Asma: mono, bi o triplice terapia

Dr. Claudio Micheletto

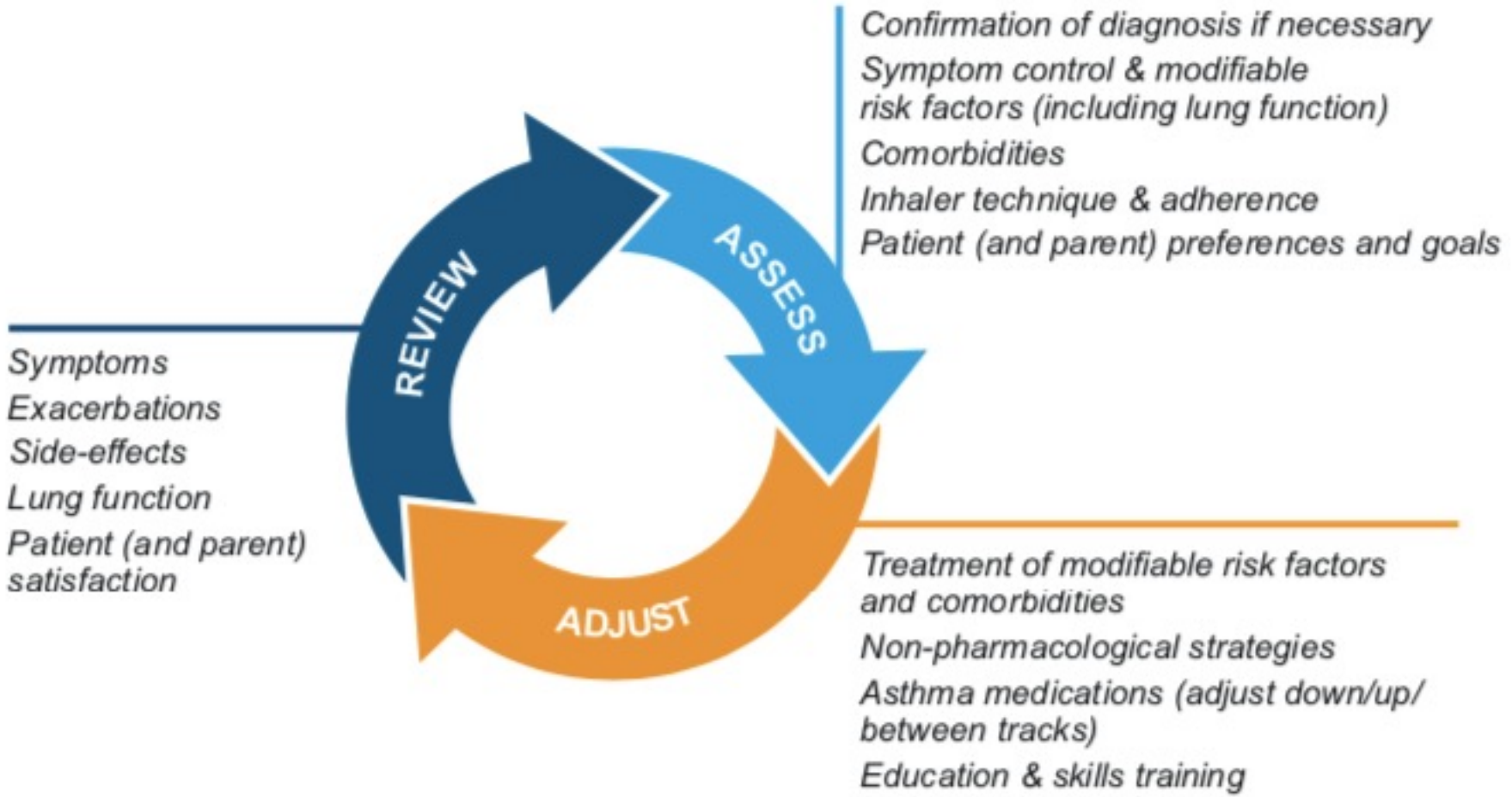
UOC di Pneumologia

Azienda Ospedaliera

Universitaria Integrata

Verona

claudio.micheletto@univr.it



Reddel HK, Bacharier LB, Bateman ED, et al. Eur Respir J 2022;

What is asthma step-up therapy?

- Because asthma is a chronic condition, treatment focuses on managing a person's symptoms.
- First, a doctor will diagnose and assess the severity of a person's asthma. Then, they will decide where to start them in step-up therapy.
- Asthma step-up therapy includes regular follow-up appointments. This allows the doctor to evaluate how an individual is responding to treatment
- After a person's symptoms are consistently under control for a specific amount of time, the doctor may begin a step-down method. This reduces medication intensity while still managing symptoms.

Obiettivi a lungo termine della gestione dell'asma bronchiale

- Raggiungere un buon controllo dei sintomi e mantenere normali livelli di attività
- Minimizzare il rischio di esacerbazioni, limitazione fissa delle vie aeree ed effetti collaterali

Monoterapia

Medications and strategies for symptom control and risk reduction

Asthma medications are categorized as controllers, relievers, and add-on therapies:

- **Controllers** contain ICS, which reduce airway inflammation, control symptoms, and reduce the risks of exacerbations [20], even in mild asthma [14, 15, 21], and of asthma death [22]. Treatment with ICS may reduce exacerbation-related declines in lung function [23]. "Maintenance" therapies are controllers that are prescribed for daily use.
- **Relievers** (low-dose ICS–formoterol or SABA) contain rapid-onset bronchodilators. They are used "as needed" (*i.e.* for quick relief of symptoms, including during exacerbations). Using ICS–formoterol as a reliever (often called an "anti-inflammatory reliever" or "AIR") also reduces the risk of severe exacerbations, compared with a SABA reliever, both with [24, 25] or without [15, 21] maintenance controller treatment. SABA or ICS–formoterol is also recommended before exercise if needed to prevent exercise-induced bronchoconstriction [26, 27].
- **Add-on therapies** are mainly for patients with difficult-to-treat or severe asthma (see below).

When choosing medications, consider local guidelines, regulatory approvals, and payer criteria.

Reddel HK, Bacharier LB, Bateman ED, et al.
Global Initiative for Asthma Strategy 2021: executive summary and rationale for key changes. Eur Respir J 2022;

Recommendation against SABA-only treatmen

Since 2019, GINA has recommended against SABA-only treatment of asthma in adults and adolescents after consideration of its risks and the evidence for a safer alternative.

Instead, to reduce the risk of serious exacerbations and control symptoms, all adults and adolescents with asthma should receive ICS-containing treatment, either regularly or, in mild asthma, as needed to relieve symptoms.

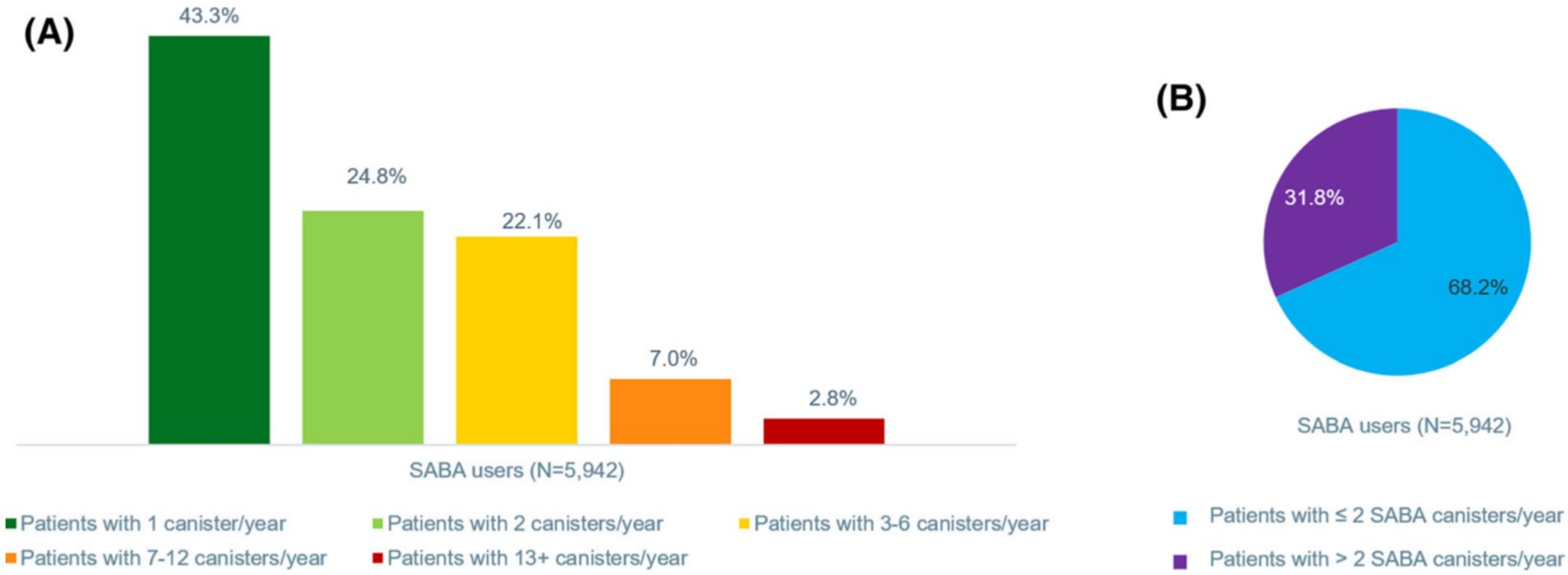
ICS is now also recommended for all children 6–11 years with asthma, either regularly or, in mild asthma, whenever SABA is taken for symptom relief.

Adv Ther (2021) 38:3816–3830
https://doi.org/10.1007/s12325-021-01772-0

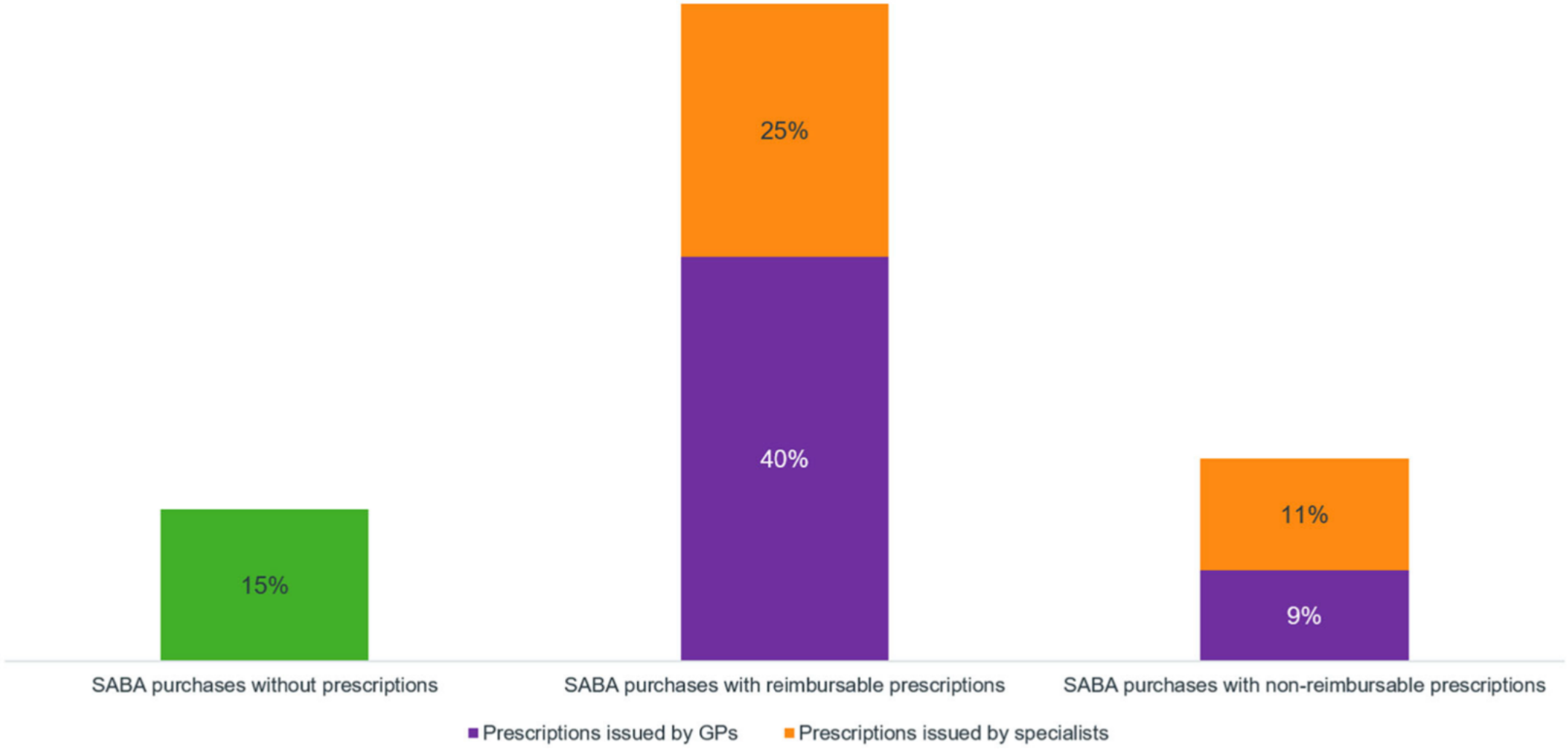
ORIGINAL RESEARCH

The Burden of Short-Acting β_2-Agonist Use in Asthma: Is There an Italian Case? An Update from SABINA Program

Fabiano Di Marco · Mariella D'Amato · Francesco P. Lombardo · Claudio Micheletto · Franca Heiman · Valeria Pegoraro · Silvia Boarino · Giandomenico Manna · Francesca Mastromauro · Simona Spennato · Alberto Papi



Adv Ther (2021) 38:3816–3830



Adv Ther (2021) 38:3816–3830

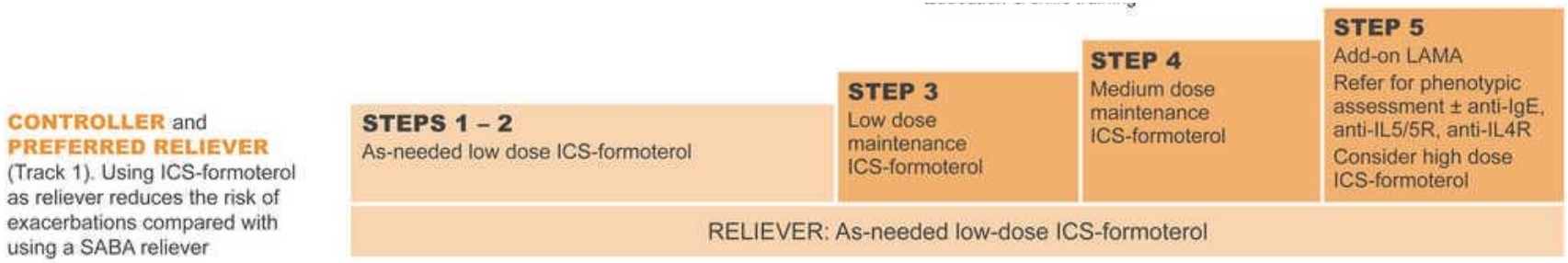
Initiate medication

- GINA outlines two “tracks” for starting asthma medication.
- Both tracks include controller medication, which is a long-term medicine for asthma maintenance, and reliever medication, which is a fast-acting medicine for quick symptom relief. The main difference between the two tracks is the type of reliever medication used.
- Each track includes five steps. Typically, step one starts with the lowest appropriate dosage. Each successive step gradually increases the dosage, and some later steps include additional medications for symptom relief. A person’s doctor may choose to add other medications, too.

Reddel HK, Bacharier LB, Bateman ED, et al.
Global Initiative for Asthma Strategy 2021: executive summary and rationale for key changes. Eur Respir J 2022;

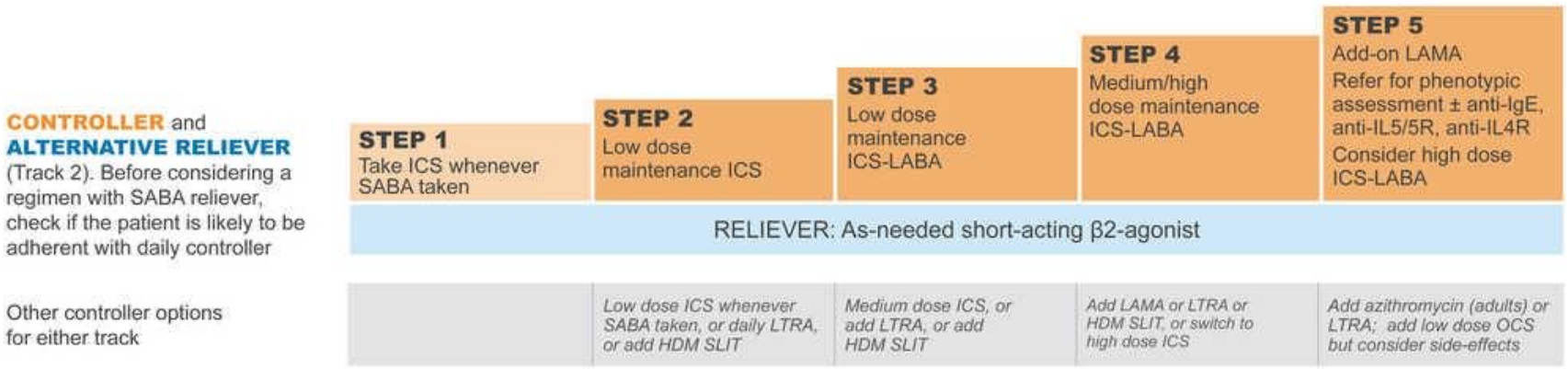
Track one

- This track includes a controller for long-term relief as an inhaled corticosteroid (ICS). Steps 1–4 gradually increase the ICS dosage. People on this track can use a low-dose reliever medication for fast-acting relief as needed.
- Step 5 introduces a long-acting muscarinic antagonist (LAMA) as an add-on medication.

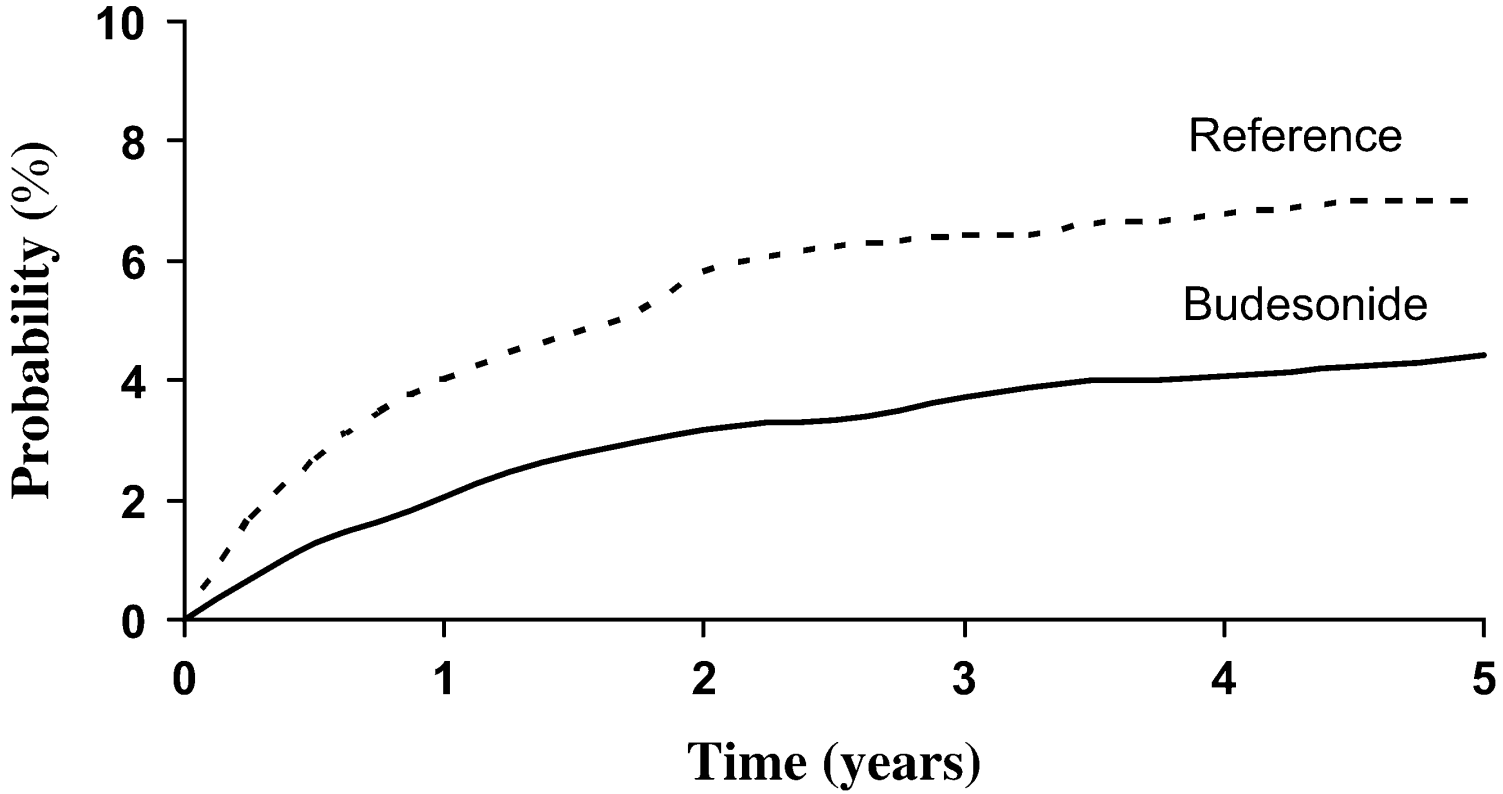


Track two

- This track also includes a controller medication. For a reliever, it has a short-acting beta-antagonist (SABA).
- Step 3 introduces a long-acting beta-antagonist (LABA), and step 5 introduces a LAMA as an add-on medication.



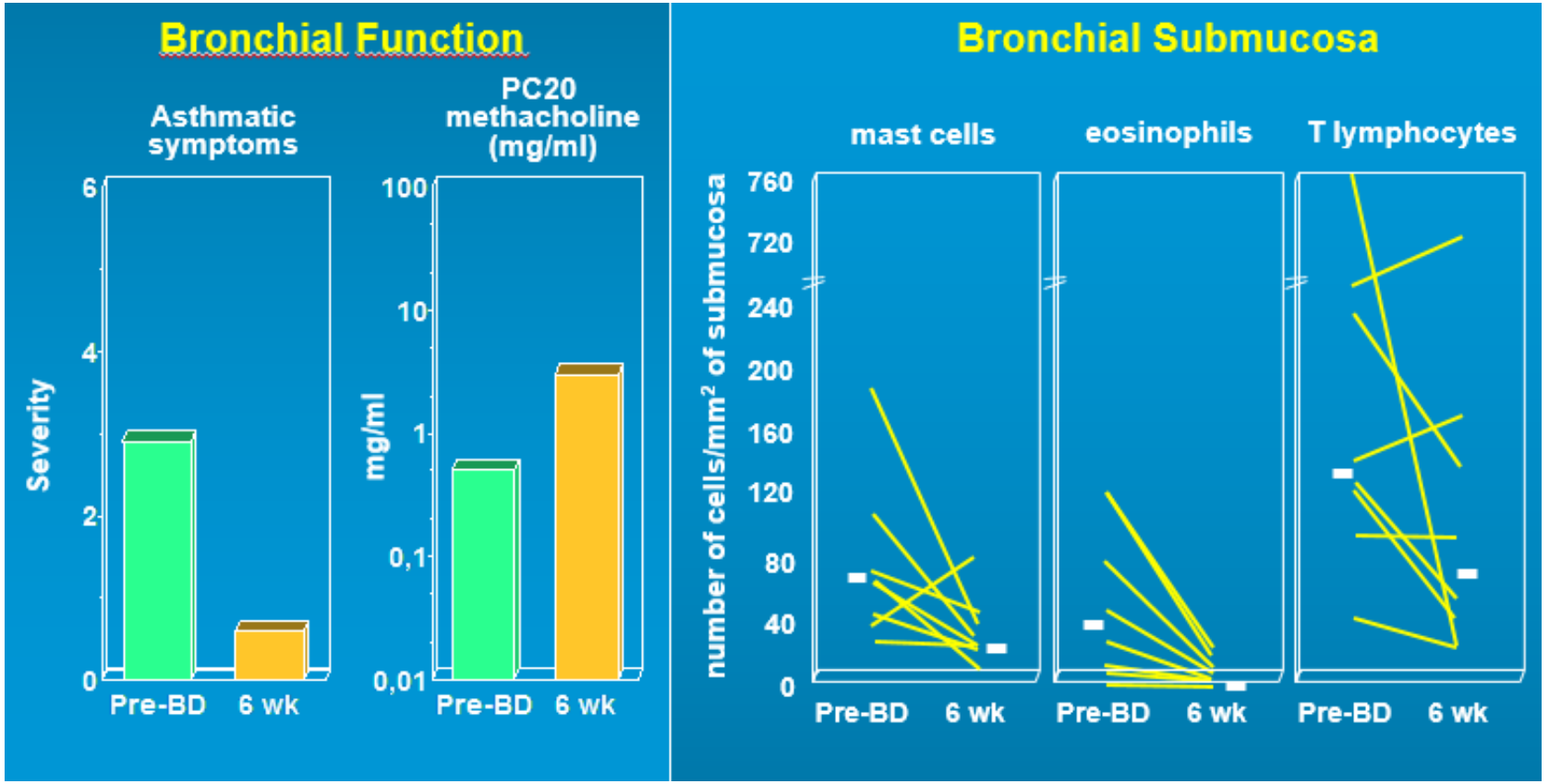
The Inhaled Steroid Treatment As Regular Therapy in Early Asthma (START) study 5-year follow-up: Effectiveness of early intervention with budesonide in mild persistent asthma



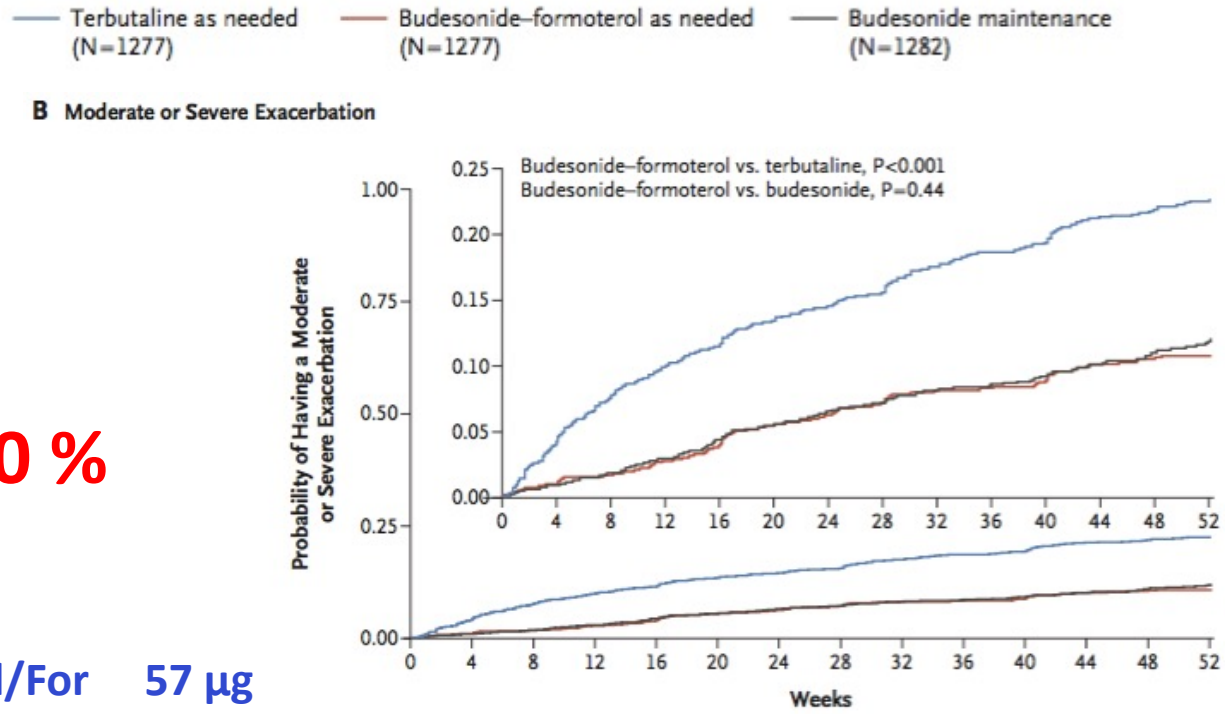
Time to the first severe asthma-related event (SARE)

Busse WW, et al. J All Clin Immunol 2008

Effects of Inhaled Beclomethasone Dipropionate in Clinical Asthma



Djukanovic et al, Am Rev Respir Dis 1992;145(3):669-74



- 60 %

Bud/For 57 µg
Bud 340 µg

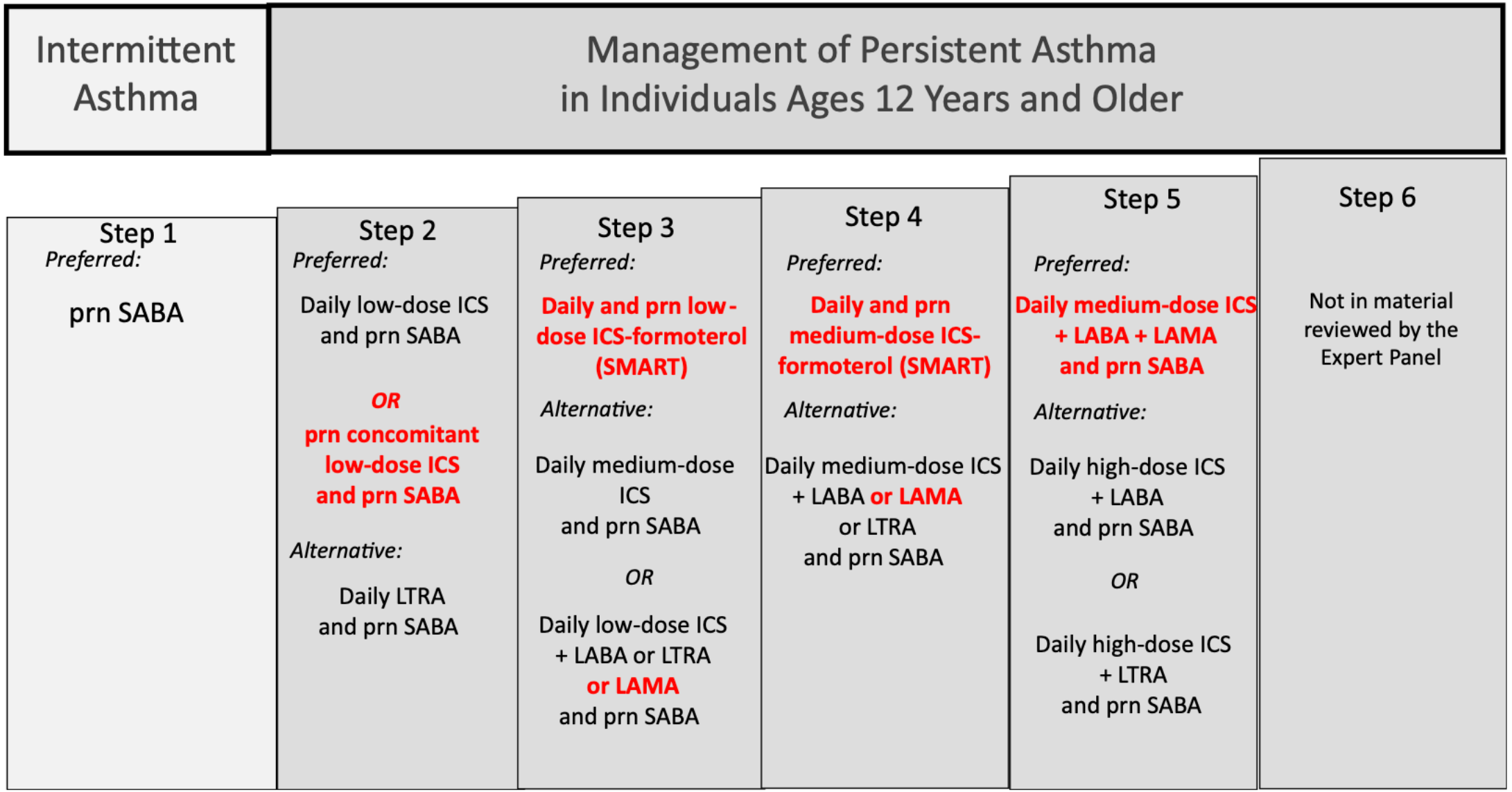
O'Byrne, et. N Engl J Med 2018;378:1865-76

Rostrum

2020 NAEPP Guidelines Update and GINA 2021—Asthma Care Differences, Overlap, and Challenges

Bradley E. Chipps, MD[a], Kevin R. Murphy, MD[b], and John Oppenheimer, MD[c] *Sacramento, Calif; Boystown, Neb; and Newark, NJ*

The NAEPP Expert Panel suggests that individuals aged 12 years and older with mild persistent asthma and a low or high perception of symptoms may not be good candidates for intermittent ICS treatment. Daily low-dose ICS with SABA for quick-relief therapy may be preferred for such patients to avoid ICS undertreatment (low symptom perception) or overtreatment (high symptom perception).



J ALLERGY CLIN IMMUNOL PRACT JANUARY 2022

Duplice terapia

Monoterapia

Pazienti sintomatici nonostante trattamento: cosa ci garantiscono i farmaci?

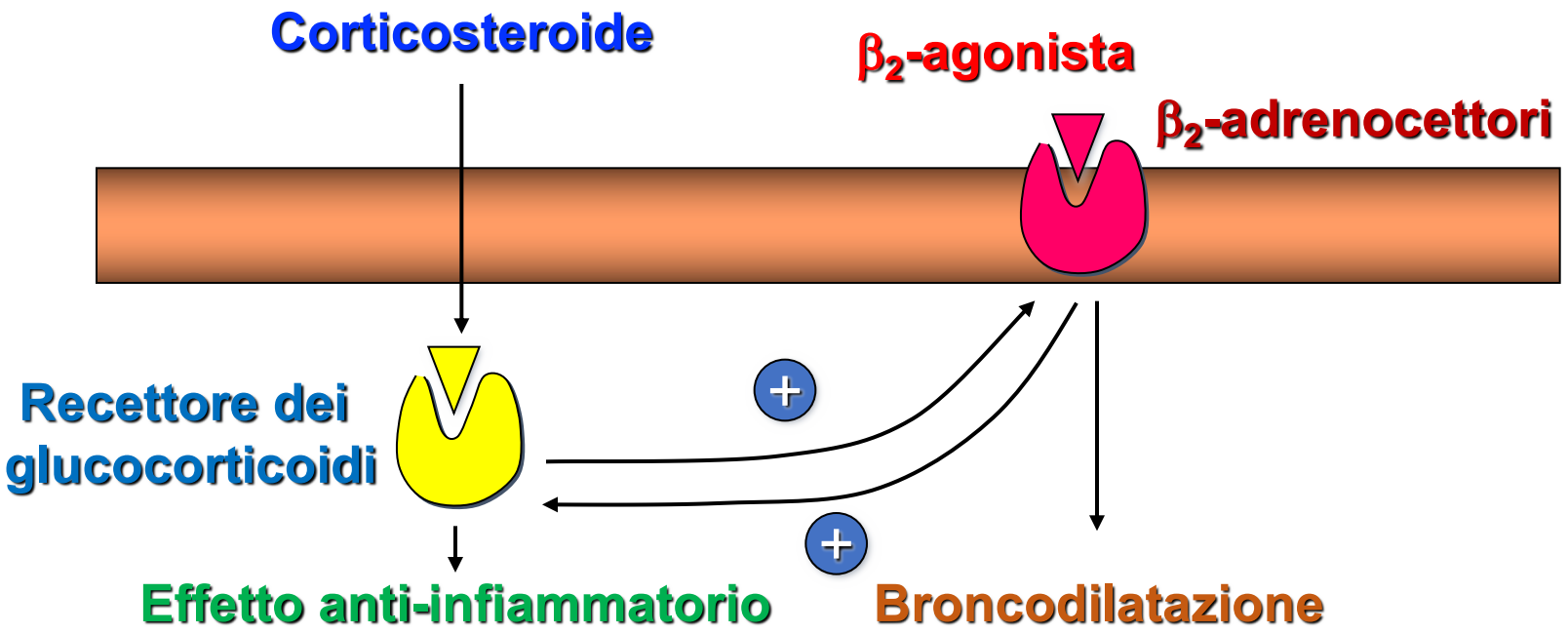
- Per i Pazienti con sintomi persistenti e/o con riacutizzazioni nonostante una bassa dose di ICS, considera uno «step up», ma prima controlla tecnica inalatoria, aderenza, comorbidità ed esposizione allergenica persistente.
- Per adulti e adolescenti, lo «step up» di prima scelta è la combinazione ICS/long-acting beta$_2$-agonist (LABA).

Gina 2018

Pazienti sintomatici nonostante trattamento: cosa garantiscono le associazioni ICS/LABA?

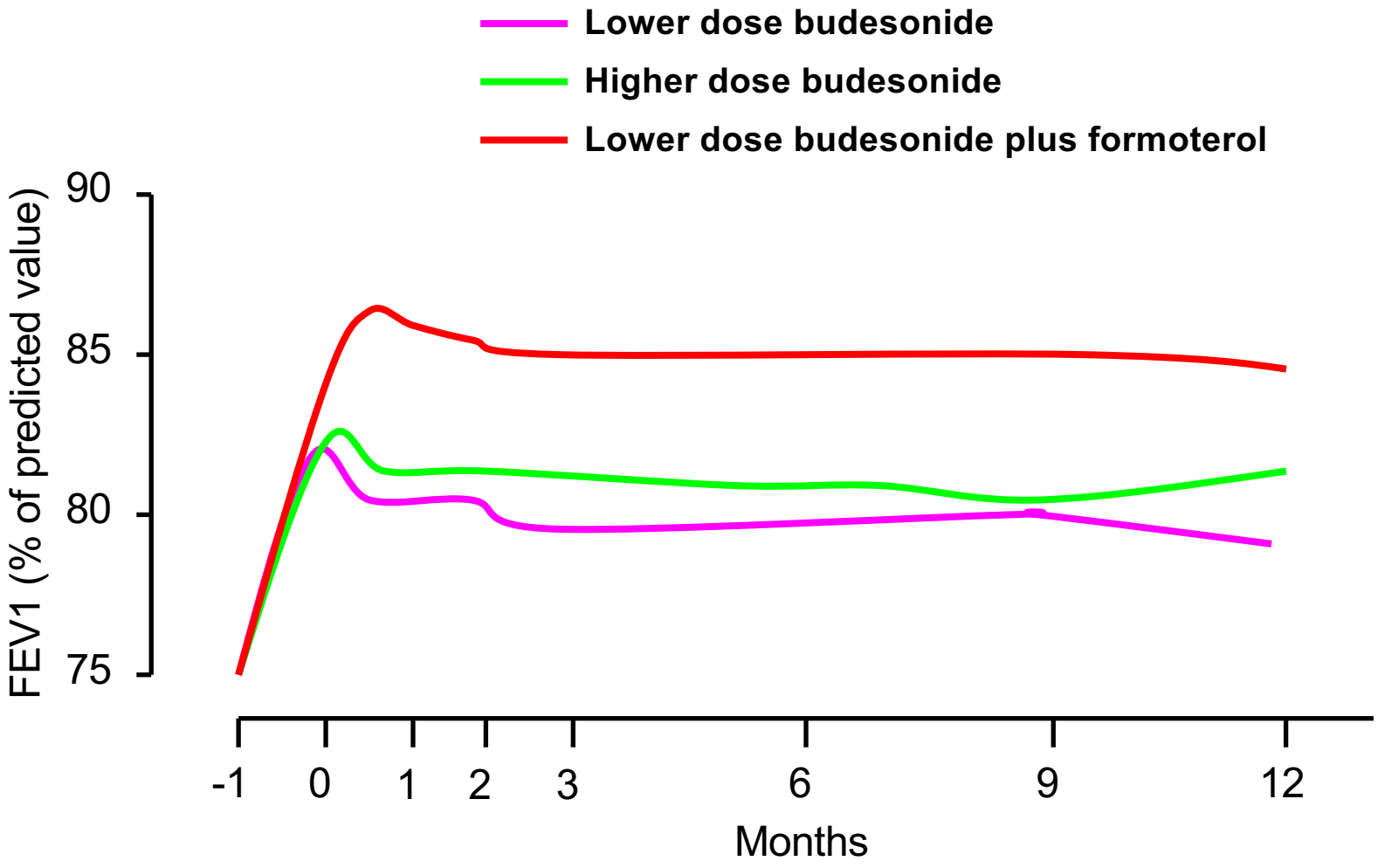
- Miglioramento della funzione
- Miglioramento dei sintomi
- Riduzione delle riacutizzazioni
- Riduzione delle ospedalizzazioni

Interazioni fra corticosteroidi e beta$_2$-agonisti a livello cellulare



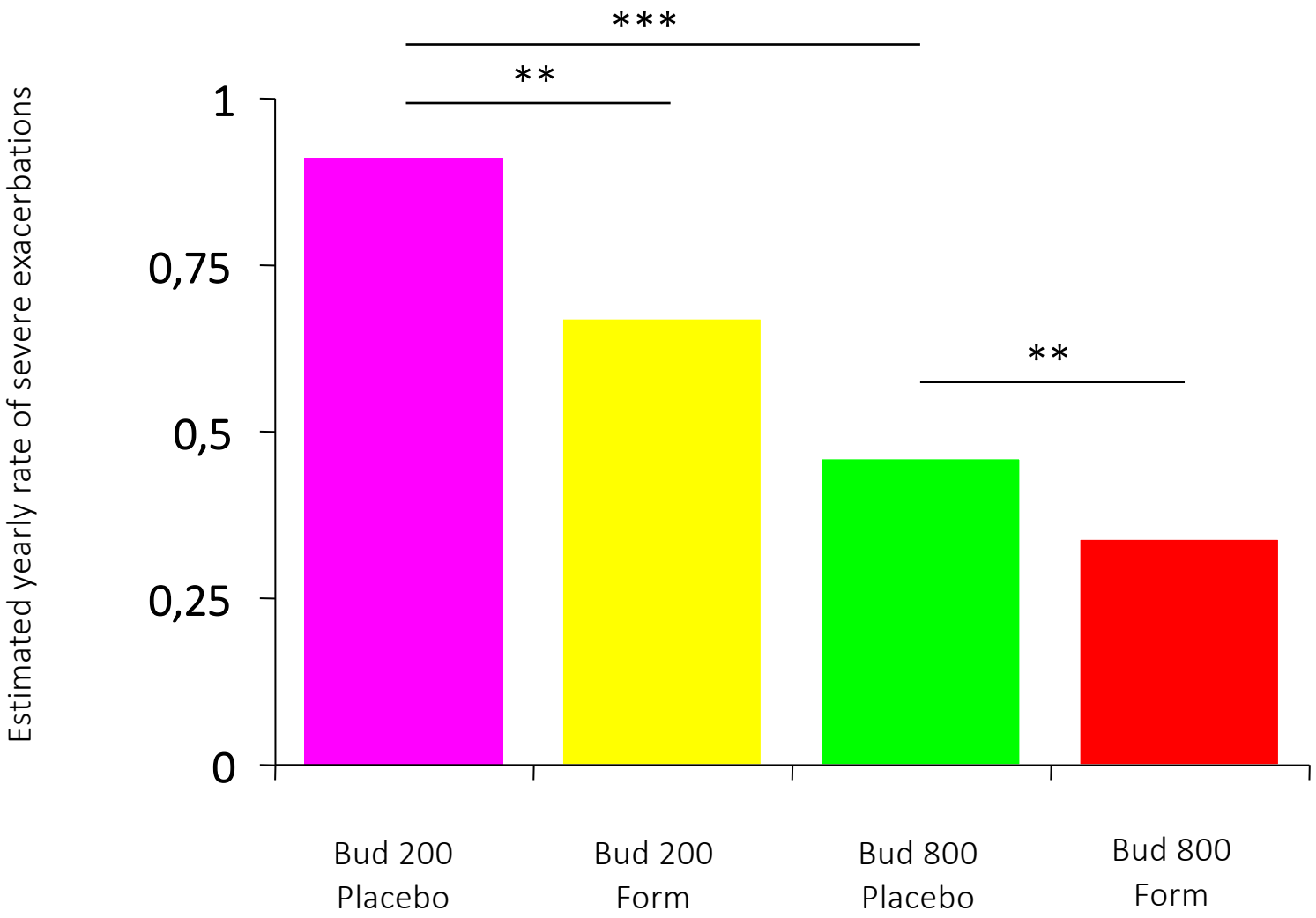
Barnes PJ. Eur Respir J 2002;19:182

Combination therapy in asthma



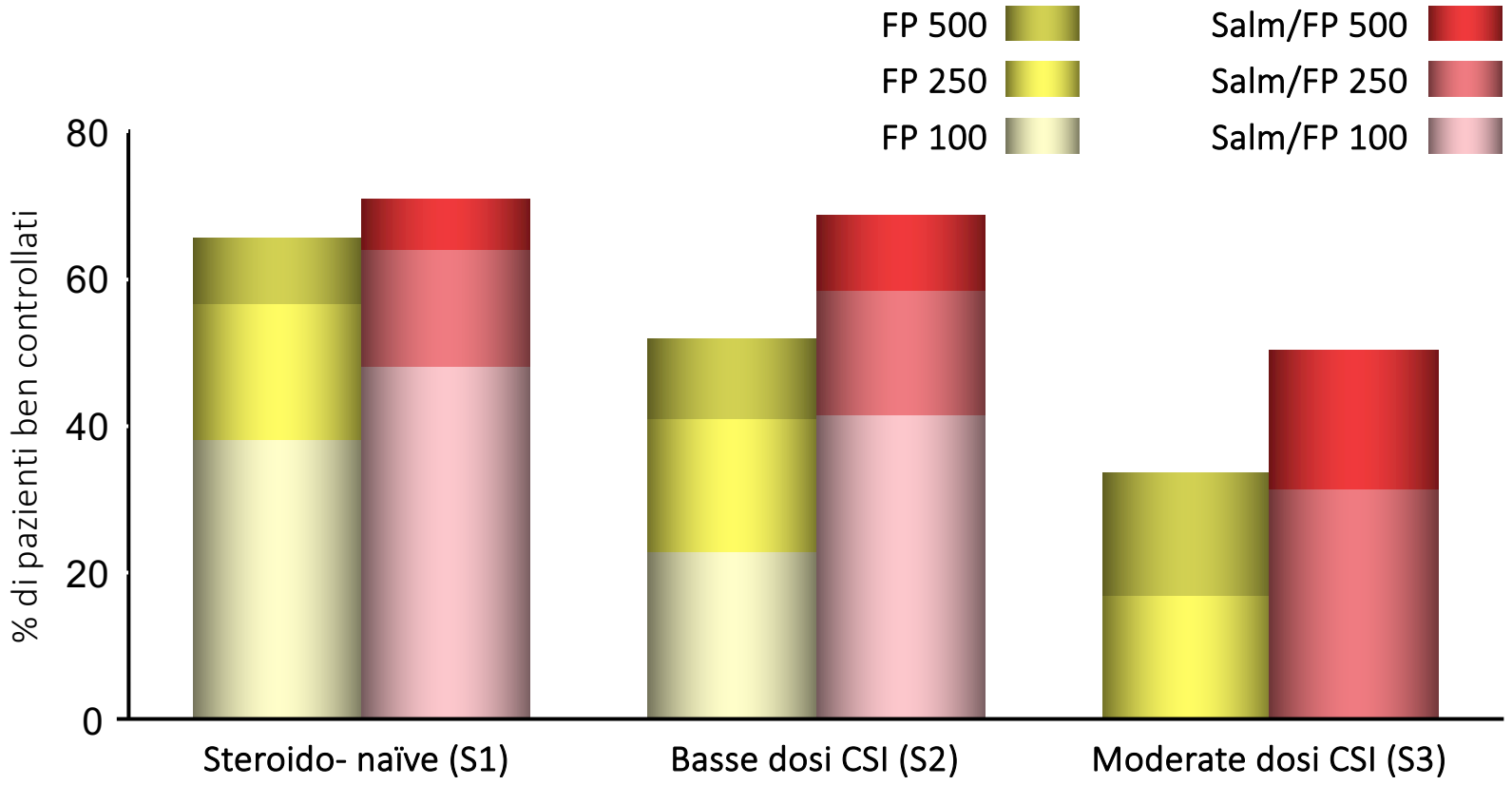
Pauwels et al. NEJM 1997

Terapia di combinazione nell'asma



Pauwels et al. NEJM 1997

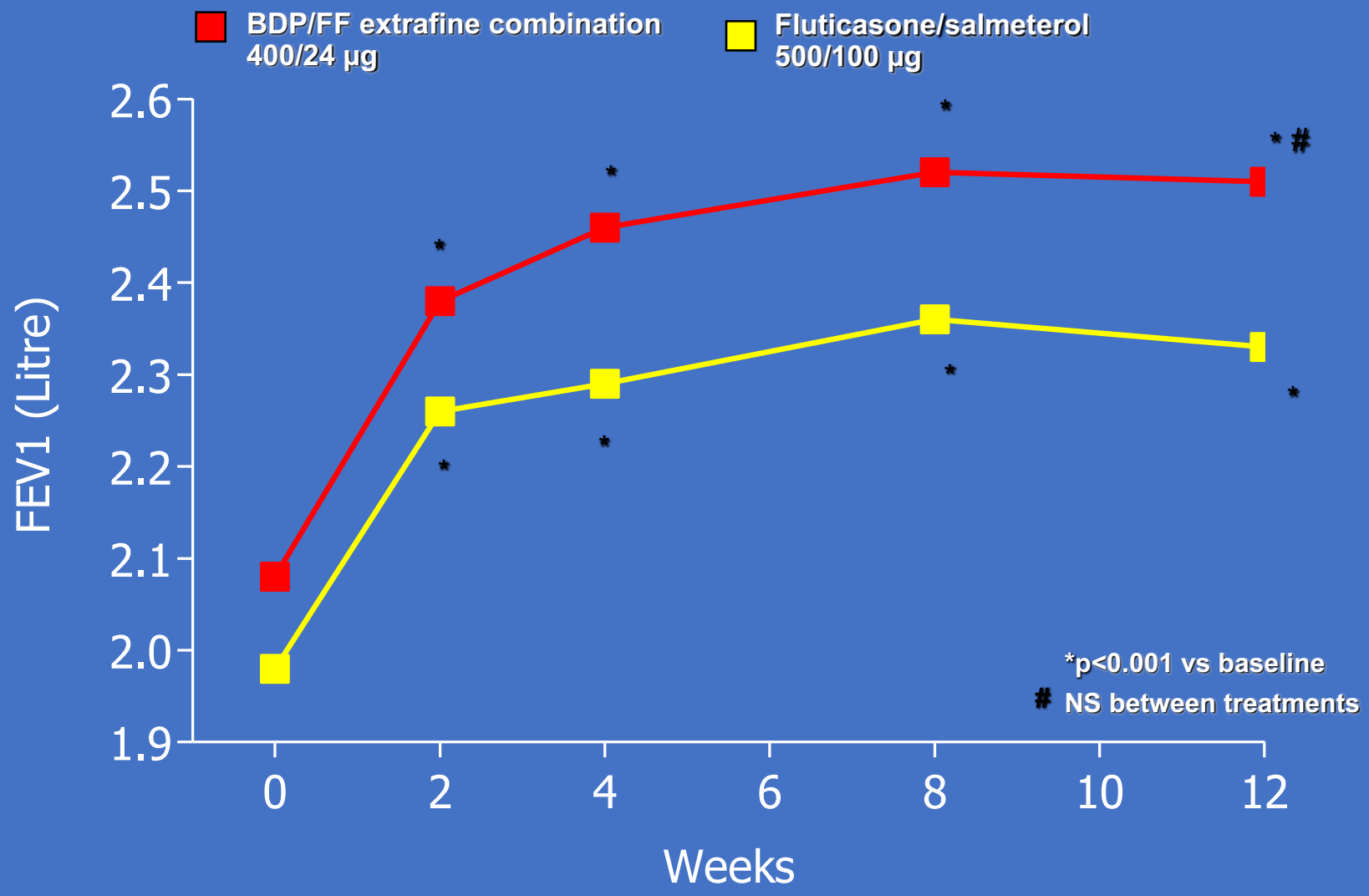
Il buon controllo dell'asma è raggiungibile in una elevata percentuale di soggetti con terapia regolare



Bateman et al, GOAL Study, AJRCCM 2004

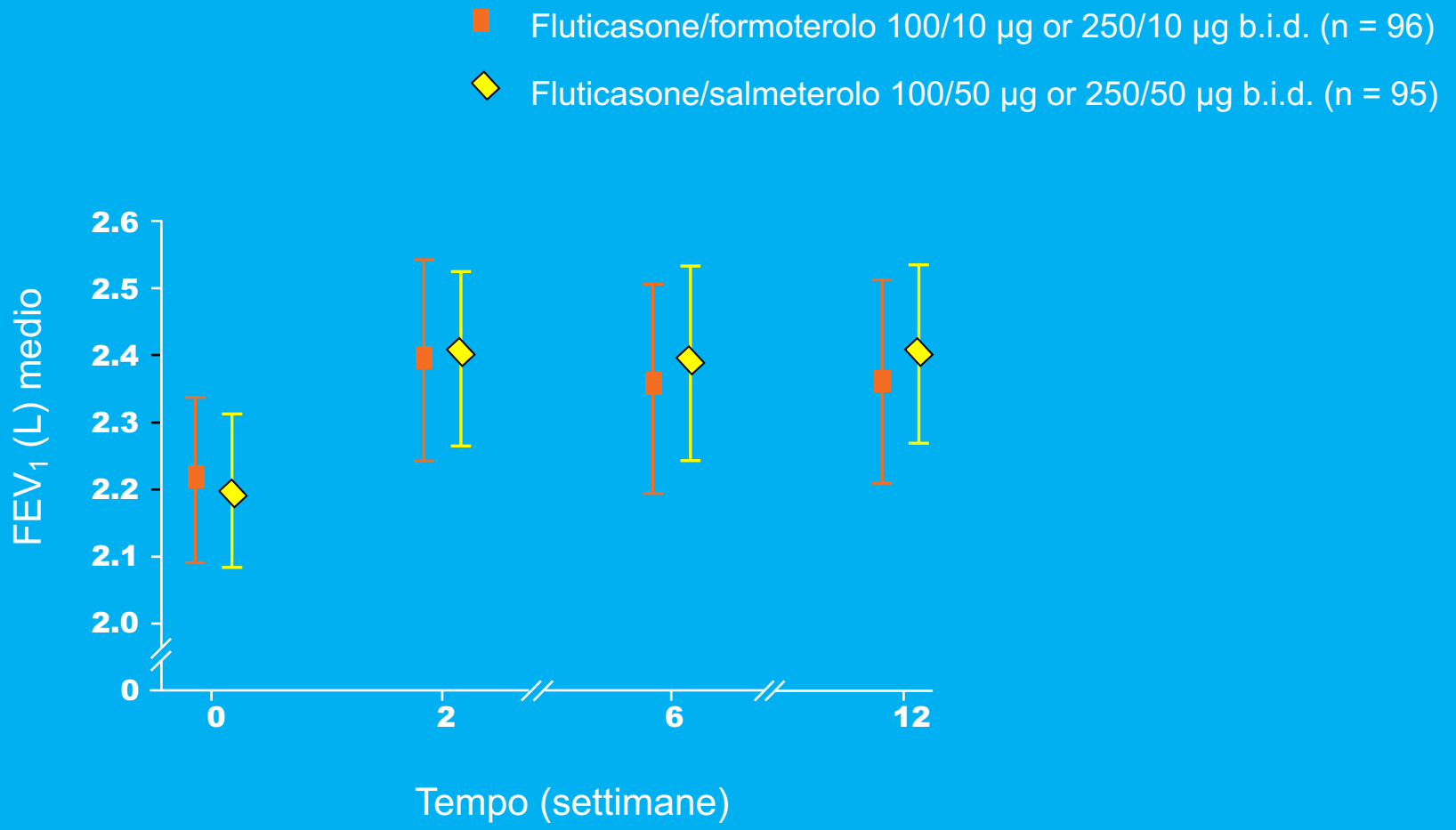
ICAT SE. FEV_1

Comparable improvement for both BDP/FF extrafine combination and fluticasone/salmeterol



Papi A, et al. Allergy 2007; 62, 1182 - 1188

Fluticasone/formoterolo simile a fluticasone/salmeterolo per il FEV_1 medio pre-dose dopo 12 settimane



Bodzenta-Lukaszyk A, Dymek A et al. BMC Pulm Med 2011

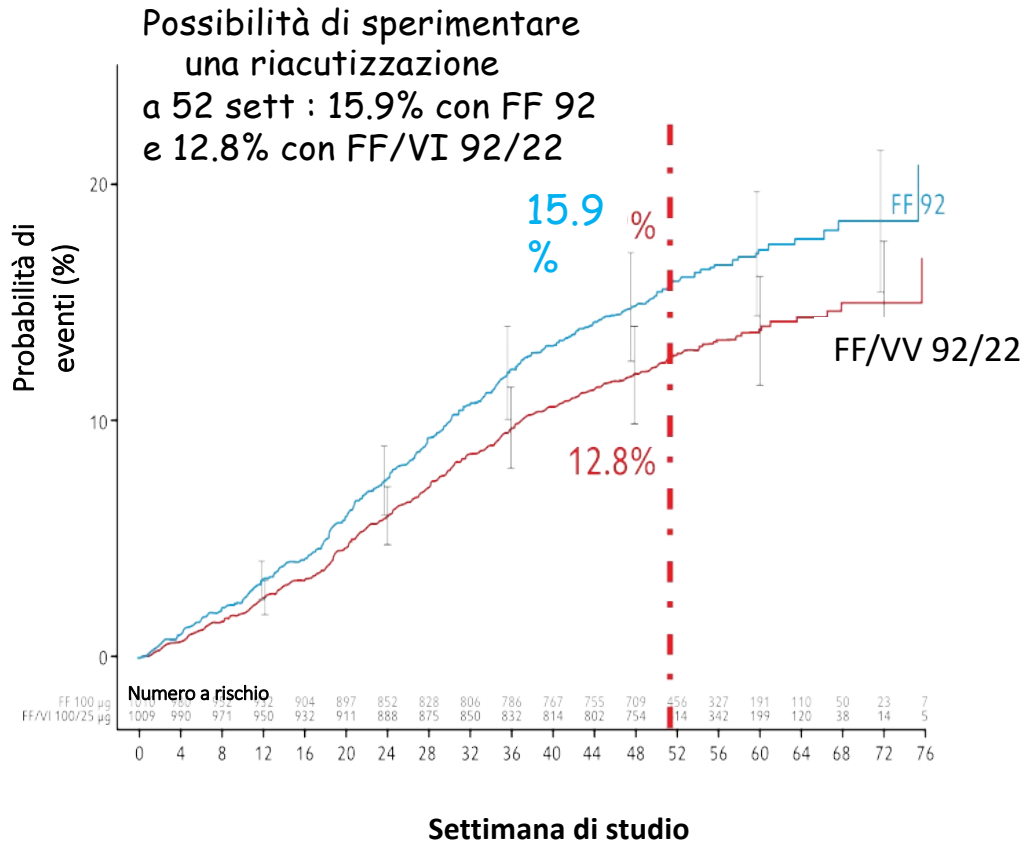
Rischio di gravi riacutizzazioni

CONFRONTO: Fluticasone Furoato/VilanteroloOD *vs* FF 92 mcg OD

ENDPOINT PRIMARIO: Tempo alla prima riacutizzazione grave (peggioramento dei sintomi che richiede l'uso di corticosteroidi sistemici per almeno 3 giorni o un ricovero ospedaliero o una visita in una struttura di emergenza)

DURATA: Variabile (da min 24 a max 76 settimane con la maggior parte dei pazienti trattati per almeno 52 settimane).

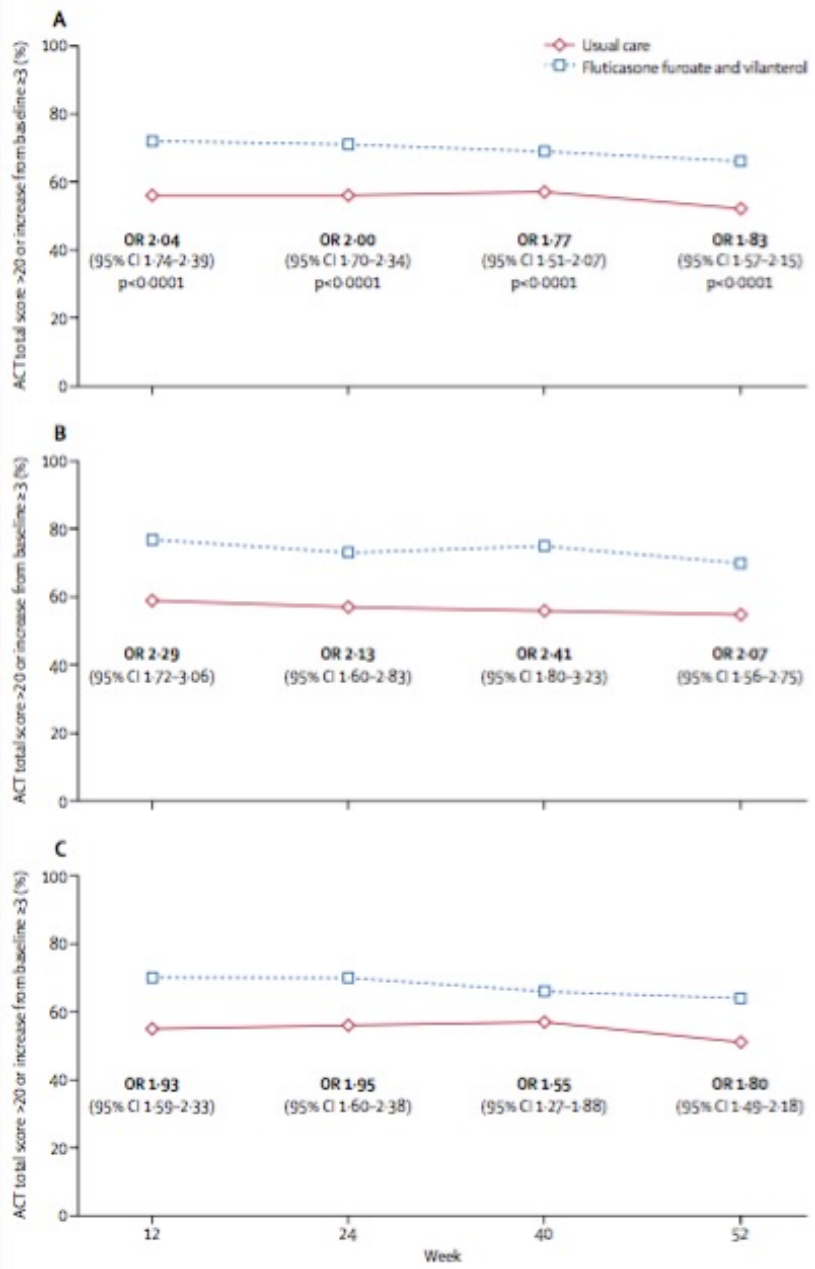
PAZIENTI: 2019 asmatici non controllati con ICS e con storia di ≥1 riacutizzazione grave nei 12 mesi precedenti (media 1.74/ anno)



Rischio di riacutizzazioni gravi ridotto significativamente del 20% FF/VI 92/22 *vs* il solo steroide (FF)

Bateman ED et al. Thorax. (2014)

Cosa garantisce la terapia di associazione nella «real life» ?



All patients

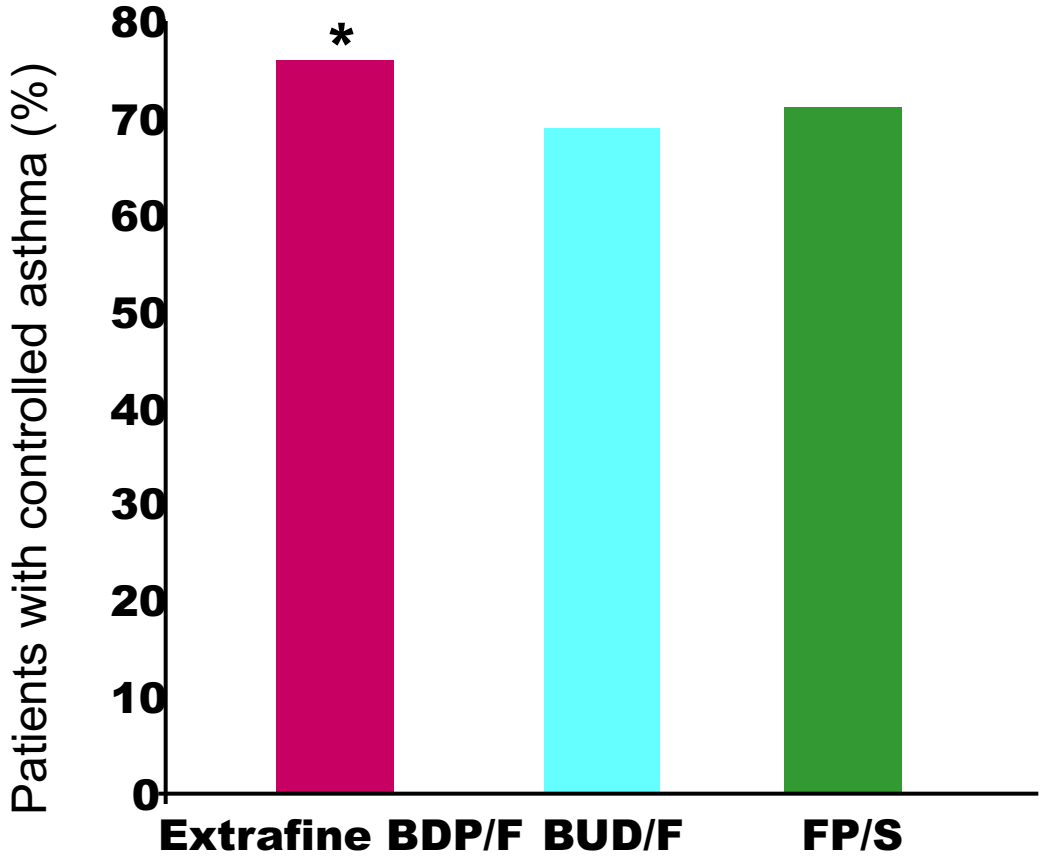
Confronto con
ICS in monoterapia

Confronto con
Altri ICS/LABA

71 % dei
Pazienti
ACT < 20

The Lancet 2017

In a real-life study, extrafine BDP/F provides a greater percentage of controlled patients than larger particle formulations

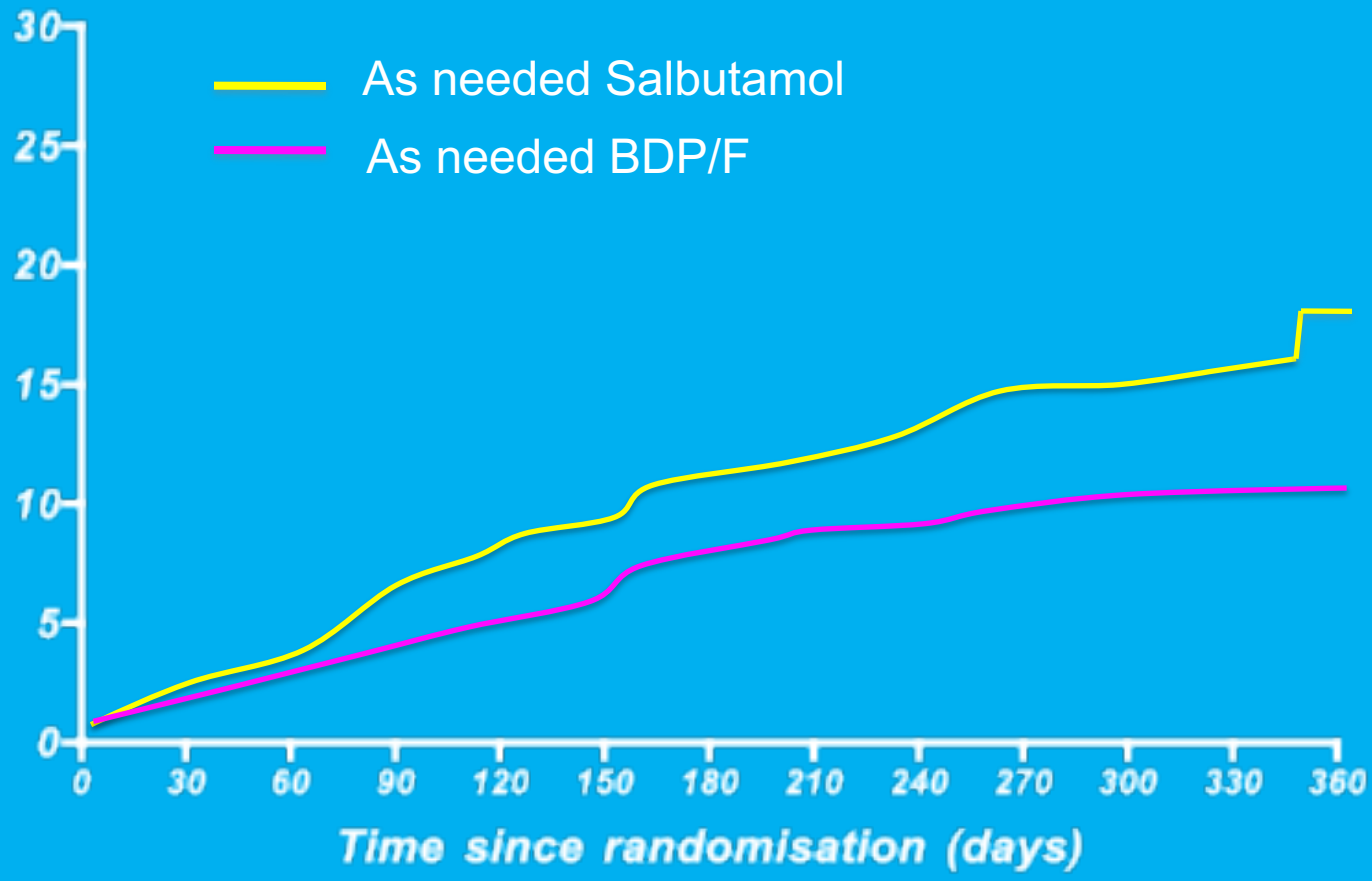


*p<0.05 vs BUD/F

Cross-sectional phase of a prospective study involving 2848 patients (1358 patients using ICS/LABA fixed combinations). No difference in asthma severity between groups at the time of diagnosis.

Allegra et al., Respir Med 2011

MART-2: Time to first severe exacerbation[1] (1)
Primary Outcome



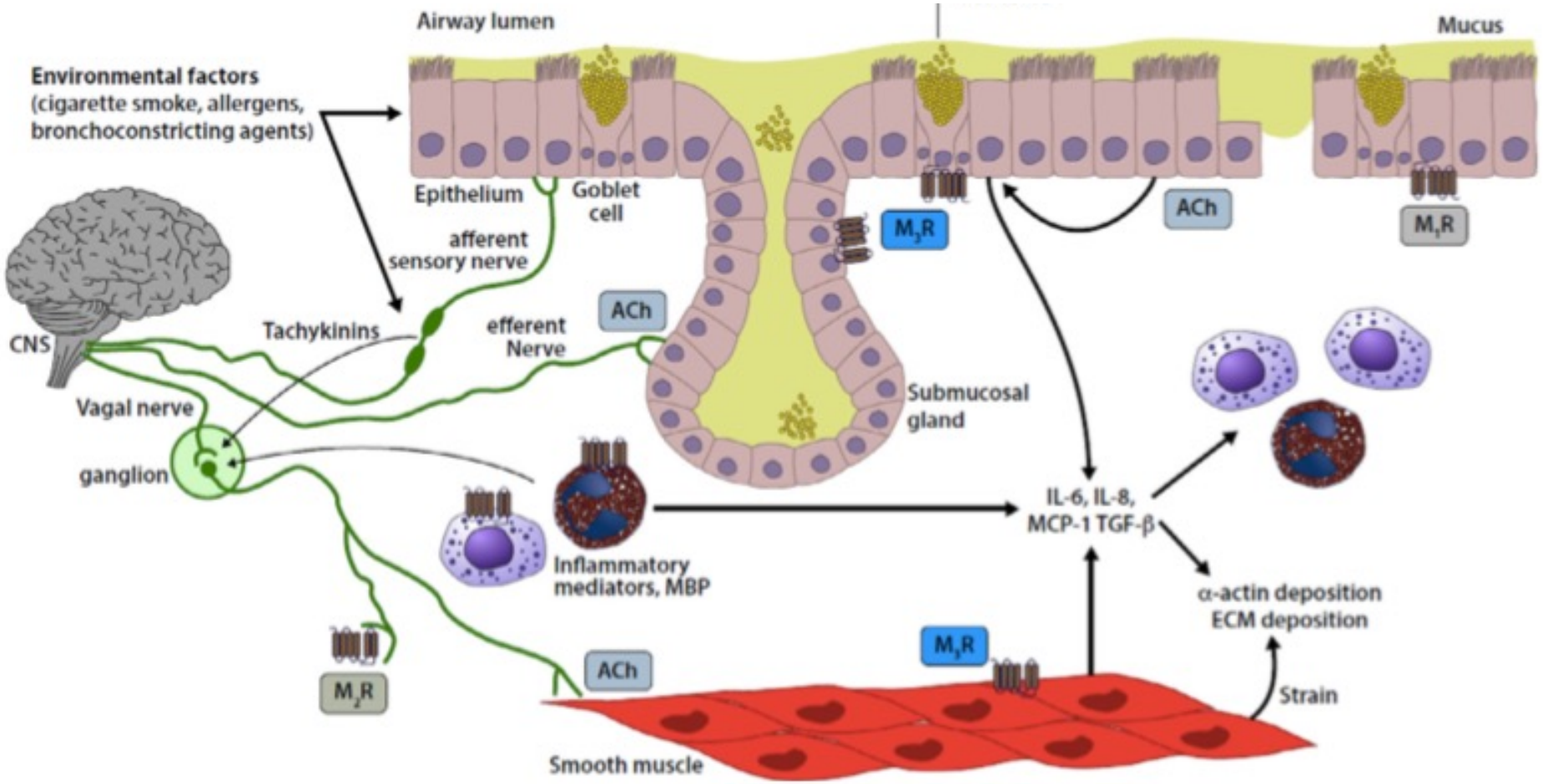
Papi A, Fabbri LM, Rabe K et al. Lancet Resp Med 2013

Triplice terapia

Duplice terapia

Monoterapia

Understanding the role of long-acting muscarinic antagonists in asthma treatment



S. Muiser et al. Ann Allergy Asthma Immunol 128 (2022) 352–360

Understanding the role of long-acting muscarinic antagonists in asthma treatment

Key Messages

- Long-acting muscarinic antagonists (LAMAs) improve lung function, reduce exacerbations, and modestly improve asthma control when added to inhaled corticosteroid plus long-acting β-agonist in patients with moderate to severe asthma who are uncontrolled.
- LAMAs are effective in all asthma phenotypes and endotypes.
- LAMAs are equally effective as long-acting β-agonists with potentially even a higher efficacy in improving lung function.
- LAMAs have additional anti-inflammatory effects in animals and in vitro, but human studies in asthma have not yet been concluded.

S. Muiser et al. / Ann Allergy Asthma Immunol 128 (2022) 352−360

Tiotropium in asthma poorly controlled with standard combination therapy

BACKGROUND

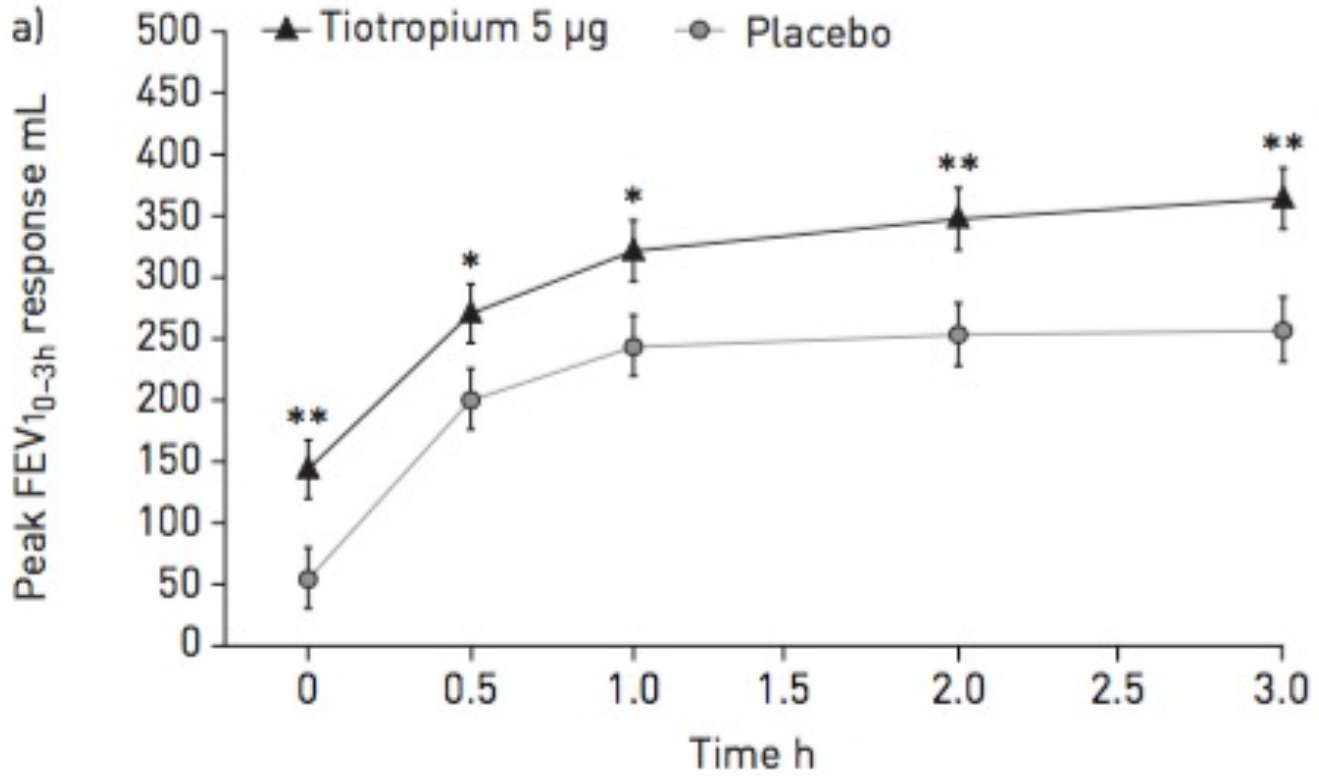
Some patients with asthma have frequent exacerbations and persistent airflow obstruction despite treatment with inhaled glucocorticoids and long-acting beta-agonists (LABAs).

METHODS

In two replicate, randomized, controlled trials involving 912 patients with asthma who were receiving inhaled glucocorticoids and LABAs, we compared the effect on lung function and exacerbations of adding tiotropium (a total dose of 5 μg) or placebo, both delivered by a soft-mist inhaler once daily for 48 weeks. All the patients were symptomatic, had a post-bronchodilator forced expiratory volume in 1 second (FEV_1) of 80% or less of the predicted value, and had a history of at least one severe exacerbation in the previous year.

All patients at least on ICS maintenance therapy > 800 mcg budesonide or equivalent

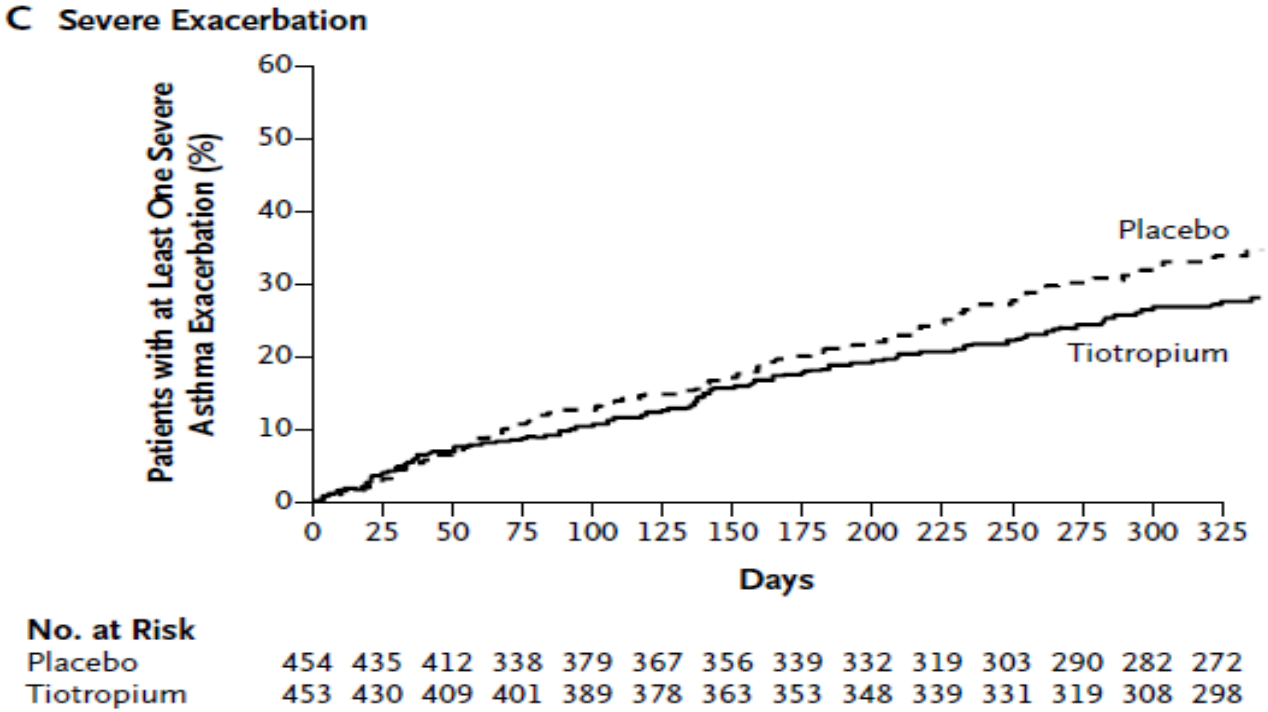
Kerstjens HAM, et al. New Engl J Med 2012



Kerstjens et al, NEJM 2012

Third coprimary endopoint (time to first severe exacerbation)

Severe exacerbation rate - 21% Time to first ex: + 56 days



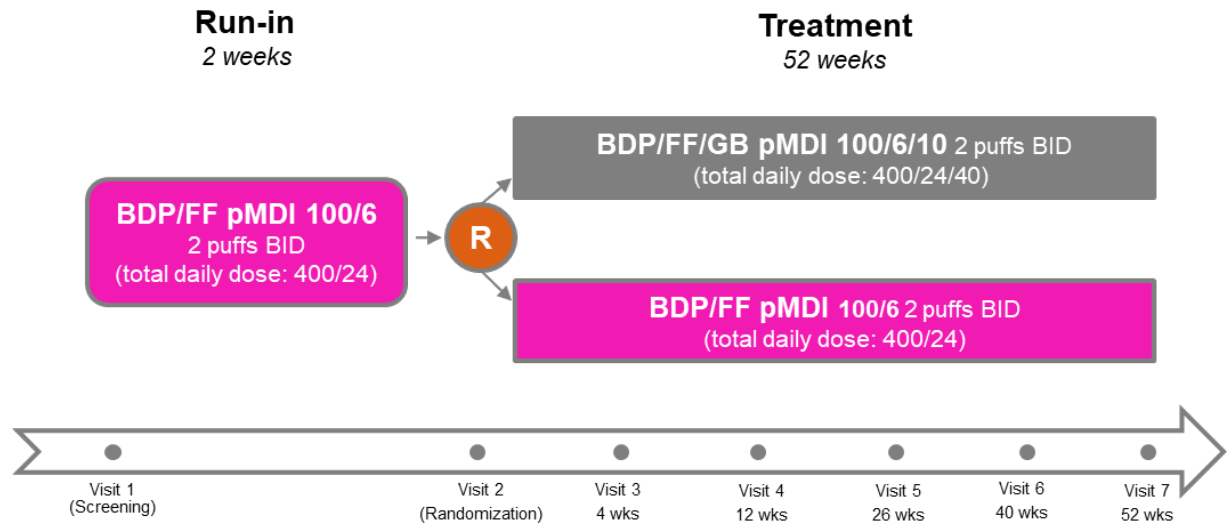
Minor changes in symptoms

- ACQ7
  - -0.09 in trial 1 (n.s.)
  - -0.13 in trial 2 (p=0.06)
- AQLQ
  - -0.04 in trial 1 (n.s.)
  - -0.18 in trial 2 (p=0.02)

Kerstjens et al, NEJM 2012

TRIMARAN Study - design

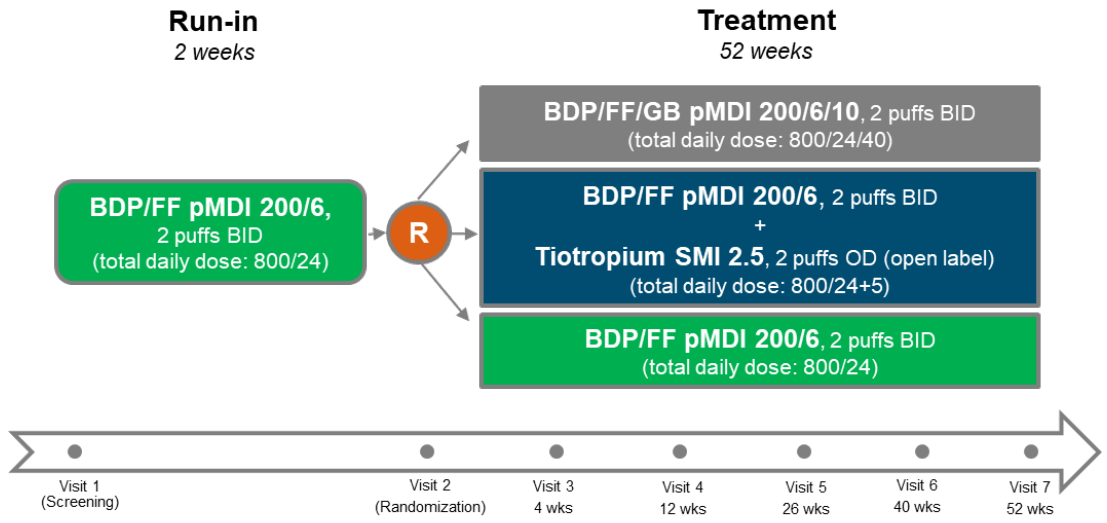
- 52 weeks, randomized, double blind, multinational, multicentre, active controlled, parallel group trial comparing BDP/FF/GB (100/6/12.5) to BDP/FF (100/6) (both pMDI extrafine formulations) in terms of lung functions parameters and rate of exacerbations, in patients with uncontrolled asthma on medium doses of ICS in combination with LABA.



Virchow JC, et al.; Lancet. 2019 Sep 30. pii: S0140-6736(19)32215-9.

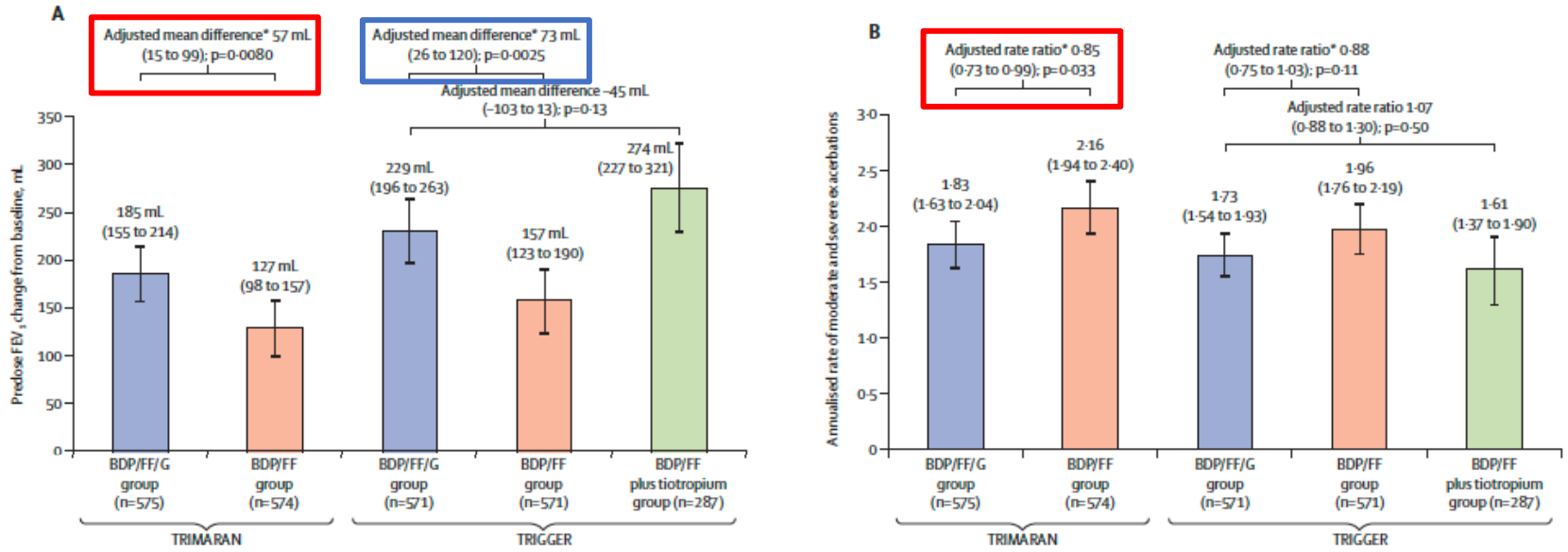
TRIGGER Study - Design

52 weeks, randomized, multinational, multicentre, active controlled, parallel group trial comparing BDP/FF/GB (200/6/10) to BDP/FF (200/6) and BDP/FF (200/6) + tiotropium (2.5) in terms of lung functions parameters and rate of exacerbations in patients with uncontrolled asthma on high doses of ICS in combination with LABA.



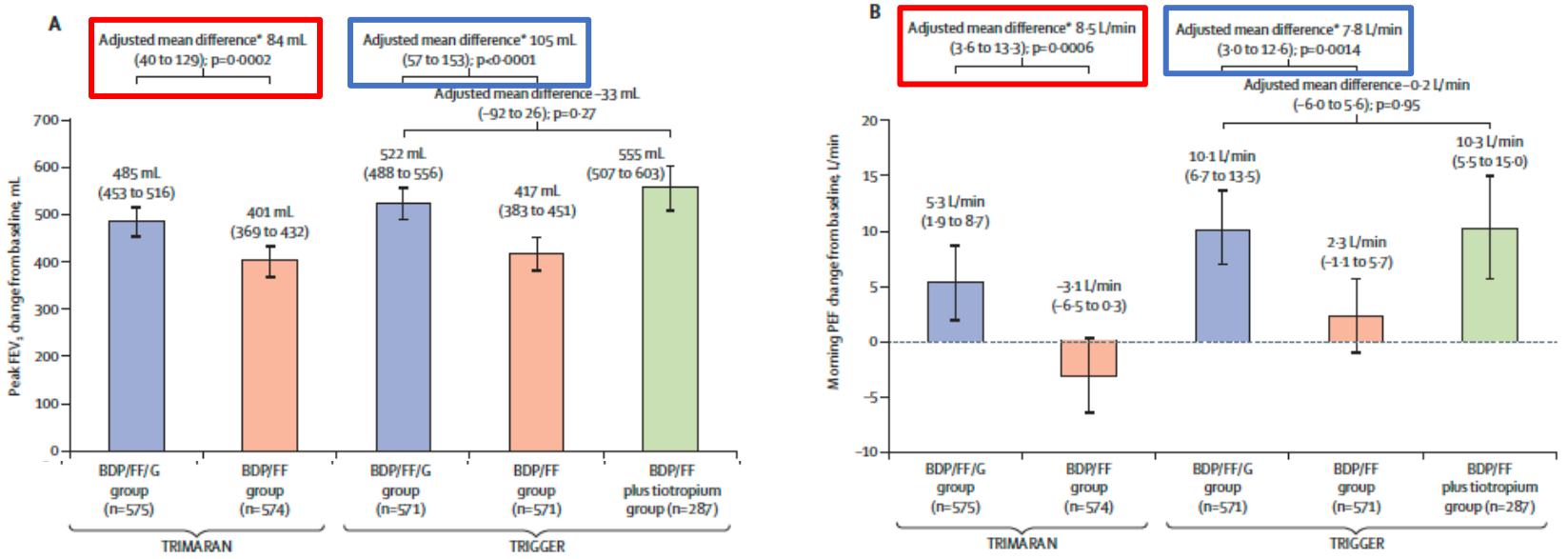
Virchow JC, et al.; Lancet. 2019 Sep 30. pii: S0140-6736(19)32215-9.

Co-primary endpoints



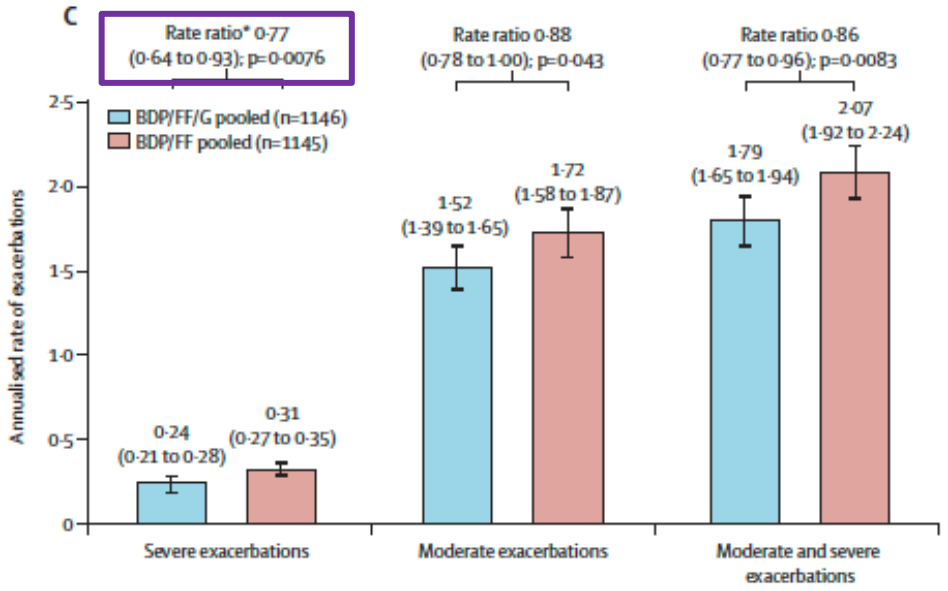
Virchow JC, et al.; Lancet. 2019 Sep 30. pii: S0140-6736(19)32215-9.

Key secondary endpoints



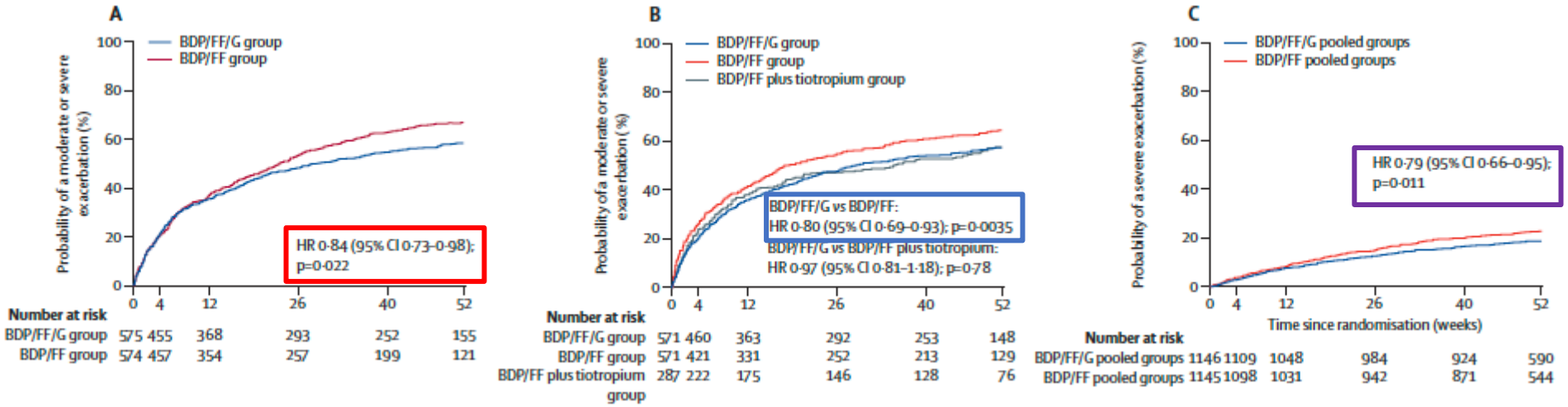
Virchow JC, et al.; Lancet. 2019 Sep 30. pii: S0140-6736(19)32215-9.

Key secondary endpoints (pooled analysis)



Virchow JC, et al.; Lancet. 2019 Sep 30. pii: S0140-6736(19)32215-9.

Other secondary endpoints



Virchow JC, et al.; Lancet. 2019 Sep 30. pii: S0140-6736(19)32215-9.

Conclusions

- The lung function co-primary endpoint was met in both studies, with a slightly larger effect size in TRIGGER. These improvements persisted for the whole duration of the studies.

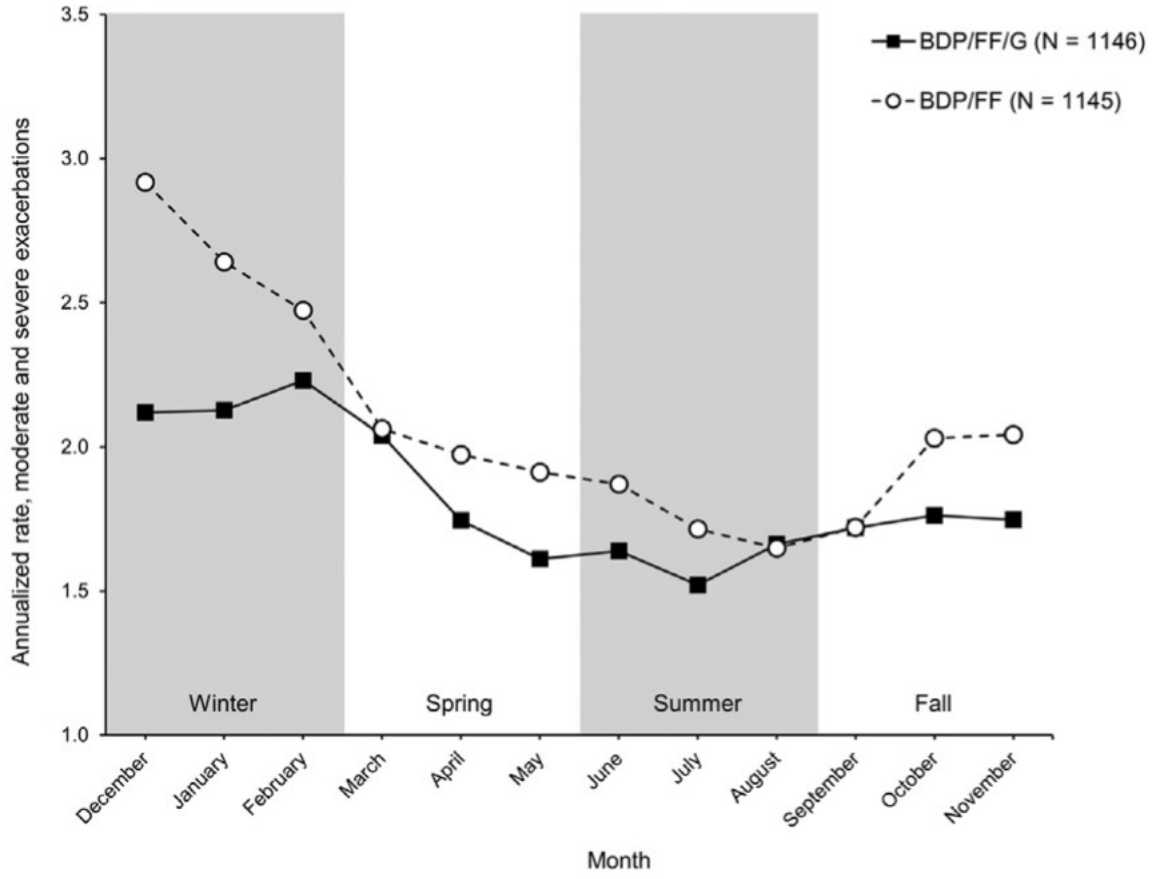
- The moderate and severe exacerbations co-primary endpoint was met in TRIMARAN. Although there was similar effect size in TRIGGER, statistical significance was not achieved.
  - When data were pooled, BDP/FF/G significantly reduced the rate of the more clinically relevant severe exacerbations, the rate of moderate and combined moderate and severe exacerbations compared with BDP/FF, and prolonged the time to first moderate, moderate or severe, and severe exacerbation.

- Asthma control, symptom endpoints and rescue medication use improved from baseline with all treatments.
  - Interestingly, in TRIMARAN BDP/FF/G and BDP/FF resulted in similar improvements in symptom-free days and asthma control days, whereas in TRIGGER there was a separation between BDP/FF/G and BDP/FF, particularly over the second half of the study.

- All treatments were similarly well tolerated. This is consistent with the results of a number of other triple therapy studies in asthma, in which the addition of long-acting muscarinic antagonist did not impact the overall adverse event profile.

Virchow JC, et al.; Lancet. 2019 Sep 30. pii: S0140-6736(19)32215-9.

Extrafine triple therapy and asthma exacerbation seasonality: TRIMARAN and TRIGGER post hoc analyses



Clinical implications: Studies have demonstrated substantial seasonal variation in asthma exacerbations. In these *post hoc* analyses, we show that inhaled triple therapy reduces this seasonal variation, demonstrating particular efficacy in the winter.

Papi A, et al. J Allergy Clin Immunol 2021;148:262-5

Once daily single inhlaer (Breezhaler)

Indacaterol/Mometasone (QMF149) and Indacaterol/Glycopyrronium/Mometasone (QVM 149)

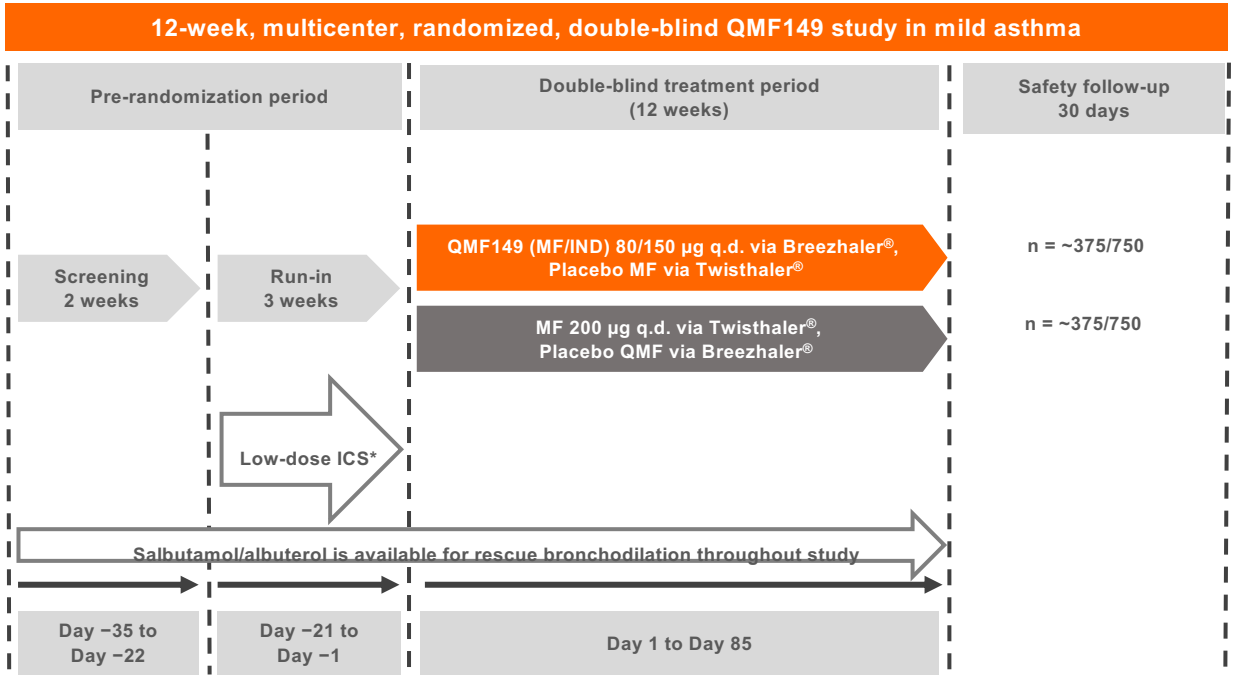
QVM149 (ICS + LABA + LAMA)

- Inhaled **fixed-dose triple combination** of:
  - LABA: Indacaterol acetate*
  - ICS: Mometasone furoate
  - LAMA: Glycopyrronium bromide
- In development for **once-daily treatment of asthma**

QMF149 (ICS + LABA)

- Inhaled **fixed-dose combination** of:
  - LABA: Indacaterol acetate*
  - ICS: Mometasone furoate
- Development of QMF149 is part of QVM149 development program
- In development for **once-daily treatment of asthma**

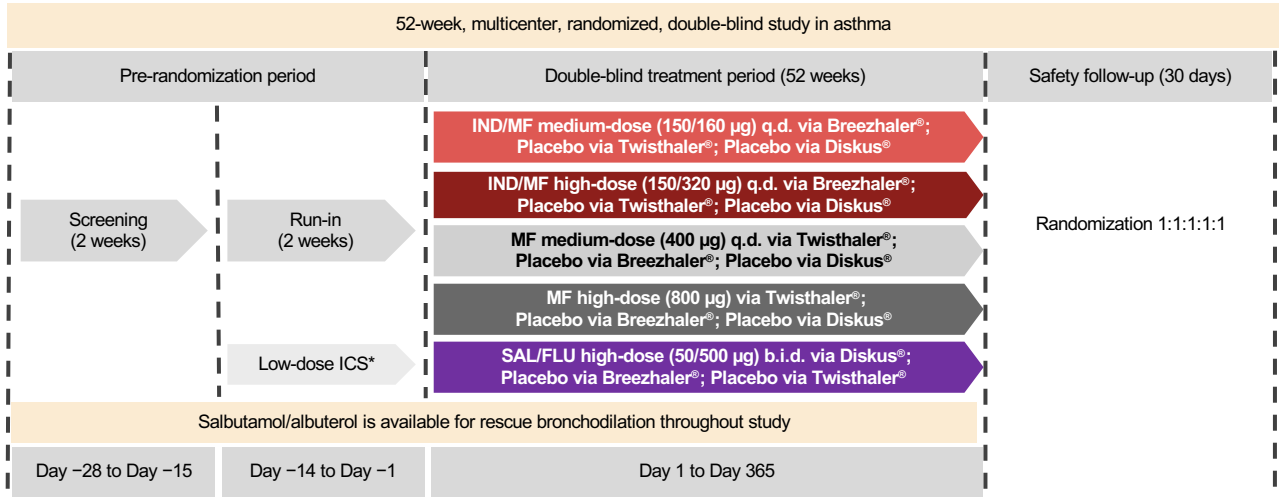
QUARTZ trial design
QVM149B2303



Kornmann et al. Respir Med. 2020 Jan;161:105809

PALLADIUM: study design

Efficacy/safety of two doses of IND/MF compared to MF monotherapy



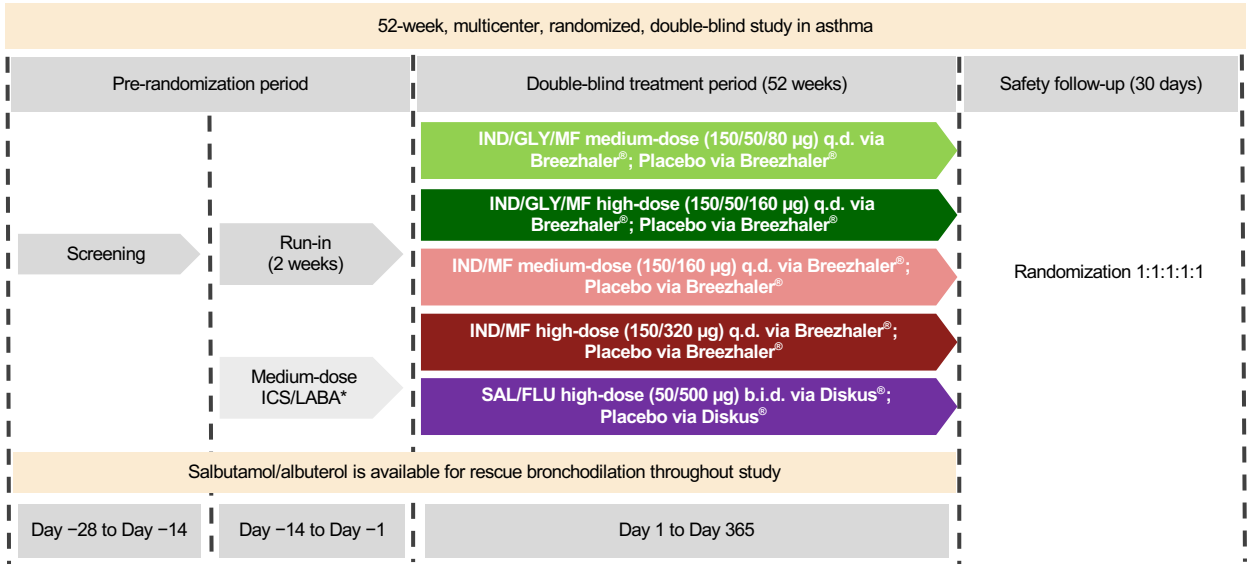
All treatments were administered in the evening

*e.g. fluticasone propionate 100 µg b.i.d.
IND/MF high-dose = IND/MF 150/320; IND/MF medium-dose = IND/MF 150/160; MF high-dose = MF 800 µg (400 b.i.d); MF medium-dose = MF 400 µg. SAL/FLU high-dose = SAL/FLU 50/500 µg; b.i.d. = twice daily; ICS = inhaled corticosteroid; IND = indacaterol acetate; MF = mometasone furoate; q.d. = once daily; SAL/FLU = salmeterol/fluticasone propionate

Study identifier: QVM149B2301.

van Zyl-Smit RN et al.; Respir Med. 2020 Jul 9:S2213-2600(20)30178-8.

IRIDIUM: study design

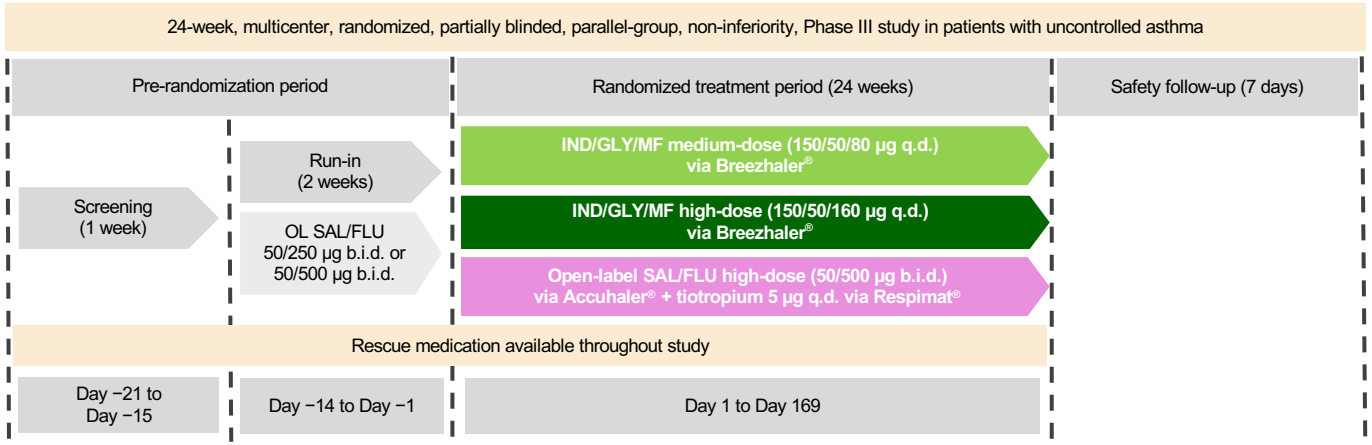


All treatments were administered in the evening

*SAL/FLU 50/250 µg b.i.d. IND/GLY/MF high-dose = IND/GLY/MF 150/50/160; IND/GLY/MF medium-dose = IND/GLY/MF 150/50/80;
IND/MF high-dose = IND/MF 150/320; IND/MF medium-dose = IND/MF 150/160; SAL/FLU high-dose = SF 50/500. b.i.d. = twice daily;
GLY = glycopyrronium bromide; ICS = inhaled corticosteroid; IND = indacaterol acetate; LABA = long-acting β_2-agonist; MF = mometasone furoate q.d. = once daily; . SAL/FLU = salmeterol/fluticasone propionate combination. Study identifier: QVM149B2302.

Huib A M Kerstjens et al., The Lancet Respiratory Medicine 2020

ARGON: study design



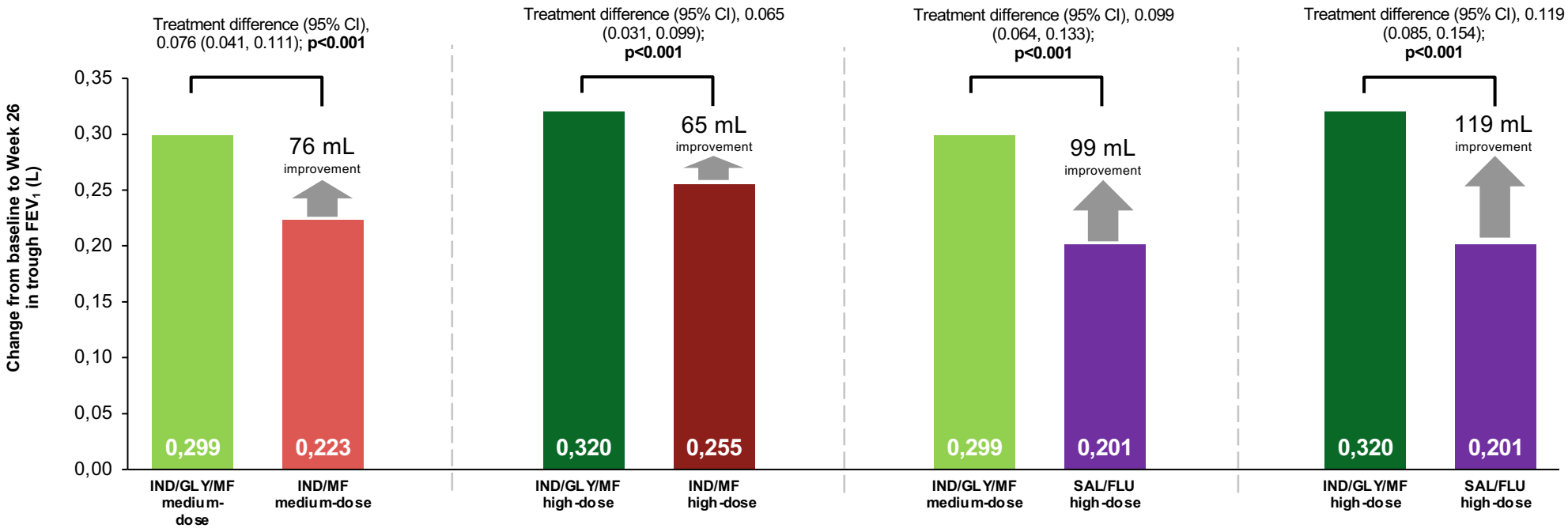
b.i.d. = twice-daily; IND/GLY/MF = indacaterol acetate/glycopyrronium bromide/mometasone furoate; q.d. = once daily; OL = open-label; SAL/FLU = salmeterol/fluticasone propionate

Gessner et al Resp Med 2020.106021

IND/GLY/MF significantly improved lung function vs IND/MF and high-dose SAL/FLU

IRIDIUM

Primary endpoint met (p<0.001 for all treatment comparisons):Superiority of medium or high doses of IND/GLY/MF to corresponding doses of IND/MF in terms of trough FEV1 **at 26 weeks**



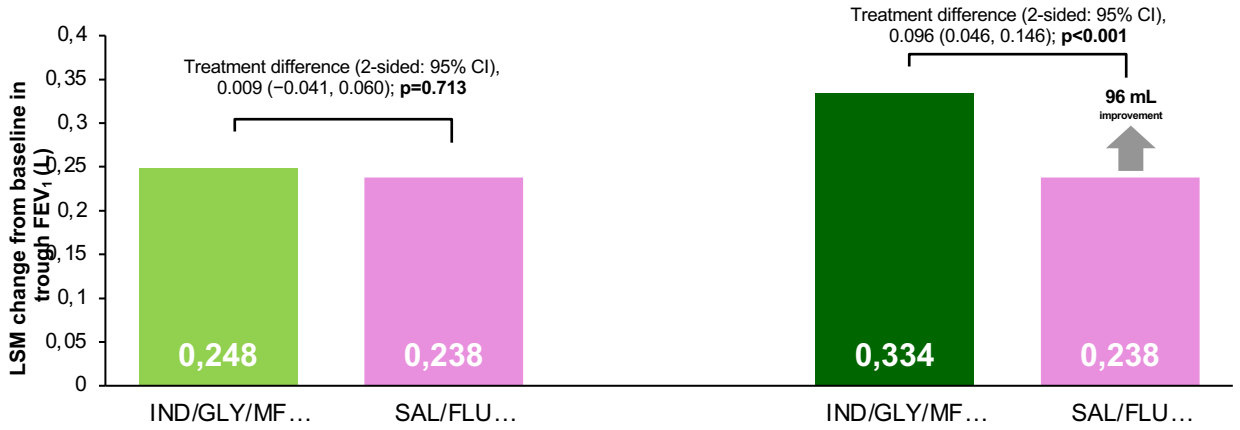
***IRIDIUM population:** **Symptomatic despite treatment with medium/high-dose LABA/ICS**
80% patients had ≥1 exacerbation requiring systemic corticosteroids in the past year

IND/GLY/MF high-dose = IND/GLY/MF 150/50/160 µg; IND/GLY/MF medium-dose = IND/GLY/MF 150/50/80 µg; IND/MF high-dose = IND/MF 150/320 µg; IND/MF medium-dose = IND/MF 150/160 µg; SAL/FLU high-dose = SAL/FLU 50/500 µg
FEV_1 = forced expiratory volume in 1 second; GLY = glycopyrronium; IND = indacaterol acetate; MF = mometasone furoate

Huib A M Kerstjens et al., The Lancet Respiratory Medicine 2020

IND/GLY/MF significantly improved lung function compared with free combination high-dose SAL/FLU + TIO

Significant **improvements in trough FEV_1 at week 24** achieved with high-dose IND/GLY/MF compared with high-dose SAL/FLU (p<0.001)[1]



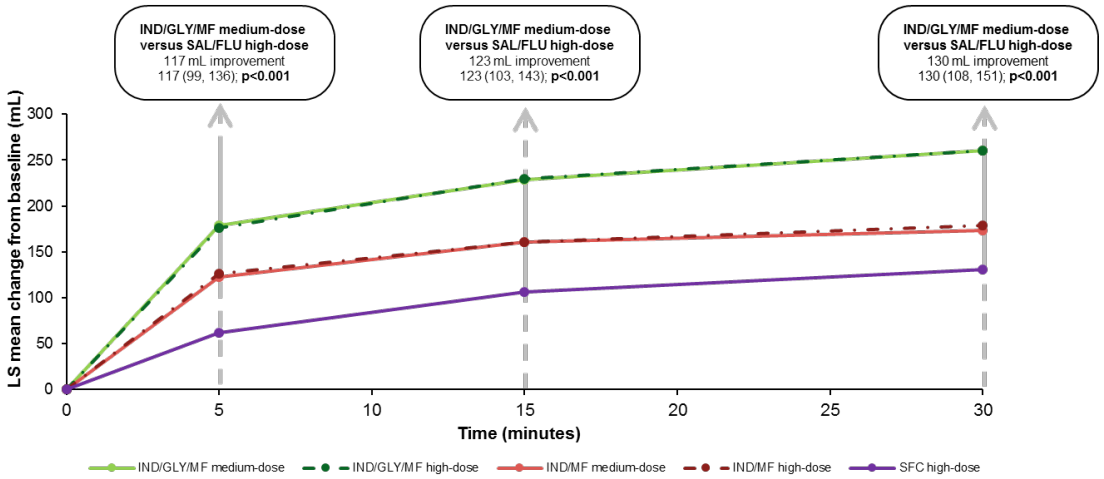
ARGON population: Symptomatic despite treatment with medium/high stable dose of LABA/ICS
80% patients had ≥1 exacerbation requiring treatment in the past year

Data presented are least squares mean treatment differences (95% confidence intervals)
IND/GLY/MF high-dose = indacaterol/glycopyrronium/mometasone furoate 150/50/160 µg; IND/GLY/MF medium-dose = IND/GLY/MF 150/50/80 µg; IND/MF high-dose = IND/MF 150/320 µg; IND/MF medium-dose = IND/MF 150/160 µg; MF high-dose = MF 800 µg; MF medium-dose = MF 400 µg; SAL/FLU high-dose = sameterol/fluticasone 50/500 µg; tio =
TIO = tiotropium 5 µg q.d.

Gessner et al Resp Med 2020.106021

IND/GLY/MF had a faster onset of action compared with SAL/FLU

Significant improvements in post-dose FEV_1 on Day 1 were **achieved at 5 minutes** with both medium- and high-dose IND/GLY/MF compared with high-dose SAL/FLU (p<0.001)[1*]



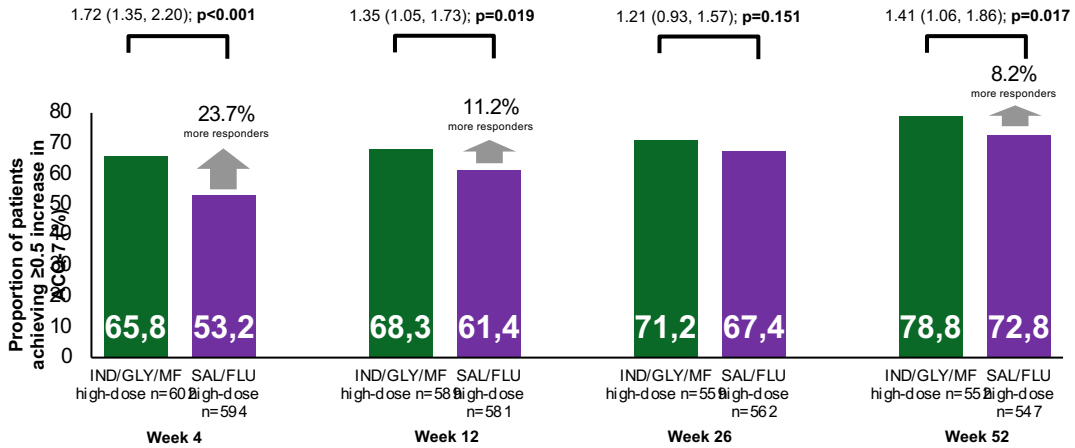
***IRIDIUM population: Symptomatic despite treatment with medium/high-dose LABA/ICS**
80% patients had ≥1 exacerbation requiring systemic corticosteroids in the past year

Data presented are LS mean, treatment differences (95% confidence intervals)
IND/GLY/MF high-dose = indacaterol/glycopyrronium/mometasone furoate 150/50/160 µg; IND/GLY/MF medium-dose = IND/GLY/MF 150/50/80 µg; IND/MF high-dose = IND/MF 150/320 µg; IND/MF medium-dose = IND/MF 150/160 µg; MF high-dose = MF 800 µg; MF medium-dose = MF 400 µg; SAL/FLU high-dose = sameterol/fluticasone 50/500 µg
LS = least squares

Huib A M Kerstjens et al., The Lancet Respiratory Medicine 2020

More patients achieved clinically important improvements in asthma control with IND/GLY/MF than with SAL/FLU

Significant improvements in **ACQ-7** responder rates at Weeks 4, 12 and 52 were achieved with high-dose IND/GLY/MF compared with high-dose SAL/FLU (p≤0.019). Improvements were non-significant at Week 26[1]*



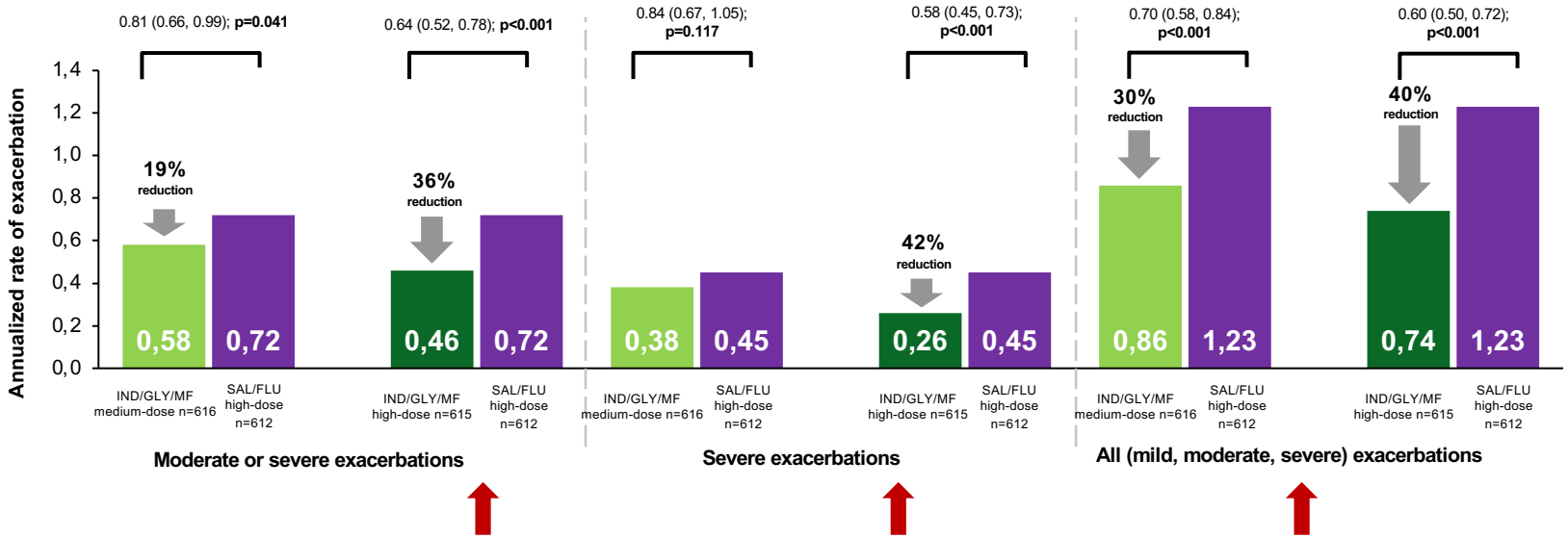
All treatments achieved clinically relevant improvements in ACQ-7 (MCID ≥0.5)[2] (–0.974, –0.975 and –0.889 for medium/high IND/GLY/MF and SAL/FLU respectively). Improvements with both doses of IND/GLY/MF were significantly greater than with SAL/FLU (–0.084 and –0.086 respectively [p≤0.038])

***IRIDIUM population: Symptomatic despite treatment with medium/high-dose LABA/ICS**
80% patients had ≥1 exacerbation requiring systemic corticosteroids in the past year

Responders were patients who achieved ≥0.5 reduction in ACQ-7 score (MCID)[2]
Data presented are odds ratios (95% confidence intervals)
IND/GLY/MF high-dose = indacaterol/glycopyrronium/mometasone furoate 150/50/160 µg; SAL/FLU high-dose = SAL/FLU 50/500 µg;
ACQ = asthma control questionnaire

Huib A M Kerstjens et al., The Lancet Respiratory Medicine 2020

IND/GLY/MF significantly reduced the rate of exacerbations vs high-dose SAL/FLU



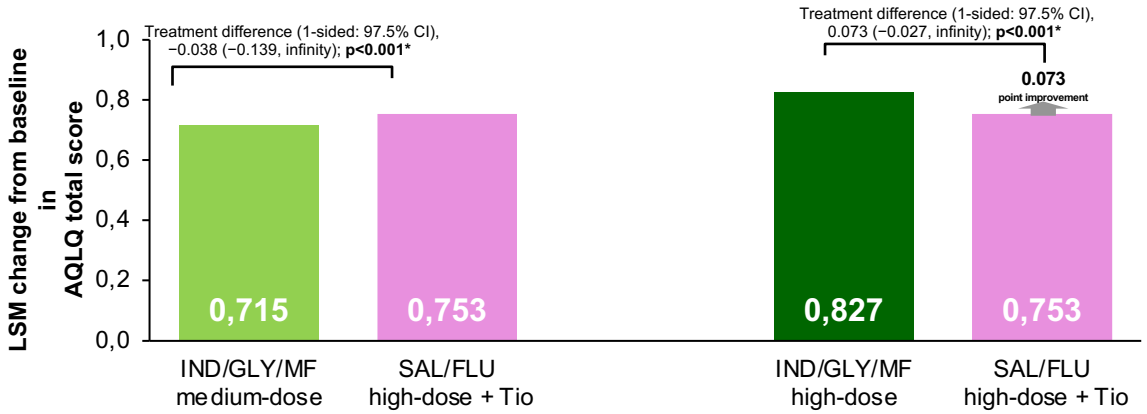
***IRIDIUM population: Symptomatic despite treatment with medium/high-dose LABA/ICS**
80% patients had ≥1 exacerbation requiring systemic corticosteroids in the past year

Data presented are annualized rate ratios (95% confidence intervals) based on 26 weeks data
IND/GLY/MF high-dose = indacaterol/glycopyrronium/mometasone furoate 150/50/160 µg; IND/GLY/MF medium-dose = IND/GLY/MF 150/50/80 µg; IND/MF high-dose = IND/MF 150/320 µg; IND/MF medium-dose = IND/MF 150/160 µg; SAL/FLU high-dose = salmeterol/fluticasone 50/500 µg.

Huib A M Kerstjens et al., The Lancet Respiratory Medicine 2020

IND/GLY/MF met the primary endpoint* demonstrating non-inferiority on AQLQ vs high dose SAL/FLU + TIO

Two IND/GLY/MF doses were non-inferior* in improving quality of life versus SAL/FLU high-dose + TIO



*Primary analysis was to demonstrate non-inferiority with a 0.25 points reduction in AQLQ score

ARGON population: Symptomatic despite treatment with medium/high stable dose of LABA/ICS
80% patients had ≥1 exacerbation requiring treatment in the past year

IND/GLY/MF high-dose = 150/50/160 µg; IND/GLY/MF medium-dose = 150/50/80 µg; SAL/FLU high-dose = 50/500 µg; Tio = Tiotropium 5 µg
*One sided non-inferiority p-value for both the comparisons. n, number of patients included in the analysis.
AQLQ = Asthma Quality of Life Questionnaire; IND/GLY/MF = indacaterol acetate/glycopyrronium/mometasone furoate; LSM = least squares mean; SAL/FLU = salmeterol/fluticasone propionate; Tio = tiotropium

Gessner et al Resp Med 2020.106021

Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomised, phase 3A trial

Interpretation In patients with uncontrolled moderate or severe asthma on ICS/LABA, adding UMEC improved lung function but did not lead to a significant reduction in moderate and/or severe exacerbations. For such patients, single-inhaler FF/UMEC/VI is an effective treatment option with a favourable risk–benefit profile. Higher dose FF primarily reduced the rate of exacerbations, particularly in patients with raised biomarkers of type 2 airway inflammation. Further confirmatory studies into the differentiating effect of type 2 inflammatory biomarkers on treatment outcomes in asthma are required to build on these exploratory findings and further guide clinical practice.

Lancet Respir Med 2020

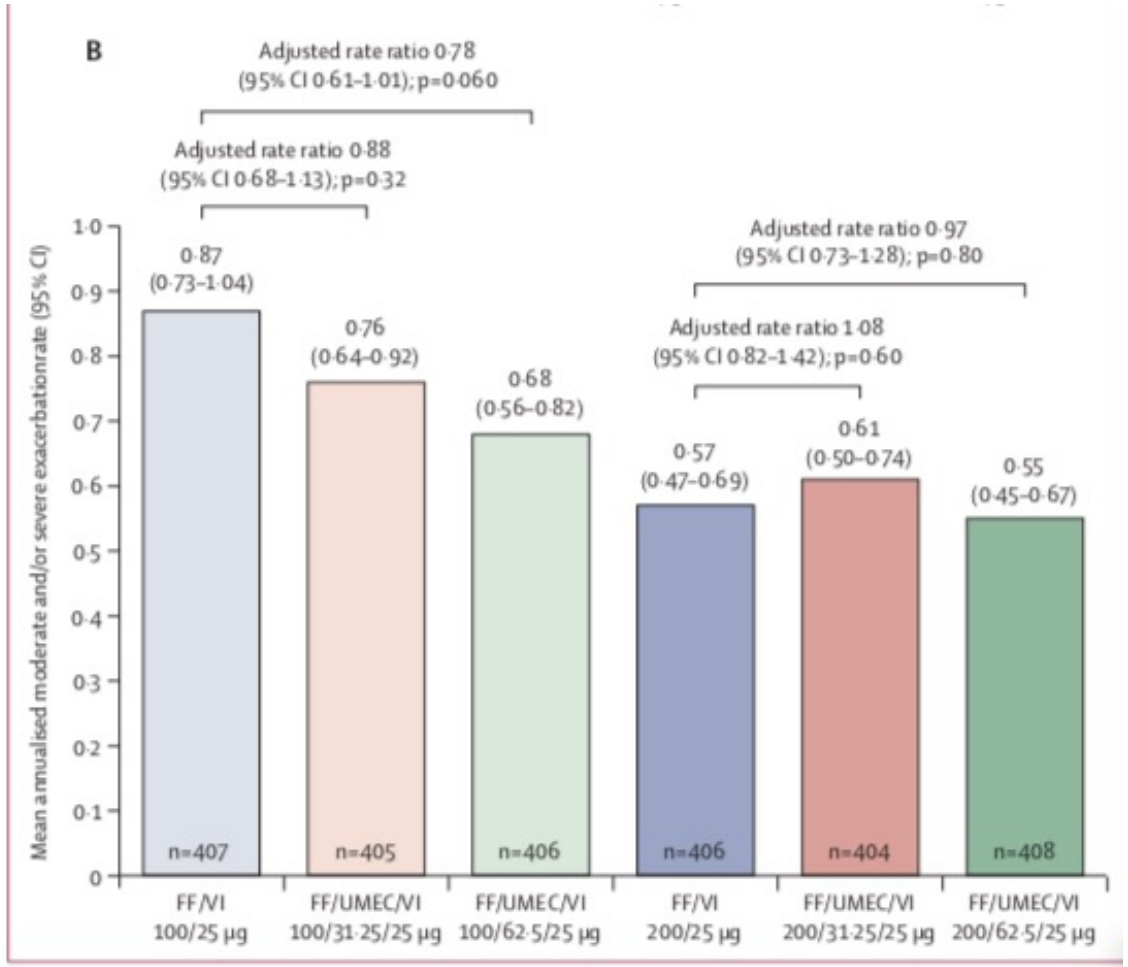


***Figure 3*: Analysis of mean annualised rate of moderate and/or severe exacerbations in the pooled (A) and unpooled (B) intention-to-treat population, weeks 1–52**

Rate ratios are adjusted for covariates (for additional detail, see appendix p 1). p values were not adjusted for multiplicity. FF=fluticasone furoate. UMEC=umedidinium. VI=vilanterol.

Lancet Respir Med 2020

JAMA | Original Investigation

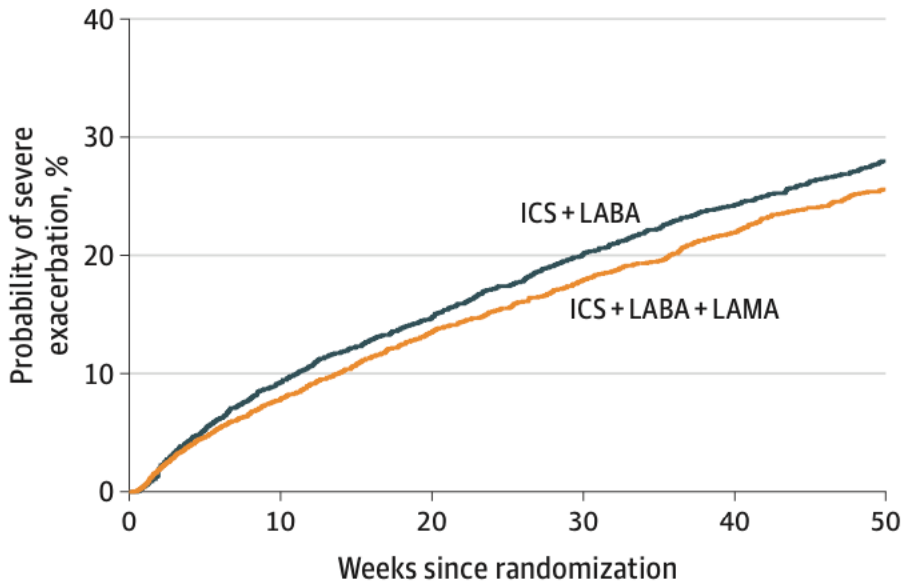
Triple vs Dual Inhaler Therapy and Asthma Outcomes in Moderate to Severe Asthma
A Systematic Review and Meta-analysis

Lisa H. Y. Kim, MD; Carol Saleh, MD; Anna Whalen-Browne, MD; Paul M. O'Byrne, MB; Derek K. Chu, MD, PhD

CONCLUSIONS AND RELEVANCE Among children (aged 6 to 18 years) and adults with moderate to severe asthma, triple therapy, compared with dual therapy, was significantly associated with fewer severe asthma exacerbations and modest improvements in asthma control without significant differences in quality of life or mortality.

JAMA. 2021;325(24):2466-2479

Figure 3. Kaplan-Meier Failure Curves of Time to First Severe Exacerbation in Patients Assigned to Triple vs Dual Asthma Inhaler Therapy

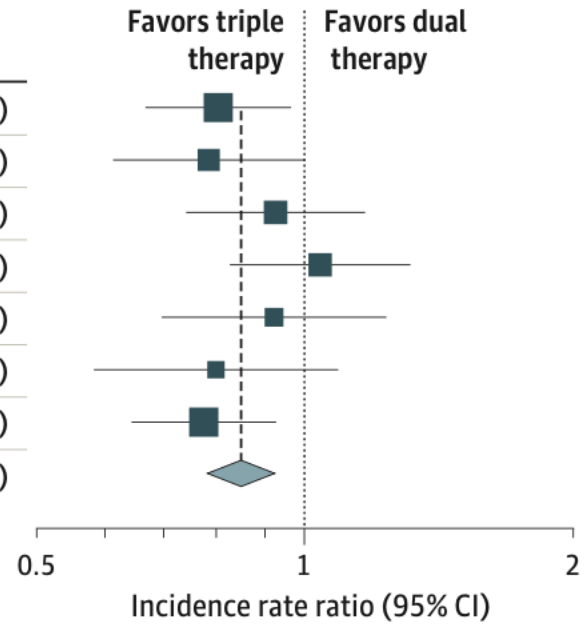


No. at risk						
ICS + LABA	4137	3650	3320	2922	2540	1760
ICS + LABA + LAMA	4159	3774	3396	2871	2332	1475
No. of studies	6	6	6	6	6	4

JAMA. 2021;325(24):2466-2479

A Incidence rate ratio of exacerbations

Source	Mean annualized exacerbation rate[a]		Incidence rate ratio (95% CI)	Weight, %
	Triple	Dual		
Kerstjens et al,[46] 2012	0.53	0.66	0.80 (0.66-0.96)	21
Kerstjens et al,[55] 2020[b]	0.26	0.33	0.78 (0.61-1.00)	12
Kerstjens et al,[55] 2020[b]	0.38	0.41	0.93 (0.74-1.17)	14
Lee et al,[56] 2020[b]	0.38	0.41	1.04 (0.82-1.31)	14
Lee et al,[56] 2020[b]	0.39	0.38	0.92 (0.69-1.23)	9
Pearl Therapeutics,[57] 2017	0.44	0.55	0.79 (0.58-1.09)	8
Virchow et al,[45] 2019	0.27	0.35	0.77 (0.64-0.93)	22
Overall: $I^2 = 0\%$			0.85 (0.78-0.92)	100



Conclusioni: asma oggi

Il controllo totale, con un trattamento regolare, è un obiettivo raggiungibile per tutti gli stadi di asma.

Triplice terapia

↑

Duplice terapia

↑

Monoterapia

Bateman et al AJRCC 2004
O'Byrne et al Chest 2008