



# **ASTMA bij volwassenen**

**Prof Dr Guy BRUSSELLE**

**Dienst Longziekten**

**UZ Gent**

**27/02/2019**

# Casus: Sofie, 33 jaar

- VG: astma sinds 14-jarige leeftijd;  
allergisch aan dierenepitheel (kat, hond)
- HA: sinds maanden dyspneu d'effort,  
frequent nachtelijke dyspneu en hoest;  
vorige maand astma opstoot (Medrol kuur)
- Medicatie:
  - Relvar 92/22 $\mu$ g;
  - Ventolin 100 $\mu$ g

# Casus: Sofie, 33 jaar

- VG: astma sinds 14-jarige leeftijd; allergisch aan dierenepitheel (kat, hond)
- HA: sinds maanden dyspneu (dag en nacht); vorige maand astma opstoot (Medrol kuur)
- Huisdieren: kat (binnenshuis)

## ■ Medicatie:

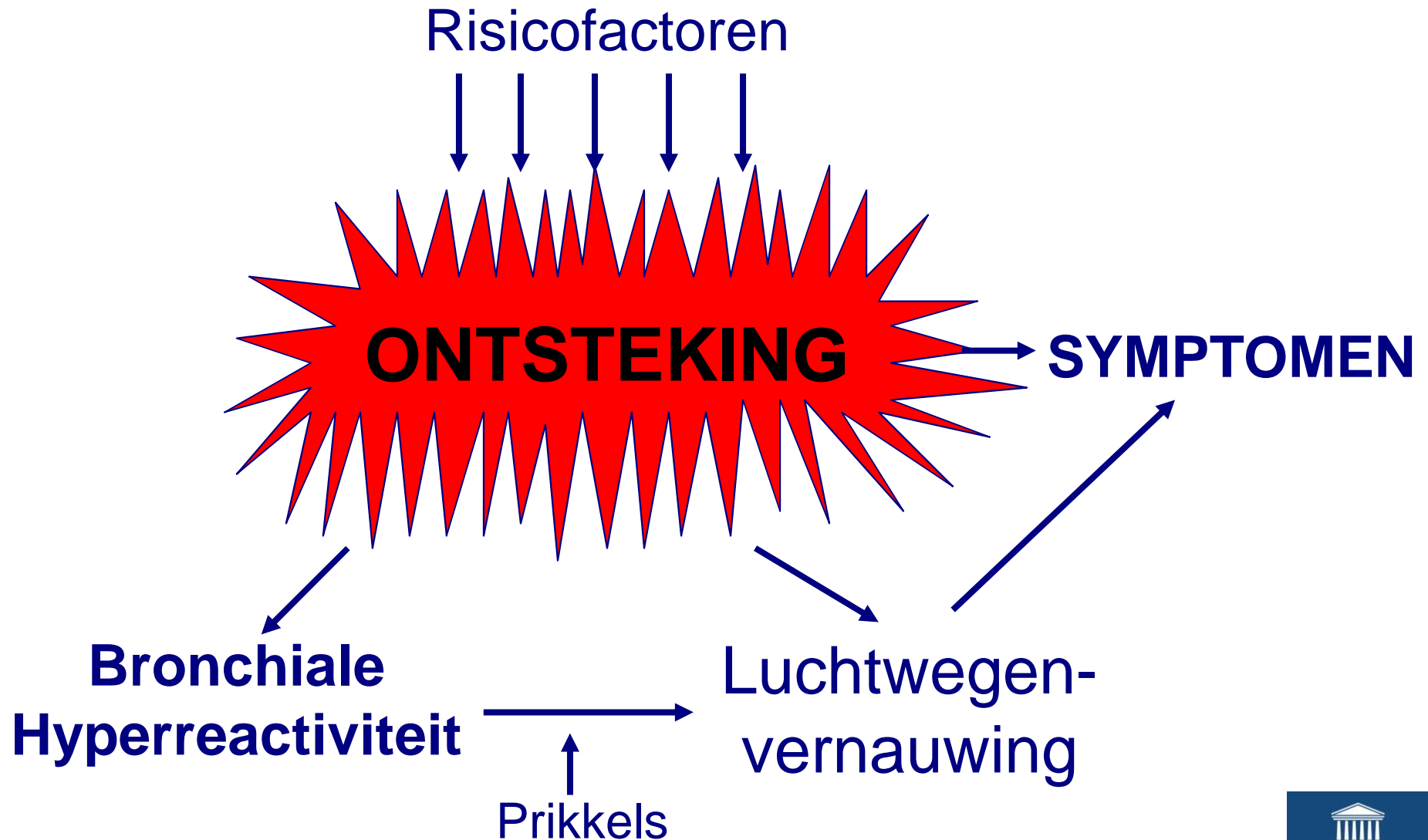
Relvar 92/22 $\mu$ g: *1x 1 puff?* Zeer onregelmatig!  
(episodisch)

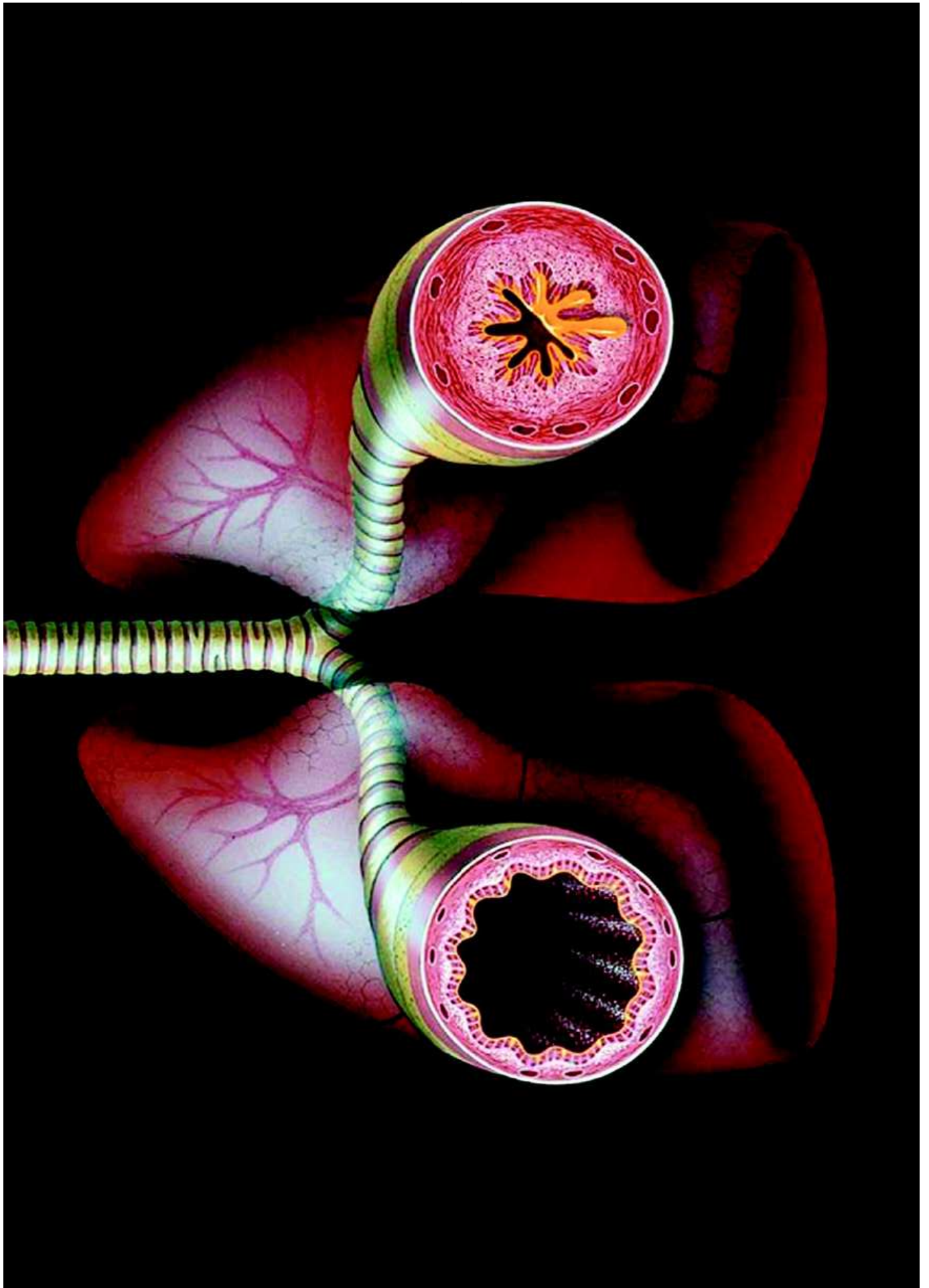
Ventolin: *zo nodig (SOS)?* Abusus! 4 tot 6x daags!

# Astma: overzicht

- Astma: (DD) diagnose
- Astma: behandeling
- Mild astma: paradoxes in management
- Ernstig astma: biologics
- Conclusie

# Definitie van astma

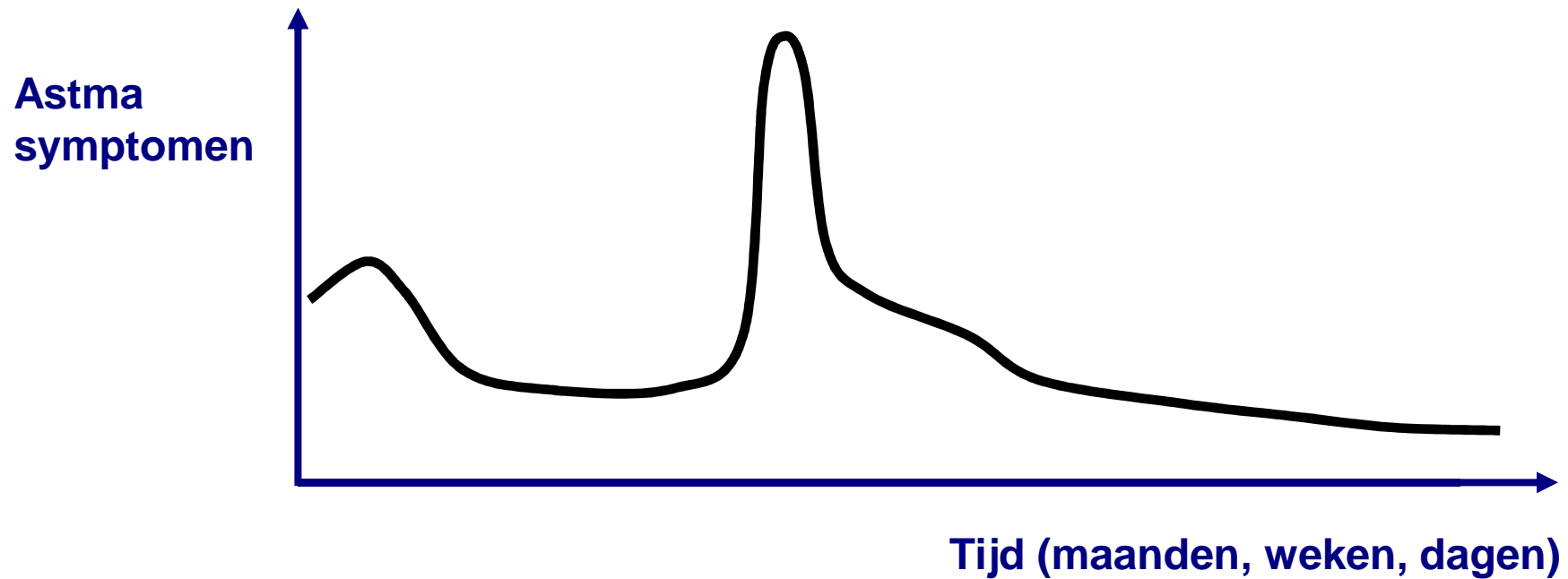




# Diagnose van astma

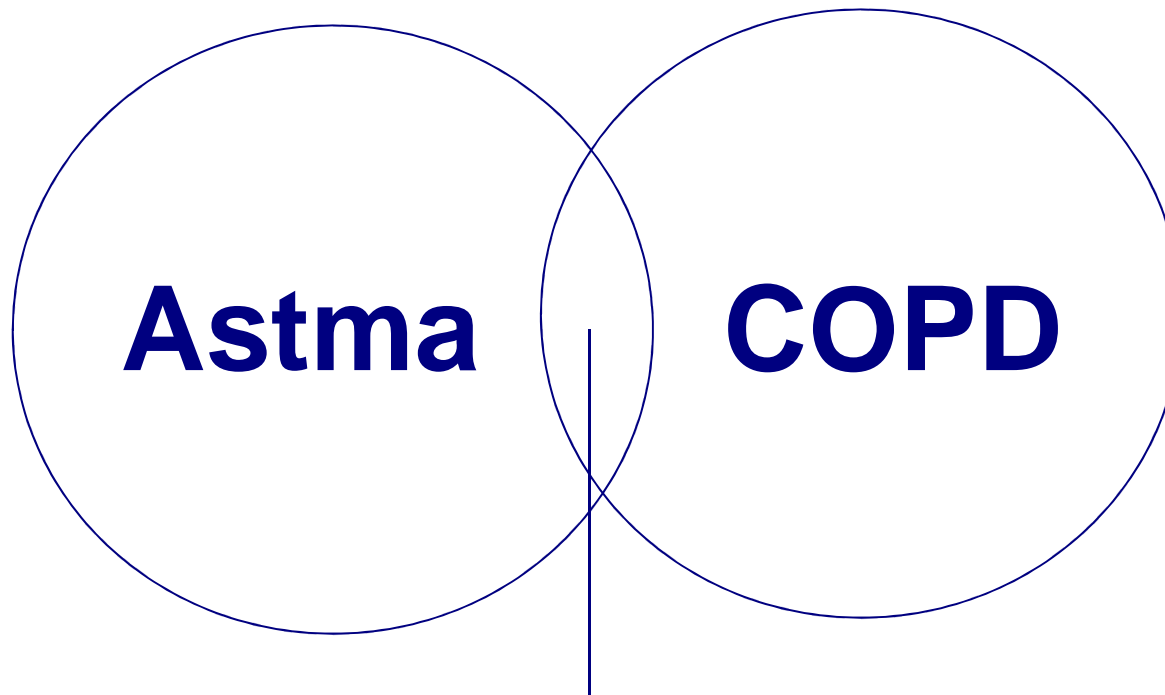
- Anamnese
- Klinisch Onderzoek
- Longfunctie:
  - aantonen van reversibele luchtwegenvernauwing
  - aantonen van bronchiale hyperreactiviteit
- Allergietesten
- Bloedonderzoek: eosinofilie
- FeNO

# Astma is een variabele aandoening





# Obstructieve Longaandoeningen



10-20% van de patiënten hebben beide  
aandoeningen: astma EN COPD:

**ACO(S)** = **Astma en COPD Overlap (Syndroom)**

# ASTMA

Allergeen



Luchtwegen inflammatie  
CD4+ T-lymfocyten  
Eosinofielen



Volledig  
reversibel

Luchtwegenvernauwing

Niet  
volledig  
reversibel

# COPD

Sigarettenrook



Long inflammatie  
CD8+ T-lymfocyten  
Macrofagen  
Neutrofielen



<b><u>DIAGNOSE</u></b>	<b><u>ASTMA</u></b>	<b><u>COPD</u></b>
Leeftijd Begin (leeftijd)	Alle leeftijden Meestal jong (vaak als kind)	Ouder dan 40 j. Later (mid-life)
Symptomen	wisselend	langzaam progressief
Nachtelijke klachten	ja	zelden
Voorgeschiedenis	eczema hooikoorts	roken
Familiale anamnese	astma	(COPD)

<b><u>DIAGNOSE</u></b>	<b><u>ASTMA</u></b>	<b><u>COPD</u></b>
<b>Kortademig</b>	<b>Na</b> inspanning	<b>Tijdens</b> inspanning
<b>BHR</b> (Bronchiale hyperreactiviteit)	<b>+++</b>	<b>±</b>
<b>Vernauwing luchtwegen</b>	omkeerbaar	niet volledig omkeerbaar
<b>Oorzaak</b>	> Allergie < APA syndroom	roken
<b>Diagnose</b>	Spirometrie Piekstroom	Spirometrie

# Astma: overzicht

- Astma: (DD) diagnose
- Astma: behandeling
- Mild astma: paradoxes in management
- Ernstig astma: biologics
- Conclusie



Asthma Management and Prevention Program

# Goals of Long-term Management

---

1. Achieve and maintain control of symptoms
2. Maintain normal activity levels, including exercise
3. Maintain pulmonary function as close to normal levels as possible
4. Prevent asthma exacerbations
5. Prevent asthma mortality
6. Avoid adverse effects from asthma medications



Asthma Management and Prevention Program

# Goals of Long-term Management

---

1. Achieve and maintain control of symptoms
2. Maintain normal activity levels, including exercise
3. Maintain pulmonary function as close to normal levels as possible
- 4. Prevent asthma exacerbations**
- 5. Prevent asthma mortality**
6. Avoid adverse effects from asthma medications

# Inhalatie CorticoSteroïden (ICS)

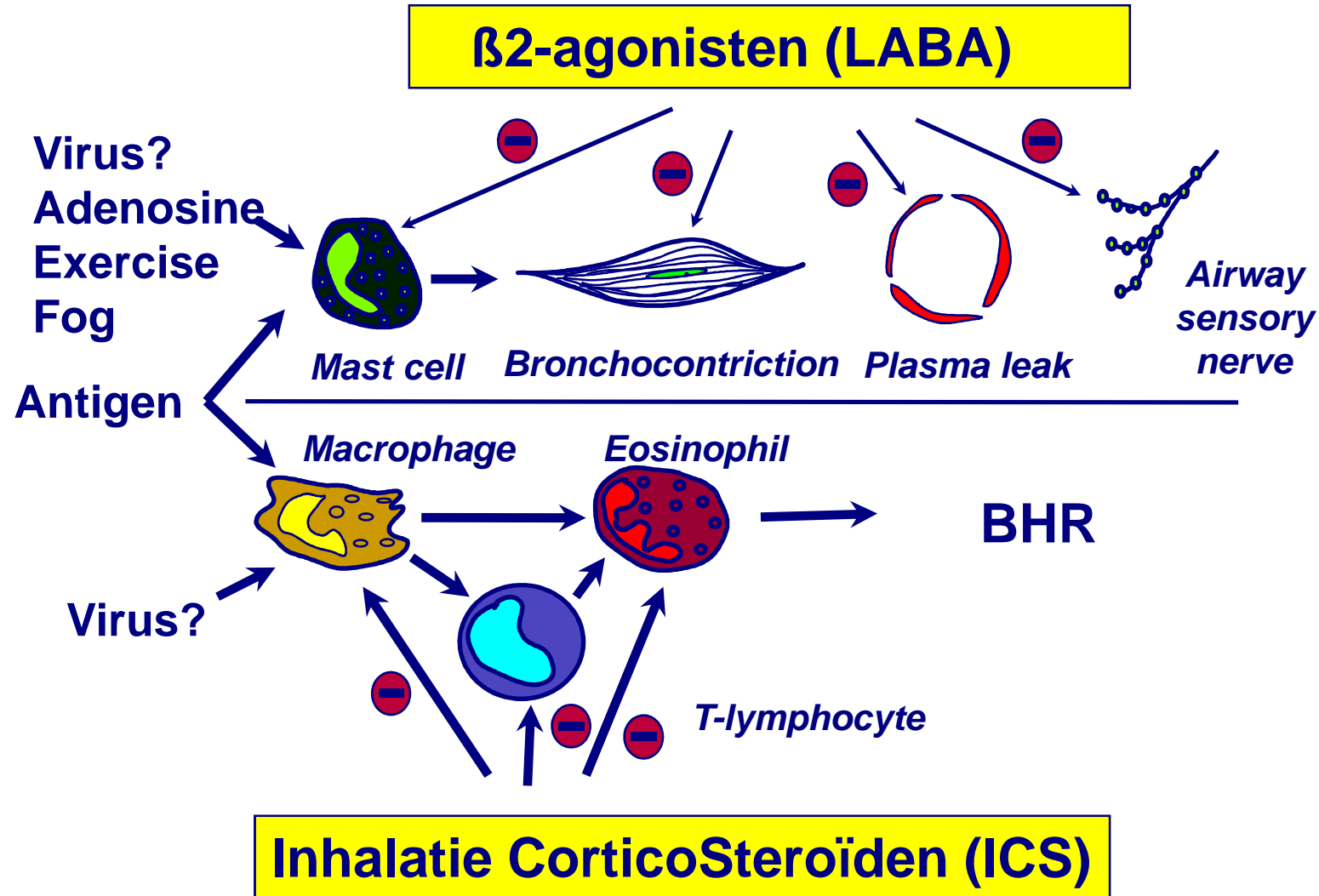
<u>ICS</u>	<u>Merknaam</u>	<u>Inhalator</u>	<u>Dosis</u>	<u>Dosering</u>
Beclometason	Qvar ®	Doseeraërosol Autohaler	50 µg	2x
			100 µg	2x
Budesonide	Pulmicort ®	<i>Turbohaler</i>	200 µg	2x
	Miflonide ®	<i>Aerolizer</i>	200 µg	2x
	Budesonide	<i>Easyhaler</i>	200 µg	2x
	Budesonide	<i>Novolizer</i>	200 µg	2x
Fluticason propionaat	Flixotide ®	<i>Diskus</i>	100 µg	2x
			250 µg	2x
			500 µg	2x
		Doseeraërosol pMDI	50 µg	2x
			250 µg	2x

## **Droog Poeder Inhalatoren (DPI):**

*Aerolizer, Diskus, Easyhaler, Novolizer, Turbohaler.*



# Vaste combinatie van LABA + ICS



# LABA + ICS vaste combinaties

ICS	LABA	Merknaam	Inhalator	Dosis	Dosering
<u>Fluticason</u>	Salmeterol	Seretide ®	Doseeraërosol  <i>Diskus</i>	<u>25/50</u> <u>25/125</u> <u>25/250</u> <u>50/100</u> <u>50/250</u> <u>50/500</u>	2x 2 puffs  2x 1 inhalatie
<u>Fluticason</u>	Formoterol	Flutiform ®	Doseeraërosol	<u>50/5</u> <u>125/5</u> <u>250/10</u>	2x 2 puffs
<u>Budesonide</u>	Formoterol	Symbicort ® Symbicort Forte Bufomix ®	<i>Turbohaler</i>  <i>Easyhaler</i>	<u>160/4,5</u> <u>320/9</u> <u>200/6</u>	2x 1 à 2 inh. 2x 1 inhalatie
<u>Beclometason</u>	Formoterol	Inuvair ®	Doseeraërosol <i>Nexthaler</i>	<u>100/6</u> <u>100/6</u> <u>200/6</u>	2x 1 à 2 puffs 2x 1 à 2 inh. 2x 1 à 2 inh.
<u>Fluticasonfuroaat</u>	Vilanterol	Relvar ®	<i>Ellipta</i>	<u>92/22</u> <u>184/22</u>	1x 1 inhalatie 1x 1 inhalatie

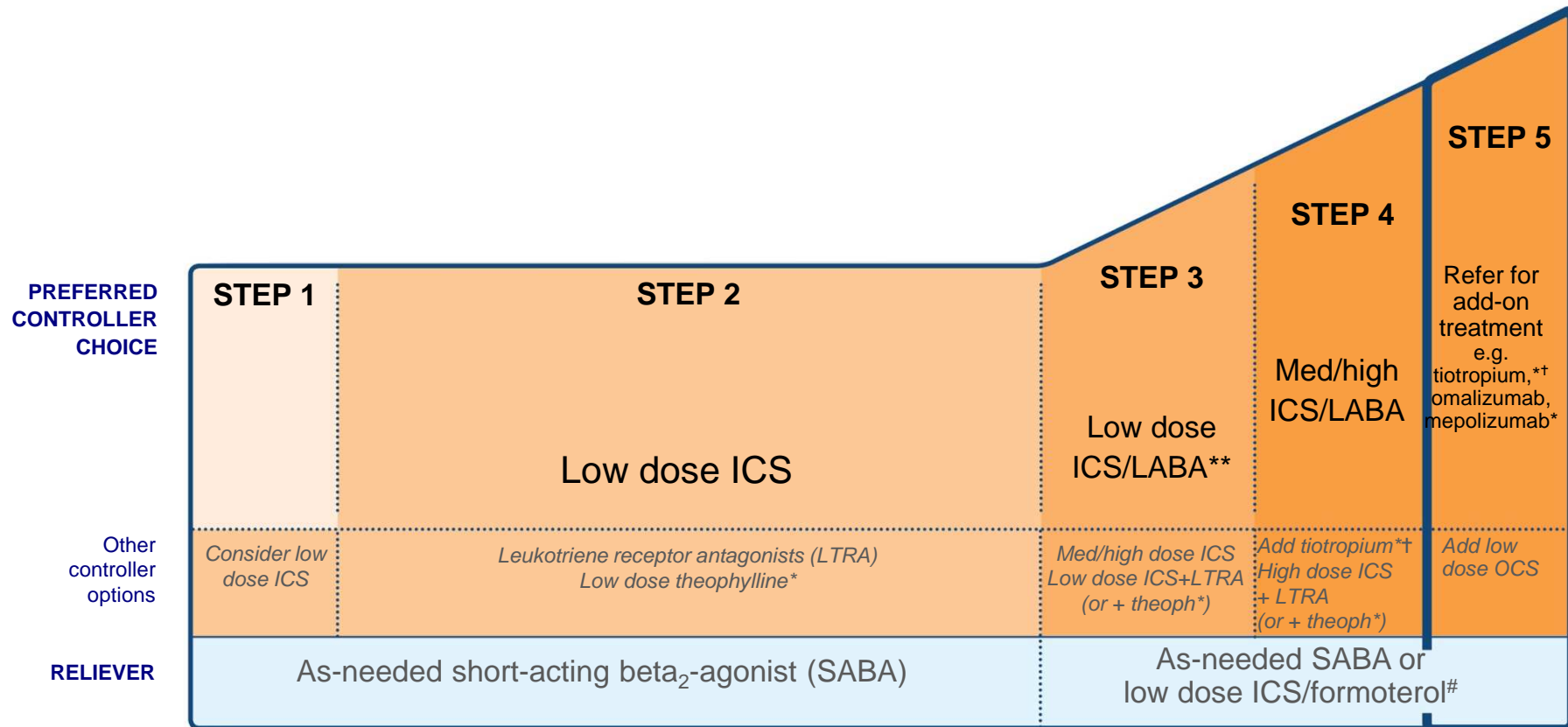
[www.bvp-sbp.org](http://www.bvp-sbp.org)  
[www.apb.be](http://www.apb.be)

App: My Puff



Voorschrift: R/ GGG = Goed Gebruik Geneesmiddelen

# Behandeling van astma (GINA 2018)





# Levels of Asthma Control

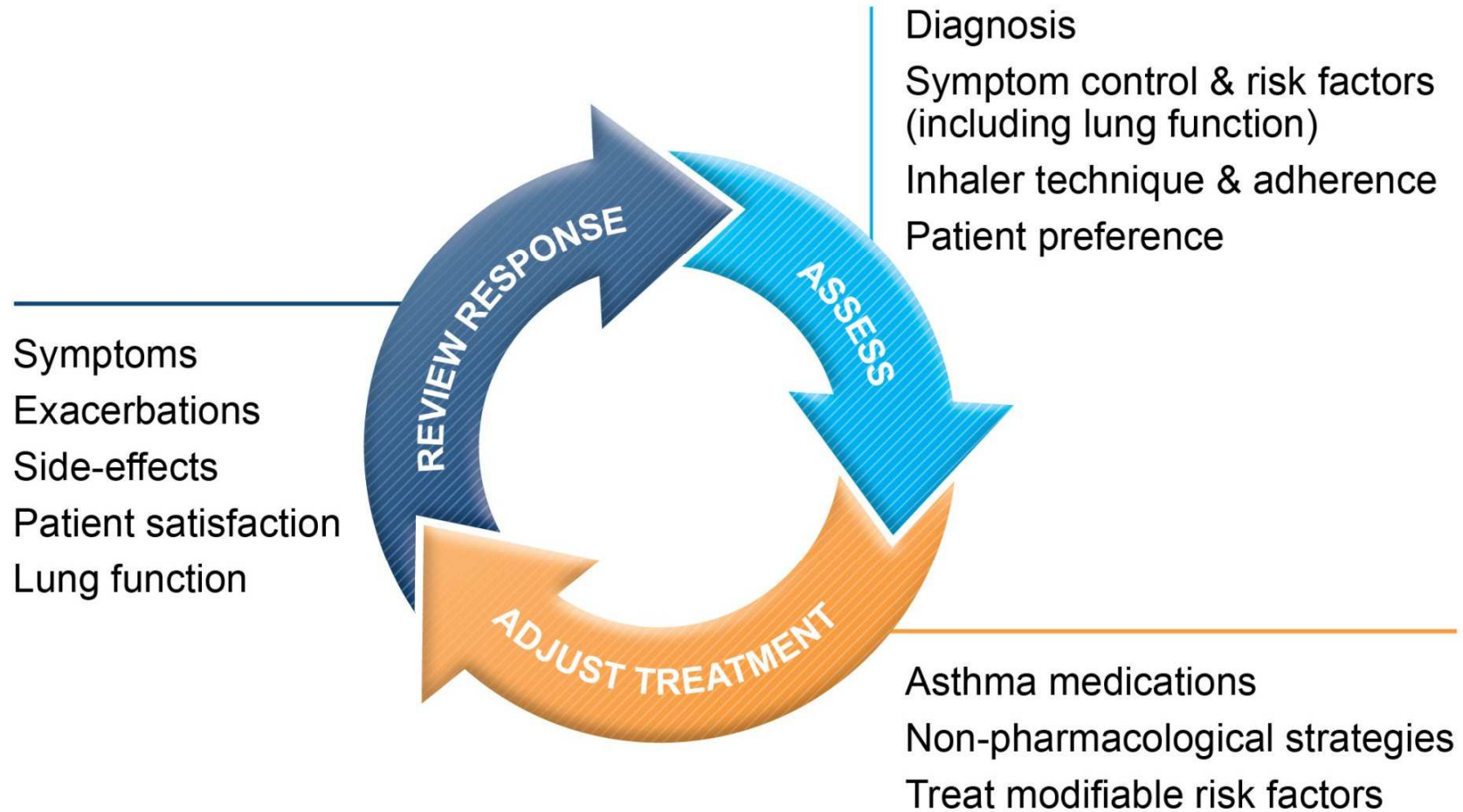
<b>Characteristic</b>	<b>Controlled</b>	<b>Partly controlled (Any present in any week)</b>	<b>Uncontrolled</b>
<b>Daytime symptoms</b>	<b>None (2 or less / week)</b>	<b>More than twice / week</b>	<b>3 or more features of partly controlled asthma present in any week</b>
<b>Limitations of activities</b>	<b>None</b>	<b>Any</b>	
<b>Nocturnal symptoms / awakening</b>	<b>None</b>	<b>Any</b>	
<b>Need for rescue / "reliever" treatment</b>	<b>None (2 or less / week)</b>	<b>More than twice / week</b>	
<b>Lung function (PEF or FEV<sub>1</sub>)</b>	<b>Normal</b>	<b>&lt; 80% predicted</b>	
<b>Exacerbation</b>	<b>None</b>	<b>One or more / year</b>	

# Als astma niet onder controle is

- **Slechte therapietrouw (ICS)**
- **Slechte inhalatietechniek**
- **Roken**
- **Blijvende blootstelling aan allergenen**
- **Significante comorbiditeit**
- **Foute diagnose**
- **Ernstig astma**

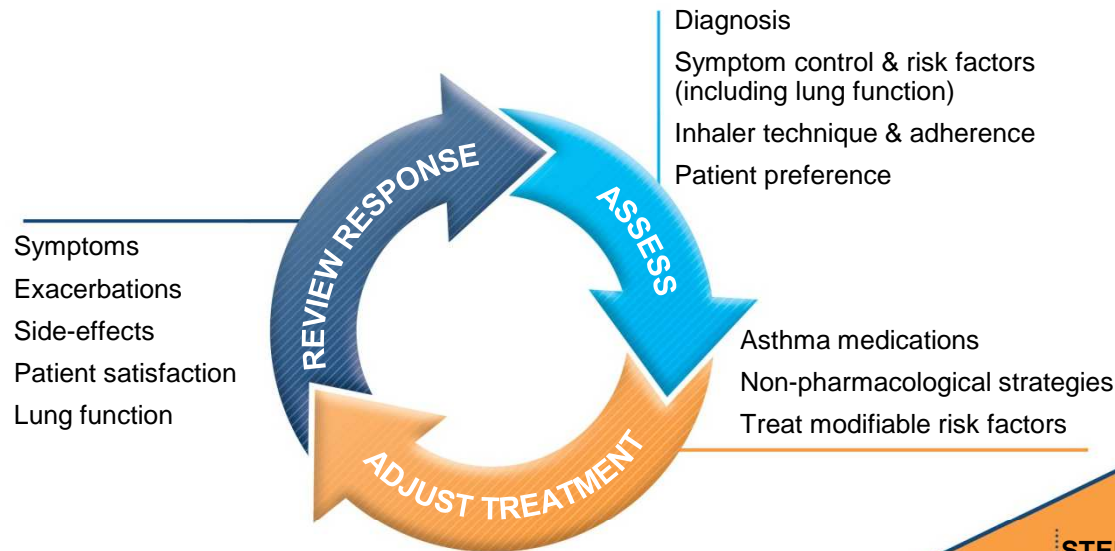


# The control-based asthma management cycle



# Stepwise management of asthma: pharmacotherapy

UPDATED  
2017



	<b>STEP 1</b>		<b>STEP 2</b>		<b>STEP 3</b>	<b>STEP 4</b>	<b>STEP 5</b>
<b>PREFERRED CONTROLLER CHOICE</b>			Low dose ICS		Low dose ICS/LABA**	Med/high ICS/LABA	Refer for add-on treatment e.g. tiotropium,** anti-IgE, anti-IL5*
Other controller options	Consider low dose ICS	Leukotriene receptor antagonists (LTRA) Low dose theophylline*		Med/high dose ICS Low dose ICS+LTRA (or + theoph*)	Add tiotropium*† High dose ICS + LTRA (or + theoph*)	Add low dose OCS	
<b>RELIEVER</b>	As-needed short-acting beta2-agonist (SABA)				As-needed SABA or low dose ICS/formoterol#		

#For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations





# Acute exacerbatie van astma: Behandeling

- Snelwerkende Bronchodilatoren: SABA  
(salbutamol: Ventolin®) als rescue: SOS
- Onderhoudsmedikatie:  
opdrijven van ICS+LABA
- Systemische corticosteroiden:  
methylprednisolone 32mg 1co daags  
gedurende 5 dagen
- Zo nodig zuurstof:  
streefdoel O<sub>2</sub> saturatie ≥ 92%

# Astma: overzicht

- Astma: (DD) diagnose
- Astma: behandeling
- **Mild astma: paradoxes in management**
- Ernstig astma: biologics
- Conclusie

# The paradoxes of asthma management: time for a new approach?

Paul M. O'Byrne<sup>1</sup>, Christine Jenkins<sup>2</sup> and Eric D. Bateman<sup>3</sup>

**Affiliations:** <sup>1</sup>Firestone Institute for Respiratory Health, St. Joseph's Healthcare and the Michael G DeGroote School of Medicine, McMaster University, Hamilton, ON, Canada. <sup>2</sup>The George Institute for Global Health, Sydney, Australia. <sup>3</sup>Division of Pulmonology, Dept of Medicine, University of Cape Town, Cape Town, South Africa.

**Correspondence:** Paul M. O'Byrne, Firestone Institute for Respiratory Health, St. Joseph's Healthcare and McMaster University, 1200 Main St. West, Hamilton, ON L8N 3Z5. Canada. E-mail: [obyrne@mcmaster.ca](mailto:obyrne@mcmaster.ca)



@ERSpublications

Paradoxes in asthma management, counterproductive in achieving optimal control, highlight a need for new approaches <http://ow.ly/7ikh30e2tOV>

P. O'Byrne et al, ERJ 2017.

# Paradoxes in (mild) asthma management

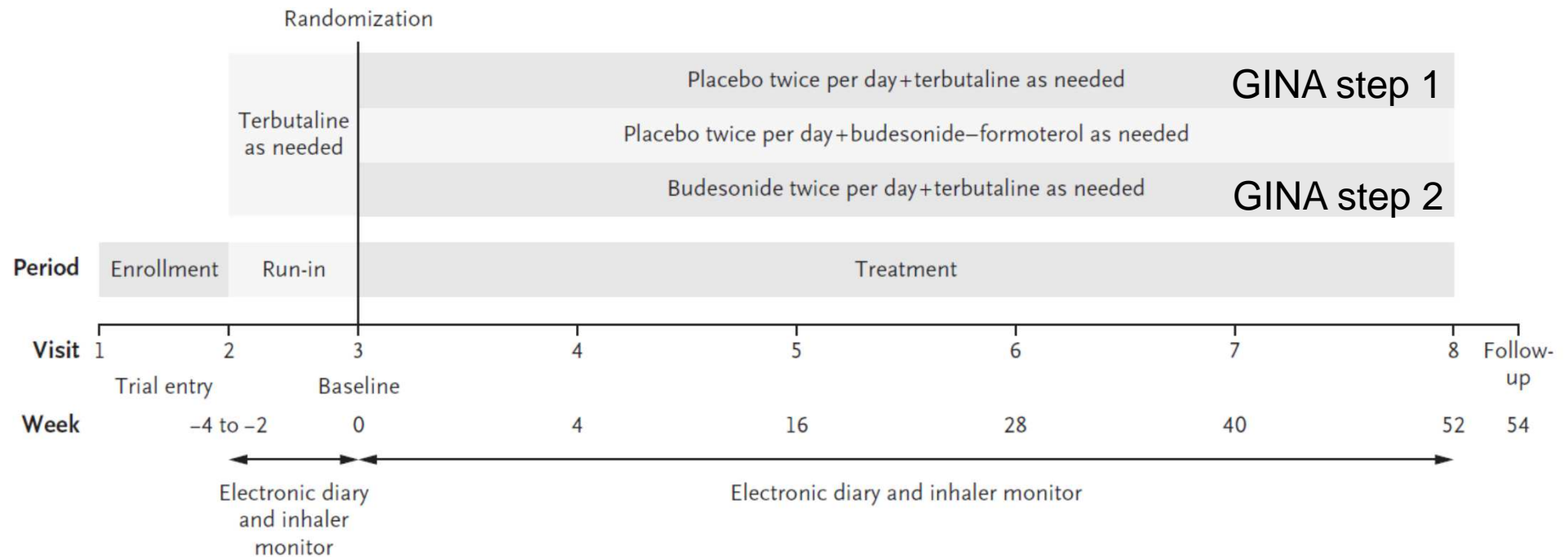
TABLE 1 Paradoxes in current asthma management

Paradox	Description
---------	-------------

- |   |   |
|---|---|
| 1 | In step 1 treatment, a SABA bronchodilator alone is recommended despite the fact that asthma is a disease of chronic airway inflammation with increased inflammation at the times of exacerbations.   |
| 2 | In step 1 treatment, the patient has autonomy and their perception of treatment as needed to control symptoms is accepted, whereas at higher asthma treatment steps it is assumed that patients will adopt a fixed-dose approach.   |
| 3 | There is a switch in recommendation from using a SABA alone as-needed at step 1 to advising an ICS fixed-dose regimen at step 2 and minimising SABA use. The medication that treats the underlying disease, which patients are encouraged to take (the ICS) is not the one that the patient perceives is benefitting them (the SABA), which they are now discouraged from taking. |
| 4 | There is a different safety message in the advice given for the use of SABA and LABA within the guidelines; SABA alone being safe and LABA alone being unsafe.  |
| 5 | There is a dislocation between patients' understanding of "asthma control" and the frequency, impact and severity of their symptoms.  |

SABA: short-acting  $\beta_2$ -agonist; ICS: inhaled corticosteroid; LABA: long-acting  $\beta_2$ -agonist.

# Inhaled combined budesonide-formoterol as needed in mild asthma: SYGMA 1 trial design

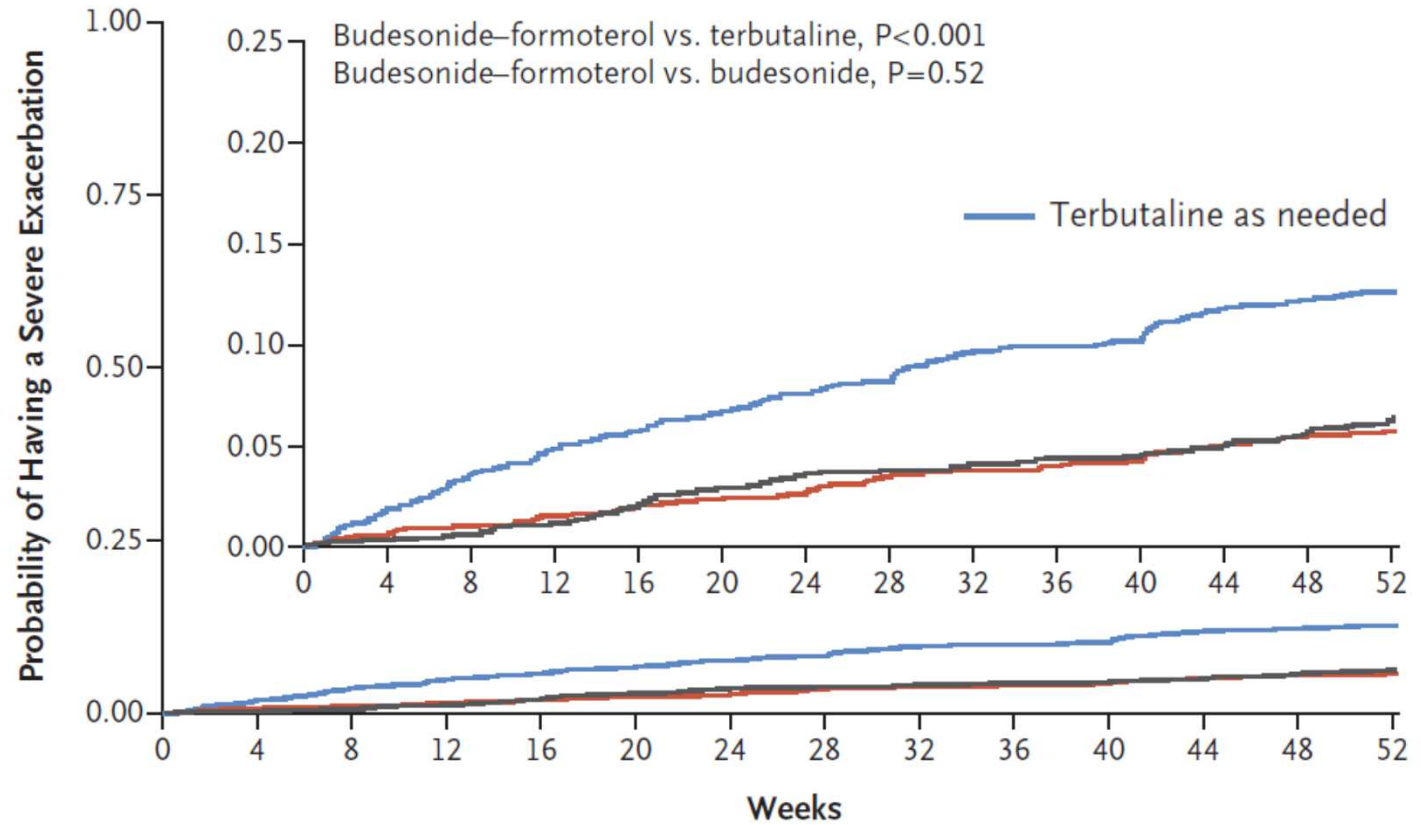


Adherence rate to maintenance treatment: 79%

P. O'Byrne et al, NEJM 2018.

# SYGMA 1 trial: severe exacerbations

## Severe Exacerbation



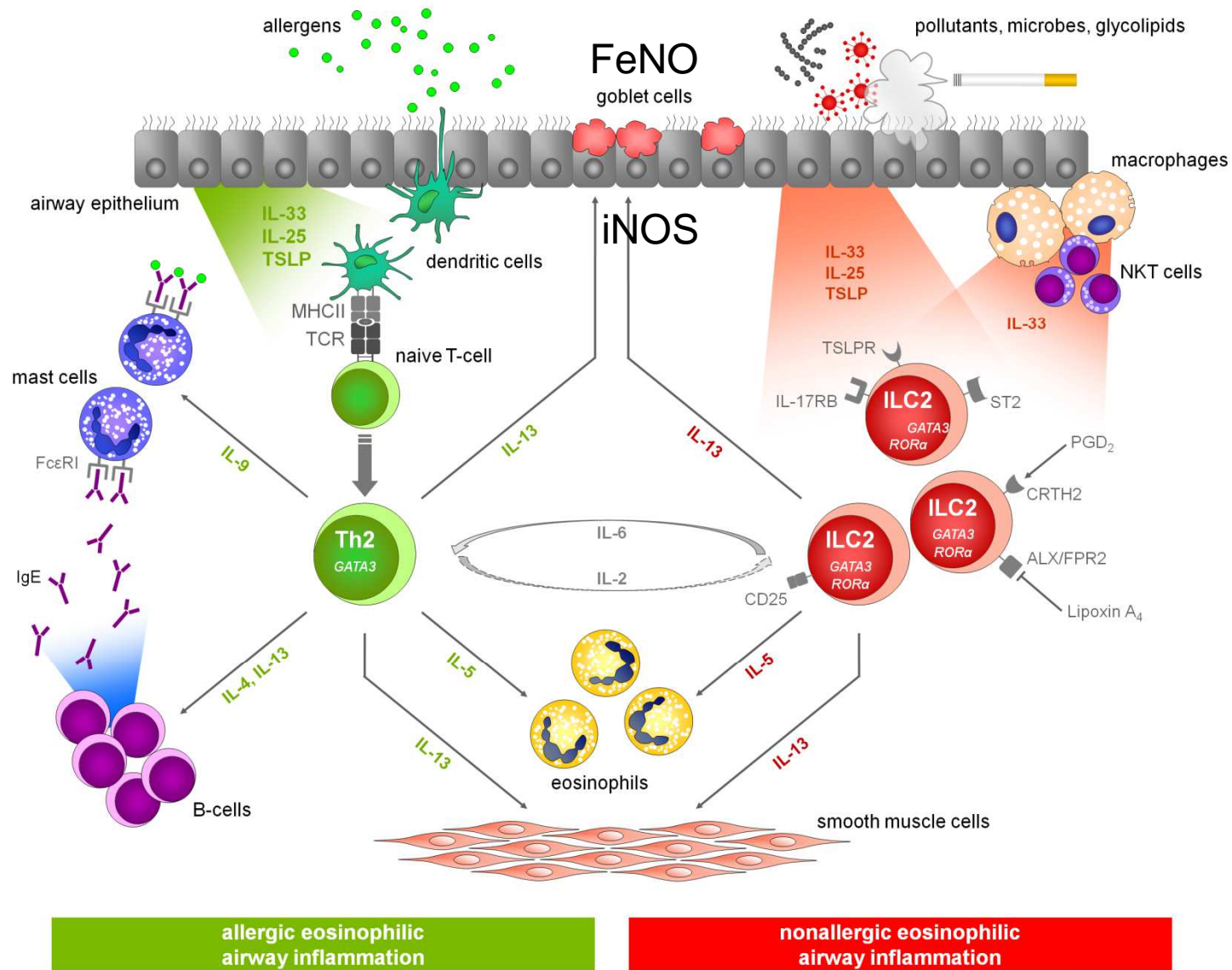
- Budesonide-formoterol as needed
- Budesonide maintenance

P. O'Byrne et al, NEJM 2018.

# Astma: overzicht

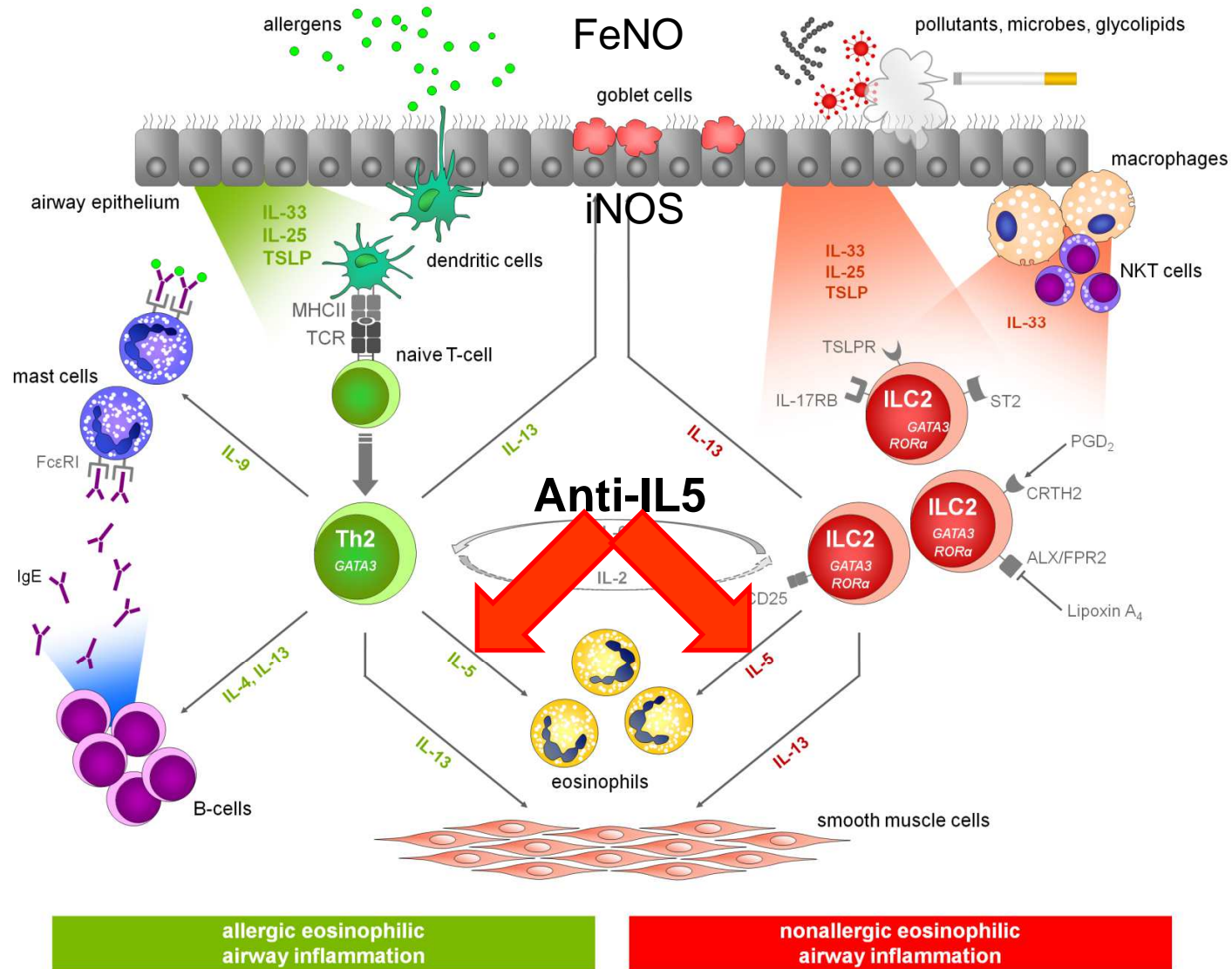
- Astma: (DD) diagnose
- Astma: behandeling
- Mild astma: paradoxes in management
- Ernstig astma: biologics
- Conclusie

# Fenotypes van eosinofiel astma

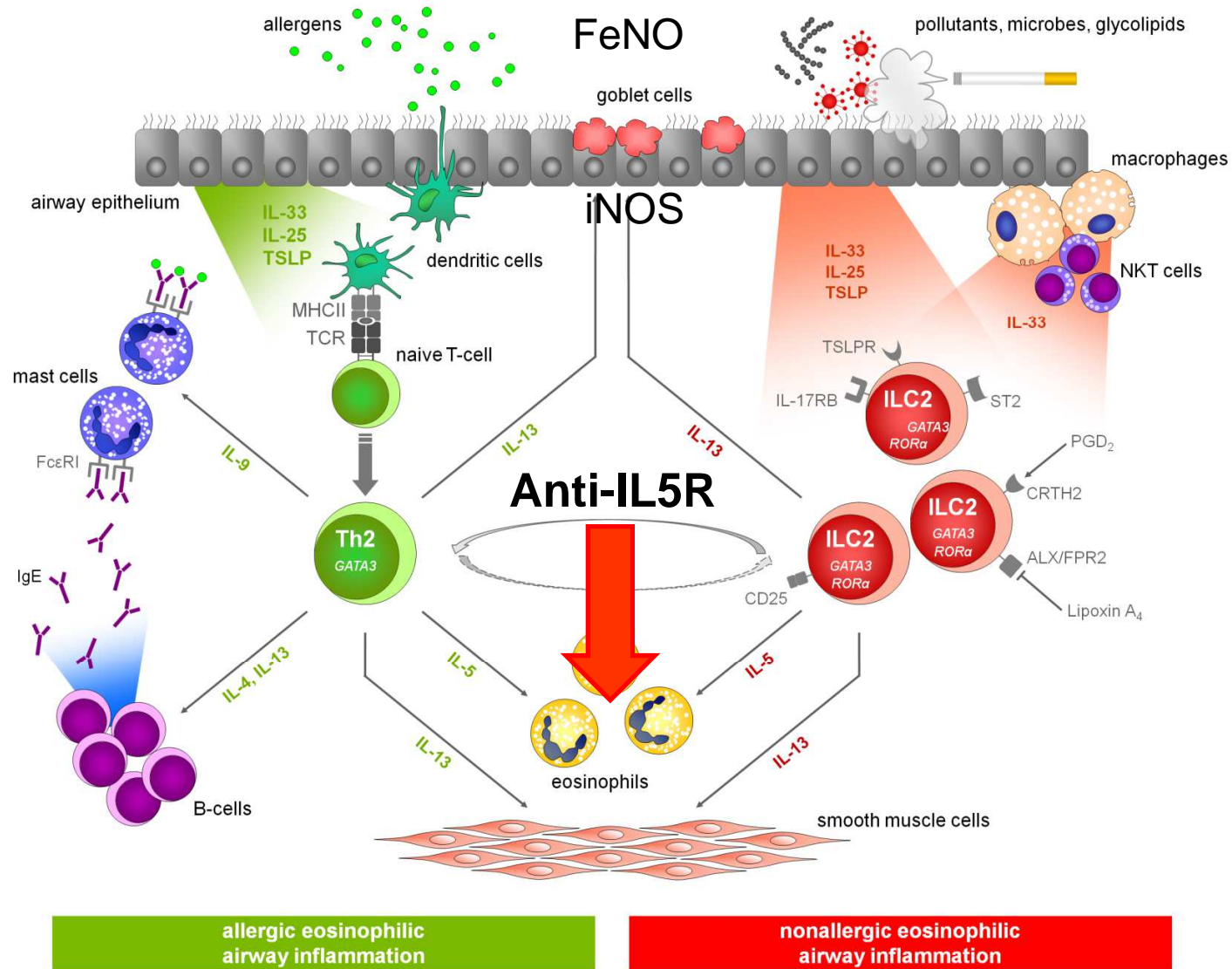




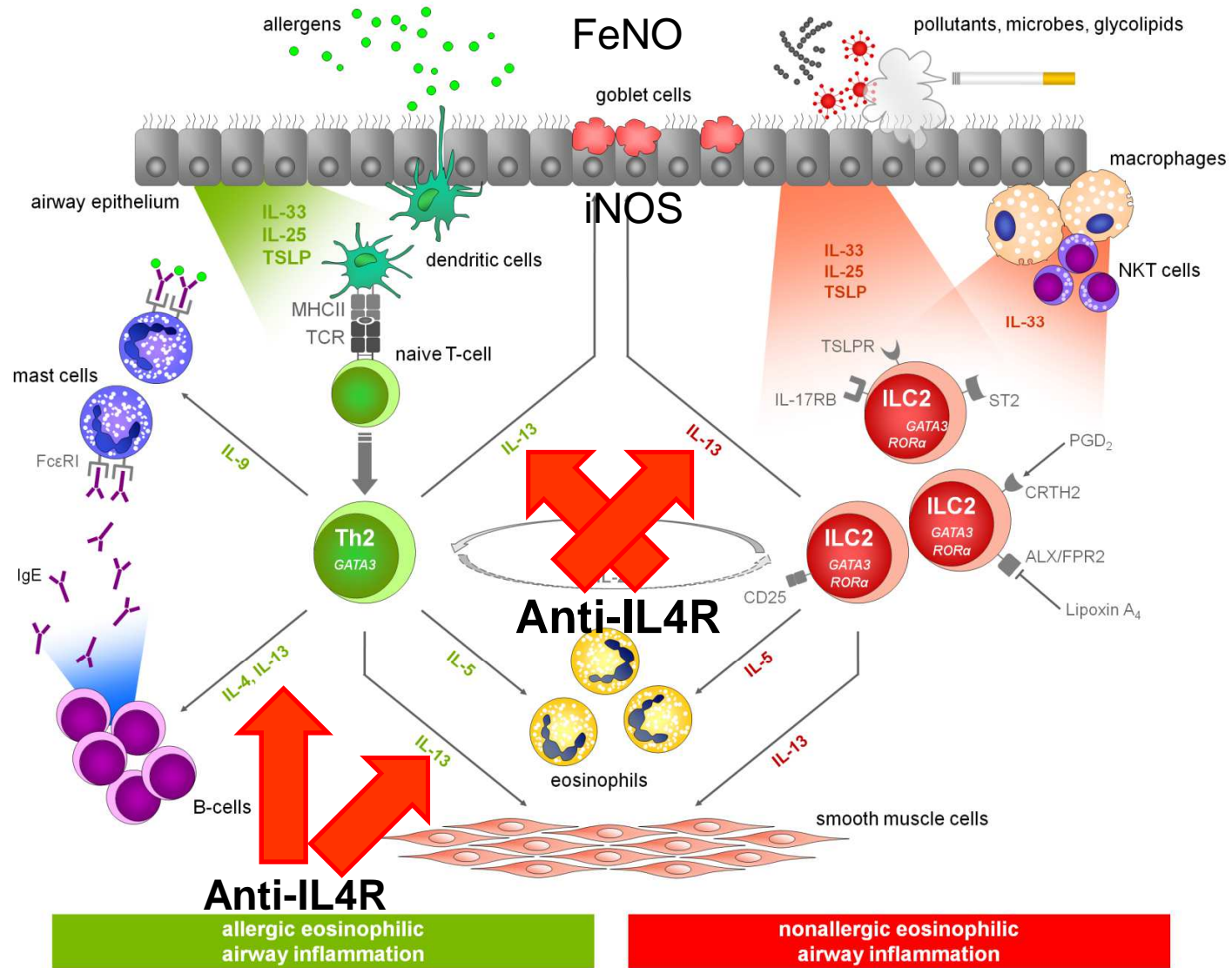
# Anti-IL5 monoclonal antibodies mepolizumab and reslizumab in severe eosinophilic asthma



# Anti-IL5 receptor monoclonal antibody benralizumab in severe eosinophilic asthma



# Anti-IL4 receptor (IL4R) monoclonal antibody dupilumab



## Anti-cytokine (receptor) monoclonal antibodies as add-on therapy in severe asthma

Monoclonal antibody	Therapeutic target	Phenotypic Biomarkers	Route of administration Dosing	Indication
Benralizumab	IL-5 Receptor alpha (IL-5R $\alpha$ )	Blood eosinophil levels <i>Sputum eosinophil levels</i>	SC 30 mg every 4 weeks (first three doses), followed by 30 mg every 8 weeks	Severe eosinophilic asthma
Dupilumab	IL-4 Receptor alpha (IL-4R $\alpha$ )	Increased FENO and/or blood eosinophil levels	SC 200 mg or 300 mg every 2 weeks	Severe type 2 asthma
Mepolizumab	IL-5	Blood eosinophil levels <i>Sputum eosinophil levels</i>	SC 100 mg every 4 weeks	Severe eosinophilic asthma
Reslizumab	IL-5	Blood eosinophil levels <i>Sputum eosinophil levels</i>	IV 3mg/kg every 4 weeks	Severe eosinophilic asthma

## Oral glucocorticoid-sparing effect of monoclonal antibodies in severe asthma

Drug	Trial Acronym	Dosing and Route of administration	Median percent reduction in daily OCS dose
mepolizumab	SIRIUS	SC 100 mg every 4 wk	-50% vs baseline; -50% vs placebo
benralizumab	ZONDA	SC 30 mg every 4 or 8 wk *	-75% vs baseline; -50% vs placebo
dupilumab	LIBERTY ASTHMA VENTURE	SC 300 mg every 2 wk	-70% vs baseline; -28% vs placebo

\* benralizumab SC 30 mg every 4 wk (first 3 doses), followed by 30 mg every 4 wk or every 8 wk

# Astma: overzicht

- Astma: (DD) diagnose
- Astma: behandeling
- Mild astma: paradoxes in management
- Ernstig astma: biologics
- Conclusie



# GINA 2019: Personal opinion

## Personal Opinion GB

**PREFERRED  
CONTROLLER  
CHOICE**

	<b>STEP 1</b>	<b>STEP 2</b>	<b>STEP 3</b>	<b>STEP 4</b>	<b>STEP 5</b>
		<b>Low dose ICS</b>	<b>Low dose ICS/LABA</b>	<b>Med/high ICS/LABA</b>	Refer for add-on treatment  e.g. tiotropium, anti-IgE, anti-IL5, anti-IL5R
<i>Other controller options</i>	<i>Consider low dose ICS</i>	<i>Leukotriene receptor antagonists (LTRA) Low dose theophylline</i>	<i>Med/high dose ICS Low dose ICS + LTRA (or + theoph)</i>	<i>Add tiotropium Med/high dose ICS + LTRA (or + theoph)</i>	<i>Add low dose OCS</i>

**PREFERRED  
RELIEVER**

	<b>As-needed low dose ICS/formoterol</b>				
<i>Other reliever options</i>	<i>As-needed short-acting beta<sub>2</sub>-agonist (SABA)</i>				

## Asthma dat niet onder controle is: first things first: adherentie en inhalatie techniek verbeteren

■ In patiënten met ongecontroleerd astma, is het zeer belangrijk om:

1) **Adherentie** te checken en optimaliseren:  
tov onderhoudsbehandeling (ICS; ICS+LABA),

en

2) **Inhalatie techniek** te checken en optimaliseren,  
vooraleer add-on therapieën met dure monoclonale  
antilichamen op te starten.



# Behandeling van astma bij volwassenen

- Farmaceutische zorg is cruciaal:  
GGG: Goed Gebruik Geneesmiddelen
- Correcte inhalatie techniek (MDI / DPI)
- Optimale adherentie aan onderhoudstherapie:
  - Astma: ICS (ICS + LABA)
- Rescue medicatie: a) vroeger: SABA: as needed (SOS): hoe minder, hoe liever;
  - b) nu: bij voorkeur: ICS/form als reliever (anti-inflammatoir).

# Casus: Sofie, 33 jaar

- VG: allergisch astma (kat, hond)
- HA: sinds maanden dyspneu (dag en nacht); vorige maand astma opstoot (Medrol kuur)
- Huisdieren: kat (binnenshuis)
- Diagnose: niet gecontroleerd astma; risico op ernstige astma aanval!      FeNO: 80 ppb (te hoog)
- Behandeling:
  - 1) blootstelling aan allergenen vermijden
  - 2) Medicatie:

Relvar 92/22 $\mu$ g: 1x 1 puff ELKE DAG (adherentie)

Symbicort (160/4,5 $\mu$ g) of Inuvair (100/6 $\mu$ g) zo nodig (SOS).



# Global Initiative for Asthma

[www.ginasthma.com](http://www.ginasthma.com)



# Global Initiative for Chronic Obstructive Lung Disease

[www.goldcopd.com](http://www.goldcopd.com)