



# Role and Expectation of Triple Inhaler in Asthma Treatment








Chin Kook Rhee, MD, PhD

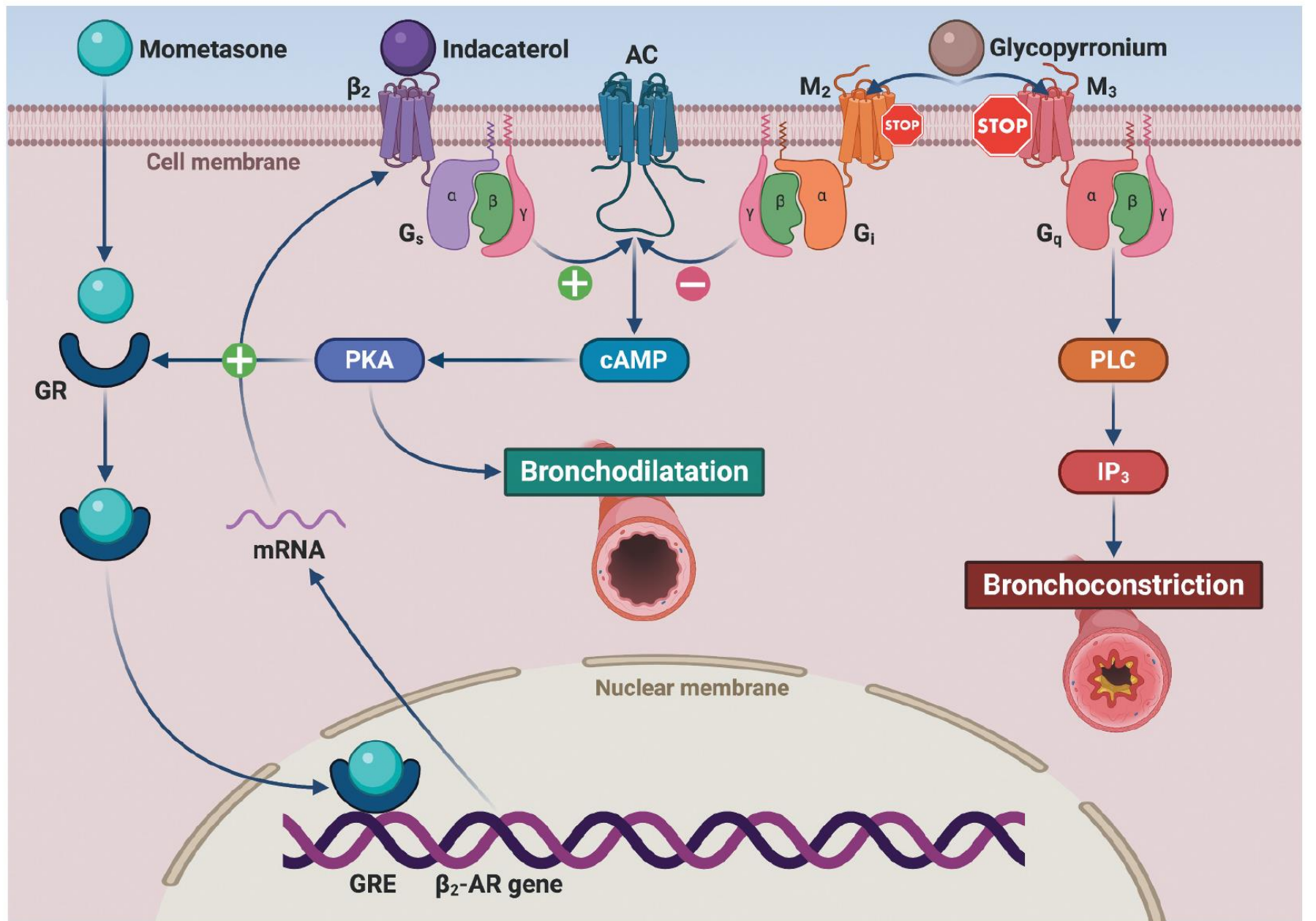
Professor  
Division of Pulmonary and Critical Care Medicine  
Department of Internal Medicine  
Seoul St. Mary's Hospital  
The Catholic University of Korea

REVIEW

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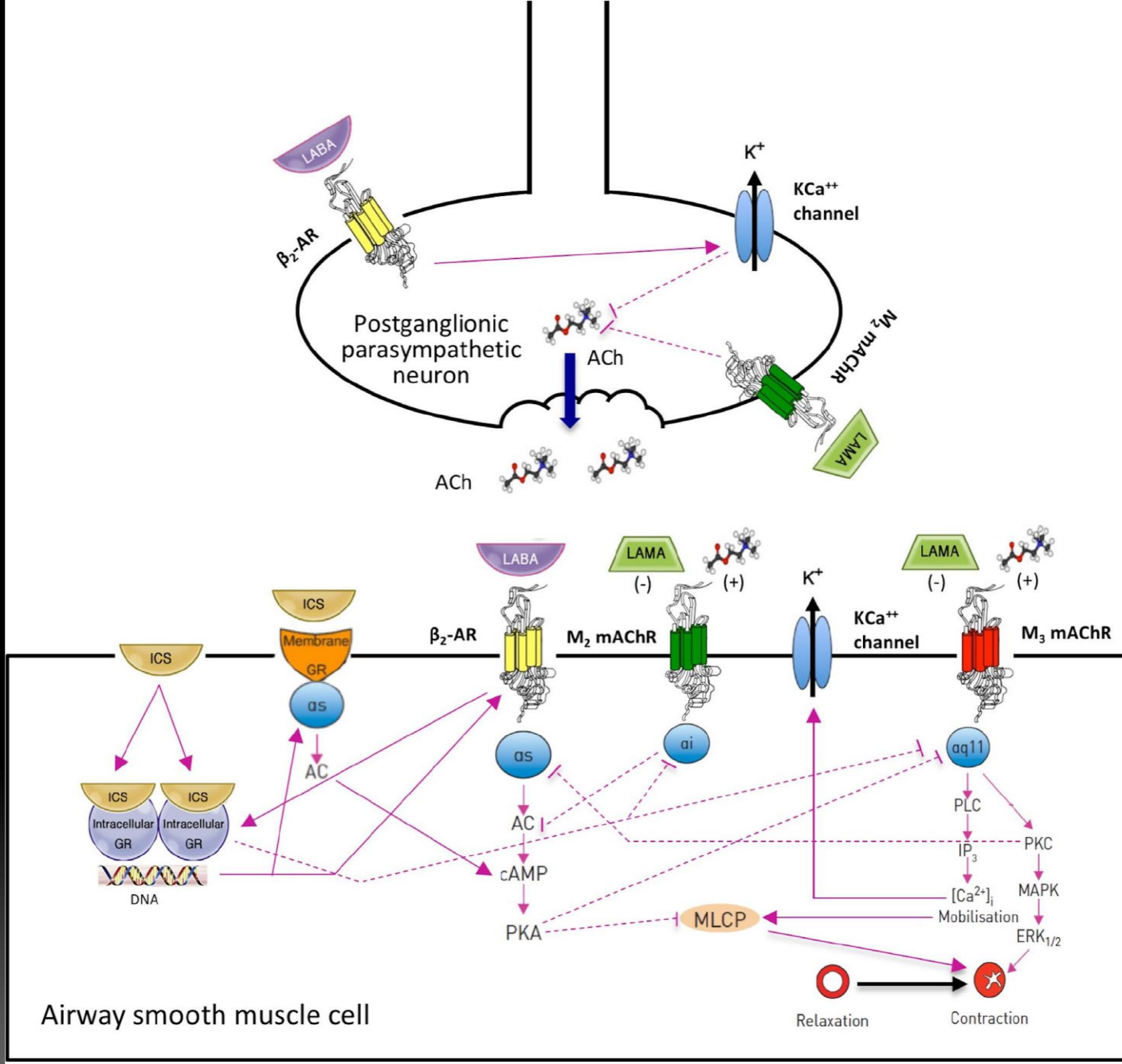
# Indacaterol/glycopyrronium/mometasone fixed dose combination for uncontrolled asthma

Corrado Pelaia <sup>a</sup>, Claudia Crimi <sup>b</sup>, Nunzio Crimi <sup>b</sup>, Luisa Ricciardi <sup>c</sup>, Nicola Scichilone <sup>d</sup>, Giuseppe Valenti <sup>e</sup>,  
Ornella Bonavita<sup>f</sup>, Stefano Andaloro<sup>f</sup>, Paolo Morini<sup>f</sup>, Andrea Rizzi<sup>f</sup> and Girolamo Pelaia <sup>a</sup>



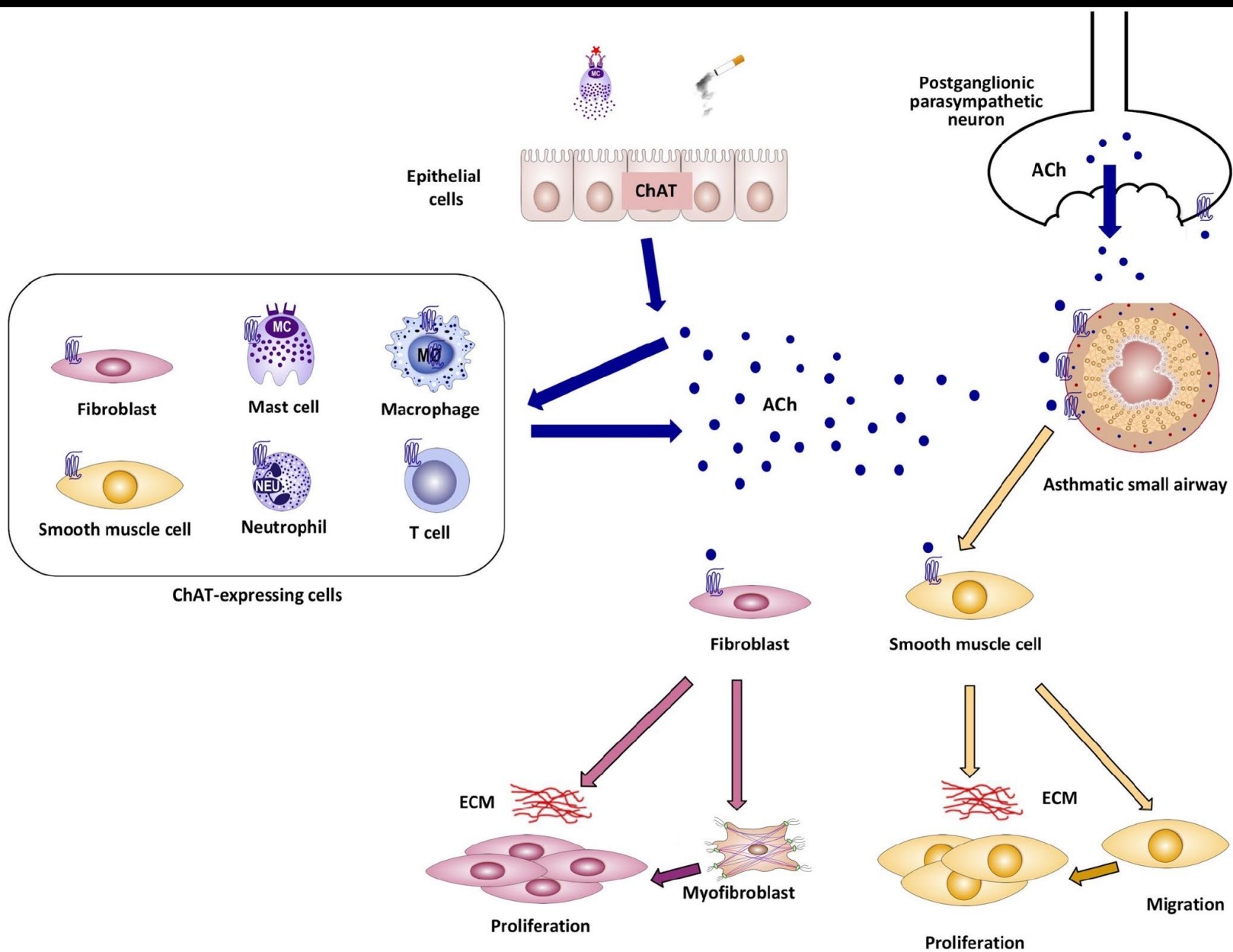
# Long-acting muscarinic antagonists and small airways in asthma: Which link?

Mario Cazzola<sup>1</sup>  | Luigino Calzetta<sup>2</sup>  | Maria Gabriella Matera<sup>3</sup>





Structure	Branch generation	Distribution of mAChR subtypes and $\beta$ -AR subtypes (abundance, fmol·mg <sup>-1</sup> of protein)			
		M <sub>2</sub> mAChR	M <sub>3</sub> mAChR	$\beta_1$ -AR	$\beta_2$ -AR
Trachea	0				
Primary bronchi	1				
Secondary bronchi	2				
Tertiary bronchi	3	47	48	0	50
Small bronchi	4				
Bronchioles	5-7				
Terminal bronchioles	8-16	11	28	0	85
Respiratory bronchioles	17-19	27	0	98	205
Alveolar ducts and sacs	20-23				



**FIGURE 3** Potential effects of ACh on asthmatic small airways. ACh, acetylcholine; ChAT, choline acetyltransferase; ECM, extracellular matrix



REVIEW

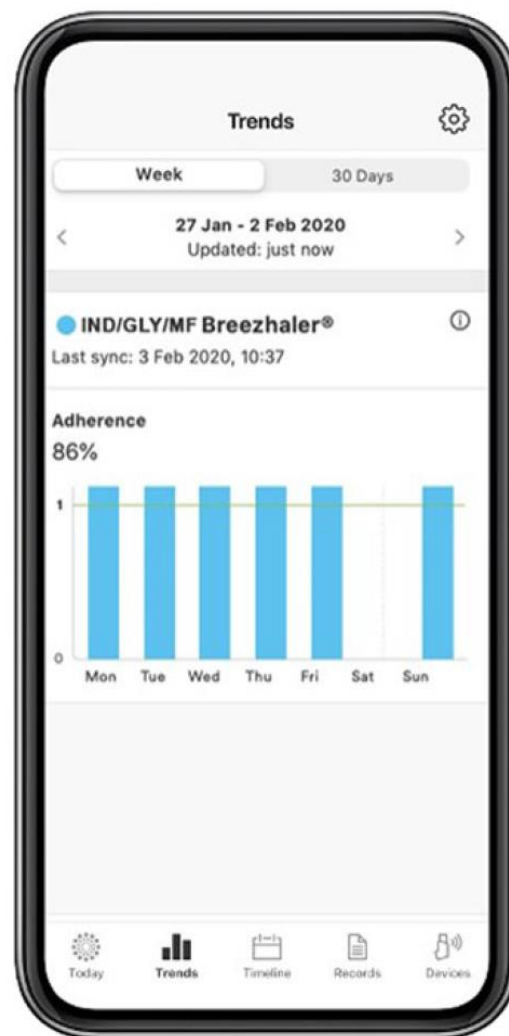
# A Review of the Unique Drug Development Strategy of Indacaterol Acetate/Glycopyrronium Bromide/Mometasone Furoate: A First-in-Class, Once-Daily, Single-Inhaler, Fixed-Dose Combination Treatment for Asthma

Dominic Brittain · Peter D'Andrea · Emilie Gruen · Motoi Hosoe · Devendra Jain ·

Juergen Jauernig · Abhijit Pethe · Emil Scosyrev · Ana-Maria Tanase · Hanns-Christian Tillmann

**Table 1** Doses of MF as monotherapy and as fixed-dose combination used in the clinical development program for IND/GLY/MF and IND/MF

	<b>Monotherapy</b>	<b>IND/MF</b>	<b>IND/GLY/MF</b>
MF			
Dose level (strength)	Via Twisthaler <sup>®</sup> [30]	Via Breezhaler <sup>®</sup> [38]	Via Breezhaler <sup>®</sup> [36]
Low	200 µg	80 µg	Not developed
Medium	400 µg	160 µg	80 µg
High	800 µg	320 µg	160 µg



**Table 2** Overview of the PLATINUM phase 3 clinical development program

Study (NCT number)	Study duration (weeks)	Study treatment arms	N
QUARTZ (NCT02892344)	12	IND/MF low-dose (150/80 µg o.d.) via Breezhaler <sup>®</sup>	398
		MF low-dose (200 µg o.d.) via Twisthaler <sup>®</sup>	404
PALLADIUM (NCT02554786)	52	IND/MF medium-dose (150/160 µg o.d.) via Breezhaler <sup>®</sup>	439
		IND/MF high-dose (150/320 µg o.d.) via Breezhaler <sup>®</sup>	445
		MF medium-dose (400 µg o.d.) via Twisthaler <sup>®</sup>	444
		MF high-dose (800 µg [400 µg b.i.d.]) via Twisthaler <sup>®</sup>	442
		SAL/FLU high-dose (50/500 µg b.i.d.) via Diskus <sup>®</sup>	446
IRIDIUM (NCT02571777)	52	IND/GLY/MF medium-dose (150/50/80 µg o.d.) via Breezhaler <sup>®</sup>	620
		IND/GLY/MF high-dose (150/50/160 µg o.d.) via Breezhaler <sup>®</sup>	619
		IND/MF medium-dose (150/160 µg o.d.) via Breezhaler <sup>®</sup>	617
		IND/MF high-dose (150/320 µg o.d.) via Breezhaler <sup>®</sup>	618
		SAL/FLU high-dose (50/500 µg b.i.d.) via Diskus <sup>®</sup>	618
ARGON (NCT03158311)	24	IND/GLY/MF medium-dose (150/50/80 µg o.d.) via Breezhaler <sup>®</sup>	474
		IND/GLY/MF high-dose (150/50/160 µg o.d.) via Breezhaler <sup>®</sup>	476
		SAL/FLU high-dose (50/500 µg b.i.d.) via Diskus <sup>®</sup> + TIO 5 µg o.d. via Respimat <sup>®</sup>	475



# Once-daily, single-inhaler mometasone–indacaterol–glycopyrronium versus mometasone–indacaterol or twice-daily fluticasone–salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study

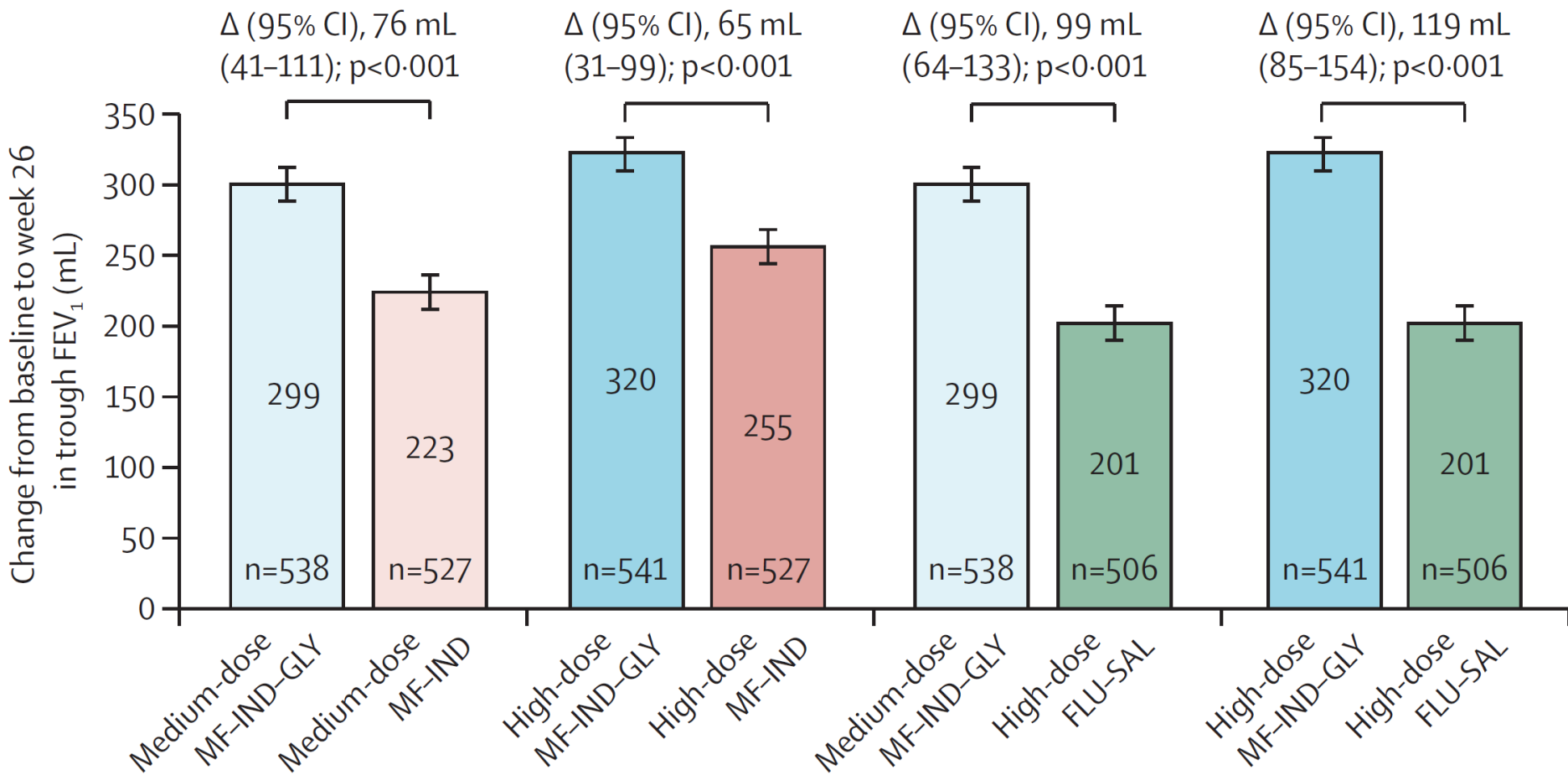
*Huib A M Kerstjens, Jorge Maspero, Kenneth R Chapman, Richard N van Zyl-Smit, Motoi Hosoe, Ana-Maria Tanase, Catherine Lavecchia, Abhijit Pethe, Xu Shu, Peter D'Andrea, on behalf of the IRIDIUM trial investigators\**

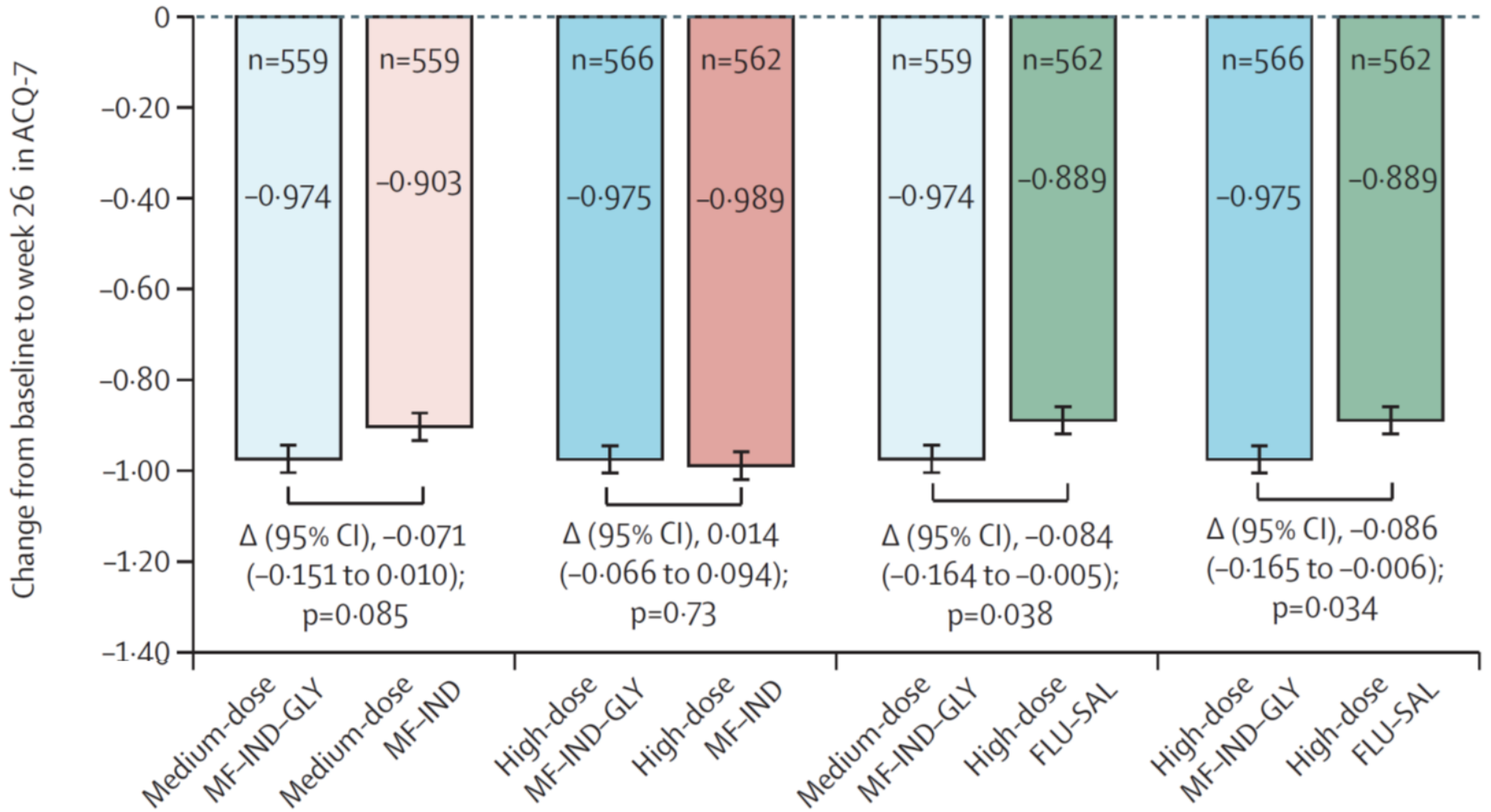
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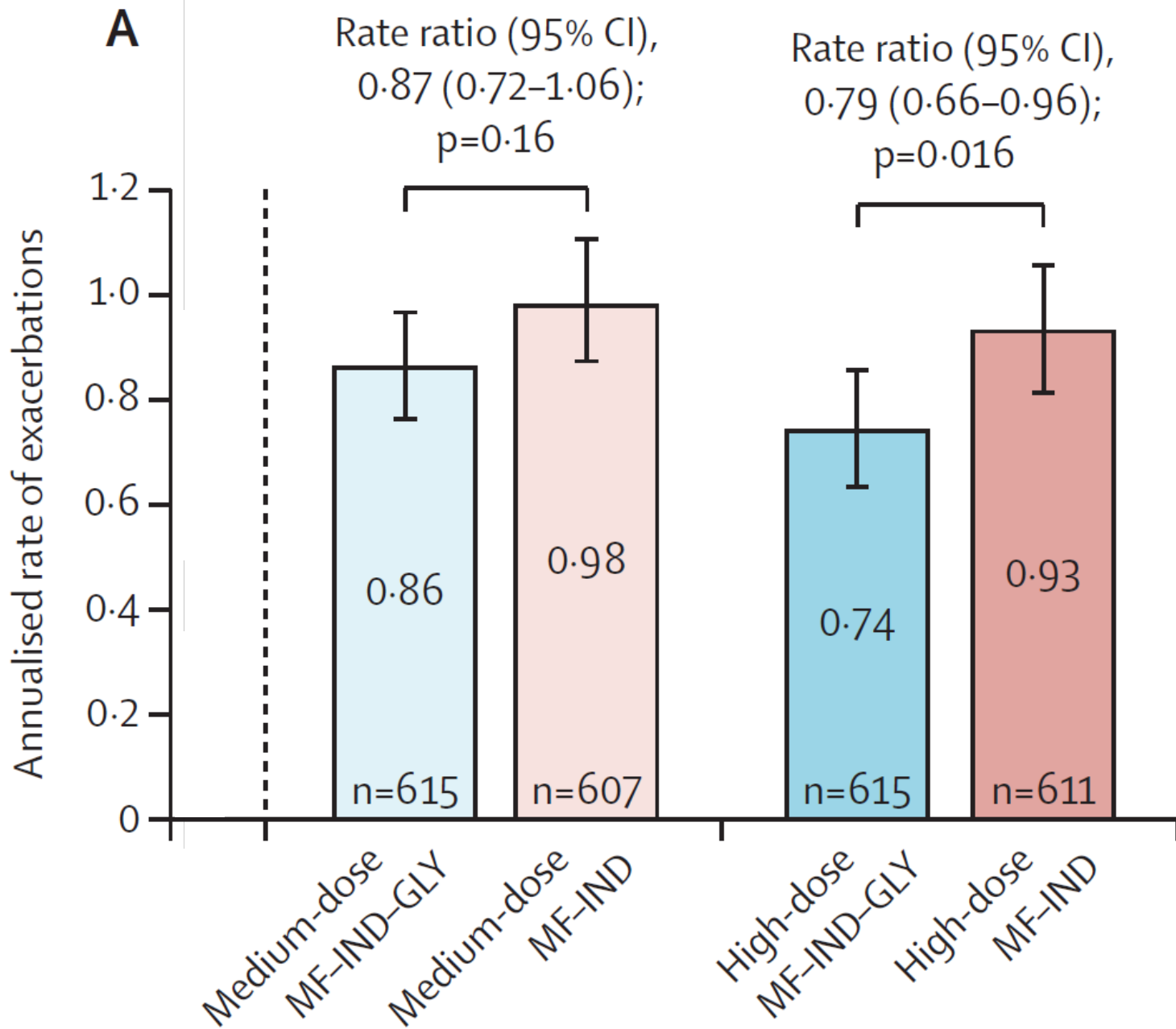
- Age 18~75
- FEV<sub>1</sub> < 80%
- BDR 12% & 200mL
- ACQ-7 at least 1.5
- At least one AE
- Medium or high dose ICSLABA

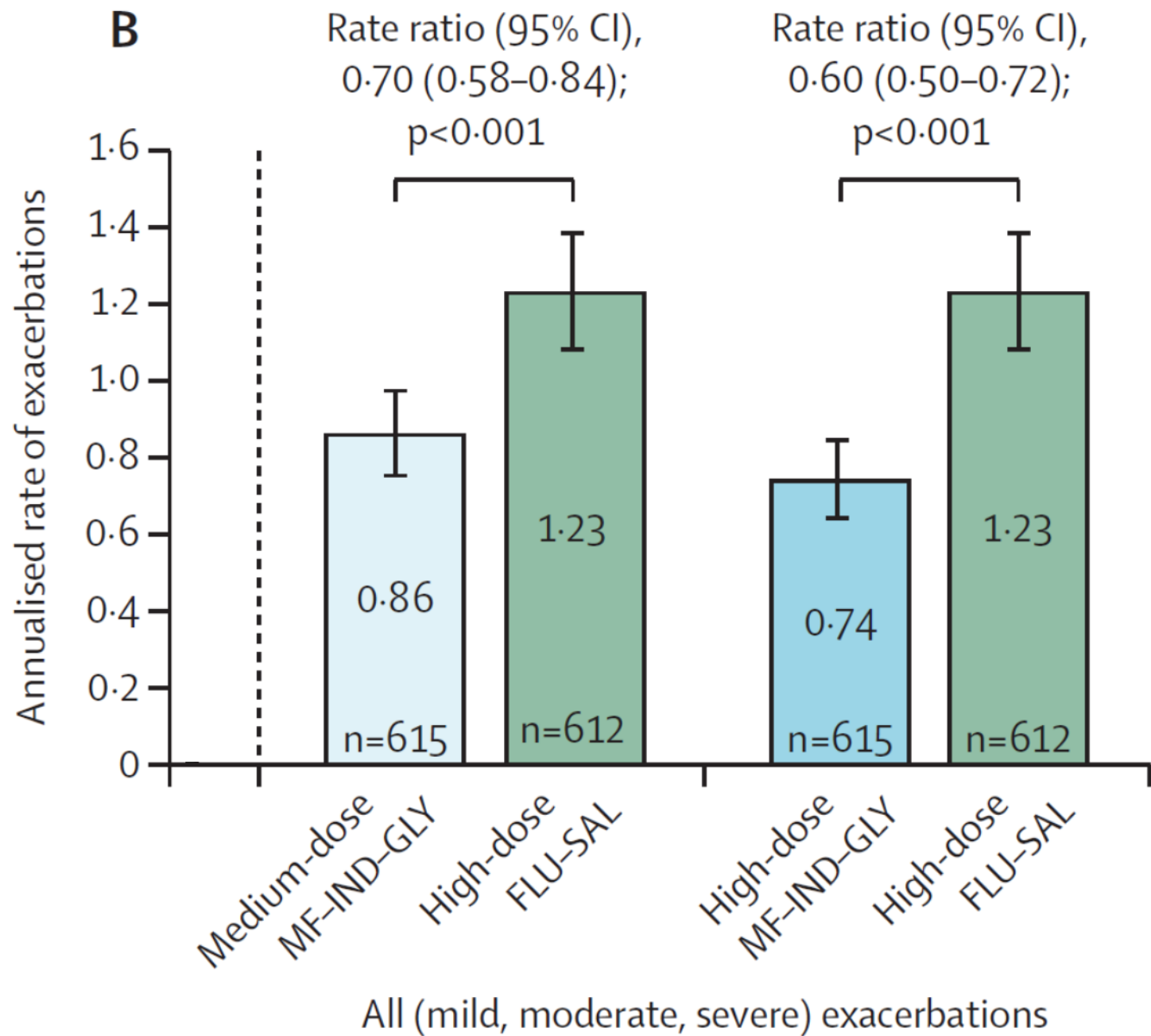
# Primary outcome

- ▣ Change from baseline in trough FEV<sub>1</sub>
  - Medium dose Triple vs Medium dose ICSLABA
  - High dose Triple vs High dose ICSLABA

**A**

**A**








# **Efficacy of one time per day, single-inhaler indacaterol/glycopyrronium/mometasone in patients with inadequately controlled asthma: post hoc analysis of IRIDIUM study in Asian population**

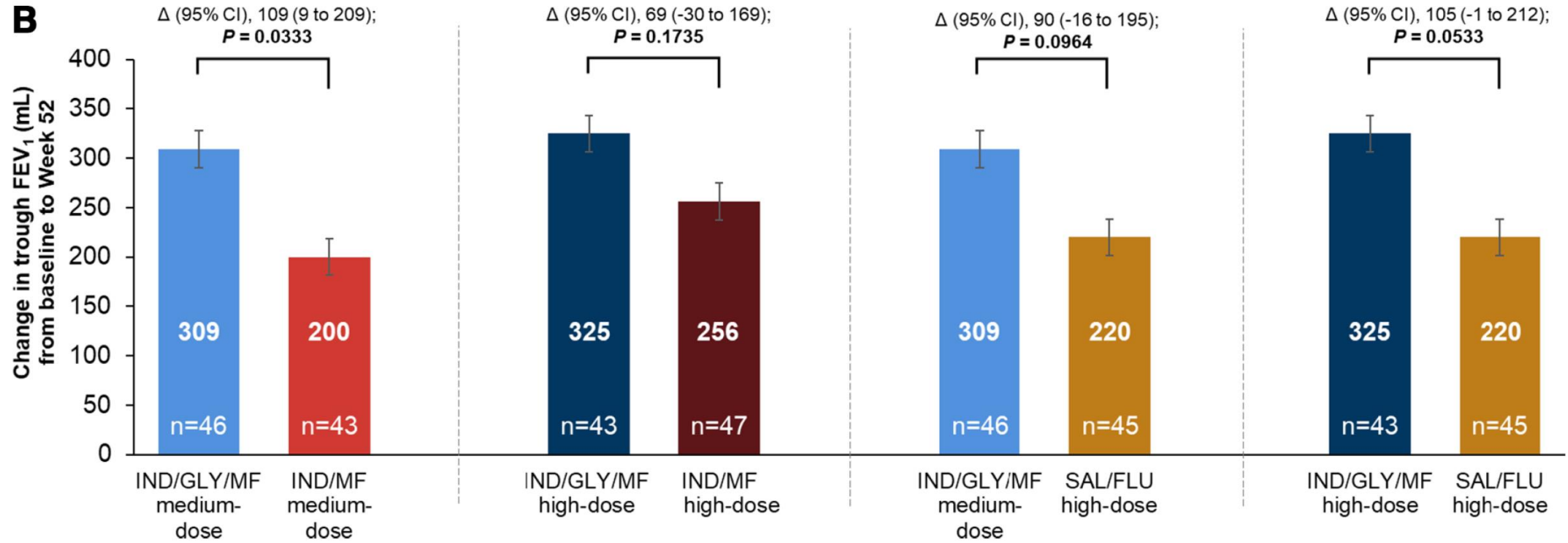
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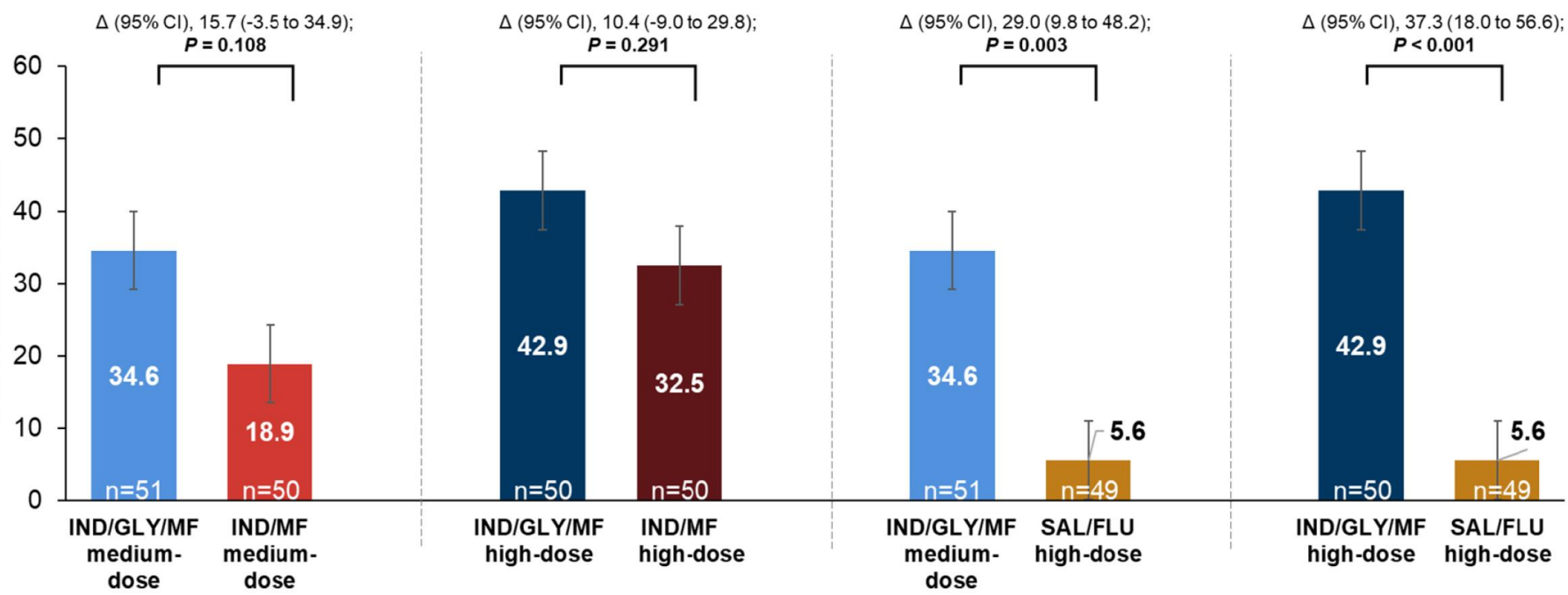
Hironori Sagara,<sup>1</sup> Nathalie Barbier,<sup>2</sup> Tsuyoshi Ishii,<sup>3</sup> Hajime Yoshisue ,<sup>3</sup> Ivan Nikolaev,<sup>2</sup> Motoi Hosoe,<sup>2</sup> Yasuhiro Gon<sup>4</sup>

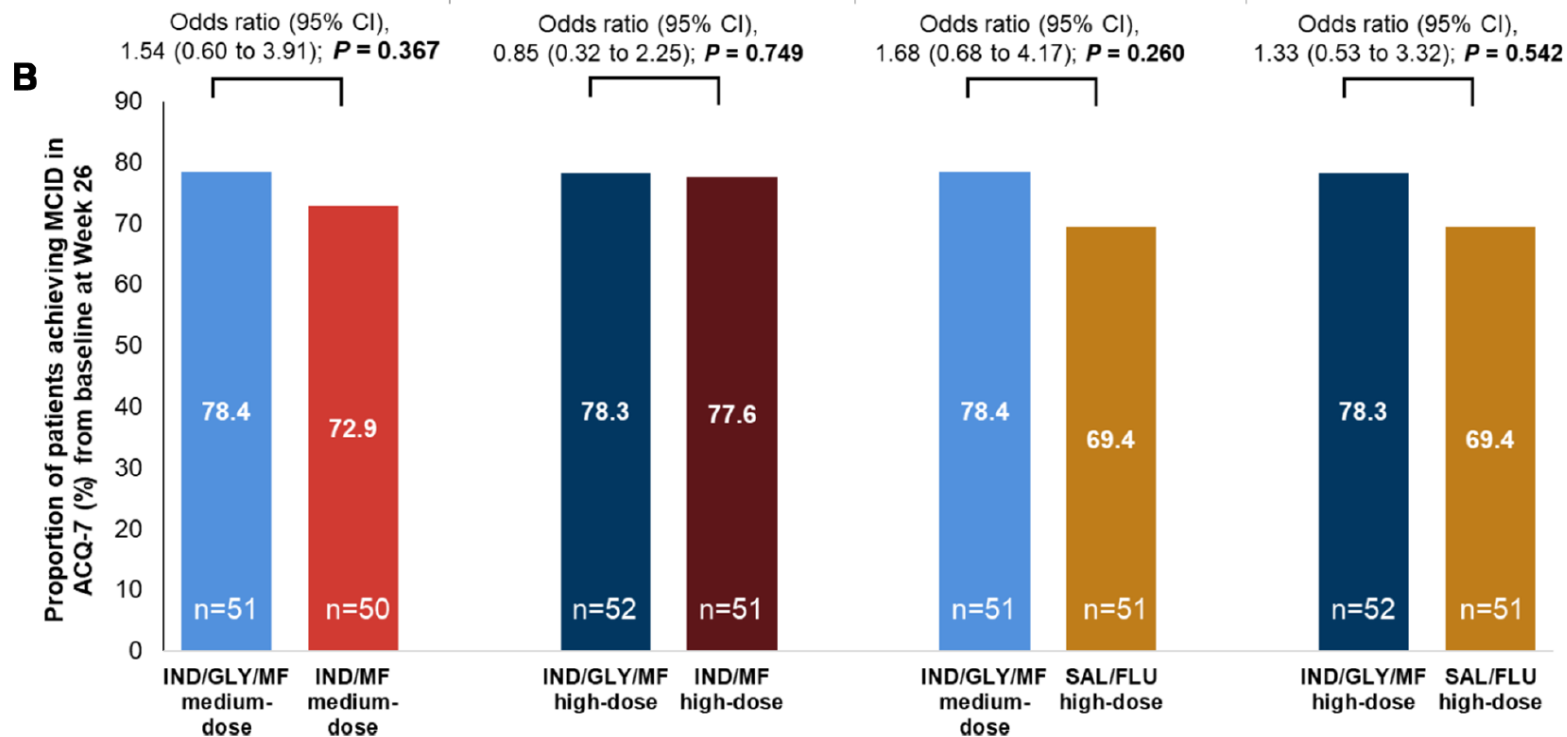
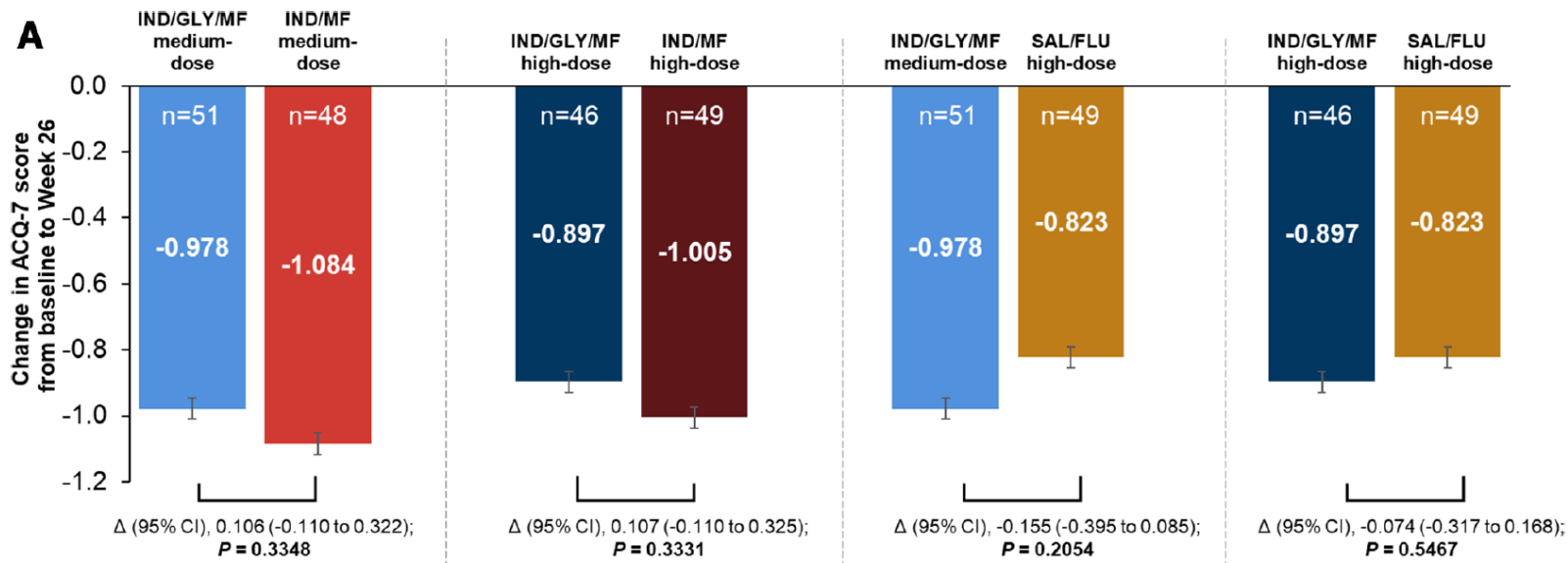
This is a post hoc analysis of data from the IRIDIUM study<sup>14</sup> in patients from Asian countries (Japan, China, Philippines, Vietnam and Thailand).

**Table 1** Baseline demographics and clinical characteristics (randomised set)

	IND/GLY/MF medium-dose N=52	IND/GLY/MF high-dose N=52	IND/MF medium-dose N=51	IND/MF high- dose N=51	SAL/FLU high-dose N=52
Age, years	52.4±11.57	49.4±11.72	50.9±12.50	52.4±10.52	51.9±12.30
Women, n (%)	28 (53.8)	37 (71.2)	37 (72.5)	34 (66.7)	36 (69.2)
Number of asthma exacerbations that required treatment in the 12 months prior to start of study, n (%)					
1	39 (75.0)	41 (78.8)	34 (66.7)	31 (60.8)	41 (78.8)
2	10 (19.2)	10 (19.2)	16 (31.4)	12 (23.5)	8 (15.4)
3	3 (5.8)	0	0	3 (5.9)	0
≥4	0	1 (1.9)	1 (2.0)	5 (9.8)	3 (5.8)
Never smoked, n (%)	44 (84.6)	48 (92.3)	47 (92.2)	45 (88.2)	45 (86.5)
Baseline ACQ-7 score*	2.2±0.46	2.3±0.67	2.3±0.45	2.4±0.52	2.3±0.40
Pre-bronchodilator FEV <sub>1</sub> , % predicted	55.6±14.80	57.1±13.65	56.4±11.50	53.6±14.33	54.3±13.59
FEV <sub>1</sub> reversibility after salbutamol inhalation, % increase†	26.0±15.13	28.2±12.23	27.0±13.26	29.2±13.59	26.7±13.44
Prior asthma treatment, n (%)					
LABA/ICS medium-dose	32 (61.5)	32 (61.5)	35 (68.6)	36 (70.6)	29 (55.8)
LABA/ICS high-dose	19 (36.5)	19 (36.5)	15 (29.4)	15 (29.4)	23 (44.2)

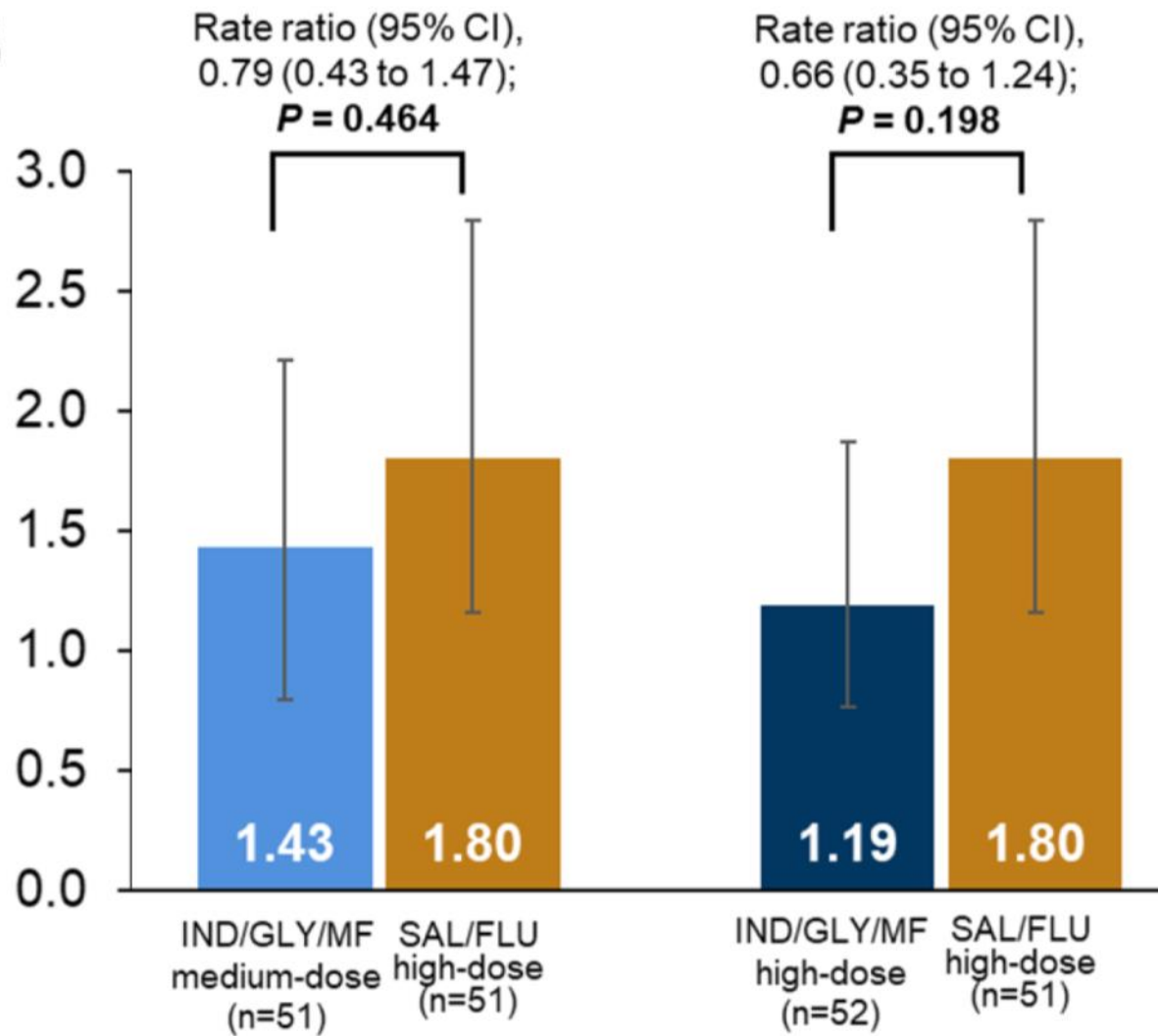
**B**

**B**Change in mean evening PEF (L/min)  
from baseline to Week 52



**B**

Annualised rate of exacerbations

**All (mild, moderate, severe) exacerbations**



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## Respiratory Medicine

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### Fixed-dose combination of indacaterol/glycopyrronium/mometasone furoate once-daily *versus* salmeterol/fluticasone twice-daily plus tiotropium once-daily in patients with uncontrolled asthma: A randomised, Phase IIIb, non-inferiority study (ARGON)

Christian Gessner<sup>a,\*</sup>, Oliver Kornmann<sup>b</sup>, Jorge Maspero<sup>c</sup>, Richard van Zyl-Smit<sup>d</sup>, Matthias Krüll<sup>e</sup>, Anna Salina<sup>f</sup>, Pritam Gupta<sup>g</sup>, Sebastien Bostel<sup>f</sup>, Sebastian Fucile<sup>h</sup>, Lorena Garcia Conde<sup>f</sup>, Pascal Pfister<sup>f</sup>





VS



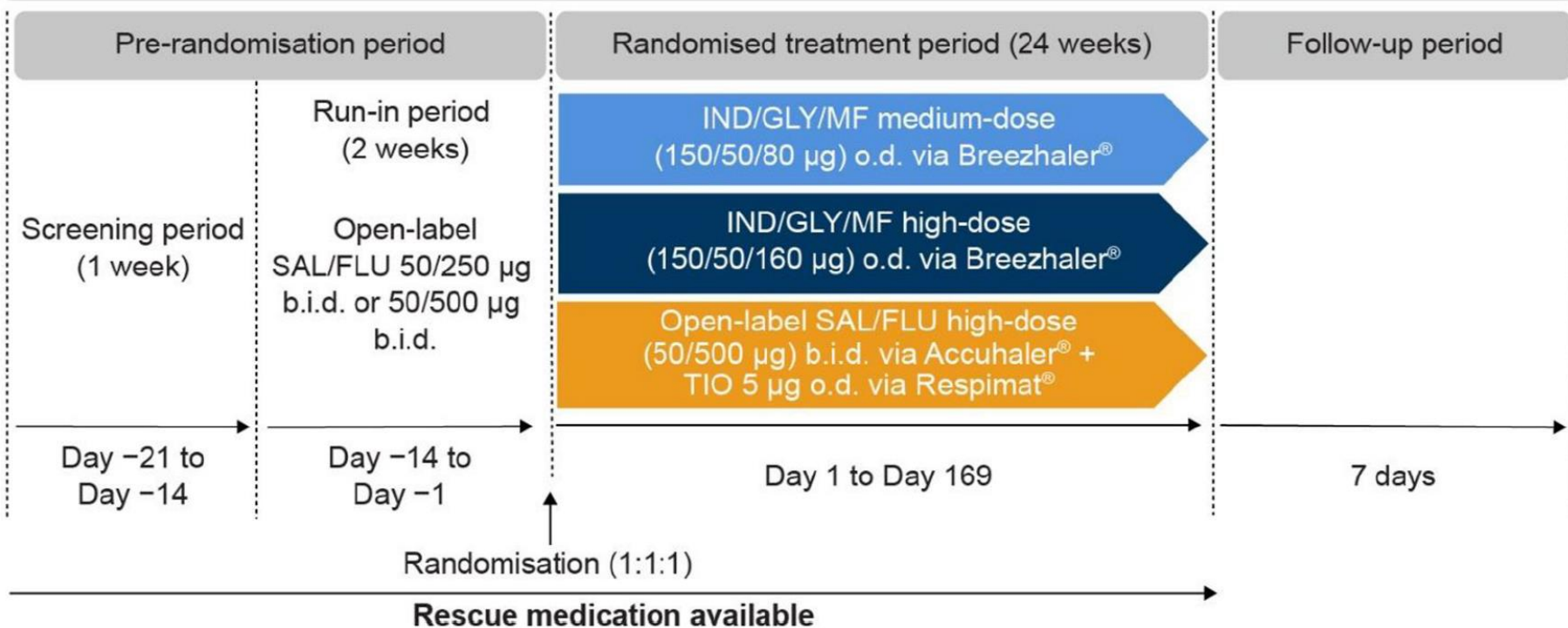
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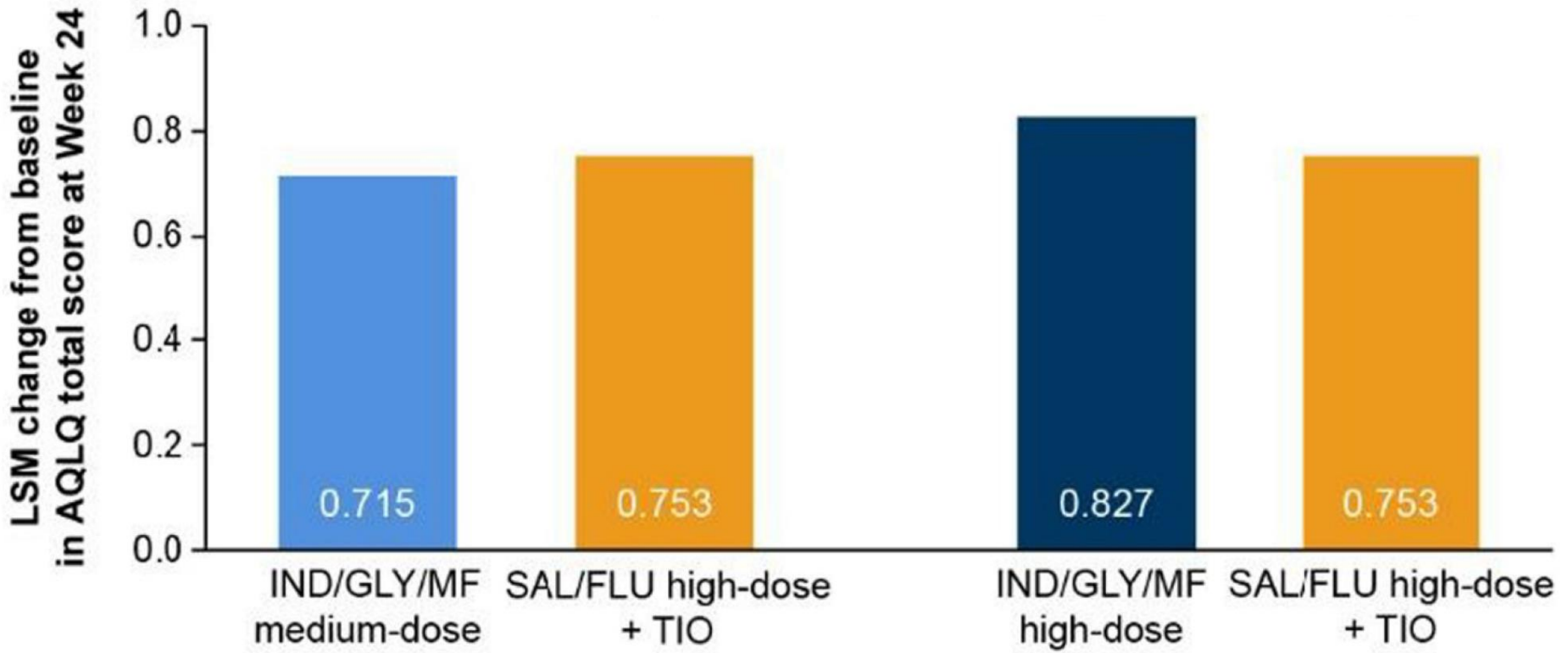
- Medium or high dose ICSLABA
- History of 1 severe exacerbation
- ACQ-7  $\geq 1.5$
- FEV<sub>1</sub> < 85%

# Primary endpoint

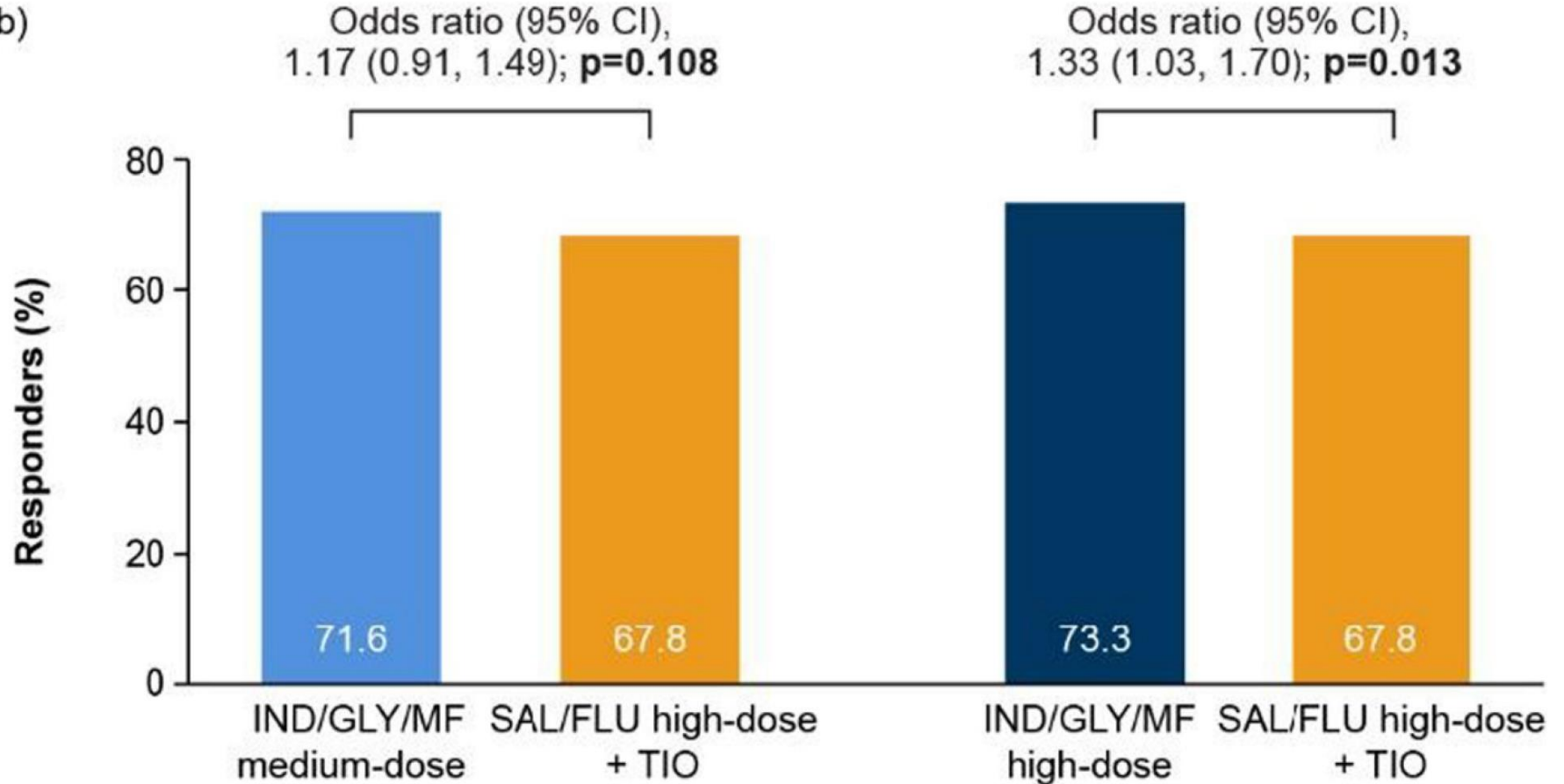
## ■ Non-inferiority of AQLQ

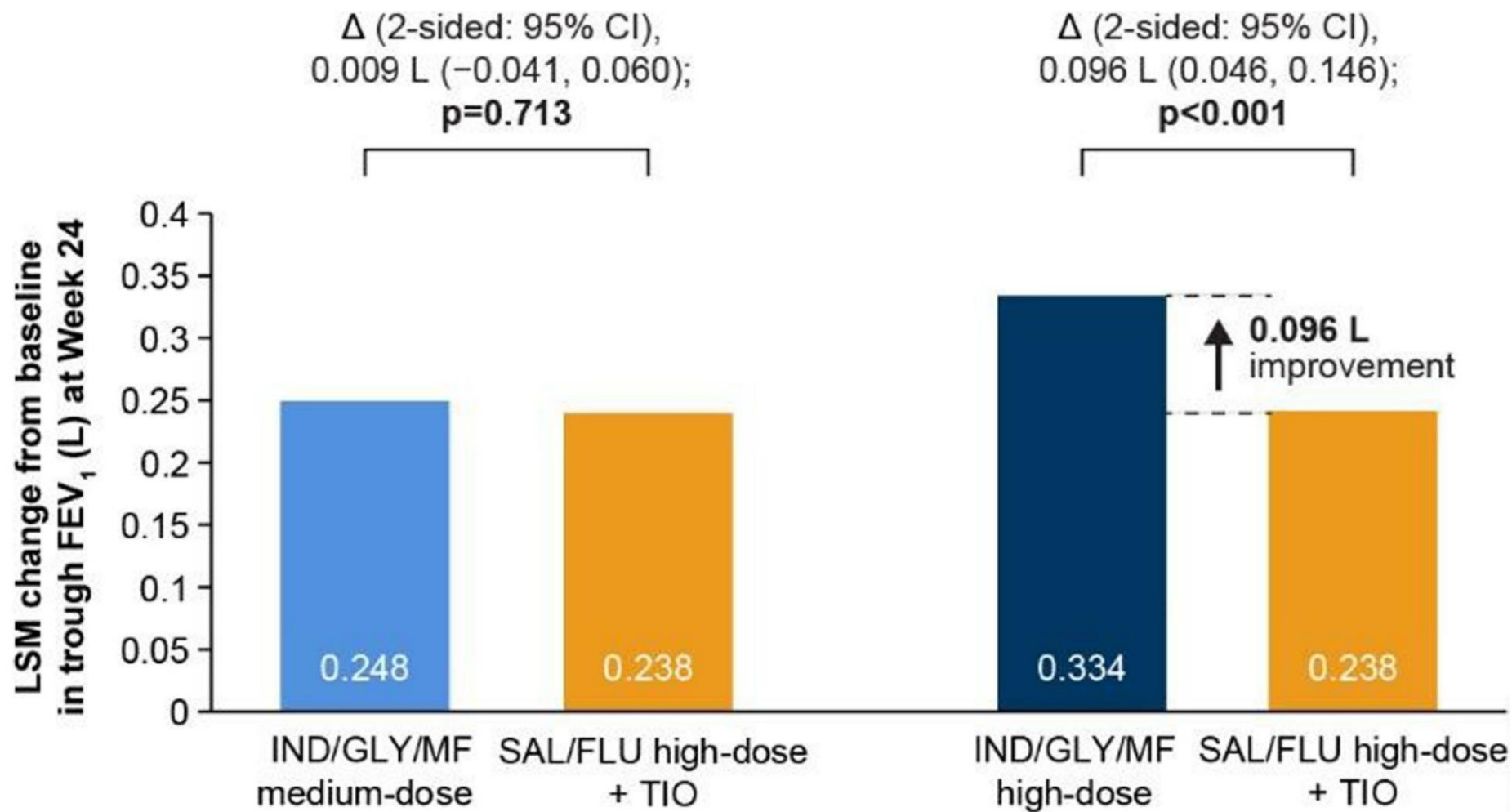
24-week, multicentre, randomised, partially-blinded, parallel-group, Phase III study in patients with uncontrolled asthma

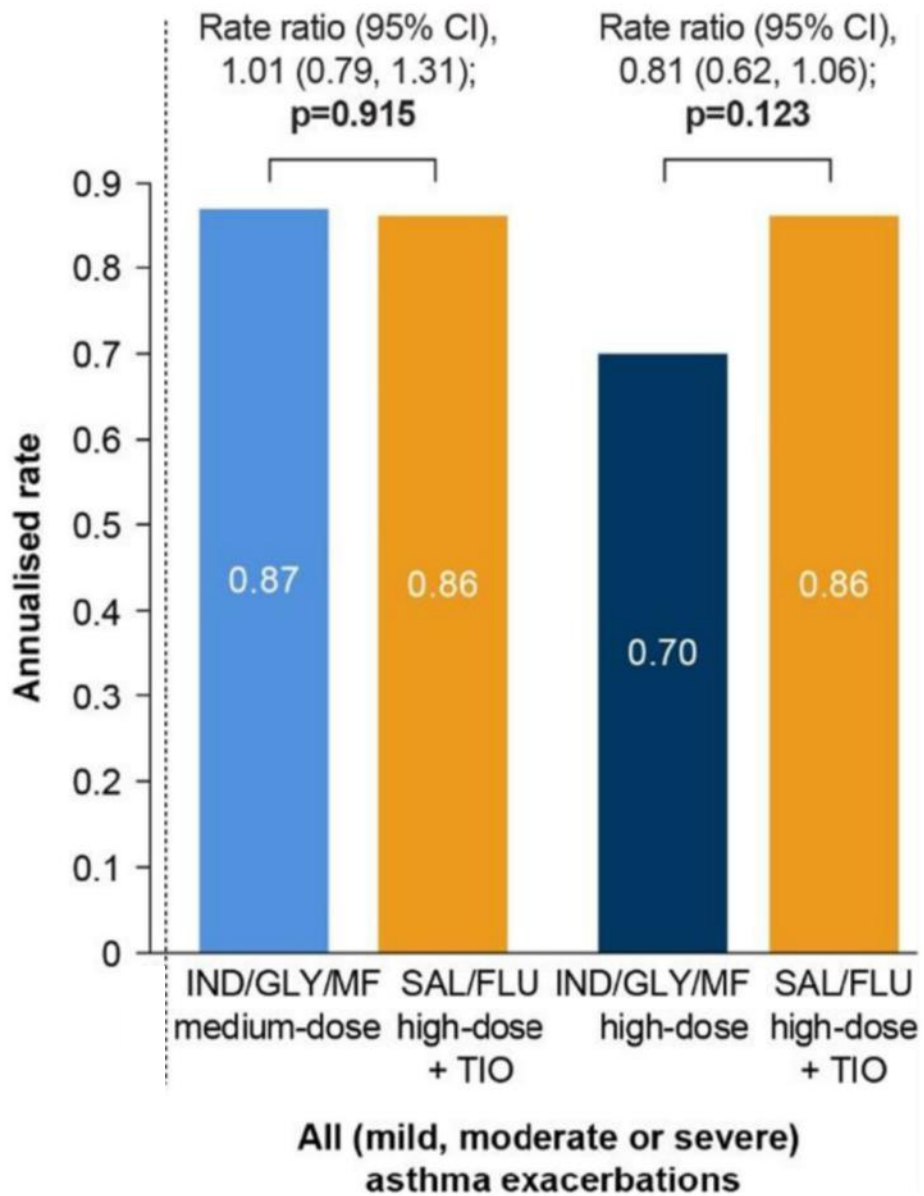






(b)







# Clinical Interpretation of Efficacy Outcomes in Pharmacological Studies on Triple Fixed-Dose Combination Therapy for Uncontrolled Asthma: Assessment of IRIDIUM and ARGON Studies

Paola Rogliani <sup>1</sup>  
Luigino Calzetta <sup>2</sup>

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**Abstract:** The IRIDIUM and ARGON studies provided positive findings concerning the benefits of the once-daily triple mometasone furoate/indacaterol/glycopyrronium (MF/IND/GLX) fixed-dose combination (FDC) for the treatment of uncontrolled asthma, at the least by

**Table 1** Clinical effect of MF/IND/GLY FDC administered at different ICS doses compared to active comparators on efficacy outcomes in asthmatic patients as reported in the IRIDIUM<sup>5</sup> and ARGON<sup>6</sup> studies

Outcome	Treatment	Active comparator	Delta	Suggested MCID	Beneficial clinically relevant effect
FEV <sub>1</sub>	MD-MF/IND/GLY	MD-MF/IND	76 mL	>60 mL*	Yes
	MD-MF/IND/GLY	HD-FLU/SAL	99 mL		Yes
	HD-MF/IND/GLY	HD-MF/IND	65 mL		Yes
	HD-MF/IND/GLY	HD-FLU/SAL	119 mL		Yes
	HD-MF/IND/GLY	HD-FLU/SAL + TIO	96 mL		Yes
Morning PEF	HD-MF/IND/GLY	HD-FLU/SAL + TIO	26.67%	>5.39% <sup>#</sup>	Yes
Evening PEF	HD-MF/IND/GLY	HD-FLU/SAL + TIO	28.72%		Yes
All exacerbations (mild, moderate, and severe)	MD-MF/IND/GLY	HD-FLU/SAL	-30%	>-20%	Yes
	HD-MF/IND/GLY	HD-MF/IND	-21%		Yes
	HD-MF/IND/GLY	HD-FLU/SAL	-40%		Yes
Moderate or severe exacerbations	MD-MF/IND/GLY	HD-FLU/SAL	-19%		Borderline
	HD-MF/IND/GLY	HD-FLU/SAL	-36%		Yes
Moderate exacerbations	HD-MF/IND/GLY	HD-FLU/SAL + TIO	-43%		Yes
Severe exacerbations	HD-MF/IND/GLY	HD-MF/IND	-22%		Yes
	HD-MF/IND/GLY	HD-FLU/SAL	-42%		Yes
ACQ-7	HD-MF/IND/GLY	HD-FLU/SAL	+8.2% responders		>0.5 points
AQLQ	HD-MF/IND/GLY	HD-FLU/SAL + TIO	+8.1% responders	>0.5 points	A greater proportion of patients achieved the MCID
SGRQ	HD-MF/IND/GLY	HD-FLU/SAL + TIO	-2.00	>4 units	No



# Lung function improvements following inhaled indacaterol/glycopyrronium/mometasone furoate are independent of dosing time in asthma patients: a randomised trial

Jutta Beier<sup>1</sup>, Henrik Watz<sup>2</sup>, Zuzana Diamant<sup>3,4,5</sup>, Jens M. Hohlfeld <sup>6,7,8</sup>, Dave Singh<sup>9</sup>, Pascale Pinot<sup>10</sup>, Ieuan Jones<sup>11</sup> and Hanns-Christian Tillmann<sup>10</sup>

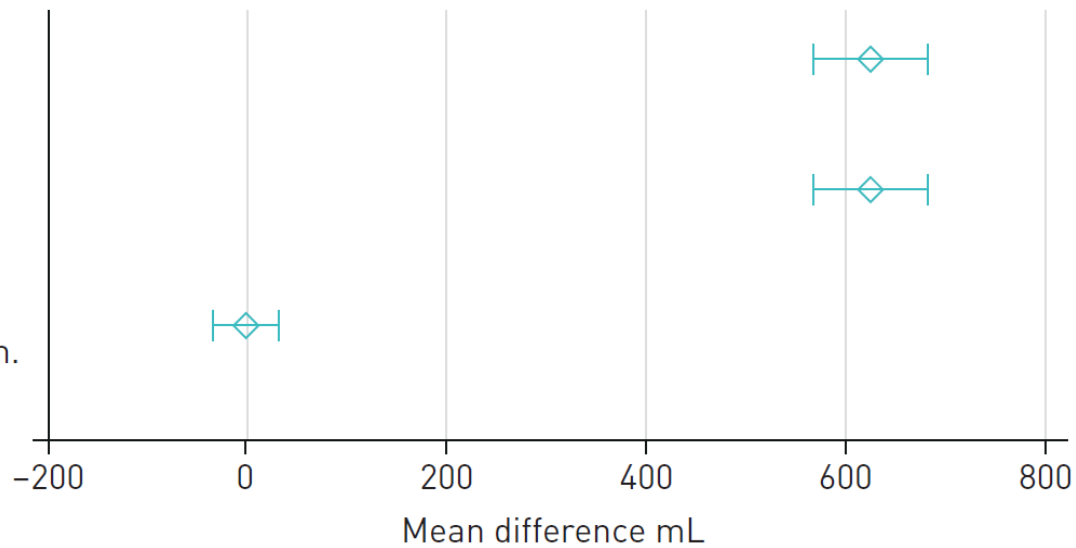
End-point

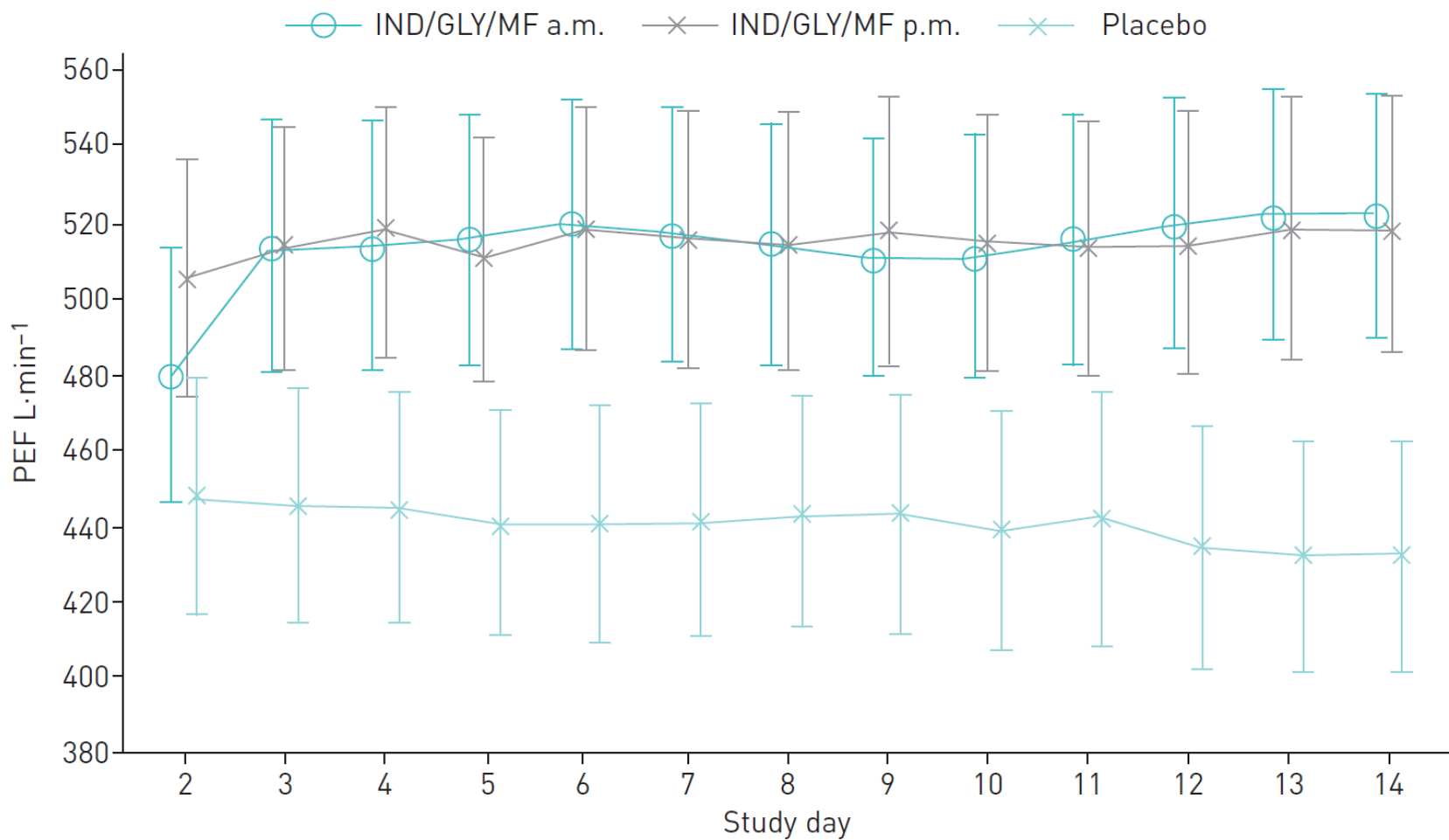
Treatment effect: test *versus* ref. (in mL)  
Difference (90% CI)

IND/GLY/MF a.m. (test)  
*versus* placebo (ref.)

IND/GLY/MF p.m. (test)  
*versus* placebo (ref.)


IND/GLY/MF a.m. (test)  
*versus* IND/GLY/MF p.m.  
(ref.)

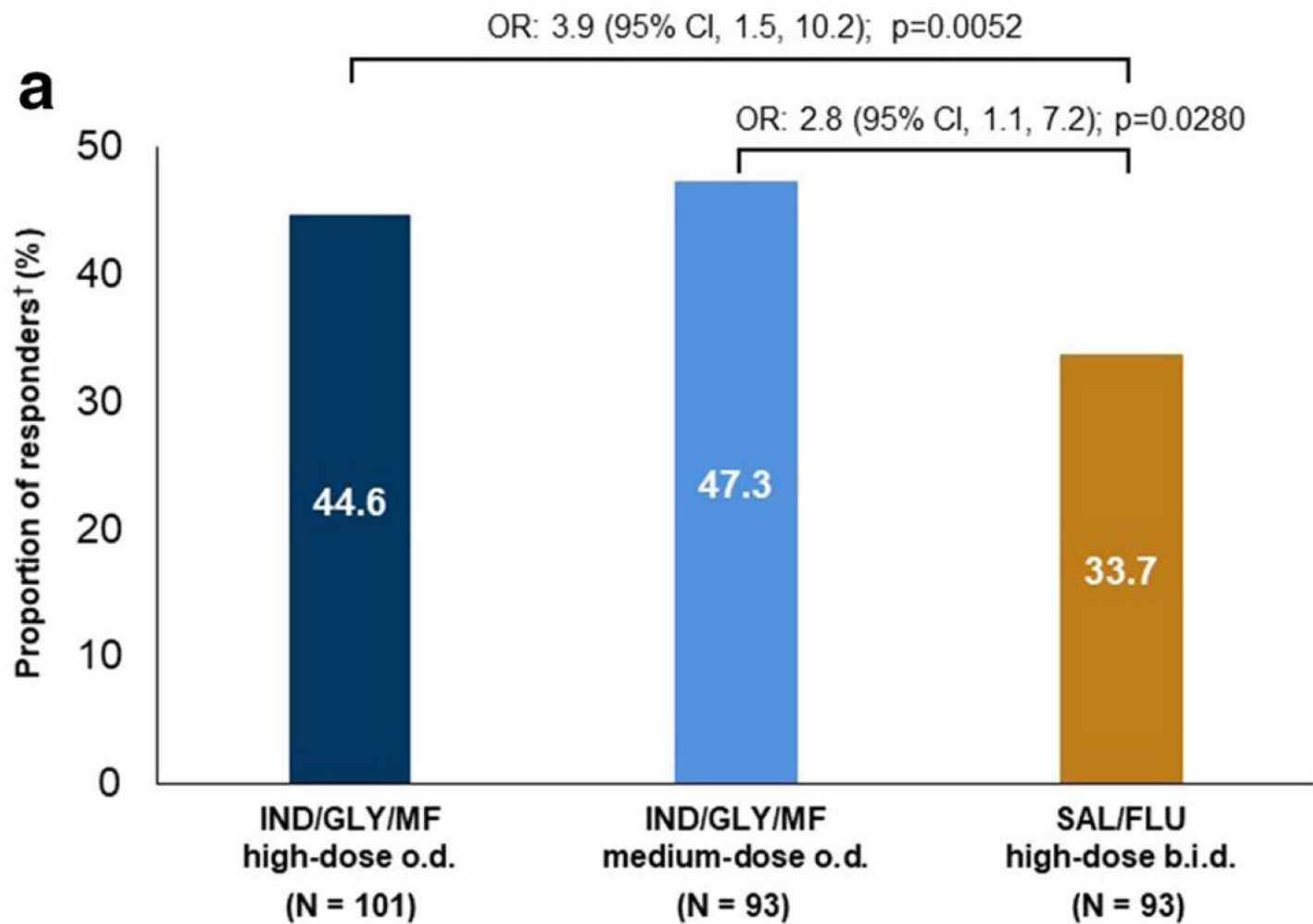




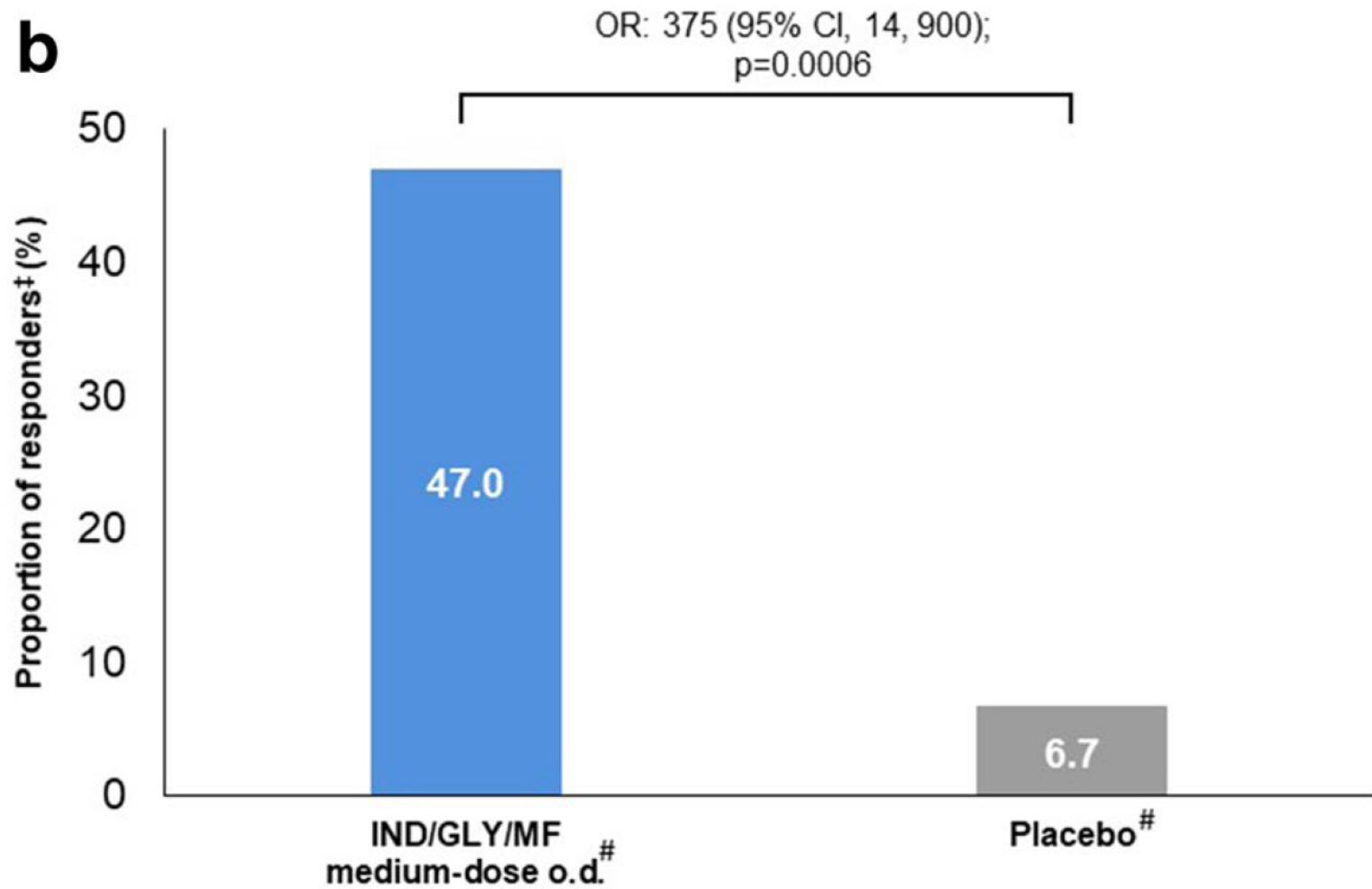


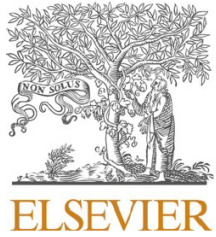
# Lung Function Normalisation with Indacaterol Acetate/ Glycopyrronium Bromide/Mometasone Furoate in Patients with Asthma

Kenneth R. Chapman<sup>1,2</sup> · Henrik Watz<sup>3</sup> · Dave Singh<sup>4</sup> · Jens M. Hohlfeld<sup>5</sup> · Zuzana Diamant<sup>6,7,8</sup> · Ieuan Jones<sup>9</sup> ·  
Hanns-Christian Tillmann<sup>10</sup> · Ivan Nikolaev<sup>9</sup> 



**b**

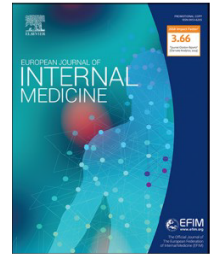




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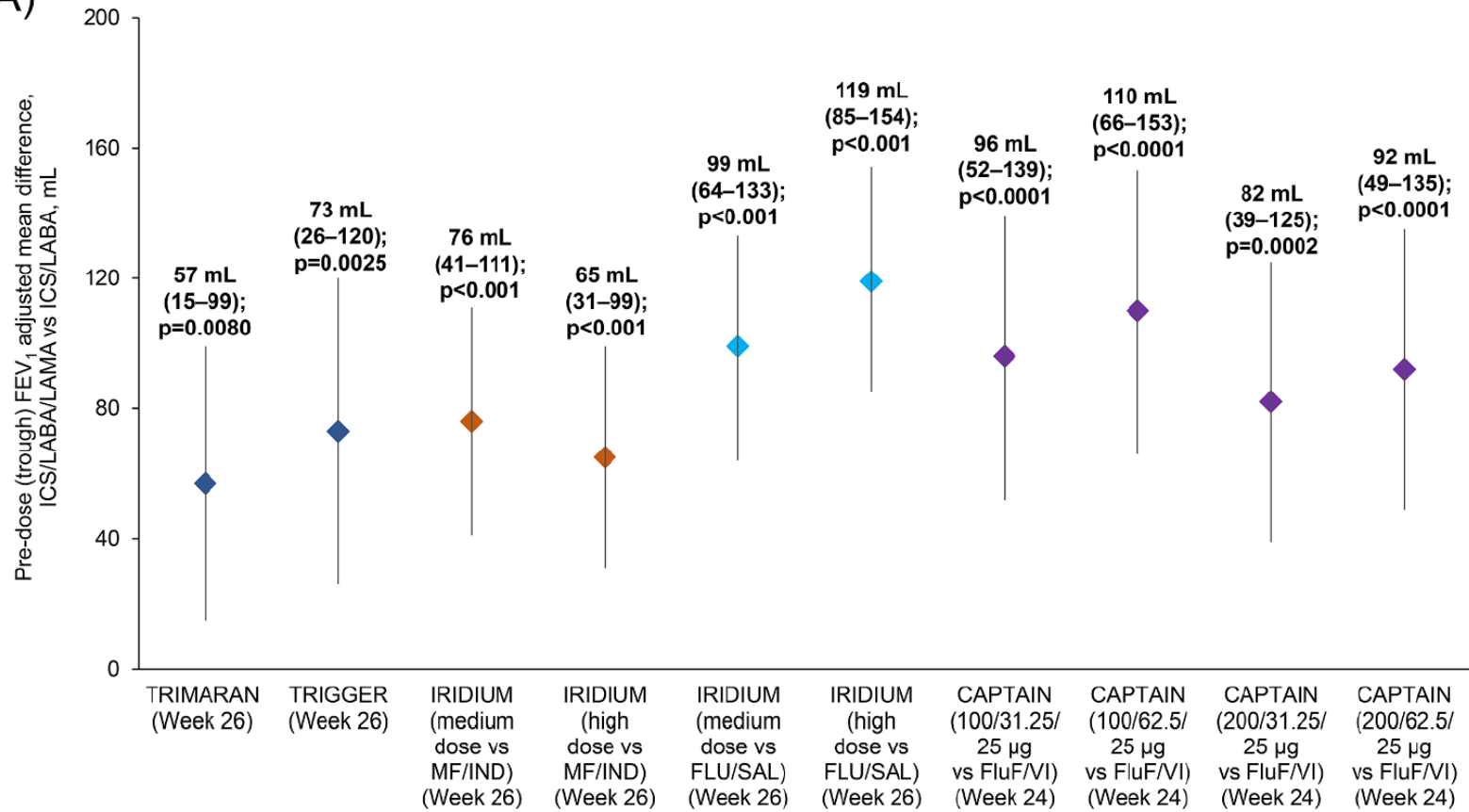


### Inhaled long-acting muscarinic antagonists in asthma – A narrative review

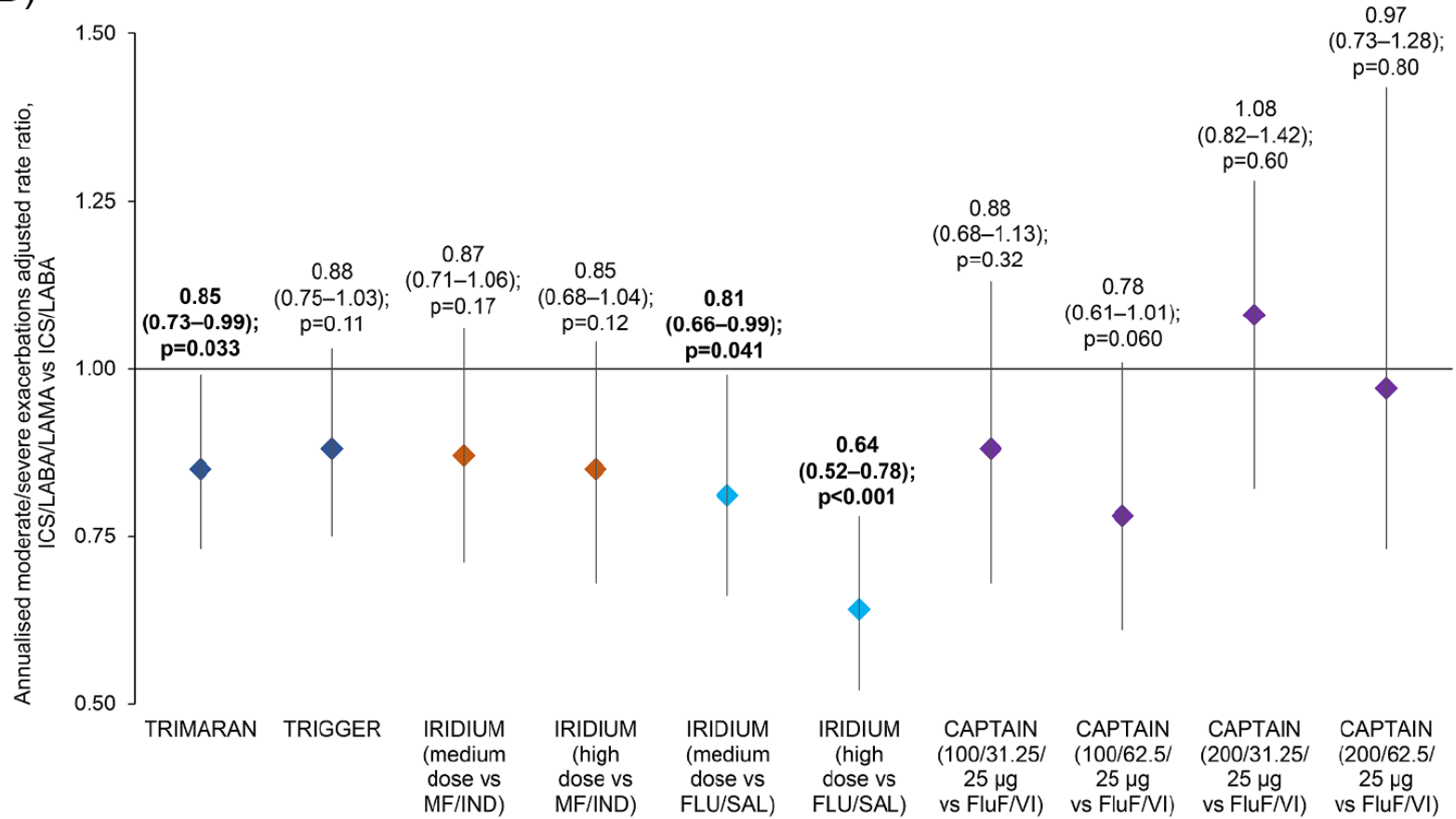


Alberto Papi<sup>a,\*</sup>, Leonardo M Fabbri<sup>b</sup>, Huib A.M. Kerstjens<sup>c</sup>, Paola Rogliani<sup>d</sup>, Henrik Watz<sup>e</sup>,  
Dave Singh<sup>f</sup>

(A)



(B)



Research

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

**A** Incidence rate ratio of exacerbations

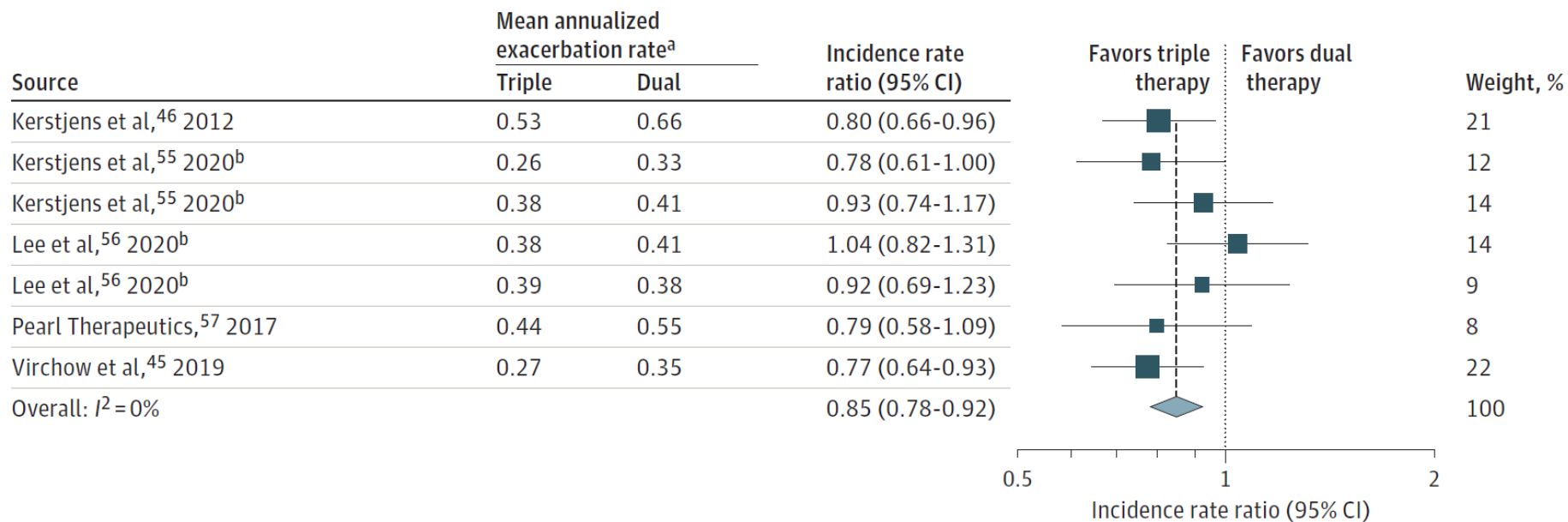
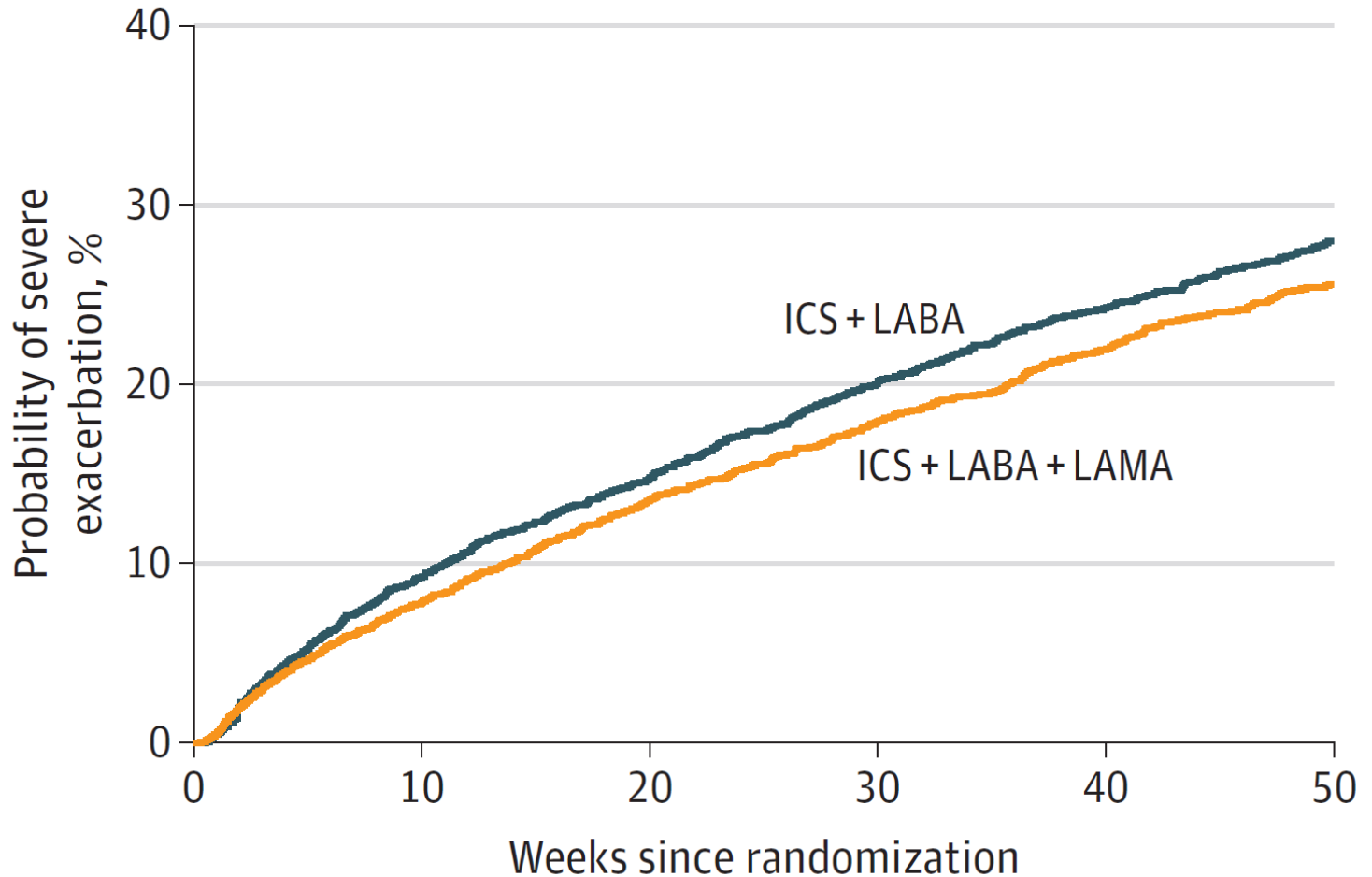


Figure 3. Kaplan-Meier Failure Curves of Time to First Severe Exacerbation in Patients Assigned to Triple vs Dual Asthma Inhaler Therapy



**A** Asthma control

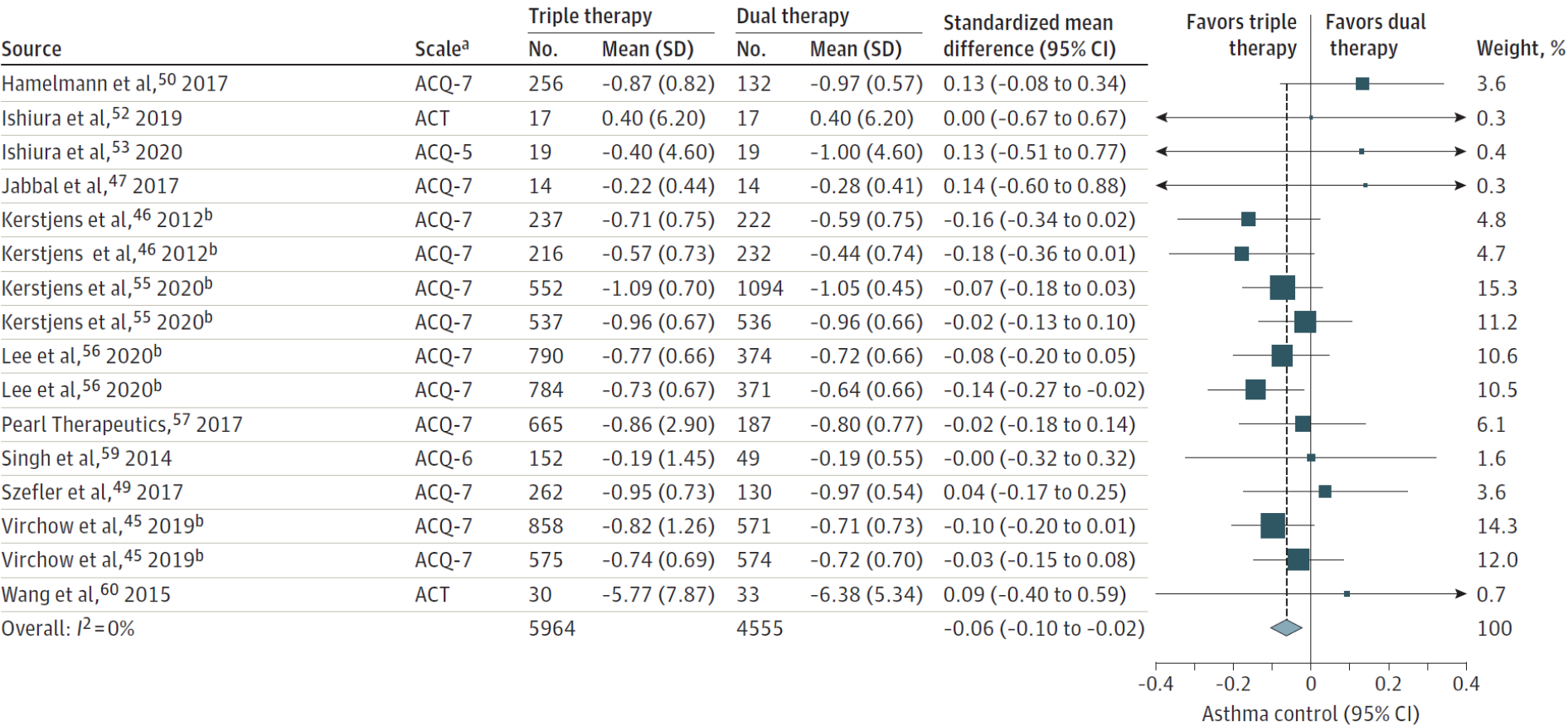
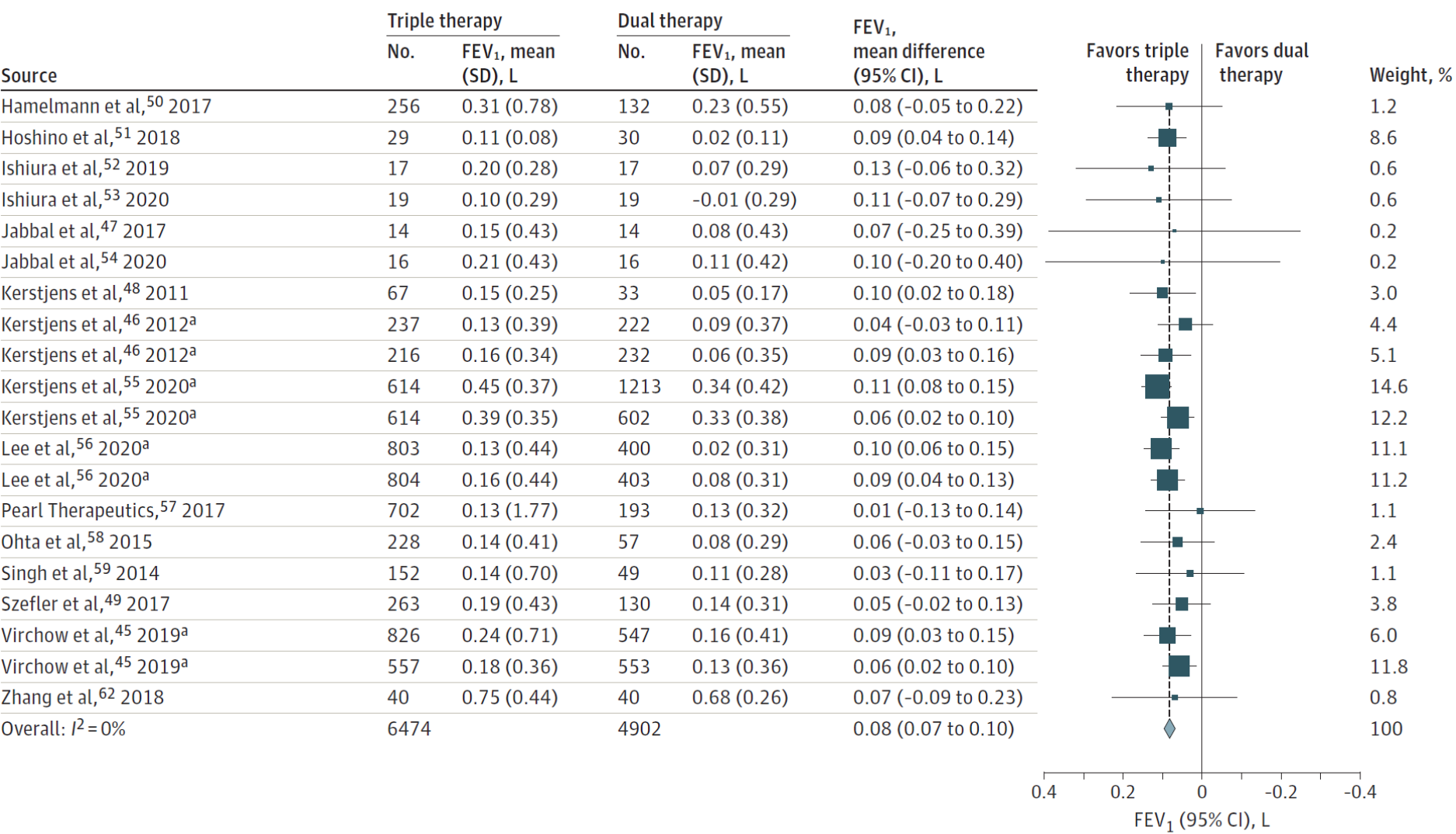
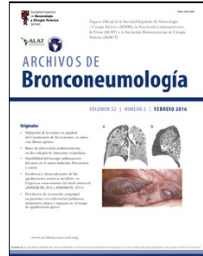


Figure 5. Lung Function as Measured by FEV<sub>1</sub> in Randomized Trials of Triple vs Dual Therapy



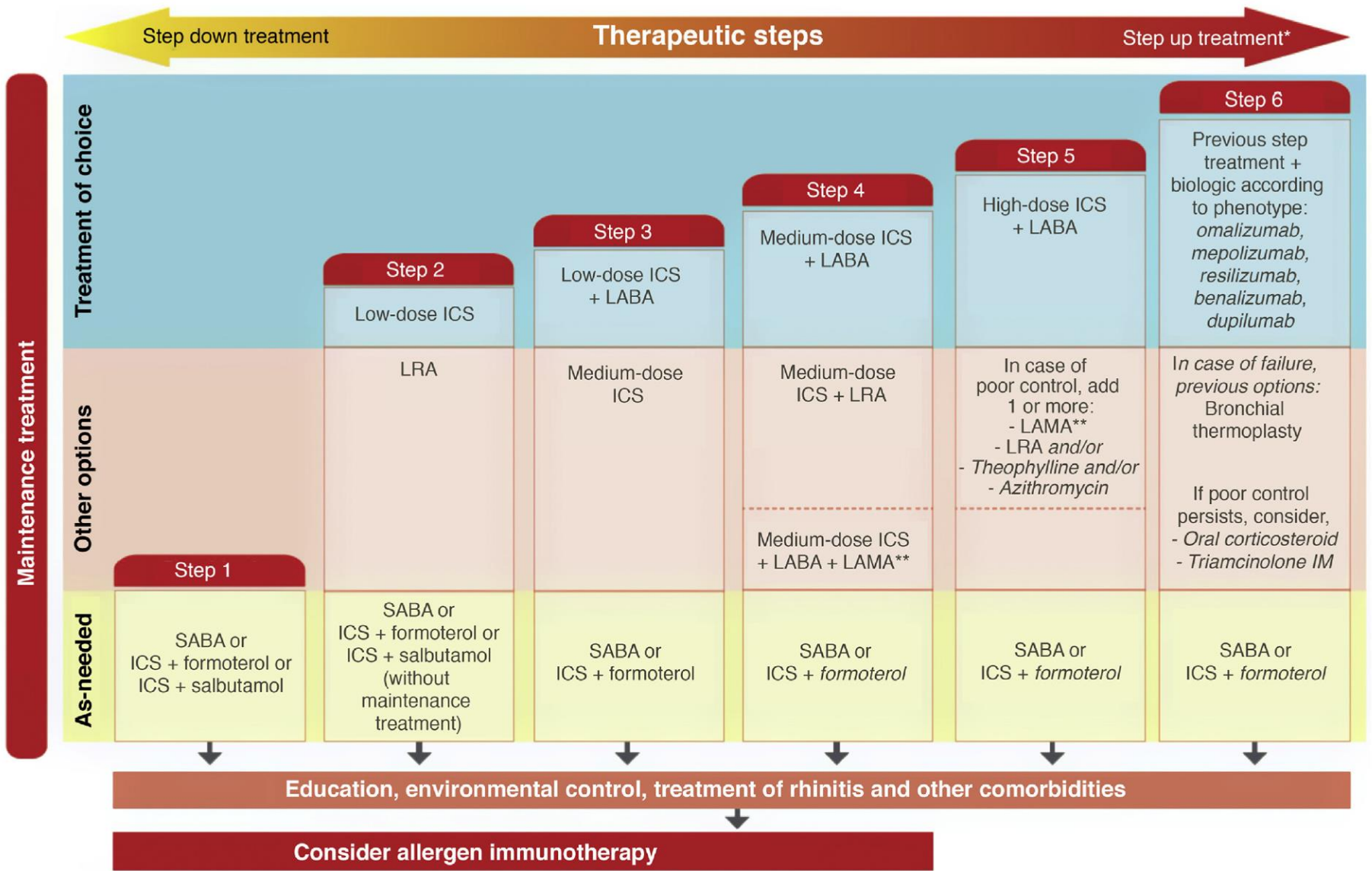


SEPAR's Voice

## [Translated article] Spanish Asthma Management Guidelines (GEMA) v.5.1. Highlights and Controversies



Vicente Plaza<sup>a,\*</sup>, Isam Alobid<sup>b</sup>, Cesáreo Alvarez<sup>c</sup>, Marina Blanco<sup>d</sup>, Jorge Ferreira<sup>e</sup>, Gabriel García<sup>f</sup>, Antonio Gómez-Outes<sup>g</sup>, Fernando Gómez<sup>h</sup>, Antonio Hidalgo<sup>i</sup>, Javier Korta<sup>j</sup>, Jesús Molina<sup>k</sup>, Francisco Javier Pellegrini<sup>l</sup>, Montserrat Pérez<sup>m</sup>, Javier Plaza<sup>n</sup>, Manuel Praena<sup>o</sup>, Santiago Quirce<sup>p</sup>, José Sanz<sup>q</sup>

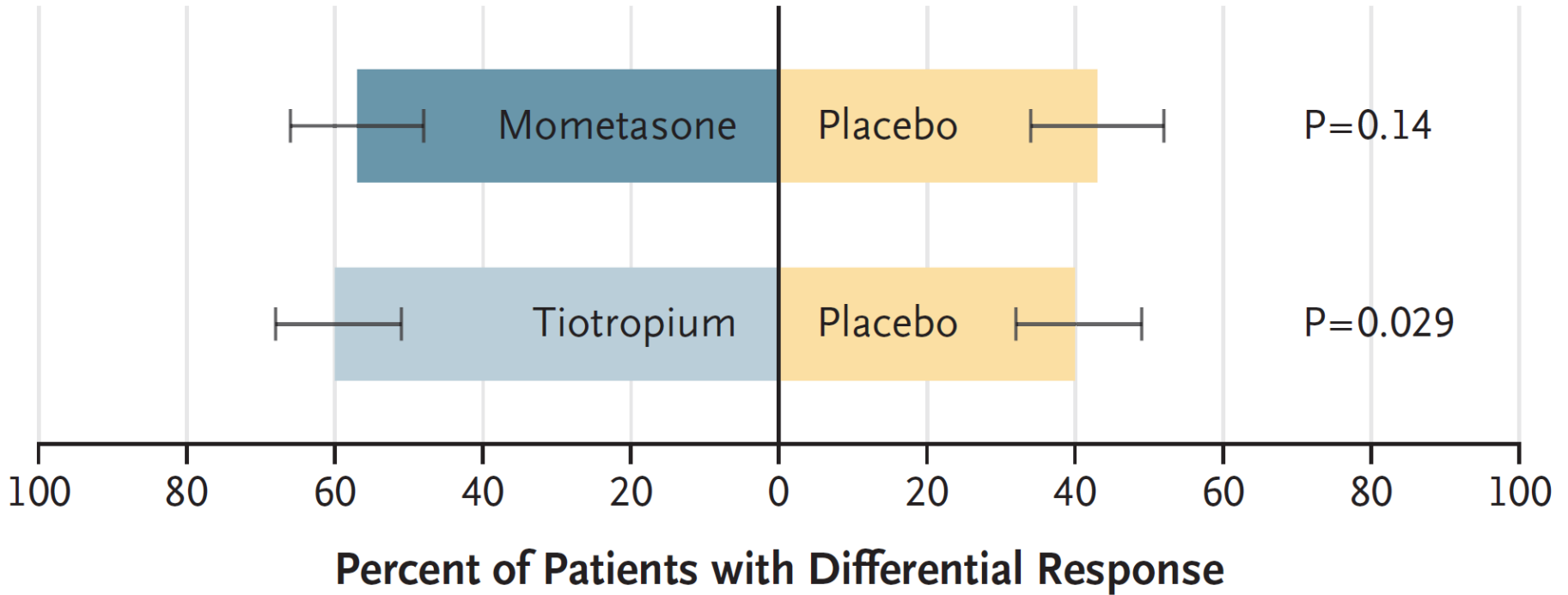


ORIGINAL ARTICLE



# Mometasone or Tiotropium in Mild Asthma with a Low Sputum Eosinophil Level

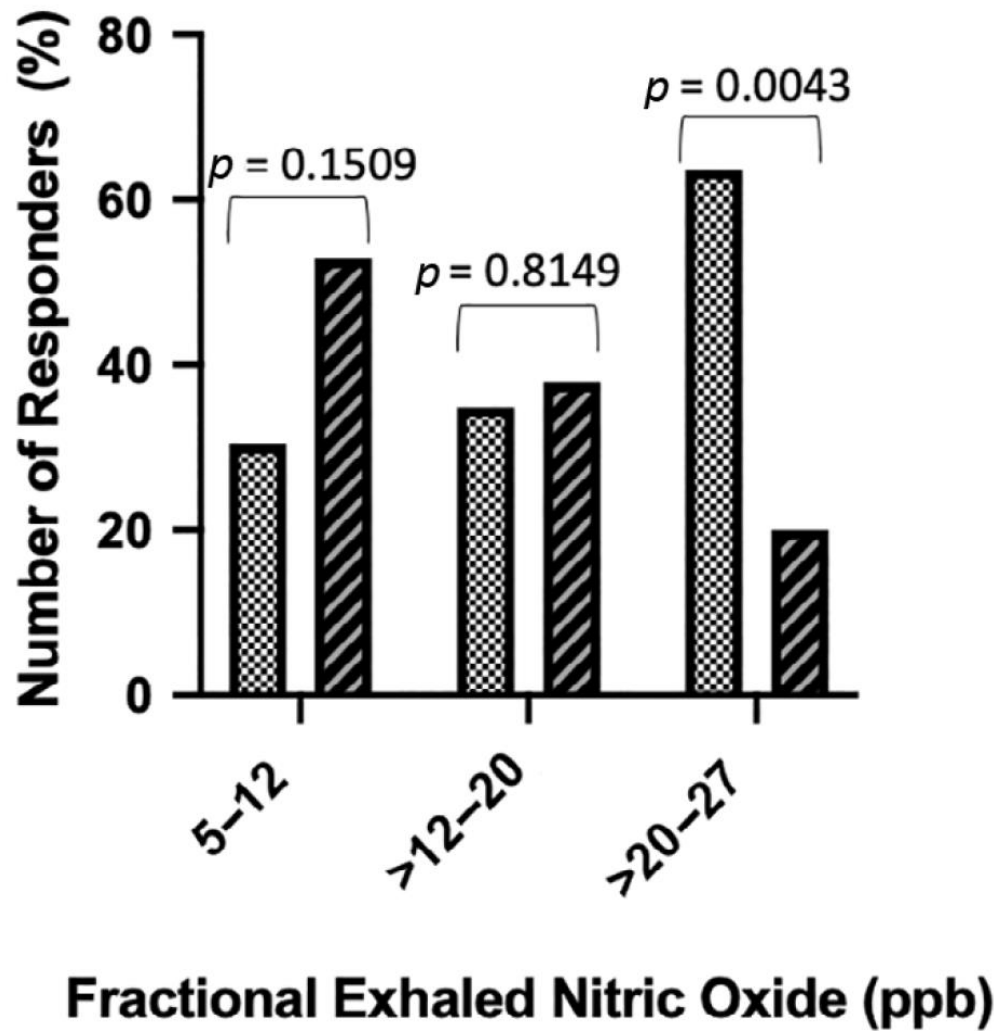
S.C. Lazarus, J.A. Krishnan, T.S. King, J.E. Lang, K.V. Blake, R. Covar, N. Lugogo, S. Wenzel, V.M. Chinchilli, D.T. Mauger, A.-M. Dyer, H.A. Boushey, J.V. Fahy, P.G. Woodruff, L.B. Bacharier, M.D. Cabana, J.C. Cardet, M. Castro, J. Chmiel, L. Denlinger, E. DiMango, A.M. Fitzpatrick, D. Gentile, A. Hastie, F. Holguin, E. Israel, D. Jackson, M. Kraft, C. LaForce, R.F. Lemanske, Jr., F.D. Martinez, W. Moore, W.J. Morgan, J.N. Moy, R. Myers, S.P. Peters, W. Phipatanakul, J.A. Pongratic, L. Que, K. Ross, L. Smith, S.J. Szeffler, M.E. Wechsler, and C.A. Sorkness, for the National Heart, Lung, and Blood Institute AsthmaNet\*



# B Primary Analysis



# A low exhaled nitric oxide level excludes a short-term benefit from inhaled corticosteroids in suspected asthma: A randomized placebo-controlled trial

Lissa Sutherland<sup>1</sup>  | Karen Shaw<sup>2</sup> | Clair Parrish<sup>2</sup> | Nicola Singleton<sup>2</sup> |  
Tricia M. McKeever<sup>2</sup> | Iain Stewart<sup>2</sup> | Dominick Shaw<sup>2</sup> | Matthew J. Martin<sup>2</sup>  |  
Tim Harrison<sup>2</sup>



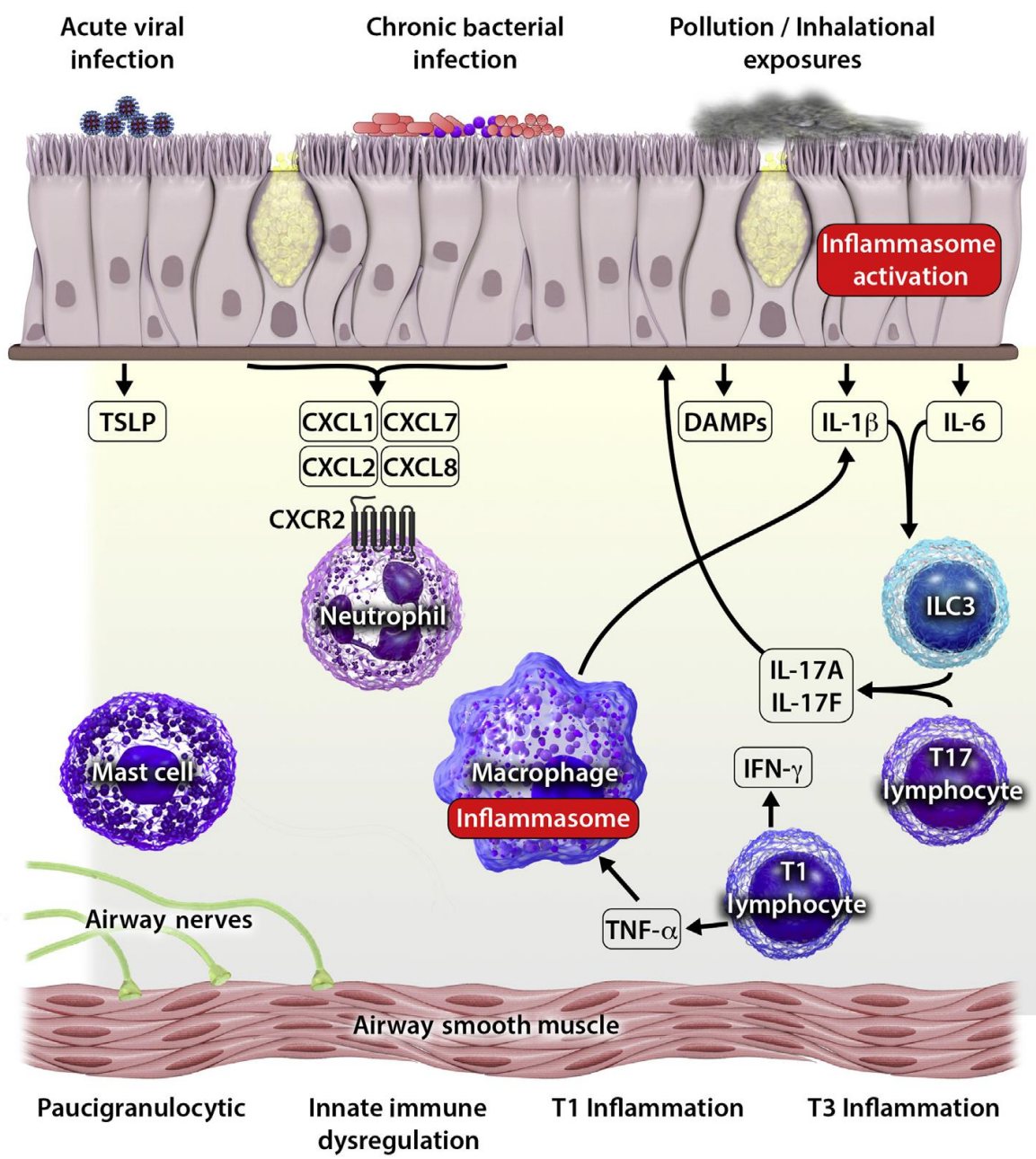
**FIGURE 3** Response to intervention according to baseline fractional exhaled nitric oxide tertiles. Budesonide , Placebo 

# Management Strategies to Reduce Exacerbations in non-T2 Asthma

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**Pharmacologic interventions**

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**Current therapies to consider**

Chronic macrolide therapy

ERS/ATS and GINA recommend use for select patients with severe asthma. Avoid use in patients with dysrhythmias and use with caution in patients with hearing loss. Risk of inducing antimicrobial resistance

Long-acting muscarinic antagonist

ERS/ATS, GINA, and NAEPP recommend use for select patients with asthma not controlled with ICS-LABA