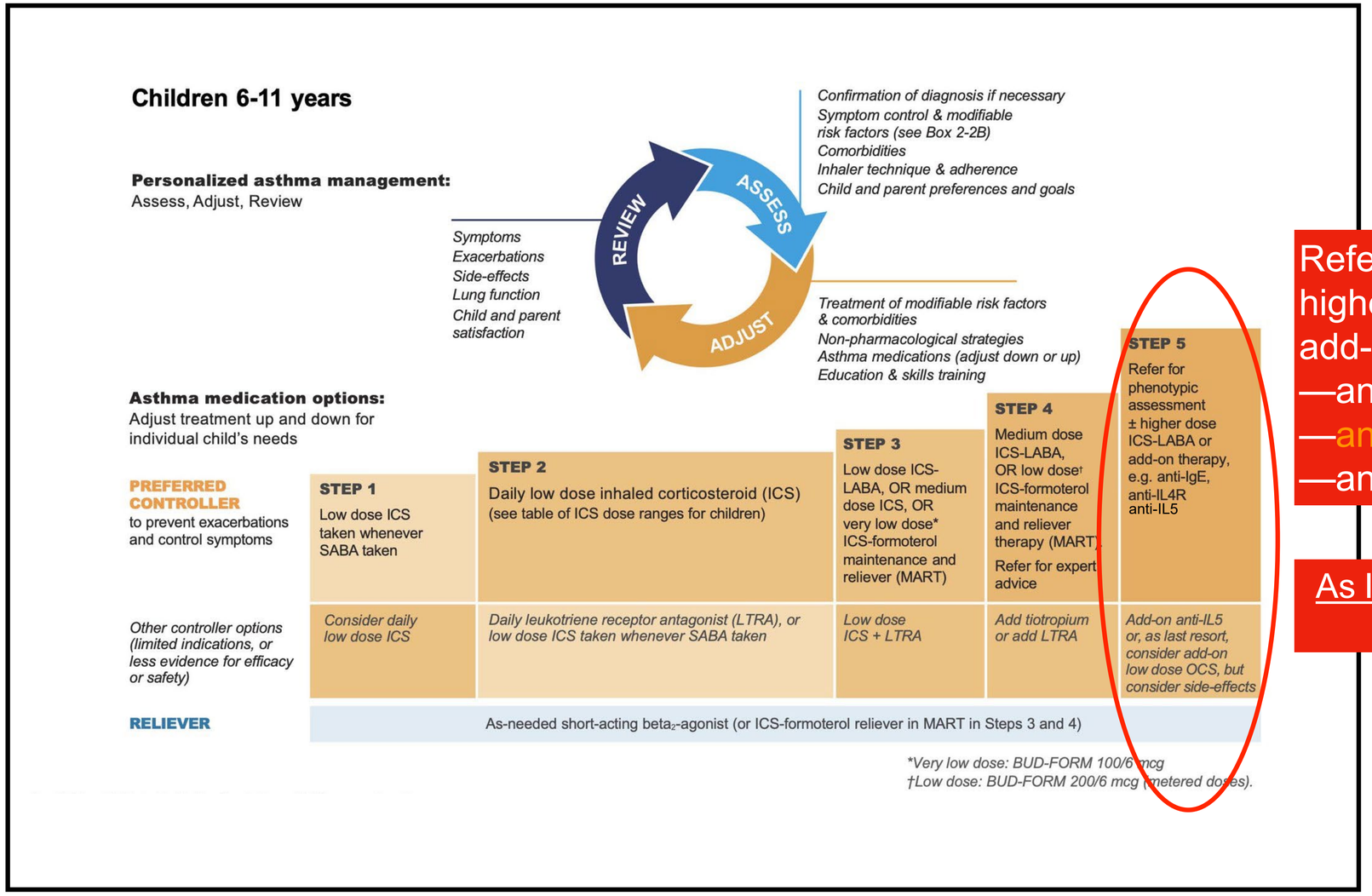
GINA 2023 Full report, p.58

Diagnosi differenziale

- Transient early wheezing
- Chronic aspiration (GER or swallowing dysfunction)
- Rhinosinusitis
- Infections (viral or bacterial, pertussis, mycoplasma, chlamydia, TB, etc.)
- BPD
- Vocal cord dysfunction or paralysis
- Smoke exposure or toxic inhalations
- Bronchiectasis
- Bronchiolitis obliterans
- Foreign body
- Anaphylaxis
- Cystic fibrosis
- Primary ciliary dyskinesia
- Eosinophilic lung diseases
- Pulmonary hemosiderosis
- Vascular tracheal compression
- Tracheobronchial malformations
- Laryngo-tracheo-bronchomalacia
- Mediastinal masses
- Immune deficiency
- Heart failure
- Hyperventilation/ panic disorder
- Interstitial lung diseases
- Medications

Liu and Covar. IN: Taussig et al, Pediatric Respiratory Medicine, 2008

Asthma therapy: 6-11 years

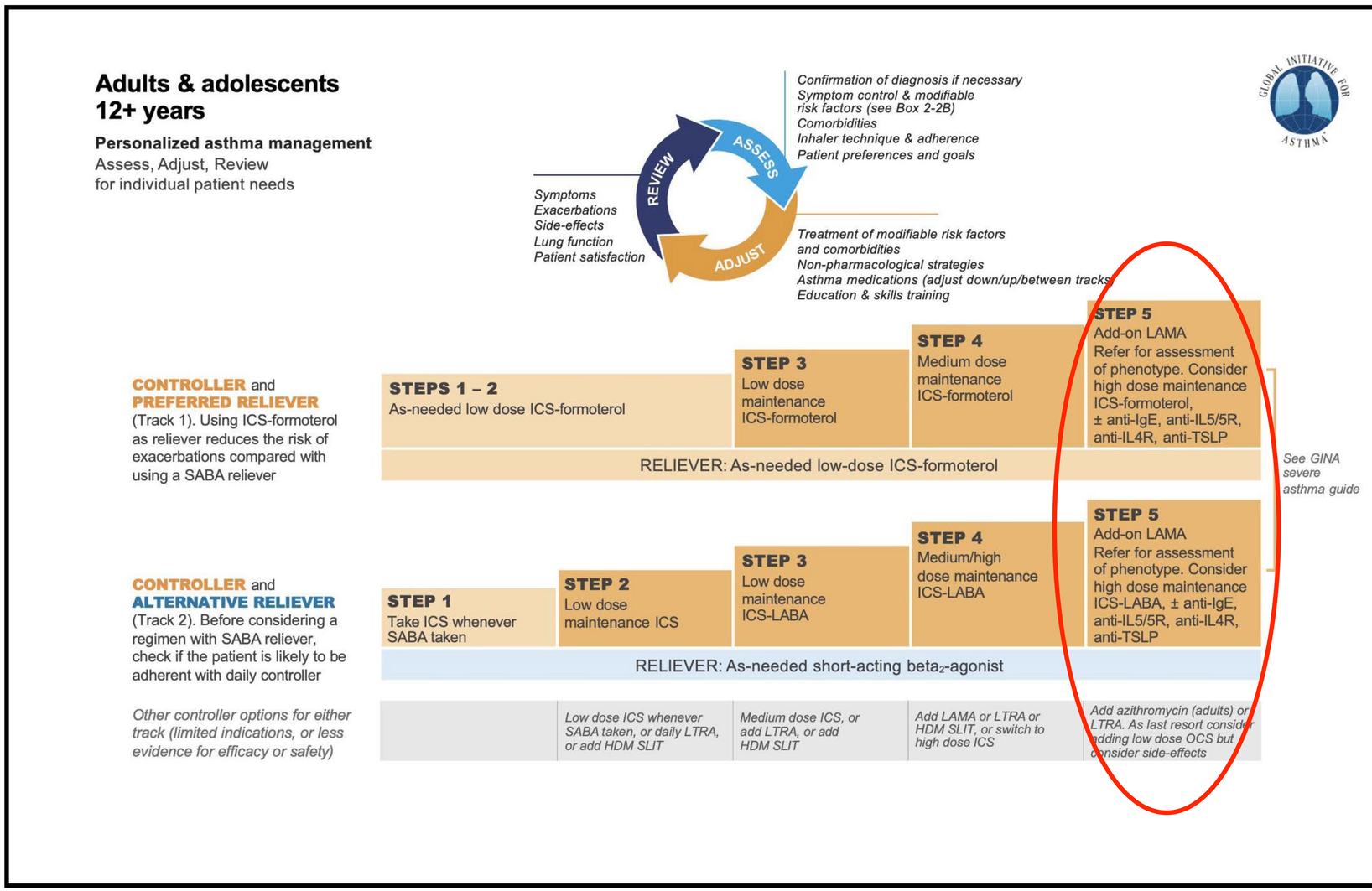


STEP 5

Refer for phenotypic assessment
higher dose ICS-LABA or
add-on therapy:
—anti-IgE
—anti-IL4R
—anti-IL5

As last resort consider add-on low dose OCS, but consider side-effects

Asthma therapy: adolescents & adults



STEP 5

Add-on LAMA
Refer for phenotypic assessment
Consider higher dose maintenance ICS-formoterol +
add-on therapy:
—anti-IgE
—anti-IL5/5R
—anti-IL4 R
—anti-TSLP

Consider higher dose maintenance ICS-LABA

Add azithromycin (adults) or LTRA
As last resort consider adding low dose OCS but consider side-effects

Attenzione alle dosi alte di steroidi inalatori!!!

Combination high dose ICS-LABA:

In most patients the increase ICS dose generally provide little additional benefit (Evidence A) and there is an increased risk of side effects, including adrenal suppression.

A high dose is only recommended on a trial basis for 3-6 months when good asthma control cannot be achieved with medium dose ICS-LABA and/or third controller.

Low, medium and high ICS doses: children 6-11 years

Children 6–11 years

Inhaled corticosteroid	Total daily ICS dose (mcg)		
	Low	Medium	High
Beclometasone dipropionate (pMDI, standard particle, HFA)	100–200	>200–400	>400
Beclometasone dipropionate (pMDI, extrafine particle*, HFA)	50-100	>100-200	>200
Budesonide (DPI)	100–200	>200–400	>400
Budesonide (nebules)	250–500	>500–1000	>1000
Ciclesonide (pMDI, extrafine particle*, HFA)	80	>80-160	>160
Fluticasone furoate (DPI)	50		n.a.
Fluticasone propionate (DPI)	50-100	>100-200	>200
Fluticasone propionate (pMDI, standard particle, HFA)	50-100	>100-200	>200
Mometasone furoate (pMDI, standard particle, HFA)	100		200

This is NOT a table of equivalence. These are suggested total daily doses for the 'low', 'medium' and 'high' dose treatment options with different ICS.

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; pMDI: pressurized metered dose inhaler (non-CFC); * see product information

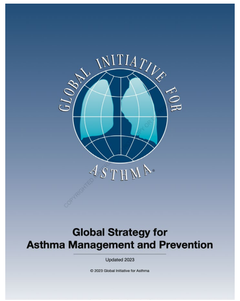
Low, medium and high ICS doses: adults/adolescents

Adults and adolescents (12 years and older)

Inhaled corticosteroid	Total daily ICS dose (mcg)		
	Low	Medium	High
Beclometasone dipropionate (pMDI, standard particle, HFA)	200-500	>500-1000	>1000
Beclometasone dipropionate (pMDI, extrafine particle*, HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle*, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	200		400
Mometasone furoate (pMDI, standard particle, HFA)	200-400		>400

This is NOT a table of equivalence. These are suggested total daily doses for the 'low', 'medium' and 'high' dose treatment options with different ICS.

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; pMDI: pressurized metered dose inhaler (non-CFC); * see product information



Asma difficile da trattare? Asma Grave?

What are difficult to treat and severe asthma?

- Difficult-to-treat asthma is asthma that is uncontrolled despite prescribing of medium or high-dose ICS-LABA treatment or that requires high-dose ICS-LABA treatment to maintain good symptom control and reduce exacerbations. It does not mean a 'difficult patient'.
- Severe asthma is asthma that is uncontrolled despite adherence with optimized high-dose ICS-LABA therapy and treatment of contributory factors, or that worsens when high-dose treatment is decreased. Approximately 3–10% of people with asthma have severe asthma.
- Severe asthma places a large physical, mental, emotional, social and economic burden on patients. It is often associated with multimorbidity.

Step 5- - -step-down ➡️ non controllo ➡️ asma grave ➡️

TASK FORCE REPORT
ERS/ATS GUIDELINES ON SEVERE ASTHMA

International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma

Kian Fan Chung[1,2,21], Sally E. Wenzel[3,21], Jan L. Brozek[4], Andrew Bush[1,2], Mario Castro[5], Peter J. Sterk[6], Ian M. Adcock[1], Eric D. Bateman[7], Elisabeth H. Bel[6], Eugene R. Bleecker[8], Louis-Philippe Boulet[9], Christopher Brightling[10], Pascal Chanez[11], Sven-Erik Dahlen[12], Ratko Djukanovic[13], Urs Frey[14], Mina Gaga[15], Peter Gibson[16], Qutayba Hamid[17], Nizar N. Jajour[18], Thais Mauad[19], Ronald L. Sorkness[18] and W. Gerald Teague[20]

- Non c'è una definizione universale per l'asma grave nei bambini, e questo riflette l'eterogeneità dell'asma e dell'asma grave in particolare.
- La gravità dell'asma viene valutata sul livello di trattamento che necessita per controllare sintomi e riacutizzazioni, in accordo con le strategie GINA (Global Initiative for Asthma)

- diagnosi di asma con test oggettivi, come la broncoreversibilità positiva oppure il test di broncoprovocazione positivo;
- i bambini sono in terapia con alte dosi di corticosteroidi per via inalatoria + almeno 1 altro controller (es. LABA) o trattamento con corticosteroidi orali di mantenimento;
- nonostante le alte dosi di farmaci, una volta affrontati i fattori modificabili,come la scarsa aderenza, persistono sintomi o frequenti esacerbazioni oppure l'asma diventa incontrollato se si fa uno step-down

Eur Respir J 2014; 43: 343–73

Chi sono questi pazienti

Pazienti (età ≥6 anni) allo step 4-5 (GINA-steps) o CS per ≥50% nell'anno precedente

Non controllati

- Scarso controllo sintomi: ACQ≥1.5, ACT <20;
- Frequenti severe riacutizzazioni: 2 o più con CS (≥3 giorni di tp) nell'anno precedente;
- Serie riacutizzazioni: almeno 1 ospedalizzazione, terapia intensiva, richiesta di ventilazione meccanica nell'anno precedente
- FEV1< 80% del pred

Controllati

- Controllo dei sintomi raggiunto con alte dosi di ICS o CS sistemici (o aggiungendo i biologici)

Chung KA et al. Eur Respir J 2014;43: 343-373

Pit stop: We phenotype! Multidisciplinary team

- 3-10% di tutti i bambini hanno l'asma

- <5% dei bambini asmatici ha l'asma grave

- 4/142 bambini asmatici **2.8%**

  de Groot EP, et al. Acta Paediatr 2015;104:916-21

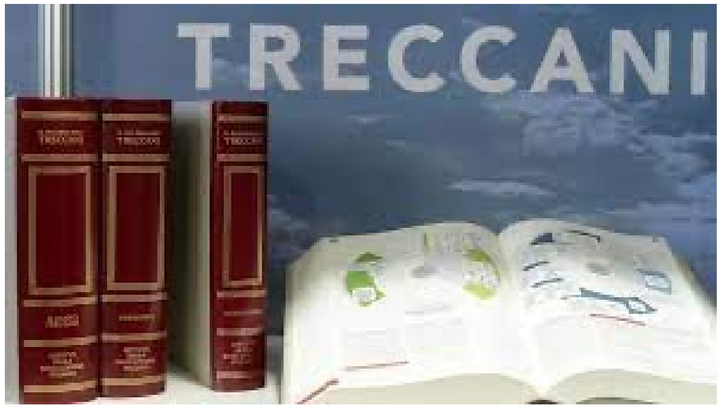
- 3/67 bambini asmatici **4.5%**

  Lang A, et al. Allergy 2008;63:1054-60

⬇️

- 95% dei bambini asmatici ha un'asma "standard"che si controlla con dosi basse-moderate di ICS senza e con secondo controller (LABA/LTRA)

Step 5: We phenotype!



fenotipo s. m. [dal ted. PhÊnotypus, comp. di phÊno- ¨ feno- 1º e del gr. τύπος ¨ tipoº].
ó In genetica, il complesso delle caratteristiche morfologiche e funzionali di un organismo, prodotto dallìinterazione [...] dei geni tra loro e con lìambiente.

Il **fenotipo** (dal greco *phainein*, che significa "**apparire**", e *týpos*, che significa "**impronta**") è l'insieme di tutte le caratteristiche manifestate da un organismo vivente, quindi la sua morfologia, il suo sviluppo, le sue proprietà biochimiche e fisiologiche comprensive del comportamento.

→ è ciò che è evidentemente il vivente,

il suo genotipo invece è la informazione genetica che è in lui contenuta, che ha generato il fenotipo; solo una parte esigua del genotipo si esprime nel fenotipo.

Il mio paziente con asma grave….Chi è?

- ✅ <u>diagnosi di asma</u>
- ✅ SPT positivo: acari +……
- 🚺 14 anni
- 🚹 12 anni
- ⬆️ <u>ICS/LABA</u> ➕/➖ LAMA ➕/➖ LTRA
- ⬆️ Eos
- ⬆️ FeNO
- ⬆️ IgE totali
- ⬆️ IgE specifiche: polisensibilizzato

Type 2 Inflammation Is Found in Up to 85% of Pediatric Asthma Patients[1-3]

GINA criteria for identifying type 2 inflammation[4]

- Blood **eosinophils** ≥150 cells/µL

and/or

- Sputum eosinophils ≥2%

and/or

- **FeNO** ≥20 ppb

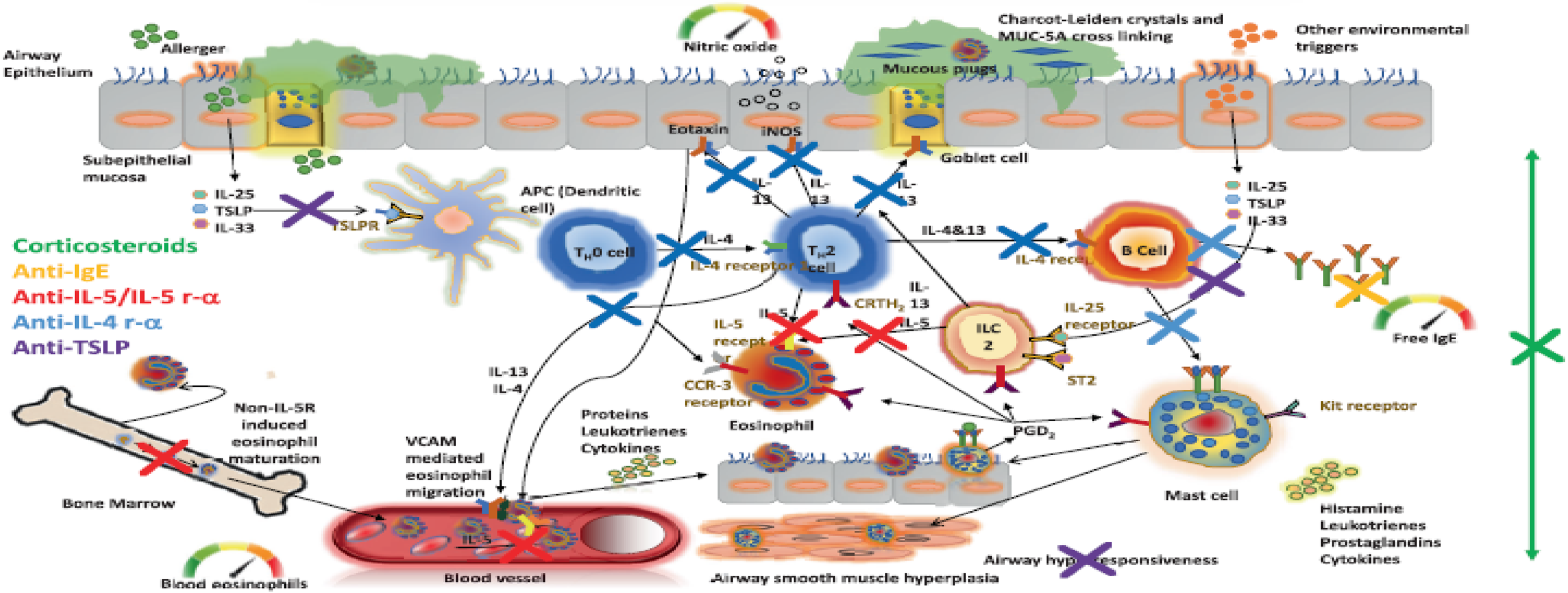
and/or

- Clinically allergen-driven* asthma (**IgE**)

(Patients requiring maintenance OCS may also have underlying type 2 inflammation. Repeat blood eosinophils and FeNO up to 3×, at least 1-2 weeks after OCS or on lowest possible OCS dose)

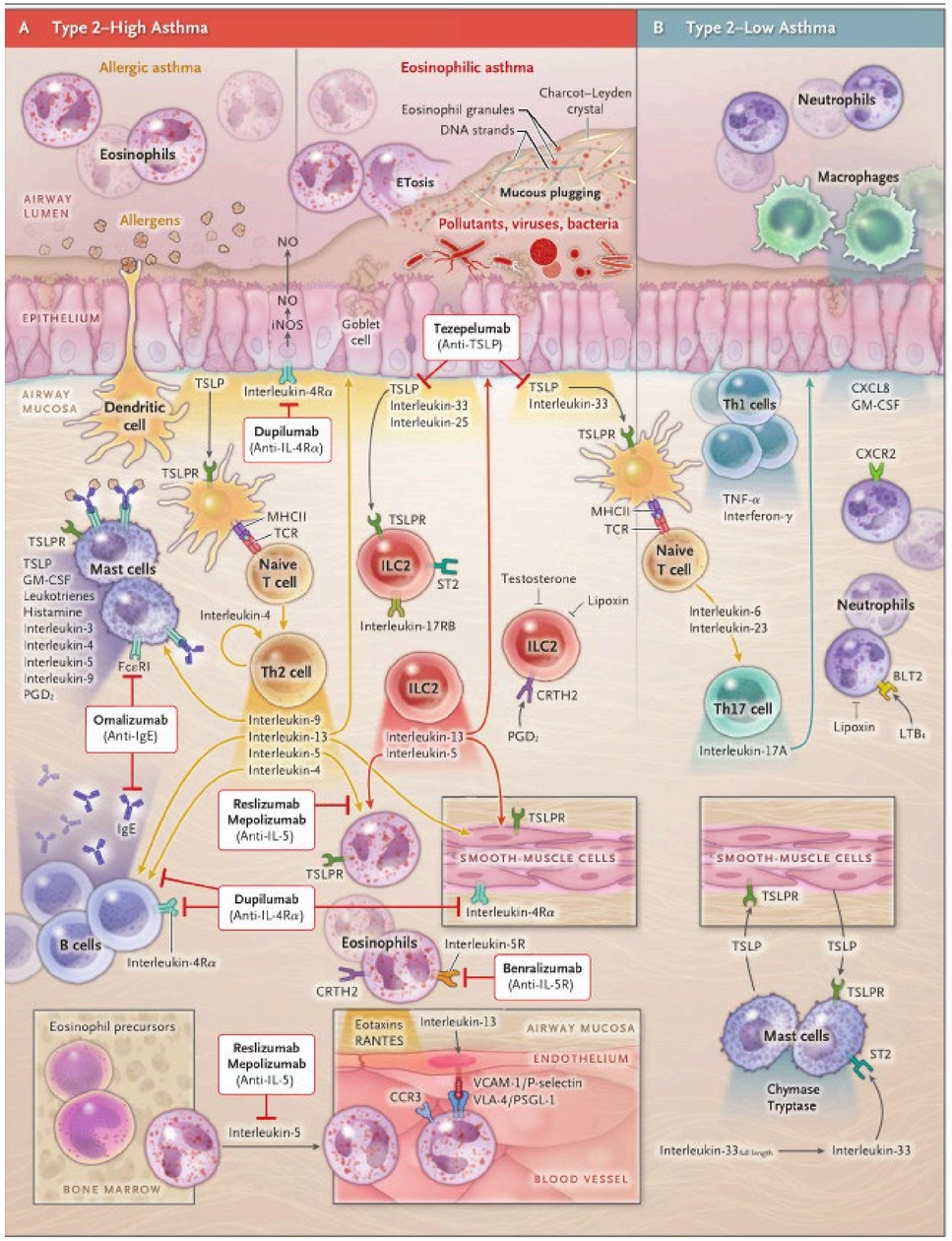
*Clinically allergen-driven as defined by specific IgE or positive skin prick test for relevant allergens.[4]
EOS, eosinophils; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E, OCS, oral corticosteroids.
1. Tran TN, et al. *Ann Allergy Asthma Immunol*. 2016;116(1):37-42. 2. Fleming L, et al. *Eur Respir J*. 2015;46(5):1322-1333. 3. Ramratnam SK, et al. *J Allergy Clin Immunol Pract*. 2017;5(4):889-898. 4. GINA. Global Strategy for Asthma Management and Prevention, Updated May 2023. Accessed August 11, 2023. https://ginasthma.org/reports/

Sub-stratification of type-2 high airway disease for therapeutic decision-making: A ‘bomb’ (blood eosinophils) meets ‘magnet’ (FeNO) framework



Couillard S, et al. *Respirology*. 2022;27(8):573-577.

Airway Inflammation in Severe Asthma and Targets of Biologic Therapies



- **Omalizumab (anti-IgE)** dai 6 aa
- **Mepolizumab (anti-IL5)** dai 6 aa
- **Dupilumab (anti-IL4/IL13 rec alfa)**
  attualmente dai 6 aa (a breve la rimborsabilità anche per la fascia 6-11 aa)
- **Benralizumab (anti-rec alfa IL5)**
  FDA dai 12 aa; EMA dai 18 aa
- **Tezepelumab (anti-TSLP)** dai 12 aa

Biologic	Trade name	Target	Indication
Omalizumab	Xolair	IgE	≥ 6 years with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICS
Mepolizumab	Nucala	IL5	≥ 6 years with severe eosinophilic asthma
Dupilumab	Dupixent	IL4/IL13 receptor alpha	≥ 6 years moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma
Benralizumab	Fasenra	IL5 receptor alpha	FDA: ≥ 12 years with severe asthma and an eosinophilic phenotype EMA: ≥ 18 years with eosinophilic asthma
Tezepelumab	Tezspire	TSLP	≥ 12 years with severe asthma who are inadequately controlled despite high dose inhaled corticosteroids + another medicinal product for maintenance treatment

Brusselle GG et al. Biologic Therapies for Severe Asthma. N Engl J MED 2022; 386; 157-71

Add-on Biologic Therapy in Pediatric Asthma (p 99)

Preferred step therapy for ages 6-11 years was separated from the adult and adolescent section – including step 5, add-on biologic therapy

Options recommended by GINA for children aged **6-11 years** with uncontrolled severe asthma despite optimized maximal therapy (see chapter 3.5 for more details) include

- Add on **anti-immunoglobulin E (anti-IgE**) (omalizumab) for patients aged ≥6 years with severe allergic asthma (Evidence A)
- Add-on **anti-interleukin-5/5Rα** (subcutaneous mepolizumab for patients aged ≥6 years with severe eosinophilic asthma (Evidence A)
- Add-on **anti-interleukin-4Rα** (subcutaneous dupilumab) for patients aged ≥6 years with severe eosinophilic/Type 2 asthma

Anti-IL-5Rα is included for the age 6-11 group as recommended add-on biologic therapy.

- **Anti-IL-5Rα (benralizumab) is approved for severe asthma in patients ages 6-11 with an eosinophilic phenotype in the US but is not approved in the pediatric population in Europe**[3,4]

Add-on anti-IL-4Rα was not given an Evidence A evaluation whereas anti-IgE and anti-IL-5/5Rα did.

- Dupilumab has demonstrated efficacy and safety in the VOYAGE and EXCURSION clinical trials in pediatric patients for up to 64 weeks[5,6]

1. https://ginasthma.org/wp-content/uploads/2024/05/GINA-2024-Main-Report-WMS-1.pdf. Accessed May 2024. 2. https://ginasthma.org/wp-content/uploads/2023/07/GINA-2023-Full-report-23_07_06-WMS.pdf. Accessed May 2024. 3. Fasenra (benralizumab) Prescribing Information. Wilmington, DE: AstraZeneca. 2024. 4. Fasenra (benralizumab) Summary of Product Characteristics. Södertälje, Sweden: AstraZeneca AB. 2022. 5. Bacharier L, et al. N Engl J Med. 2021;385:2230-2240. 6. Bacharier LB, et al. Lancet Respir Med. 2023

Omalizumab: anti-IgE

Severe pediatric asthma therapy: Omalizumab—A systematic review and meta-analysis of efficacy and safety profile

Study	Study design	Mean age	Study duration	Asthma severity	Number of patients (omalizumab/ placebo group)
Lanier 2009 (15)	Omalizumab add-on/placebo add-on	8,6 (6–12 years)	24 weeks, 52 weeks	Moderate-to-severe	421/206
Busse 2011 (16)	Omalizumab add-on/placebo add-on	8.4 (6–11 years)	24 weeks	Moderate-to-severe	117/120
Teach 2015 (17)	Omalizumab add-on/placebo add-on (third arm with ICS boost)	10,1 (6–12 years)	17–39 weeks	Moderate-to-severe	259/89
Sly 2017 (18)	Omalizumab add-on/placebo add-on	11,5 (6–15 years)	104 weeks	Moderate-to-severe	14/13

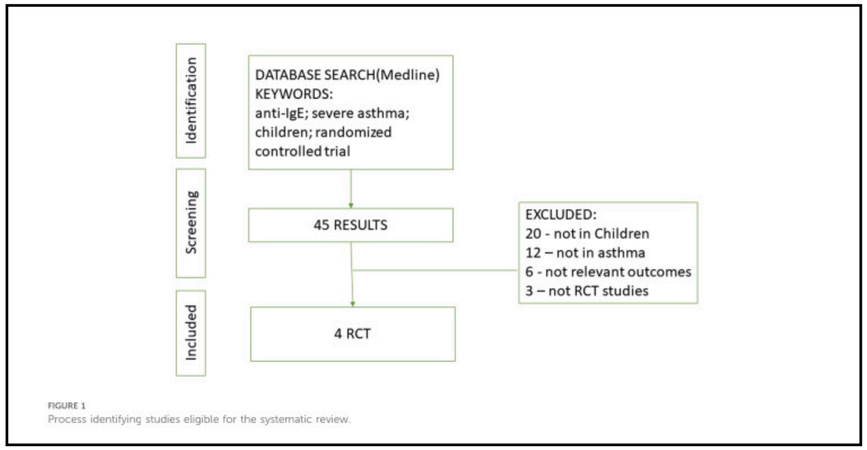
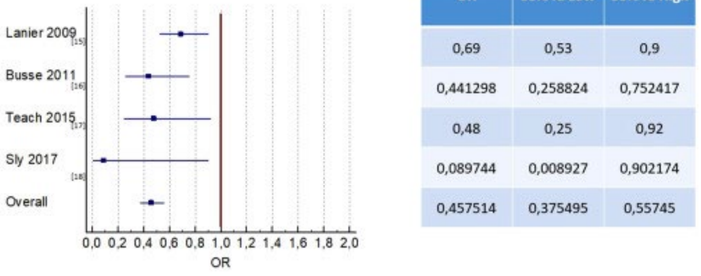


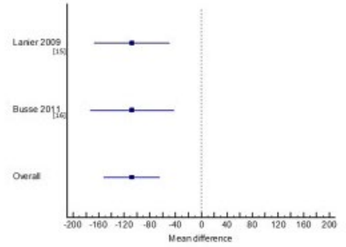
FIGURE 1
Process identifying studies eligible for the systematic review.



OR	95% IC Low	95% IC High
0,69	0,53	0,9
0,441298	0,258824	0,752417
0,48	0,25	0,92
0,089744	0,008927	0,902174
0,457514	0,375495	0,55745

FIGURE 2
Effect of omalizumab vs. placebo on the number of exacerbations.

Asthma exacerbations rate



Mean Difference	IC-H	IC-L
-108,00	-165,99	-50,01
-108,00	-172,73	-43,27
-108,00	-151,19	-64,81

FIGURE 3
Effect of omalizumab vs. placebo on reduction in ICS use.

Reduction in ICS use

Fenu G. et al. Frontiers in Pediatrics 2023 Mar 3;10:1033511

Adverse events

	Lanier 2009 (15)		Busse 2011 (16)		Teach 2015 (17)		Total	
	Placebo	Omalizumab	Placebo	Omalizumab	Placebo	Omalizumab	Placebo	Omalizumab
Severe adverse events	17	17	30	10	3	3	**50**	**30**
Blood and lymphatic system disorders	–	–	16	1	1	1	**17**	**2**
Eye, ear, and labyrinth disorders	39 (l)	70	7	2	1	6	**47**	**78**
Gastrointestinal disorders	24 (j)	34	2	11	10	19	**36**	**64**
General disorders and administration-site conditions	–	–	8	10	10	63	**18**	**73**
Immune system disorders	–	–	6	1	2	5	**8**	**6**
Infections and infestations	56 (a), 46 (b), 20 (c), 28 (d), 29 (e), 26 (f)	117, 69, 59, 51, 37, 34	26	18	22	63	**253**	**448**
Musculoskeletal and connective tissue disorders	–	–	3	3	1	8	**4**	**11**
Nervous system disorders	33 (g)	58	10	3	9	21	**52**	**82**
Psychiatric disorders	–	–	3	0	2	7	**5**	**7**
Respiratory, thoracic, and mediastinal disorders	25 (h)	44	95	57	11	29	**131**	**130**
Skin and subcutaneous tissue disorders	–	–	24	22	18	41	**42**	**63**
Other	–	–	22	31	4	37	**26**	**68**
Any adverse events	**343**	**590**	**222**	**159**	**97**	**300**	**662**	**1,049**

a, nasopharyngitis; b, URTI; c, pyrexia; d, influenza; e, bronchitis; f, viral URTI; g, headache; h, cough;, i, vomiting; l, sinusitis.

Conclusions

Omalizumab is the first biological therapy that has been used in moderate-to-severe asthma, and it is certainly the one with better evidence of safety and efficacy.

Our systematic review and meta-analysis provide further confirmation that omalizumab reduces the rate of exacerbations and inhaled steroid use in children with moderate-to-severe asthma with a great safety profile.

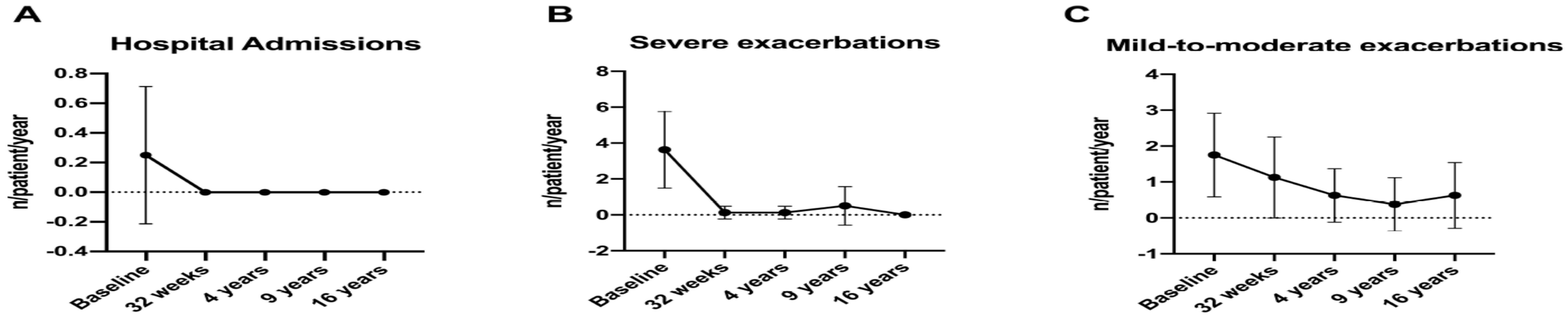
Its antiviral role is emerging more and more and finds application in pathology such as asthma, where the main actors are viruses, especially in children.

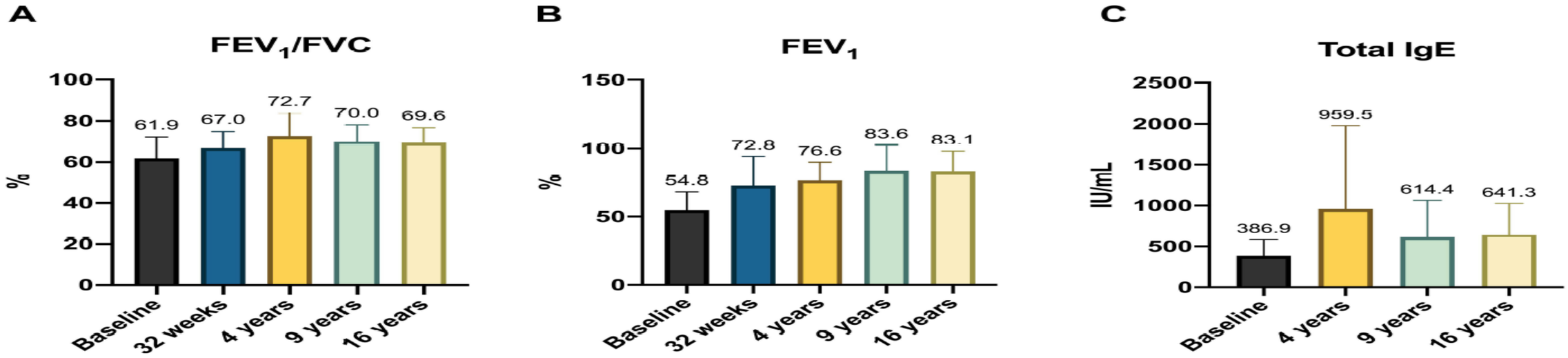
Fenu G. et al. Frontiers in Pediatrics 2023 Mar 3;10:1033511

Omalizumab: anti-IgE

Efficacy and Safety of Omalizumab Treatment Over a 16-Year Follow-Up: When a Clinical Trial Meets Real-Life

Francesco Menzella[1], Matteo Fontana[1], Marco Contoli[2], Patrizia Ruggiero[1], Carla Galeone[1], Silvia Capobelli[1], Anna Simonazzi[1], Chiara Catellani[1], Chiara Scelfo[1], Claudia Castagnetti[1], Francesco Livrieri[1], Nicola Facciolongo[1]



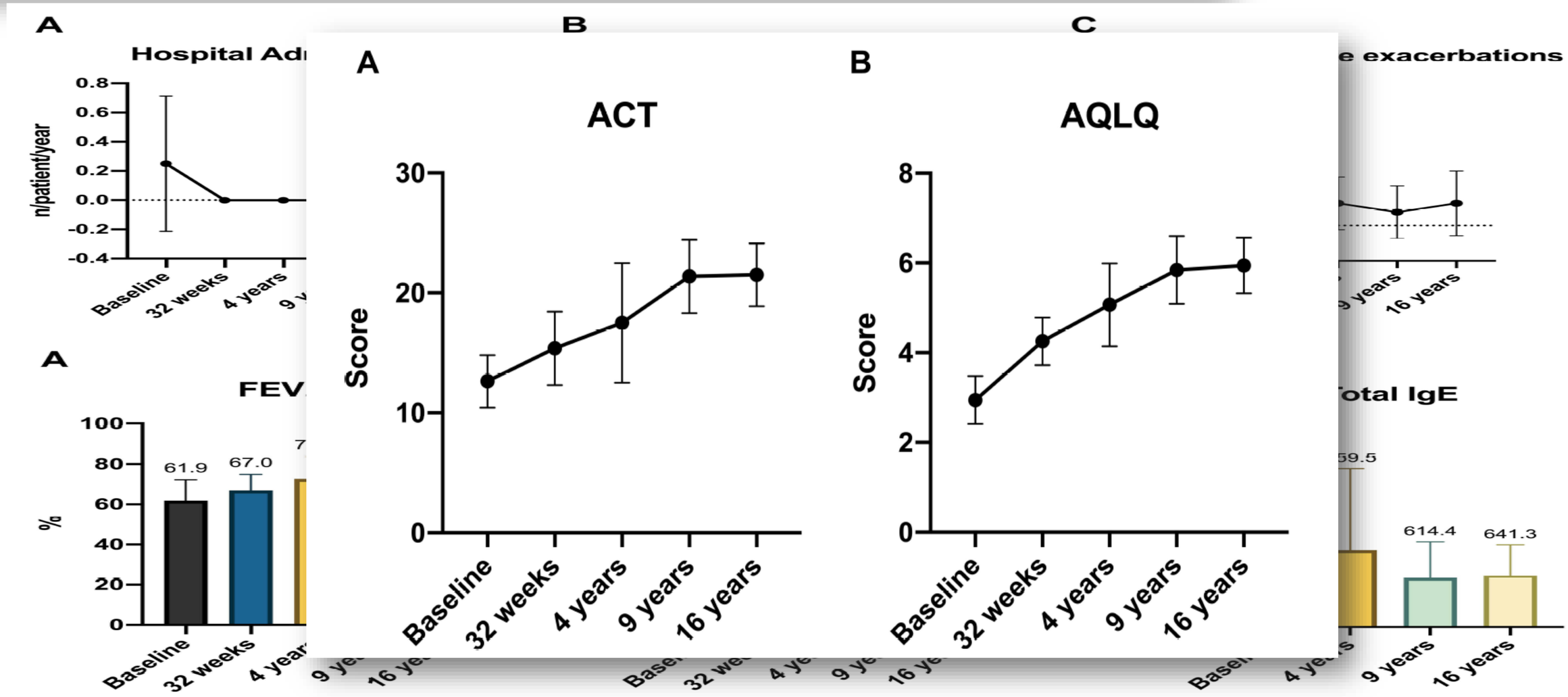


J Asthma Allergy. 2022;15:505-515.

Omalizumab: anti-IgE

Efficacy and Safety of Omalizumab Treatment Over a 16-Year Follow-Up: When a Clinical Trial Meets Real-Life

Francesco Menzella[1], Matteo Fontana[1], Marco Contoli[2], Patrizia Ruggiero[1], Carla Galeone[1], Silvia Capobelli[1], Anna Simonazzi[1], Chiara Catellani[1], Chiara Scelfo[1], Claudia Castagnetti[1], Francesco Livrieri[1], Nicola Facciolongo[1]



J Asthma Allergy. 2022;15:505-515.

Mepolizumab: anti-IL5

ORIGINAL ARTICLE: ASTHMA

WILEY

Subcutaneous mepolizumab in children aged 6 to 11 years with severe eosinophilic asthma

Atul Gupta MD(Res)[1] | Isabelle Pouliquen PharmD[2] | Daren Austin PhD[2] | Robert G. Price MSc[3] | Rodger Kempsford PhD[4] | Jonathan Steinfeld MD[5] | Eric S. Bradford MD[6] | Steven W. Yancey MSc[6]

- **Objectives**: pharmacokinetics and pharmacodynamics of mepolizumab following sc administr. Children 6-11 years with severe eosinophilic asthma
- **Study Design**: multinational (13 centers), nonrandomised open-label (NCT02377427)
- **Patient Selection:** blood eosinophil count ≥ 150 cells/μL at screening or ≥ 300 cells/μL <12 months of screening and ≥ 2 exacerbations in the prior year
- **Methodology:** mepo SC 40 mg (bodyweight < 40 kg) or 100 mg (≥ 40 kg) every 4 weeks for **12 weeks**

Conclusions

- Mepolizumab SC was associated with a **similar therapeutic effect in children to adults,** with marked reductions in blood eosinophil counts, a trend toward improved asthma control compared with baseline, and a favorable safety profile.
- The **40 and 100 mg SC** dosing regimens were deemed **acceptable for children aged 6 to 11 years with severe eosinophilic asthma** based on mepolizumab's wide therapeutic index. Results will be used as a basis for further dosing refinement.

Pediatr Pulmonol 2019 Dec;54(12):1957-1967

Mepolizumab: anti-IL5

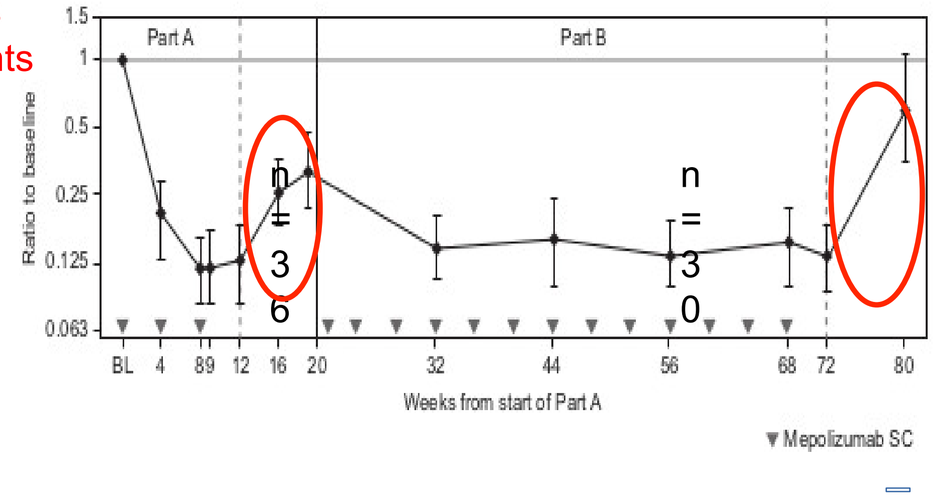
Biologics and immunotherapy

Long-term safety and pharmacodynamics of mepolizumab in children with severe asthma with an eosinophilic phenotype

Atul Gupta, MD(Res),[a] Masanori Ikeda, MD,[b] Bob Geng, MD,[c] Jay Azmi, PhD,[d] Robert G. Price, MSc,[e] Eric S. Bradford, MSc,[f] Steven W. Yancey, MSc,[f] and Jonathan Steinfeld, MD[g] *London, Uxbridge, and Stevenage, United Kingdom; Okayama, Japan; San Diego, Calif; Research Triangle Park, NC; and Philadelphia, Pa*

- open-label, uncontrolled, repeat-dose extension study (NCT02377427);
- children aged 6-11 years with severe asthma with an eosinophilic phenotype (blood eosinophil counts ≥150 cells/mL at screening or ≥300 cells/mL in the previous year);
- received a body weight–dependent dose of SC mepolizumab of 40 mg (<40 kg) or 100 mg (≥40 kg) **over 52 weeks;**
- end points included the incidence of adverse events

Blood EOS counts



In previous adult and adolescent studies
this response has been associated with a worsening of asthma symptoms (as indicated by ACQ-7 and ACQ-5 scores)

J Allergy Clin Immunol.2019 Nov;144(5):1336-1342.e.7.

Albers et al. Respiratory Research (2019) 20:169
https://doi.org/10.1186/s12931-019-1134-7

Respiratory Research

Mepolizumab: anti-IL5

RESEARCH Open Access

Mepolizumab reduces exacerbations in patients with severe eosinophilic asthma, irrespective of body weight/body mass index: meta-analysis of MENSA and MUSCA

Frank C. Albers[1,7*], Alberto Papi[2], Camille Taillé[3], Daniel J. Bratton[4], Eric S. Bradford[5], Steven W. Yancey[5] and Namhee Kwon[6]

Abstract

Background: We assessed the efficacy of the licensed mepolizumab dose (100 mg subcutaneously [SC]) in patients with severe eosinophilic asthma according to body weight/body mass index (BMI).

Methods: This was a post hoc individual patient-level meta-analysis of data from the Phase 3 studies MENSA (MEA115588/NCT01691521) and MUSCA (200862/NCT02281318). Patients aged ≥12 years with severe eosinophilic asthma and a history of exacerbations were randomised to 4-weekly placebo, mepolizumab 75 mg intravenously (IV) or 100 mg SC (MENSA) or placebo or mepolizumab 100 mg SC (MUSCA) for 32 (MENSA) or 24 (MUSCA) weeks. The primary endpoint was the annual rate of clinically significant exacerbations; other outcomes included the proportion of patients with no exacerbations, lung function, St George's Respiratory Questionnaire (SGRQ) and Asthma Control Questionnaire-5 (ACQ-5) scores and blood eosinophil counts. Analyses were performed by baseline body weight and BMI (≤60, > 60–75, > 75–90, > 90, < 100, ≥100 kg; ≤25, > 25–30, > 30, < 36, ≥36 kg/m^2).

Results: Overall, 936 patients received placebo or mepolizumab 100 mg SC. Across all body weight/BMI categories, mepolizumab reduced the rate of clinically significant exacerbations by 49–70% versus placebo. Improvements with mepolizumab versus placebo were also seen in lung function in all body weight/BMI categories except > 90 kg; improvements in SGRQ and ACQ-5 scores were seen across all categories.

Conclusions: Mepolizumab 100 mg SC has consistent clinical benefits in patients with severe eosinophilic asthma across a range of body weights and BMIs. Data show that the fixed-dose regimen of mepolizumab is suitable, without the need for weight-based dosing.

Trial registration: This manuscript is a post hoc meta-analysis of data from the Phase 3 studies MENSA and MUSCA. ClinicalTrials.gov, NCT01691521 (MEA115588; MENSA). Registered September 24, 2012. ClinicalTrials.gov, NCT02281318 (200862; MUSCA). Registered November 3, 2014.

Keywords: Asthma, Asthma pharmacology, Body mass index, Body weight, Mepolizumab

The NEW ENGLAND JOURNAL of MEDICINE

Dupilumab: anti-IL4/IL13

ORIGINAL ARTICLE

Dupilumab in Children with Uncontrolled Moderate-to-Severe Asthma

L.B. Bacharier, J.F. Maspero, C.H. Katelaris, A.G. Fiocchi, R. Gagnon, I. de Mir, N. Jain, L.D. Sher, X. Mao, D. Liu, Y. Zhang, A.H. Khan, U. Kapoor, F.A. Khokhar, P.J. Rowe, Y. Deniz, M. Ruddy, E. Laws, N. Patel, D.M. Weinreich, G.D. Yancopoulos, N. Amin, L.P. Mannent, D.J. Lederer, and M. Hardin, for the Liberty Asthma VOYAGE Investigators*

Studio VOYAGE

Aims.

To evaluate the efficacy, safety, and tolerability of dupilumab in children 6 to <12 years of age with uncontrolled persistent asthma, including the effect of dupilumab in improving exacerbation rate, lung function, PROs, and HRQOL, dupilumab systemic exposure, incidence of antidrug antibodies, biomarker levels in patients, the association between dupilumab treatment and pediatric immune responses to vaccine, and to evaluate the quality of life of caregivers of pediatric patients

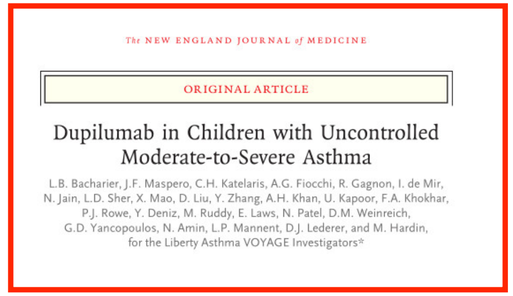
- 52 weeks
- Phase 3
- **Randomized double-blind, placebo-controlled trial**
- **408 children**
- **6-11 years** with uncontrolled moderate-severe asthma
- Dupi 100 mg/sc ≤30 kg; Dupi 200 mg/sc >30 kg or matched placebo every 2 weeks
- All children continued to receive a stable dose of standard background therapy
- Primary end point: annualized rate of severe asthma exacerbations
- Secondary end points: change from baseline in the percentage of predicted prebronchodilator forced expiratory volume in 1 second (ppFEV1) at week 12 and in the score on the ACQ-7 at week 24
- Two primary populations: Type 2 (baseline blood EOS ≥150 cells/μL or FeNO ≥20 ppb) and Baseline blood EOS ≥300 cells/μL

N Engl J Med. 2021;385:2230-2240

Dupilumab: anti-IL4/IL13

LIBERTY ASTHMA VOYAGE (NCT02948959)
Italian centers

Centre
Paediatric Section AOUI Verona, University of Verona, Verona, Italy
Pediatric Pulmonary Unit, "Anna Meyer," IRCCS Pediatric University-Hospital, Florence, Italy
Pediatric Respiratory Medicine and Allergy Unit, Women's and Children's Health Department, University of Padova, Padova, Italy
Allergy dpt., Pediatric Hospital Bambino Gesù, Rome, Italy
Pediatric Respiratory and Cystic Fibrosis Unit, Department of Clinical and Experimental Medicine, San Marco Hospital, University of Catania, 95121 Catania, Italy


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dupilumab in Children with Uncontrolled Moderate-to-Severe Asthma

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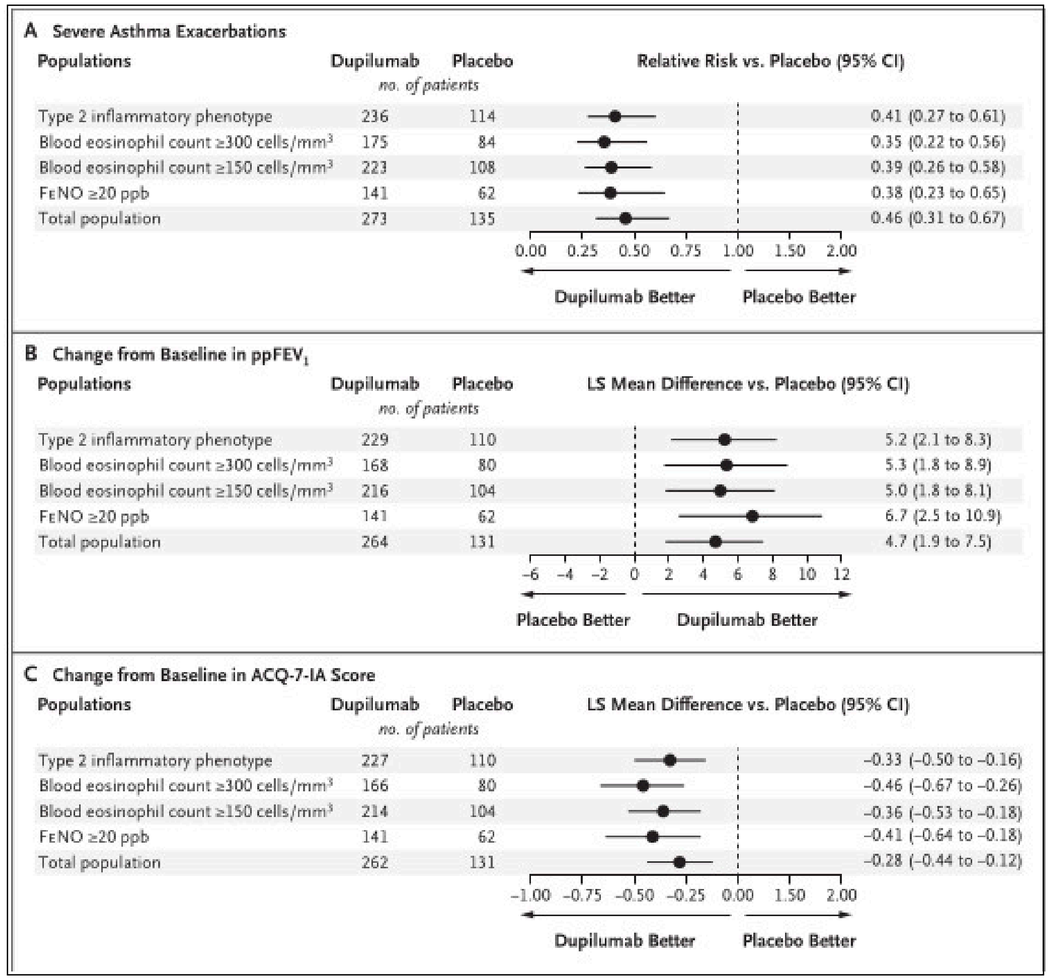
Dupilumab: anti-IL4/IL13

Primary and secondary end points



- ## Severe Asthma Exacerbations

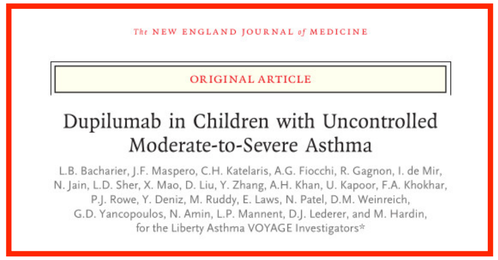
  Dupilumab Significantly Reduced the Annualized Rate of Severe Exacerbations Versus Placebo

- ## Change from Baseline in ppFEV1

  Dupilumab Significantly Improved FEV1pp Versus Placebo at Week 12

- ## Change from Baseline in ACQ-7-IA Score

  Dupilumab Significantly Improved Asthma Control Score (ACQ-7-IA) Versus Placebo at Week 24

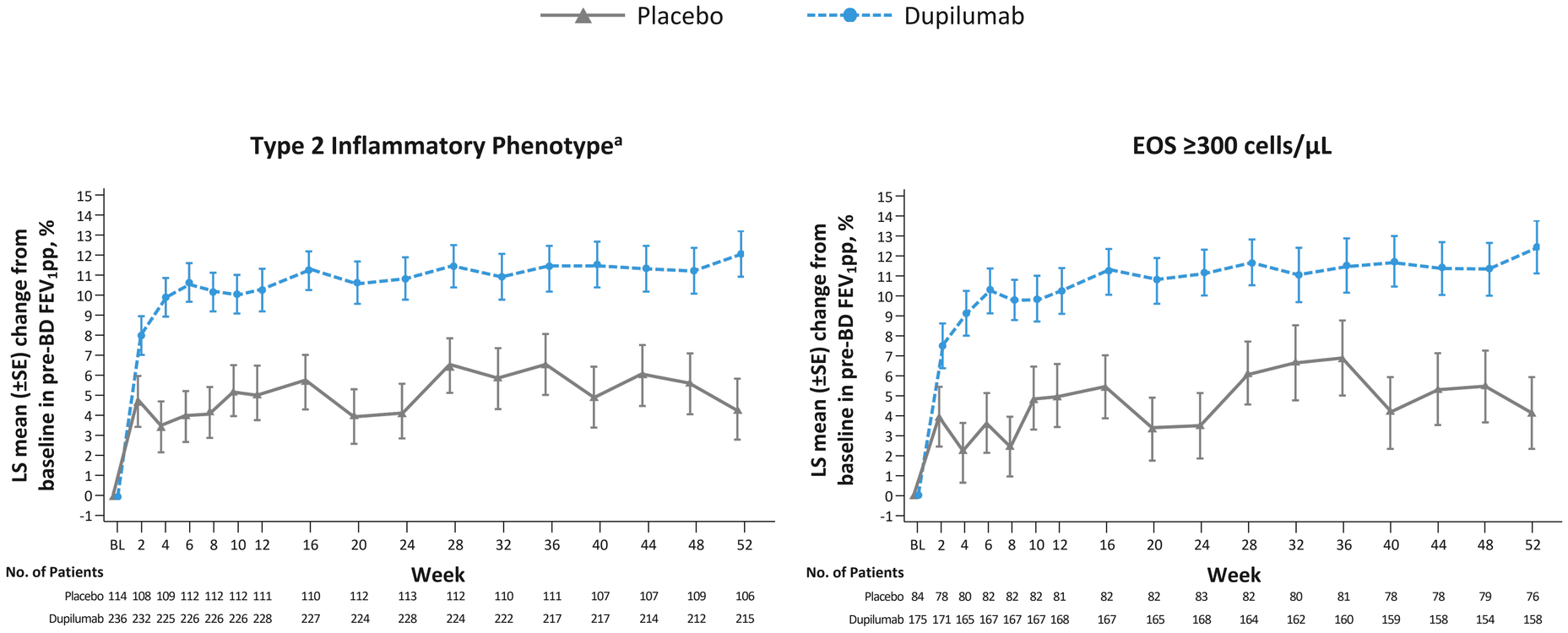

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

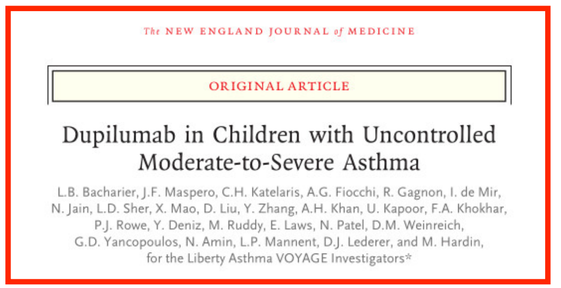
Dupilumab in Children with Uncontrolled Moderate-to-Severe Asthma

L.B. Bacharier, J.F. Maspero, C.H. Katelaris, A.G. Fiocchi, R. Gagnon, I. de Mir, N. Jain, L.D. Sher, X. Mao, D. Liu, Y. Zhang, A.H. Khan, U. Kapoor, F.A. Khokhar, P.J. Rowe, Y. Deniz, M. Ruddy, E. Laws, N. Patel, D.M. Weinreich, G.D. Yancopoulos, N. Amin, L.P. Mannent, D.J. Lederer, and M. Hardin, for the Liberty Asthma VOYAGE Investigators*

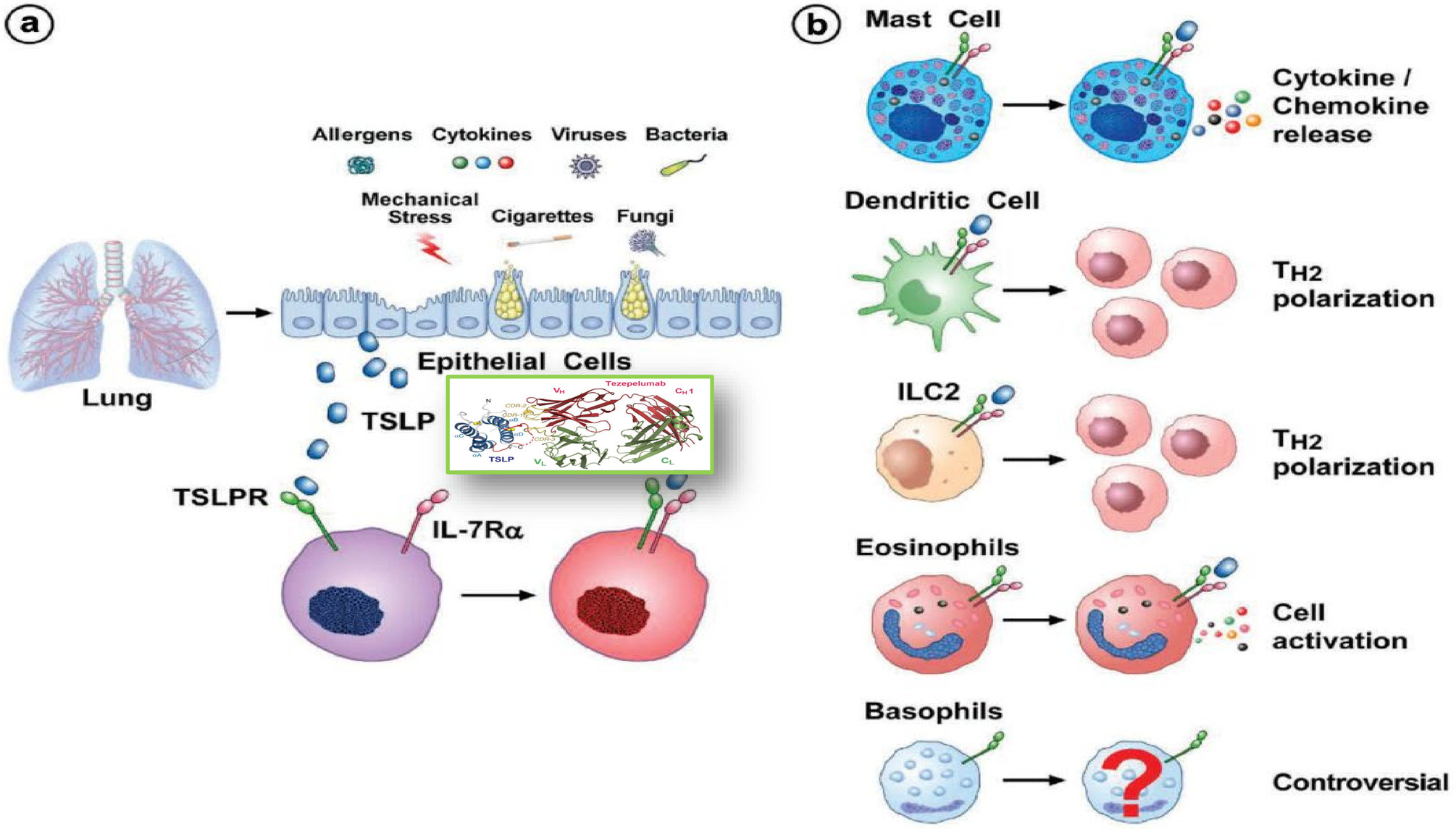
Dupilumab Led to Rapid and Sustained Lung Function Improvement Over the 52-Week Treatment Period



[a]Defined by baseline blood EOS count ≥150 cells/µL or baseline FeNO ≥20 ppb.
BD, bronchodilator; BL, baseline; EOS, eosinophils; FeNO, fractional exhaled nitric oxide; FEV_1pp, percent predicted forced expiratory volume in 1 second; LS, least squares; ppb, parts per billion; SE, standard error



A new first-in-class biologic gets FDA breakthrough status for non eosinophilic asthma: Tezepelumab



Marone G, et al. *Expert Opin Investig Drugs*. 2019;28(11):931-940.

Tezepelumab: anti-TSLP

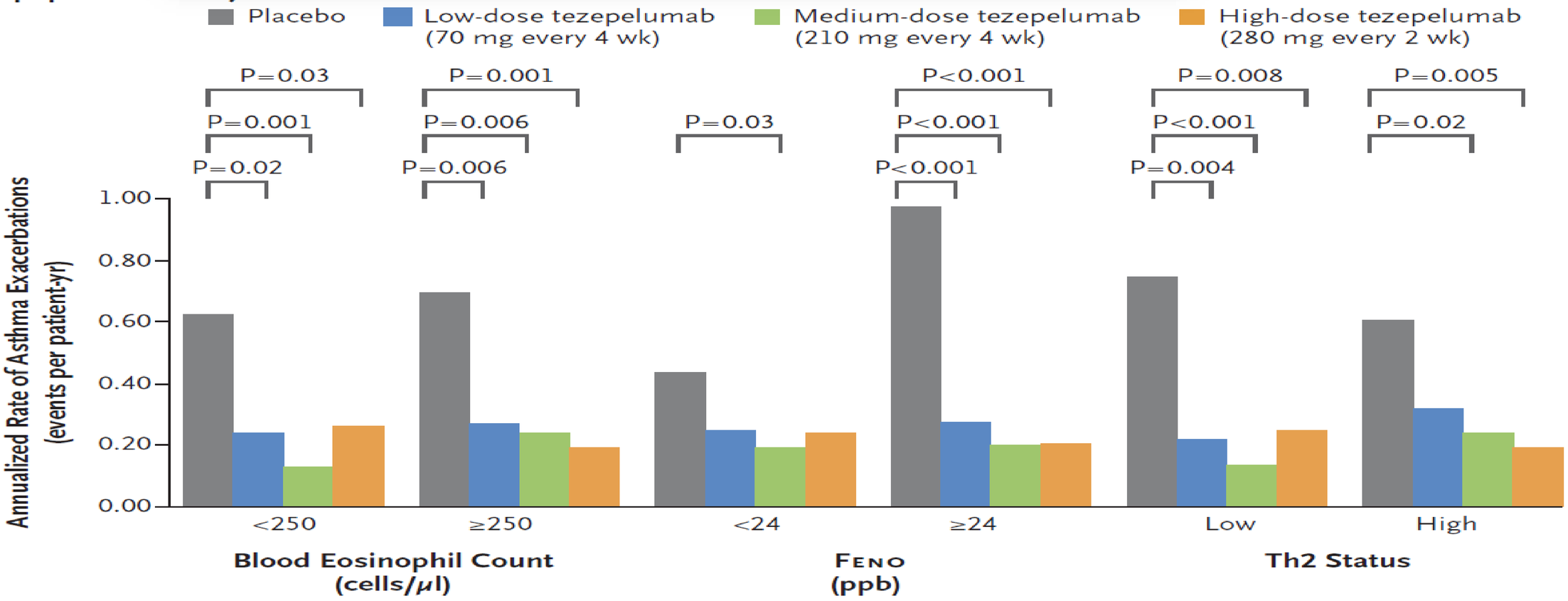
The NEW ENGLAND JOURNAL of MEDICINE

Tezepelumab in Adults with Uncontrolled Asthma

Jonathan Corren, M.D., Jane R. Parnes, M.D., Liangwei Wang, Ph.D., May Mo, M.S., Stephanie L. Roseti, A.P.N., M.S.N., Janet M. Griffiths, Ph.D., and René van der Merwe, M.B., Ch.B.

N Engl J Med. 2017;377:936-46.

A Subpopulation Analysis



✓ **The use of tezepelumab at a dose of 70 mg every 4 weeks, 210 mg every 4 weeks, or 280 mg every 2 weeks resulted in annualized asthma exacerbation rates at week 52 of 0.26, 0.19, and 0.22, respectively, as compared with 0.67 in the placebo group**

✓ **Thus, exacerbation rates in the respective tezepelumab groups were lower by 61%, 71%, and 66% than the rate in the placebo group (P<0.001 for all comparisons). Similar results were observed in patients regardless of blood eosinophil counts at enrollment**

ORIGINAL ARTICLE

Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma

Andrew Menzies-Gow, M.D., Jonathan Corren, M.D., Arnaud Bourdin, M.D., Geoffrey Chupp, M.D., Elliot Israel, M.D., Michael E. Wechsler, M.D., Christopher E. Brightling, F.Med.Sci., Janet M. Griffiths, Ph.D., Åsa Hellqvist, M.Sc., Karin Bowen, M.Sc., Primal Kaur, M.D., Gun Almqvist, M.Sc., Sandhia Ponnarambil, M.D., and Gene Colice, M.D.

Tezepelumab: anti-TSLP

PHASE 3, MULTICENTER, DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL

1061
Adults and adolescents who had ≥2 asthma exacerbations in preceding 12 mo

	Tezepelumab	Placebo
	N=529	N=532
	Subcutaneously every 4 wk	
Annualized rate of asthma exacerbations over 52 wk	0.93 95% CI, 0.80 to 1.07	2.10 95% CI, 1.84 to 2.39
	Rate ratio, 0.44; 95% CI, 0.37 to 0.53; P<0.001	
Adverse events	77.1%	80.8%
Serious adverse events	9.8%	13.7%

Tezepelumab reduced exacerbations in patients with severe, uncontrolled asthma.

The annualized rate of asthma exacerbations was 0.93 (95% confidence interval [CI], 0.80 to 1.07) with tezepelumab and 2.10 (95% CI, 1.84 to 2.39) with placebo. FEV_1 (0.23 vs. 0.09 liters; difference, 0.13 liters; 95% CI, 0.08 to 0.18; P<0.001)

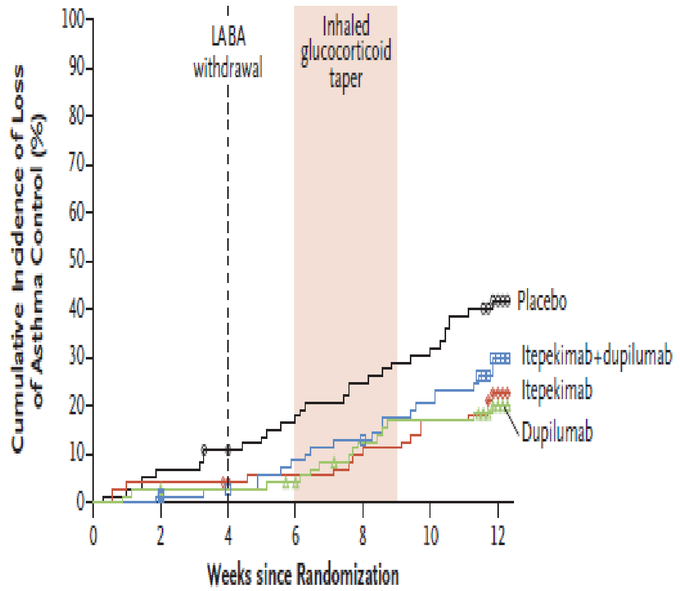
N Engl J Med. 2021;384(19):1800-1809.

Itepekimab: anti-IL33

ORIGINAL ARTICLE

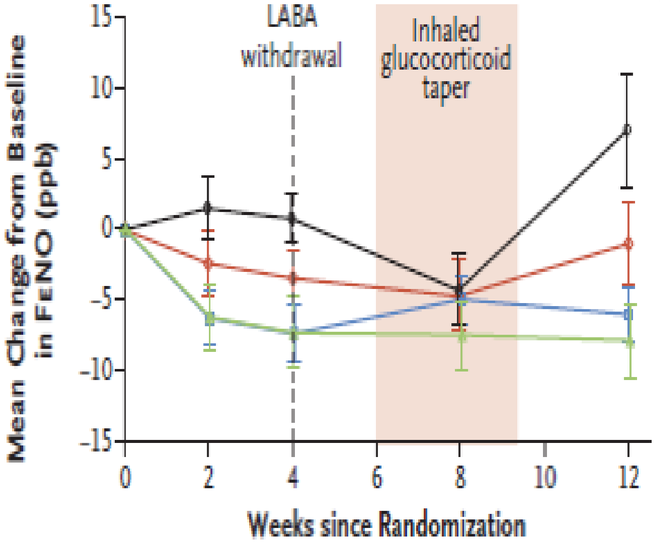
Efficacy and Safety of Itepekimab in Patients with Moderate-to-Severe Asthma

A Primary End Point: Loss of Asthma Control



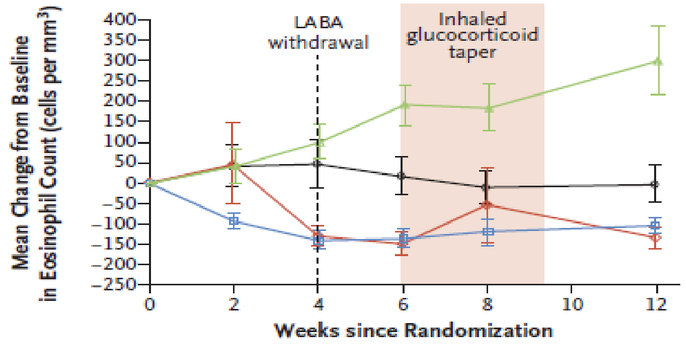
No. of Patients							
Placebo	74	69	65	60	54	50	31
Itepekimab	73	70	69	67	64	59	48
Itepekimab+dupilumab	74	73	68	63	60	54	32
Dupilumab	74	72	71	69	61	58	43

D Change in FeNO level



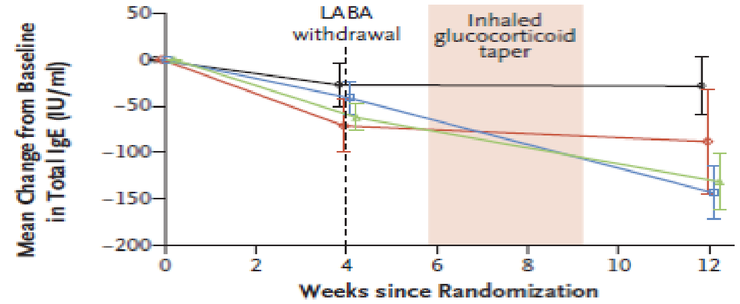
No. of Patients					
Placebo	73	69	66	58	49
Itepekimab	73	65	66	63	61
Itepekimab+ dupilumab	74	69	66	62	54
Dupilumab	72	70	70	67	58

C Change in Blood Eosinophil Count



No. of Patients						
Placebo	74	69	67	61	54	52
Itepekimab	73	68	65	62	65	62
Itepekimab+ dupilumab	74	66	68	62	58	56
Dupilumab	74	71	67	68	69	56

E Change in Total IgE Level



No. of Patients			
Placebo	74	72	56
Itepekimab	73	70	67
Itepekimab+ dupilumab	74	73	59
Dupilumab	74	73	63

Wechsler ME, et al. *N Engl J Med*. 2021;385(18):1656-1668.

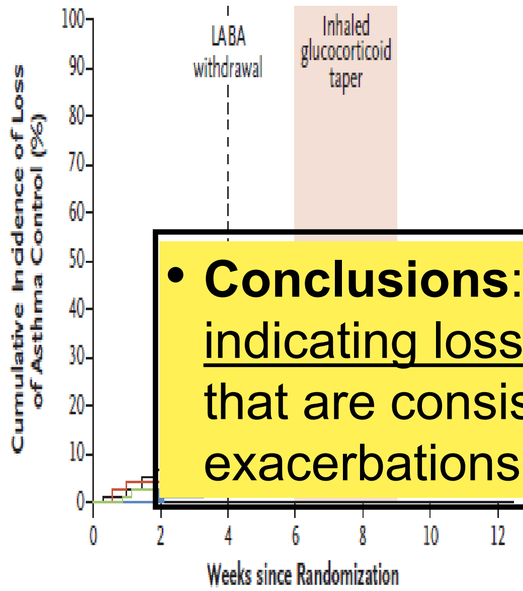
Itepekimab: anti-IL33

ORIGINAL ARTICLE

Efficacy and Safety of Itepekimab in Patients with Moderate-to-Severe Asthma

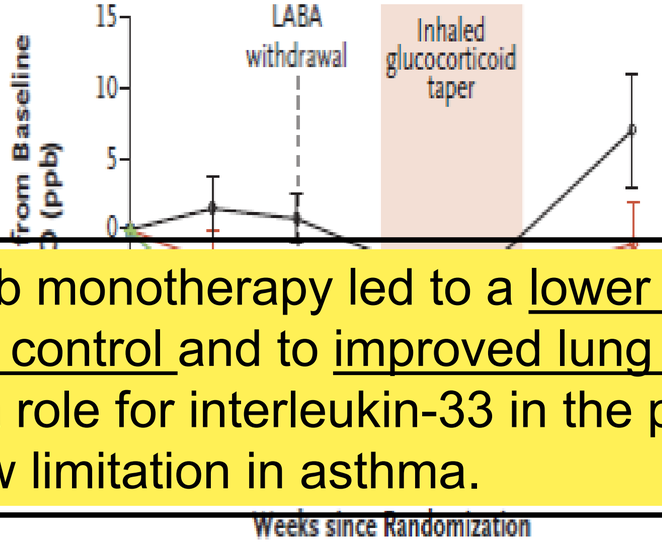
- **Conclusions**: Itepekimab monotherapy led to a lower incidence of events indicating loss of asthma control and to improved lung function, findings that are consistent with a role for interleukin-33 in the pathogenesis of exacerbations and airflow limitation in asthma.

A Primary End Point: Loss of Asthma Control



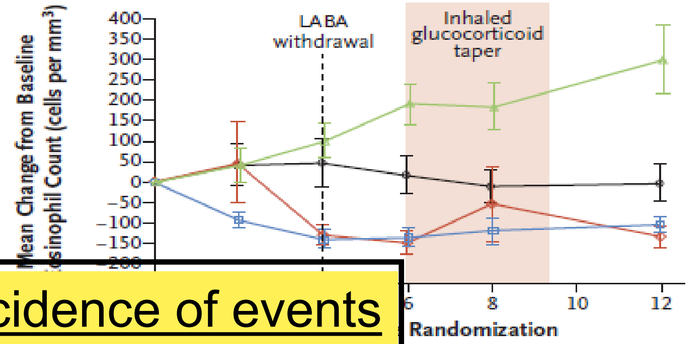
No. of Patients							
Placebo	74	69	65	60	54	50	31
Itepekimab	73	70	69	67	64	59	48
Itepekimab+dupilumab	74	73	68	63	60	54	32
Dupilumab	74	72	71	69	61	58	43

D Change in FeNO level



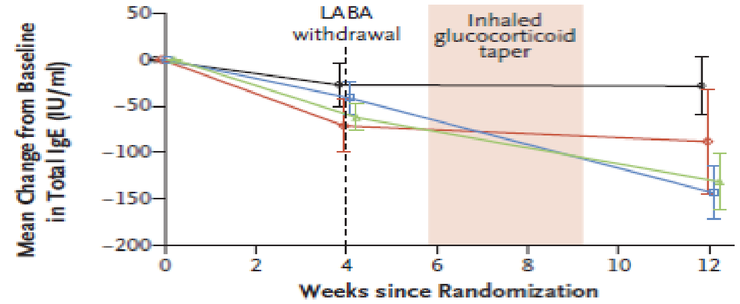
No. of Patients					
Placebo	73	69	66	58	49
Itepekimab	73	65	66	63	61
Itepekimab+ dupilumab	74	69	66	62	54
Dupilumab	72	70	70	67	58

C Change in Blood Eosinophil Count



61	54	52
62	65	62
62	58	56
68	69	56

E Change in Total IgE Level



No. of Patients			
Placebo	74	72	56
Itepekimab	73	70	67
Itepekimab+ dupilumab	74	73	59
Dupilumab	74	73	63

Wechsler ME, et al. *N Engl J Med*. 2021;385(18):1656-1668.

Depemokimab: anti-IL5

NIH U.S. National Library of Medicine

ClinicalTrials.gov

has the potential to be the first approved **ultra-long-acting biologic** with a six-month dosing schedule for severe asthma

Home > Search Results > Study Record Detail

Save this study

Placebo-controlled Efficacy and Safety Study of GSK3511294 (Depemokimab) in Participants With Severe Asthma With an Eosinophilic Phenotype

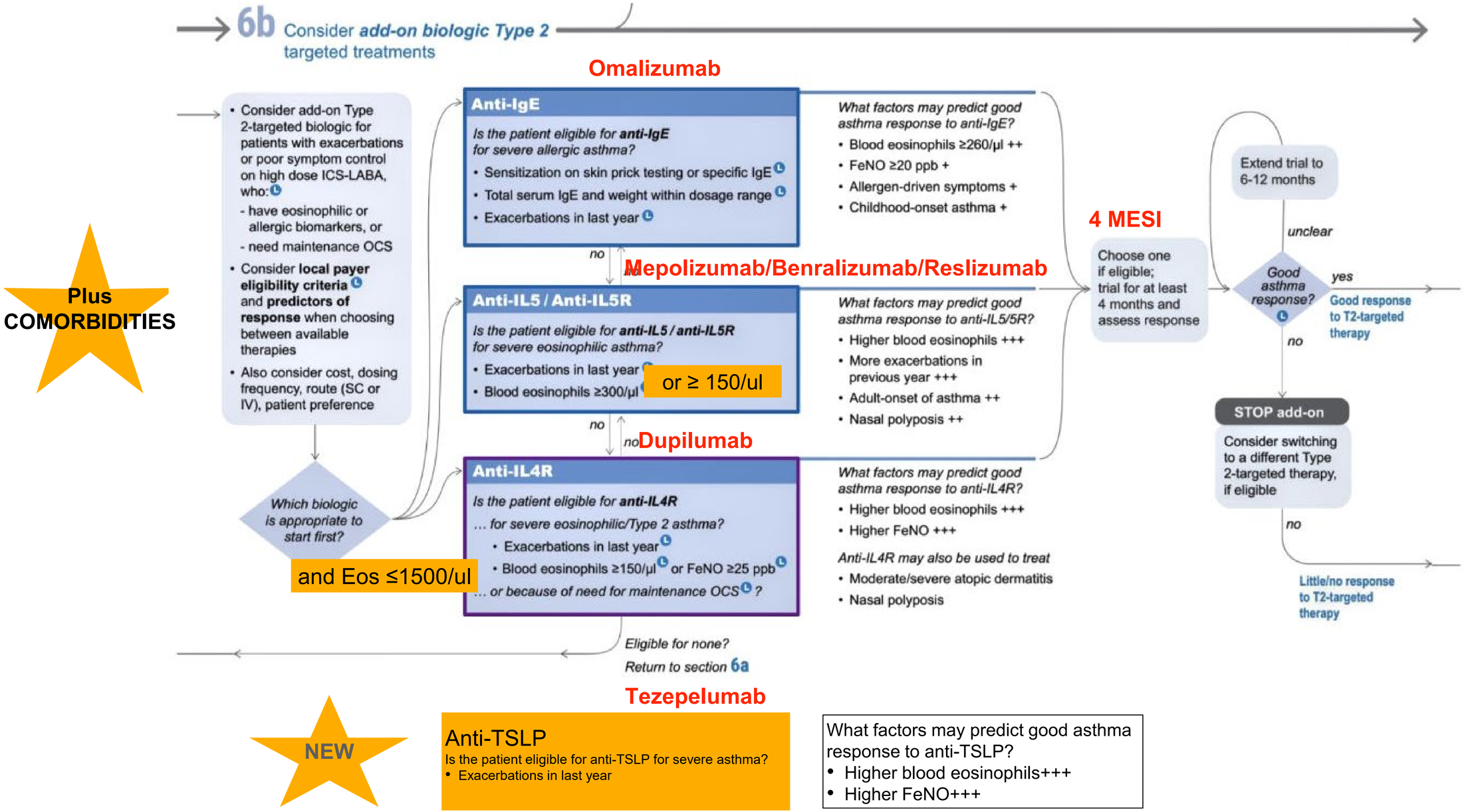
ClinicalTrials.gov Identifier: NCT04719832

Study Design

Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	375 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Double (Participant, Investigator)
Primary Purpose:	Treatment
Official Title:	A 52-week, Randomised, Double-blind, Placebo-controlled, Parallel-group, Multi-centre Study of the Efficacy and Safety of GSK3511294 Adjunctive Therapy in Adult and Adolescent Participants With Severe Uncontrolled Asthma With an Eosinophilic Phenotype
Actual Study Start Date :	March 17, 2021
Estimated Primary Completion Date :	February 16, 2024
Estimated Study Completion Date :	February 16, 2024

Step 5: add-on biologic Type 2-targeted treatments



GINA 2020 algorithm updated **GINA 2024**

Remission of Asthma (p 50)

New section summarizing the concepts of clinical and complete remission, both off-treatment and on-treatment

GINA provided examples of criteria for clinical and complete asthma remission

- Examples of criteria for **clinical remission** included **no asthma symptoms or exacerbations** for a specific period
- Examples of criteria for **complete remission** included **normal lung function, airway responsiveness, and/or inflammatory markers**

Remission of asthma

Remission of asthma has been investigated extensively in the past, most commonly remission of childhood asthma off treatment. Definitions and criteria vary, but they commonly refer to either ***clinical remission*** **(eg, no asthma symptoms or exacerbations for a specific period) or** ***complete (or pathophysiological) remission*** **(eg, also including normal lung function, airway responsiveness, and/or inflammatory markers).** There has been interest in *remission off treatment* and *remission on treatment,* for example, with biologic therapy for severe asthma. **The concept of clinical remission on treatment is consistent with the** ***long-term goal of asthma management*** **promoted by GINA, which is to achieve the best possible long-term asthma outcomes for the patient (see Box 3-2, p 50).** When discussing the best possible outcomes with a patient, consider their own asthma goals, their asthma phenotype, clinical features, multimorbidity, risk factors (including severity of airflow limitation), practical issues including the availability and cost of medications, and the potential for adverse effects of treatment (Box 3-4, p 54).

Research in patients who have (or have not) experienced clinical or complete remission of asthma, either off treatment or on treatment, provides important opportunities for understanding the heterogeneous and interconnected underlying mechanisms of asthma, and for developing new approaches to asthma prevention and management. This will be facilitated by using standardized criteria and tools.

1. https://ginasthma.org/wp-content/uploads/2024/05/GINA-2024-Main-Report-WMS-1.pdf. Accessed May 2024. 2. https://ginasthma.org/wp-content/uploads/2023/07/GINA-2023-Full-report-23_07_06-WMS.pdf. Accessed May 2024.

Take Home messages

- Stepping Down: when Asthma Symptoms have been **well controlled** and **lung function** has been stable for **3 or more months** (Evidence D);
- Before Stepping up, remember: **incorrect inhaler technique**; **poor adherence**; **persistent exposure at home/work** to agents such as allergens, tobacco smoke, indoor or outdoor air pollution, or to medications such as beta-blockers or (in some patients) non steroidal anti-infiammatory drugs (NSAIDs); **comorbidities**; **incorrect diagnosis**.
- Biologic therapy: as add-on therapy for severe asthma has revolutionized severe asthma management
- FOUR Biologics are currently licensed to treat severe asthma in children and/or adolescents: omalizumab, mepolizumab, dupilumab e tezepelumab
- Biologic therapy: Wich biologic is appropriate to start first? Trial for at least 4 months and assess response
- Remission of asthma: the long-term goal of asthma management


World Asthma Day
• May 7, 2024 •
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ASTHMA EDUCATION EMPOWERS
Information is Key
SIMRI
società italiana per le malattie respiratorie infantili
Broncopneumologia
Pulmonary Unit