보건의료전문가용

THE EFFECTIVENESS OF TRIPLE THERAPY IN RCT AND REAL WORLD EVIDENCE IN PATIENTS WITH COPD

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TRELEGY ELLIPTA
fluticasone furoate/umeclidinium/vilanterol

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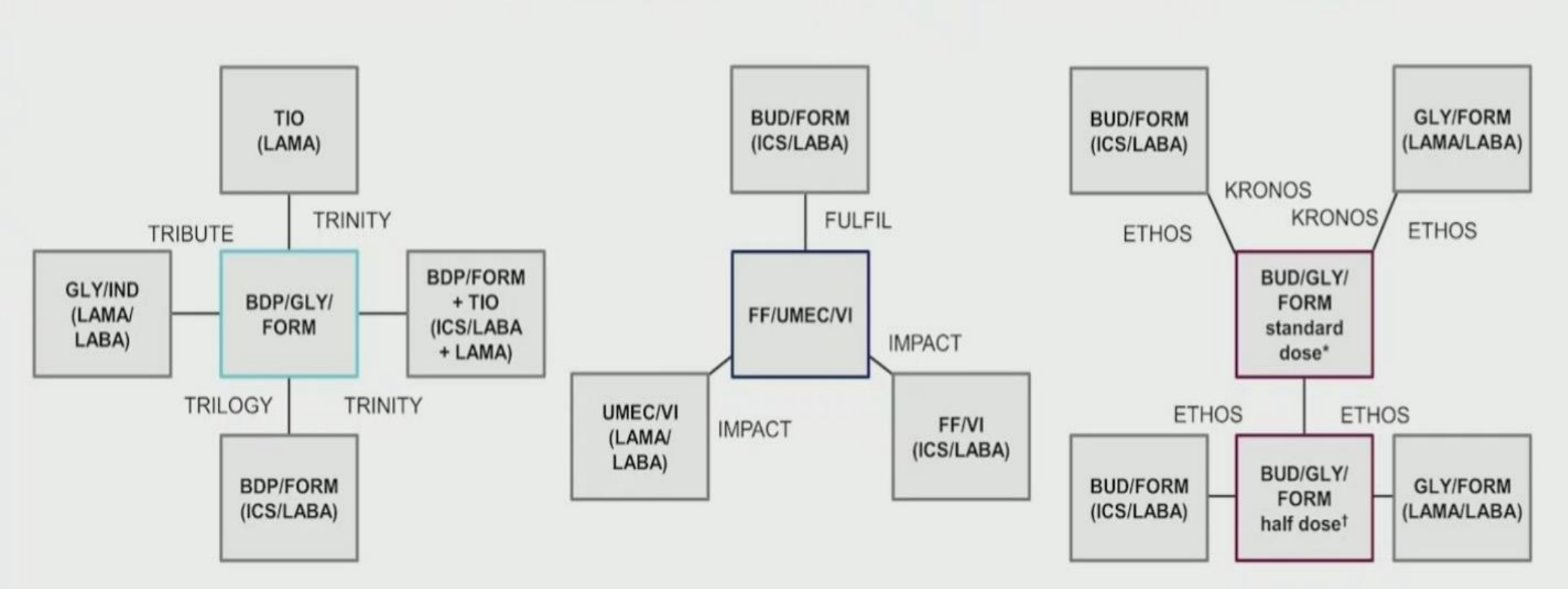
Overview of Triple therapy pivotal studies



Triple Therapy: Key Clinical Trials

Treatments	ETHOS[a] N = 8509	IMPACT[b] N = 10,355	TRIBUTE[c] N = 1532
ICS/LAMA/LABA	BUD/GLY/FORM MDI 320/14.4/10 µg BID **160/14.4/10 µg BID**	FF/UMEC/VI DPI 100/62.5/25 µg QD	BDP/FORM/GLY MDI 174/10/18 µg BID
LAMA/LABA	GLY/FORM MDI 14.4/10 µg BID	UMEC/VI DPI 62.5/25 µg QD	IND/GLY DPI 85/43 µg QD
ICS/LABA	**BUD/FORM MDI 320/10 µg BID**	**FF/VI DPI 100/25 µg QD**	N/A
Eligible patient population	Symptomatic COPD (CAT ≥ 10) with a history of exacerbations	Symptomatic COPD (CAT ≥ 10) with a history of exacerbations	Symptomatic COPD (CAT ≥ 10) with a history of exacerbations

a. Rabe KF et al. *Respir Med*. 2019;158:59-66; b. Lipson DA et al. *N Engl J Med*. 2018;378:1671-1680; c. Papi A et al. *Lancet*. 2018;391:1076-1084.

Inclusion/Exclusion Criteria

Inclusion/ exclusion criteria	ETHOS[a] N = 8509	IMPACT[b] N = 10,355	TRIBUTE[c] N = 1532
Post-BD FEV_1 % predicted	25% to 65%	≤ 80%	< 50%
Moderate or severe exacerbations in last year	≥ 1 (if post-BD FEV_1 < 50%) ≥ 2 moderate / ≥ 1 severe (if post-BD FEV_1 ≥ 50%)	≥ 1 (if FEV_1 < 50%) ≥ 2 moderate / ≥ 1 severe (if FEV_1 ≥ 50% to 80%)	≥1
Excluded patients on prior triple therapy	No	No	Yes
COPD treatment at screening	On ≥ 2 inhaled maintenance therapies* for ≥ 6 weeks prior to screening	LAMA, LABA or ICS, alone or in combination	Use of ICS/LABA, ICS/LAMA, LABA/LAMA, or LAMA alone for ≥ 2 months

*Includes scheduled SABAs and/or SAMAs.

a. Rabe KF et al. *Respir Med*. 2019;158:59-66; b. Lipson DA et al. *N Engl J Med*. 2018;378:1671-1680; c. Papi A et al. *Lancet*. 2018;391:1076-1084.

Primary and Secondary Endpoints

	ETHOS[a] N = 8509	IMPACT[b] N = 10,355	TRIBUTE[c] N = 1532
Primary endpoint	Rate of moderate or severe COPD exacerbations	Rate of moderate or severe COPD exacerbations	Rate of moderate or severe COPD exacerbations
Key secondary endpoints	• Rate of severe COPD exacerbations • Time to first moderate or severe COPD exacerbation • Rescue medication use • SGRQ response and total score • **Time to death (all-cause)** • **TDI focal score** • EXACT total score	• Rate of severe COPD exacerbations • SGRQ total score • Trough FEV_1 • Time to first moderate or severe COPD exacerbation • **Time to first moderate or severe COPD exacerbation in patients with blood eosinophils ≥150 cells/µL**	• Time to first moderate or severe COPD exacerbation • Rate of and time to first severe COPD exacerbation • FEV_1 response • SGRQ response • Rescue medication use • EXACT total score • **CAT total score**

a. Rabe KF et al. *Respir Med*. 2019;158:59-66; b. Lipson DA et al. *N Engl J Med*. 2018;378:1671-1680; c. Papi A et al. *Lancet*. 2018;391:1076-1084; d. Scuri M at al. *Am J Respir Crit Care Med*. 2018;197: Abstract A7725.

Baseline Characteristics

	ETHOS[a]* N = 8509	IMPACT[b]† N = 10,355	TRIBUTE[c]‡ N = 1532
	%*	%*	%*
COPD exacerbations in previous year, mean			
1 moderate or severe	44	45	81
≥ 2 moderate or severe	56	55	19
≥ 1 severe	21	26	-
ICS use prior to study entry	79	67†	65†
Blood eosinophils ≥ 150 cells/µL	60	57	-
COPD severity‡			
Moderate (FEV_1 50% to 80%)	29	36	0
Severe (FEV_1 30% to < 50%)	61	48	79
Very severe (FEV_1 < 30%)	11	16	20

*Unless otherwise stated; †Includes ICS/LABA and ICS/LAMA only; ‡ETHOS safety population, N = 8539..

a. Rabe KF et al. *Respir Med*. 2019;158:59-66; b. Lipson DA et al. *N Engl J Med*. 2018;378:1671-1680; c. Papi A et al. *Lancet*. 2018;391:1076-1084.

Contents

- IMPACT study and subgroup analysis
  - ✓ Exacerbation and Clinically Important Deterioration (CID)
  - ✓ Pneumonia and Composite Adverse Events
  - ✓ Mortality
  - ✓ Blood Eosinophil
- Real world evidence (INTREPID study)

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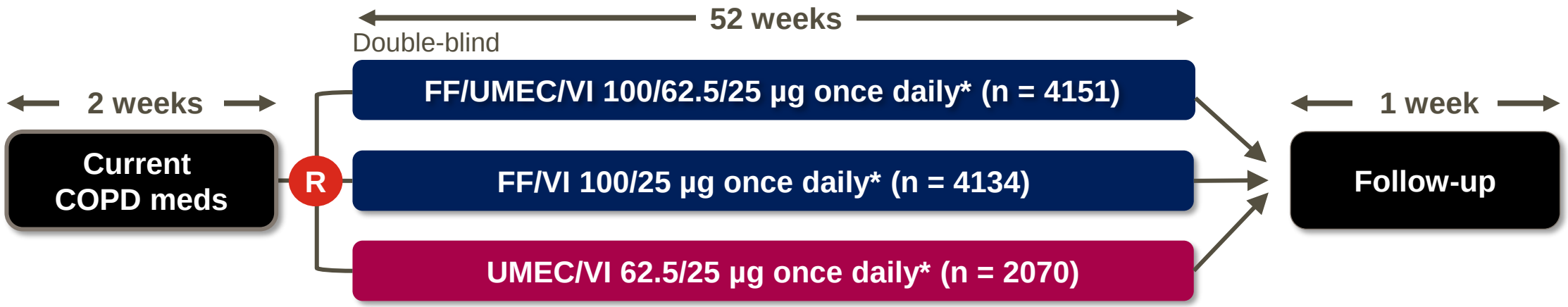
IMPACT : A landmark trial in symptomatic patients with COPD and a history of exacerbation[1,2]

First to compare single inhaler Triple Therapy with a LAMA/LABA (UMEC/VI) and with an ICS/LABA (FF/VI)



Co-primary treatment comparisons (ITT population)

- Annual rate of on-treatment moderate/severe exacerbations:
  - FF/UMEC/VI vs FF/VI
  - FF/UMEC/VI vs UMEC/VI

Secondary endpoints included:

- Trough FEV_1 and SGRQ
- Time To First on-treatment moderate/severe exacerbation
- Annual moderate/severe exacerbation by EOS

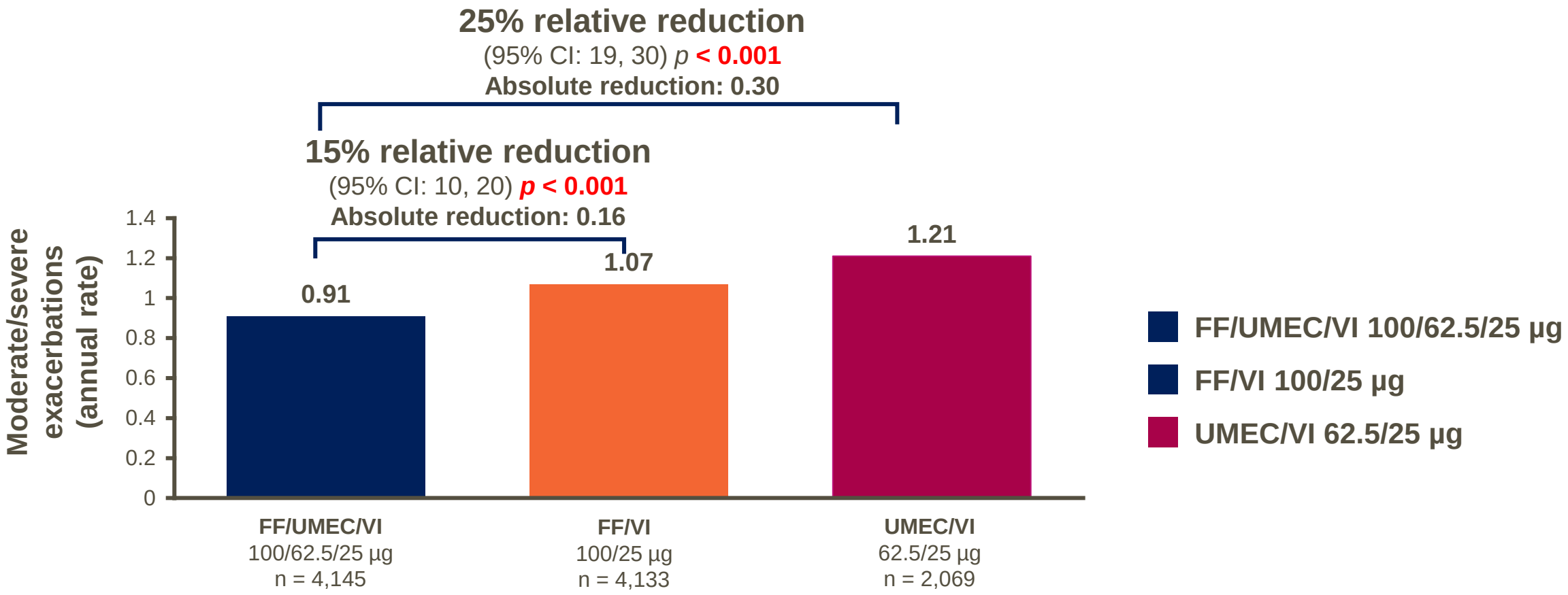
Other endpoints included:

- Time to death from any cause

1. Pascoe SJ, et al. *Eur Respir J*. 2016;48:320–330; 2. Lipson DA, et al. *N Engl J Med*. 2018;378:1671–1680 (including supplementary appendix);
3. Trelegy Ellipta Prescribing Information

IMPACT TRIAL

Significant reduction in moderate/severe exacerbations
Triple vs dual

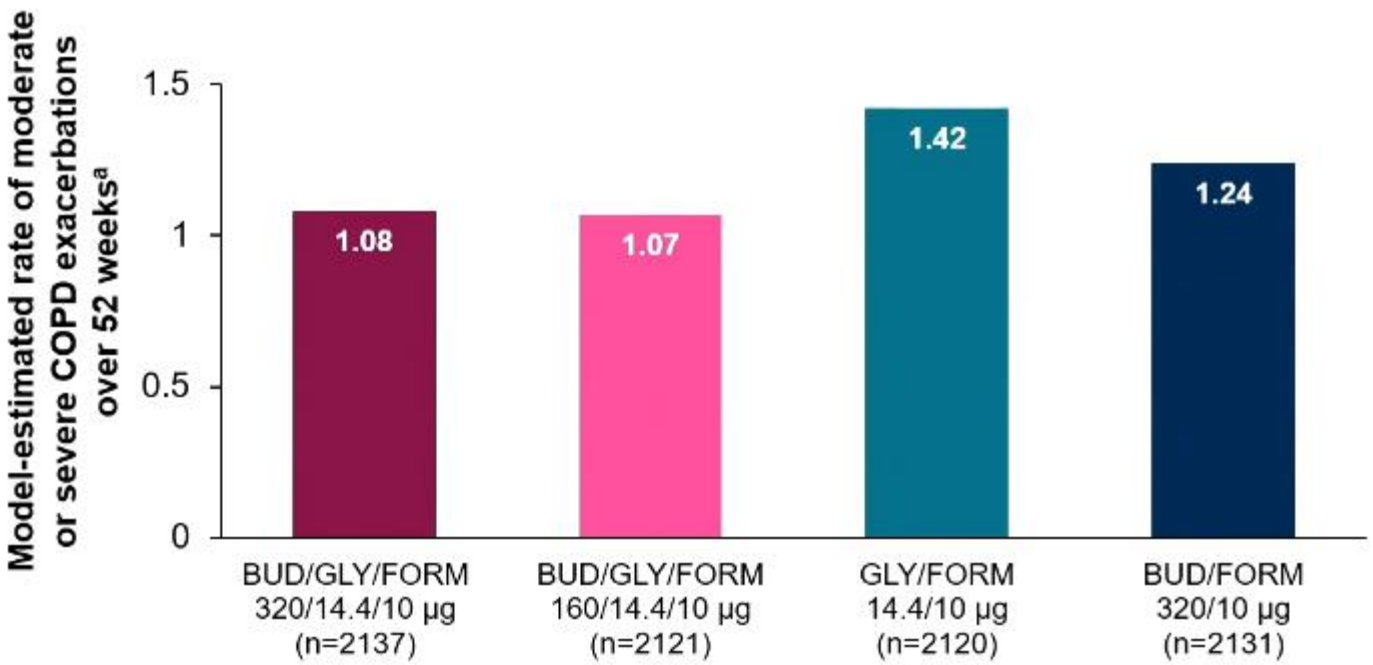


Lipson DA, et al. *N Engl J Med*. 2018;378:1671–1680.
This graph has been independently created by GSK from the original data.

IMPACT TRIAL

BUD/GLY/FORM: the Rate of Moderate or Severe Exacerbations vs. Dual Therapies

Primary Endpoint



Over 52 weeks **BUD/GLY/FORM 320/14.4/10 µg** demonstrated a:

24% significant reduction in exacerbation rate vs. LAMA/LABA

13% significant reduction in exacerbation rate vs. ICS/LABA

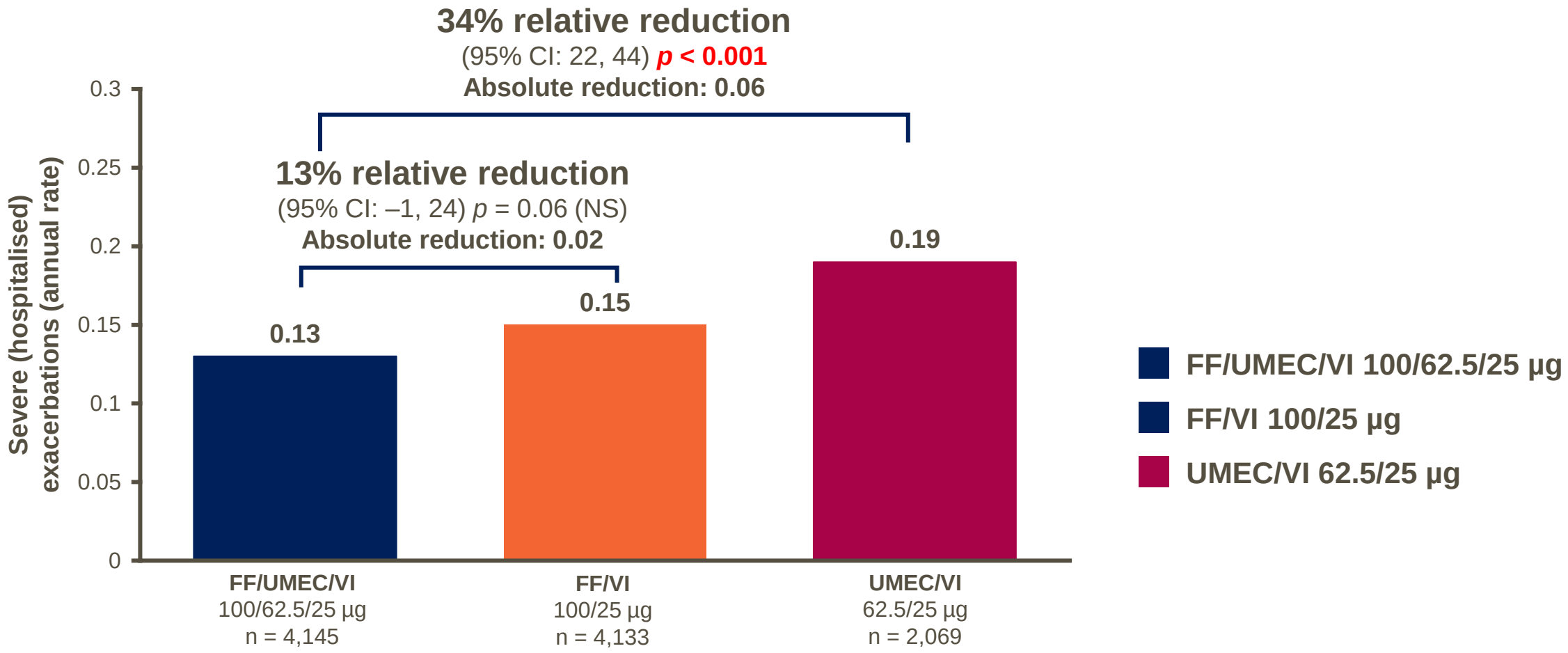
	vs. LAMA/LABA	vs. ICS/LABA
320 µg	**1.08 vs 1.42; RR: 0.76 95% CI: 0.69 to 0.83; p<0.001**	**1.08 vs 1.24; RR: 0.87 95% CI: 0.79 to 0.95; p=0.003**
160 µg	1.07 vs 1.42; RR: 0.75 95% CI: 0.69 to 0.83; p<0.001	1.07 vs 1.24; RR: 0.86 95% CI: 0.79 to 0.95; p=0.002

Notes: All treatments were administered BID. Results for moderate/severe exacerbation rate using the attributable estimand (secondary endpoint) were similar to those for the primary analysis. BUD/GLY/FORM 160/14.4/10 µg is currently not registered (off label).

[a]mITT population.

Rabe KF et al. N Engl J Med. 2020. Jul 2;383(1):35-48

Reduction in severe (hospitalised) exacerbations
Triple vs dual



Lipson DA, et al. *N Engl J Med*. 2018;378:1671–1680.
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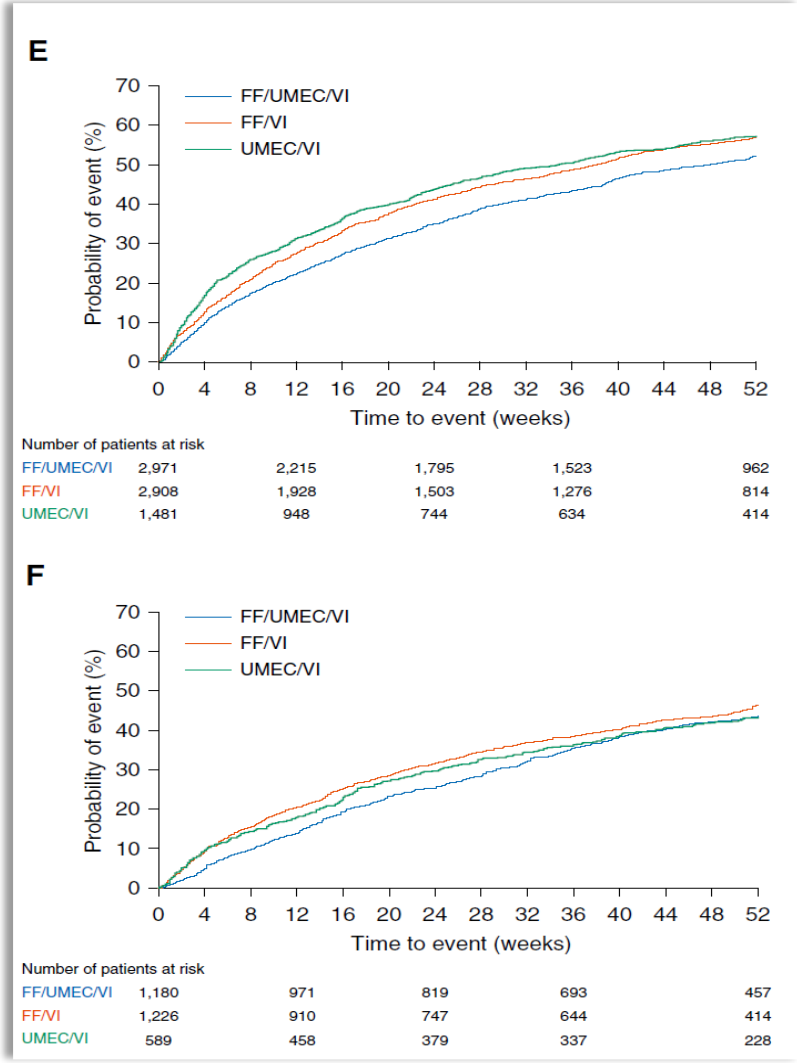
IMPACT TRIAL

Mod to severe exacerbation in prior ICS users & nonusers

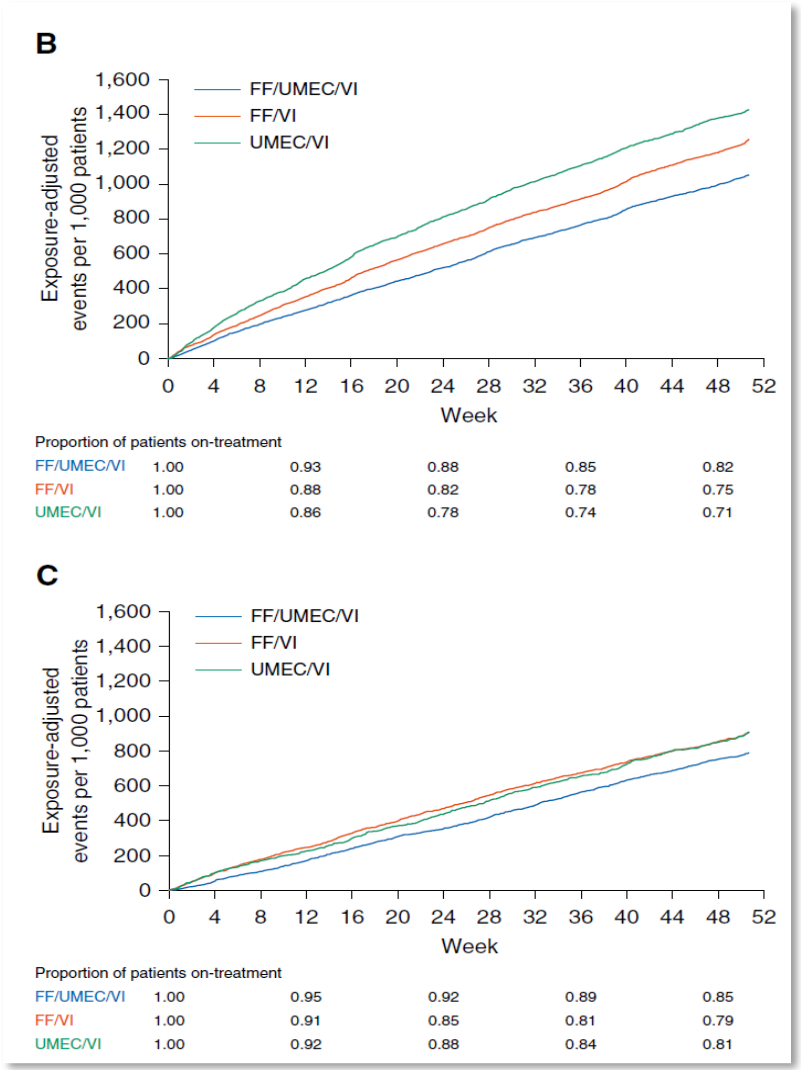
Time to first mod/severe AECOPD



ICS use at screen

No ICS use at screen

Cumulative no of mod/severe AECOPD



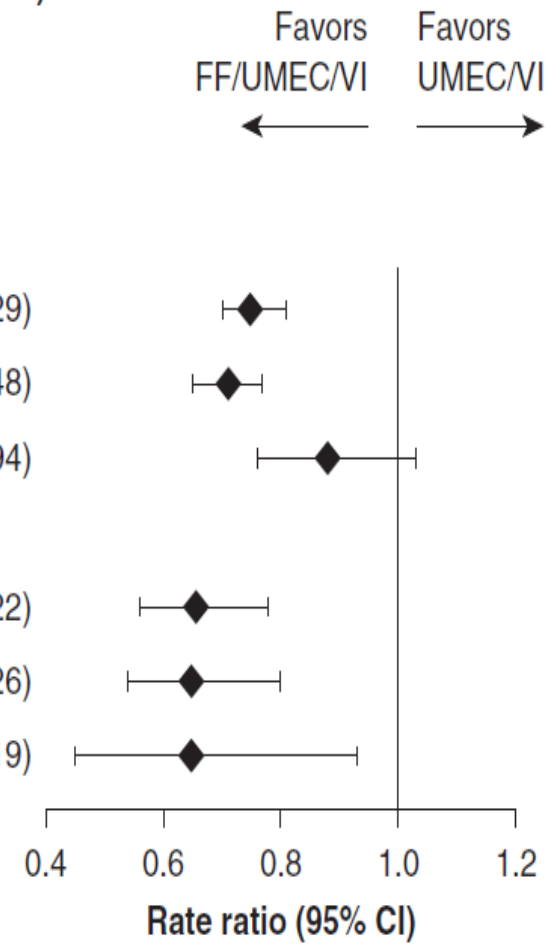
FF/UMEC/VI Reducing mod/severe AECOPD vs UMEC/VI

- **Prior ICS user : 29% (P<0.001)**
- Prior ICS nonuser: 12% (P=0.115)

Han MK et al. AJRCCM 2020

Severe exacerbation in prior ICS users & nonusers

	Model-estimated annual rates (95% CI)		Rate ratio (95% CI); p-value	Annual rate reduction, % (95% CI)
	FF/UMEC/VI	UMEC/VI		
On-treatment moderate/severe exacerbation				
Overall (n=6,214)	0.91 (0.87, 0.95)	1.21 (1.14, 1.29)	0.75 (0.70, 0.81); p<0.001	25 (19, 30)
ICS use at screening (n=4,448)	0.98 (0.93, 1.03)	1.38 (1.29, 1.48)	0.71 (0.65, 0.77); p<0.001	29 (23, 35)
No ICS use at screening (n=1,766)	0.73 (0.67, 0.80)	0.83 (0.73, 0.94)	0.88 (0.76, 1.03); p=0.115	12 (–3, 24)
On-treatment severe exacerbation				
Overall (n=6,214)	0.13 (0.12, 0.14)	0.19 (0.17, 0.22)	0.66 (0.56, 0.78); p<0.001	34 (22, 44)
ICS use at screening (n=4,448)	0.14 (0.13, 0.16)	0.22 (0.19, 0.26)	0.65 (0.54, 0.80); p<0.001	35 (20, 46)
No ICS use at screening (n=1,766)	0.09 (0.07, 0.11)	0.14 (0.10, 0.19)	0.65 (0.45, 0.93); p=0.018	35 (7, 55)

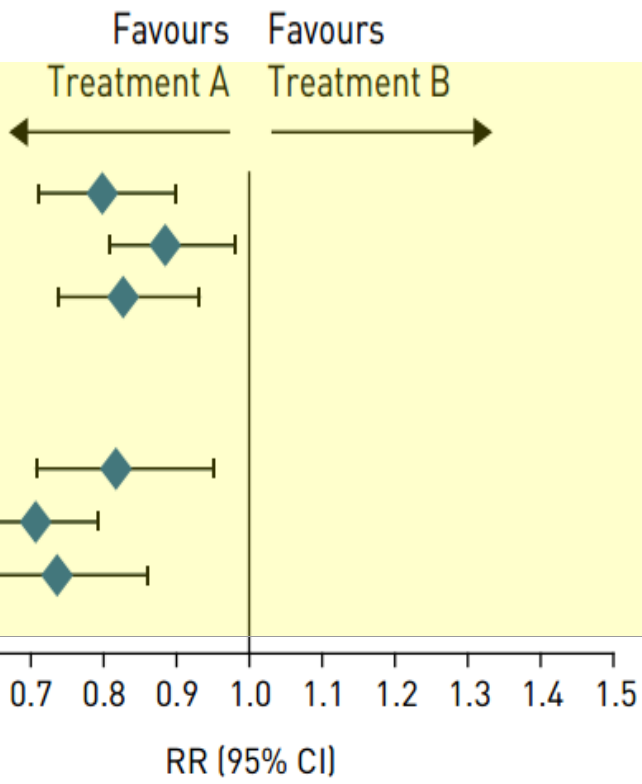


Han MK et al. AJRCCM 2020

Annual rate of on-treatment moderate or severe exacerbations (post-hoc analysis) according to exacerbation history in the year prior to screening

a)

	Treatment A FF/UMEC/VI	Treatment B FF/VI	RR (95% CI)	p-value
FF/UMEC/VI *versus* FF/VI				
Single moderate subgroup	0.85 (0.78–0.92)	1.06 (0.97–1.15)	0.80 (0.71–0.90)	<0.001
Frequent moderate subgroup	0.85 (0.80–0.91)	0.96 (0.90–1.03)	0.89 (0.81–0.98)	0.016
Severe subgroup	1.06 (0.98–1.16)	1.28 (1.18–1.39)	0.83 (0.74–0.93)	0.002
FF/UMEC/VI *versus* UMEC/VI	**FF/UMEC/VI**	**UMEC/VI**		
Single moderate subgroup	0.85 (0.78–0.92)	1.03 (0.92–1.16)	0.82 (0.71–0.95)	0.007
Frequent moderate subgroup	0.85 (0.80–0.91)	1.21 (1.10–1.32)	0.71 (0.63–0.79)	<0.001
Severe subgroup	1.06 (0.98–1.16)	1.43 (1.27–1.61)	0.74 (0.65–0.86)	<0.001

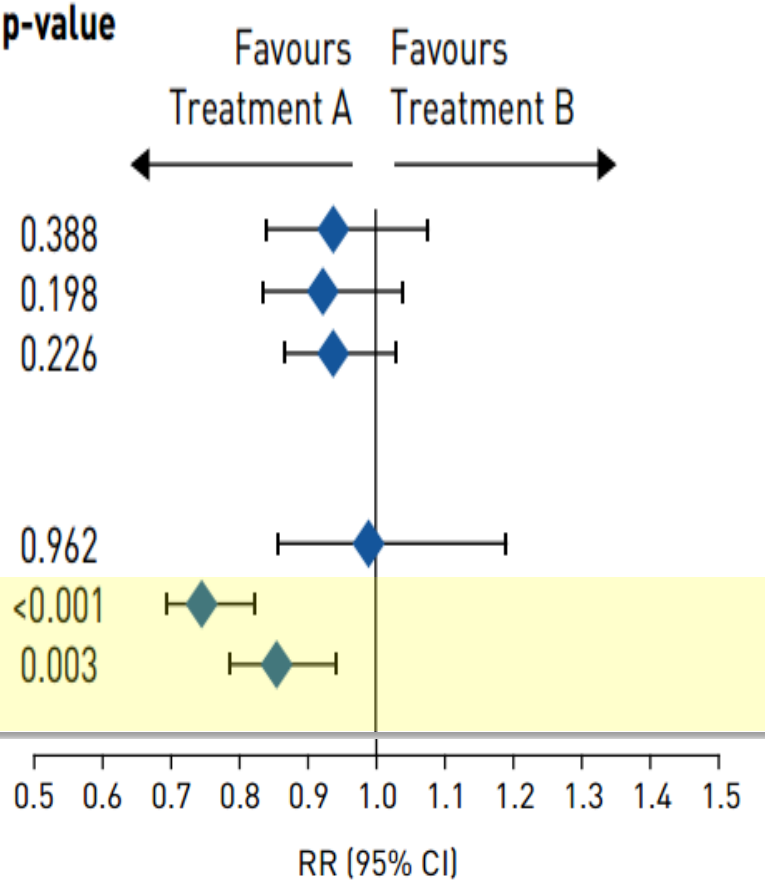


Halpin DMG;Eur Respir J;2020;55;1-12

Annual rate of on-treatment severe exacerbations (post-hoc analysis) according to exacerbation history in the year prior to screening

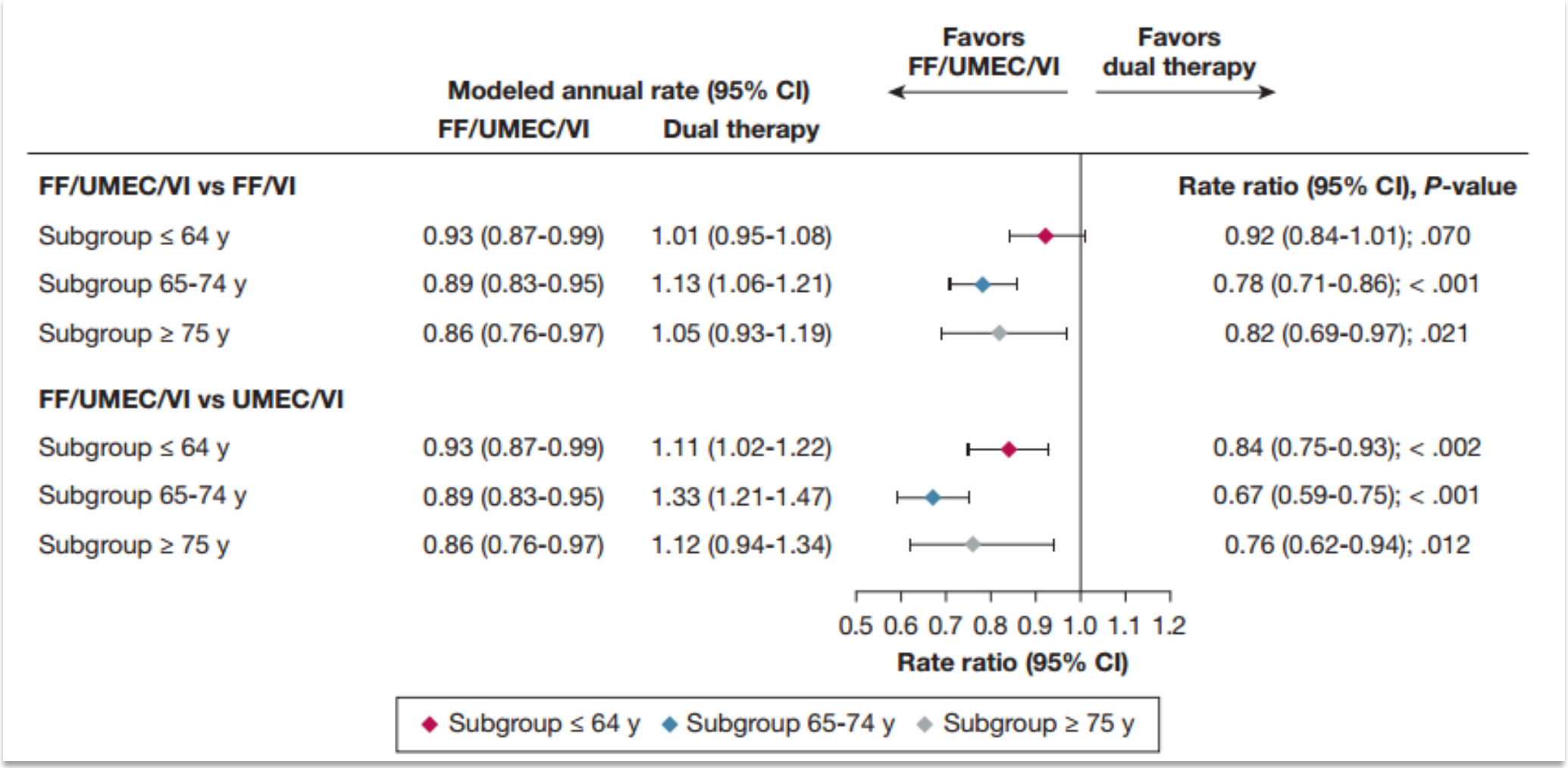
b)

	Treatment A FF/UMEC/VI	Treatment B FF/VI	RR (95% CI)	p-value
FF/UMEC/VI *versus* FF/VI				
Single moderate subgroup	0.11 (0.09–0.14)	0.13 (0.10–0.16)	0.88 (0.66–1.18)	0.388
Frequent moderate subgroup	0.06 (0.05–0.08)	0.07 (0.06–0.09)	0.84 (0.64–1.10)	0.198
Severe subgroup	0.29 (0.25–0.33)	0.33 (0.28–0.38)	0.88 (0.72–1.08)	0.226
FF/UMEC/VI *versus* UMEC/VI	**FF/UMEC/VI**	**UMEC/VI**		
Single moderate subgroup	0.11 (0.09–0.14)	0.11 (0.08–0.15)	0.99 (0.69–1.43)	0.962
Frequent moderate subgroup	0.06 (0.05–0.08)	0.14 (0.11–0.17)	0.45 (0.33–0.61)	<0.001
Severe subgroup	0.29 (0.25–0.33)	0.42 (0.34–0.51)	0.69 (0.54–0.88)	0.003



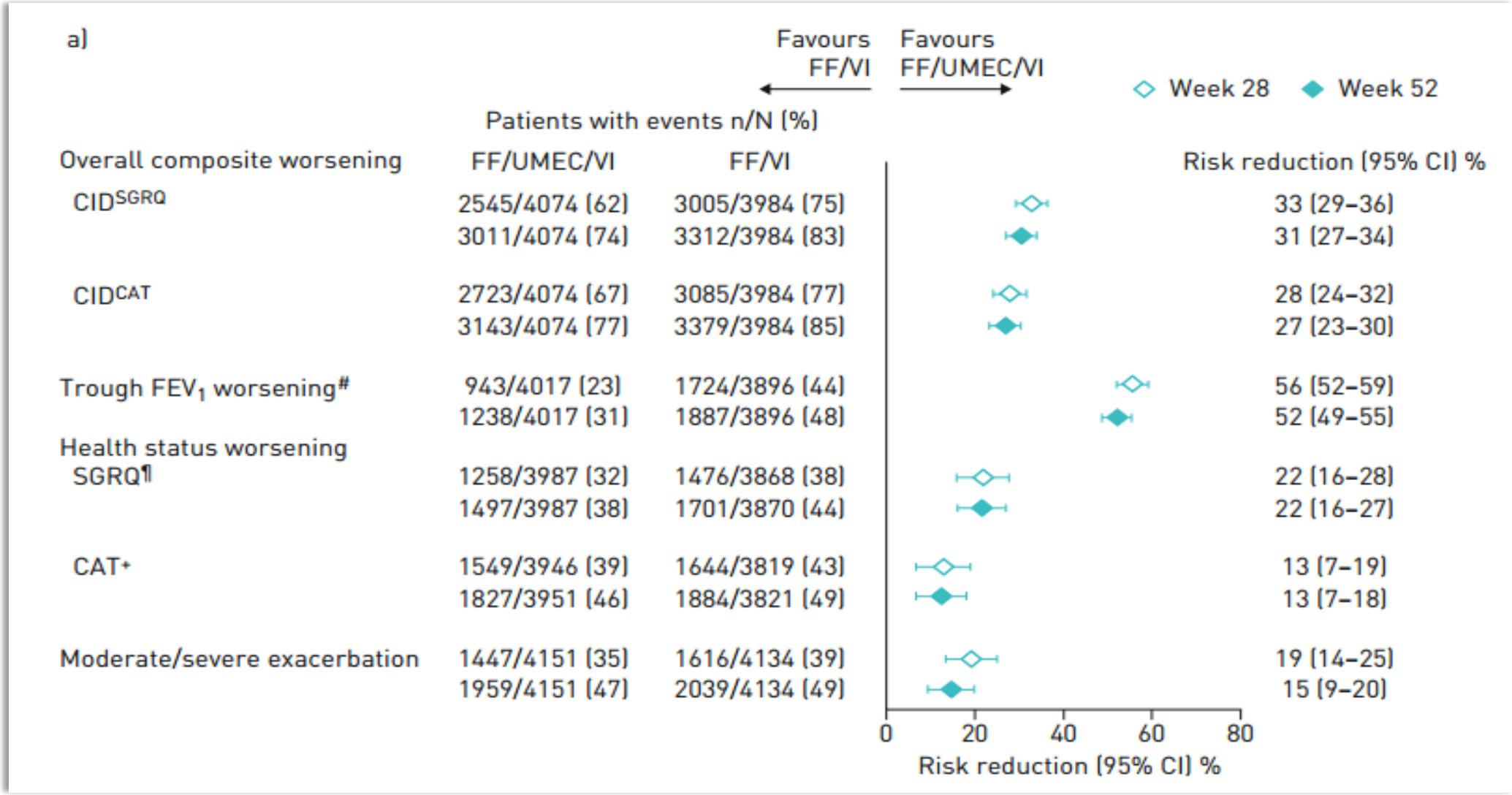
Halpin DMG;Eur Respir J;2020;55;1-12

Rate of on-treatment moderate/severe exacerbations by age group



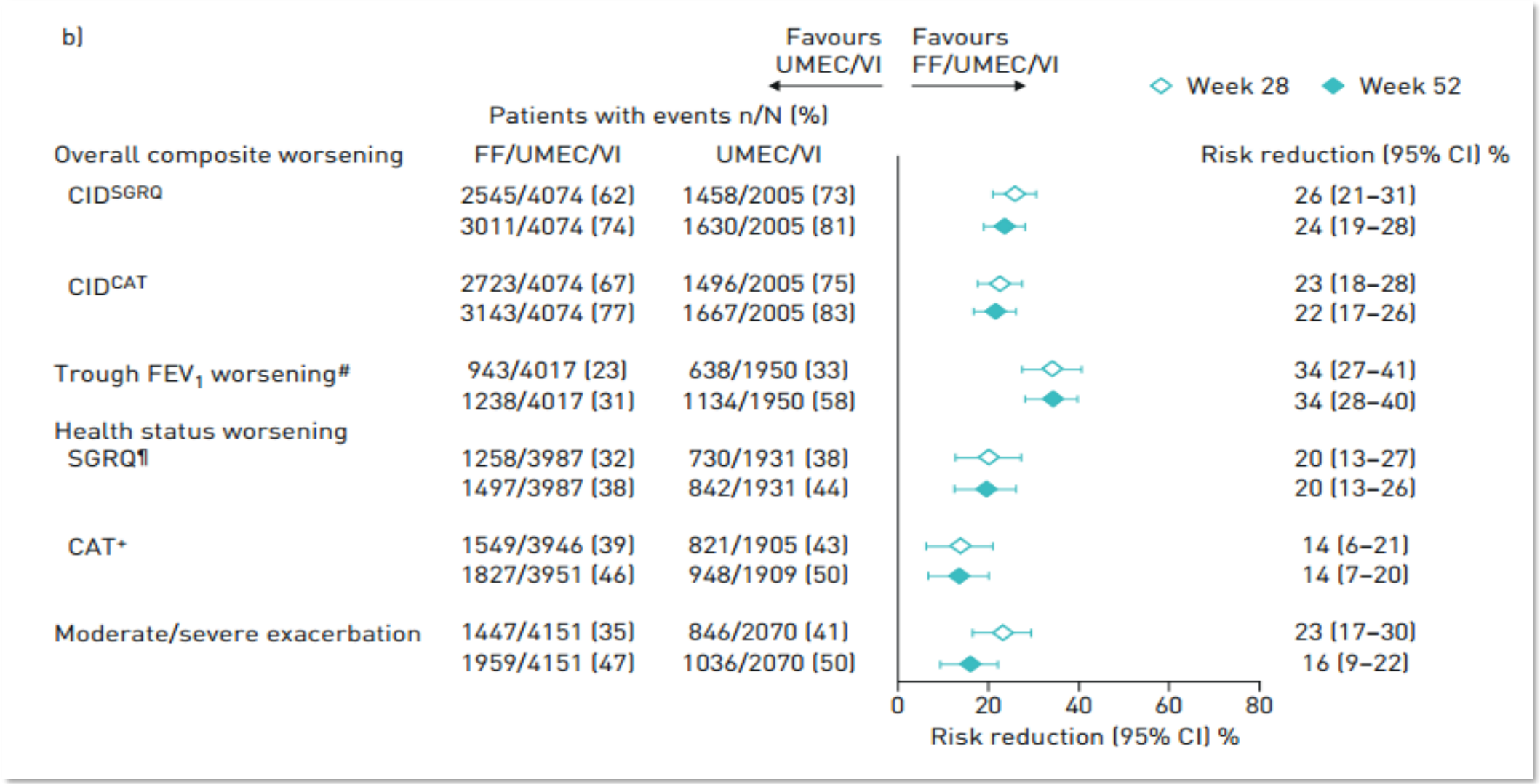
Hanania NA, et al. CHEST 2021; 159(3):985-995

Reduction in clinically important deterioration (CID) risk (time to first) with fluticasone furoate/ umeclidinium/vilanterol (FF/UMEC/VI) versus FF/VI



Han MK, et al ERJ open research ;2021;7;00663-2020

Reduction in clinically important deterioration (CID) risk (time to first) with fluticasone furoate/ umeclidinium/vilanterol (FF/UMEC/VI) versus UMEC/VI



Han MK, et al ERJ open research ;2021;7;00663-2020

Reduction in Emergency Department (ED) Visits in Patients With Chronic Obstructive Pulmonary Disease (COPD): Analysis of the IMPACT Trial

Mapel D[1], Bogart M[2], Criner GJ[3], Dransfield MT[4], Gaeckle N[5], Gotfried M[6], Halpin DMG[7], Han MK[8], Jain RG[2], Kaul V[9,10], Mammen MJ[11], Midwinter D[12], Singh D[13], Wise R[14], Lipson DA[15,16]

[1]University of New Mexico College of Pharmacy, Albuquerque, NM, USA; [2]GSK, Research Triangle Park, NC, USA; [3]Lewis Katz School of Medicine at Temple University, Philadelphia, PA, USA; [4]Division of Pulmonary, Allergy, and Critical Care Medicine, Lung Health Center, University of Alabama at Birmingham, Birmingham, AL, USA; [5]Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, University of Minnesota, Minneapolis, MN, USA; [6]Pulmonary Associates PA, Phoenix, AZ, USA; [7]University of Exeter Medical School, University of Exeter, Exeter, UK; [8]University of Michigan, Pulmonary & Critical Care, Ann Arbor, MI, USA; [9]State University of New York Upstate Medical, Syracuse, NY, USA; [10]Crouse Health, Syracuse, NY, USA; [11]Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, USA; [12]GSK, Brentford, UK; [13]University of Manchester, Manchester University NHS Foundation Trust, Manchester, UK; [14]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [15]GSK, Collegeville, PA, USA; [16]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Recording by Doug Mapel

IMPACT TRIAL

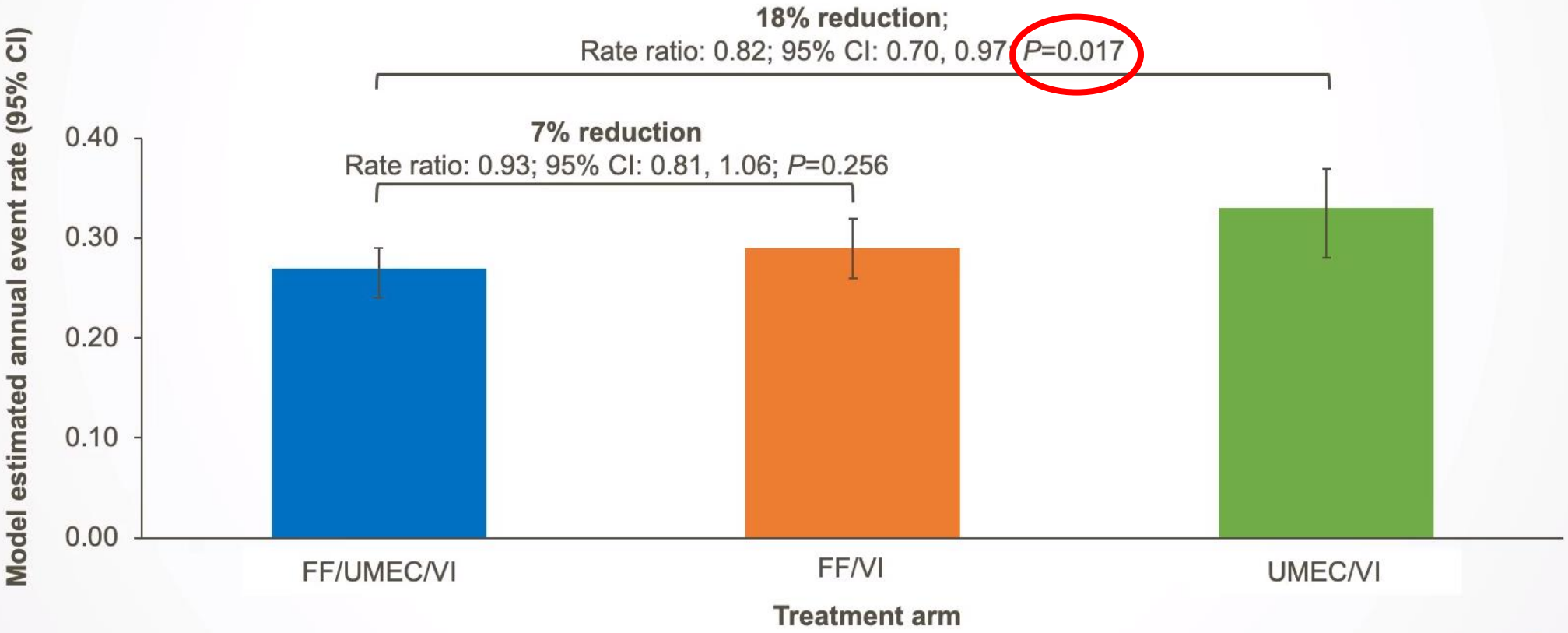
American Thoracic Society
Annual Meeting 2021
May 14–19, 2021

- The rate of ED visits in patients enrolled in IMPACT has not been published; this post hoc analysis of the IMPACT trial evaluated the annual rate of ED visits by treatment arm.

The rate of ED visits was significantly lower with FF/UMEC/VI vs UMEC/VI, with no statistically significant difference vs FF/VI

IMPACT TRIAL

The model estimated annual event rates (95% CI) were 0.27 (0.24, 0.29) for FF/UMEC/VI, 0.29 (0.26, 0.32) for FF/VI, and 0.33 (0.28, 0.37) for UMEC/VI



Analysis covariates included treatment group, sex, exacerbation history (≤1, ≥2 moderate/severe), smoking status (screening), region and post-bronchodilator percent predicted FEV_1 (screening).
CI, confidence interval; ED, emergency department; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol
Mapel D, et al. Reduction in Emergency Department (ED) Visits in Patients With Chronic Obstructive Pulmonary Disease (COPD): Analysis of the IMPACT Trial

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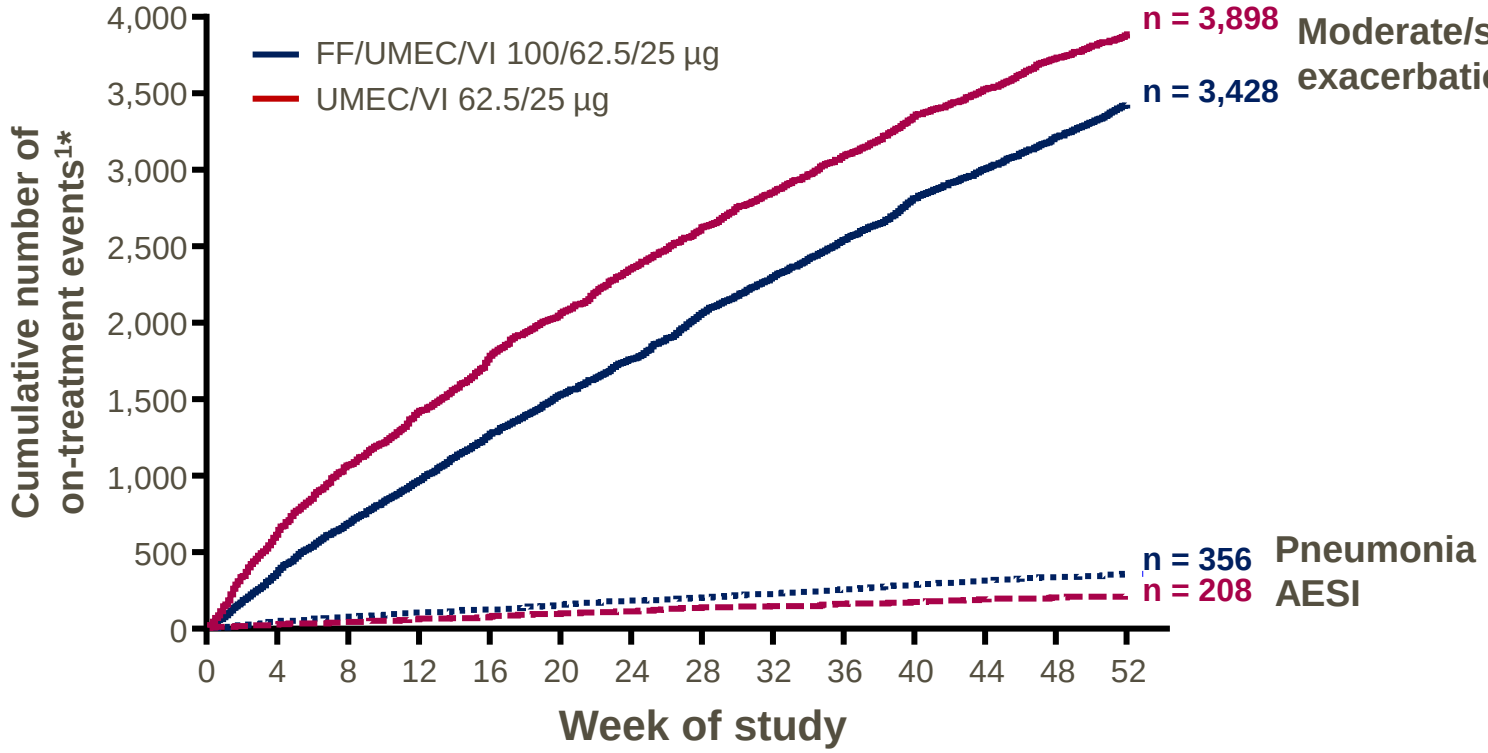
Results could support a positive benefit : risk profile

Pneumonia events taken in context with exacerbation events could support a positive benefit: risk profile with FF/UMEC/VI



Number needed to treat

- For every **4 patients** treated for 1 year, FF/UMEC/VI could help prevent 1 moderate/severe exacerbation vs UMEC/VI
- For every **16 patients** treated for 1 year, FF/UMEC/VI could help prevent 1 **severe exacerbation** vs UMEC/VI

Number needed to harm

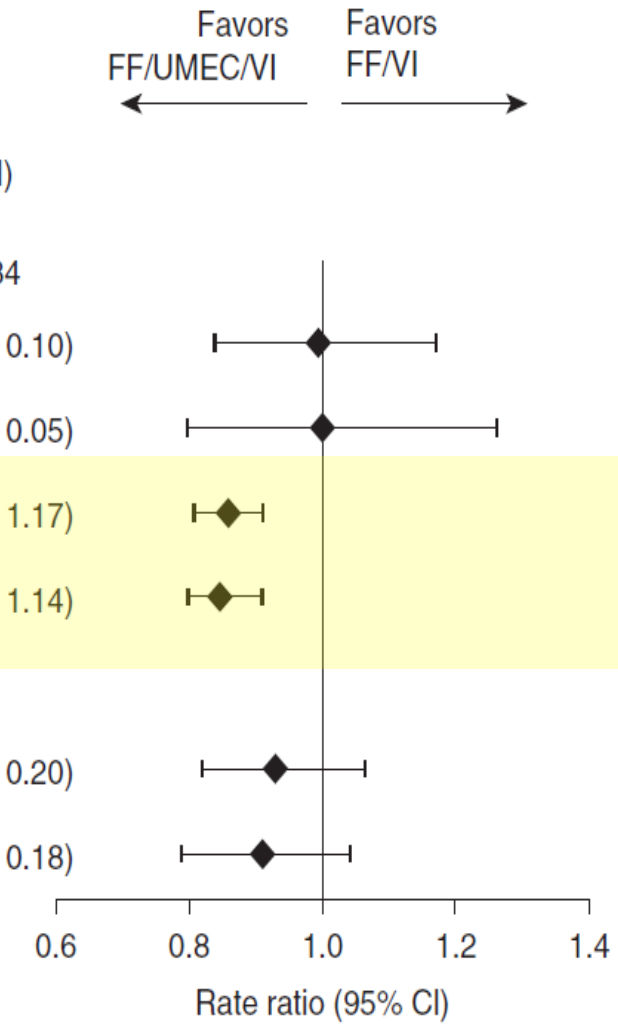
- For every **33 patients** treated for 1 year, FF/UMEC/VI may cause 1 pneumonia AESI vs UMEC/VI

Lipson DA et al, NEJM 2018;378;1671-1680(including supplementary appendix)
This graph has been independently created by GSK from the original data.

IMPACT TRIAL

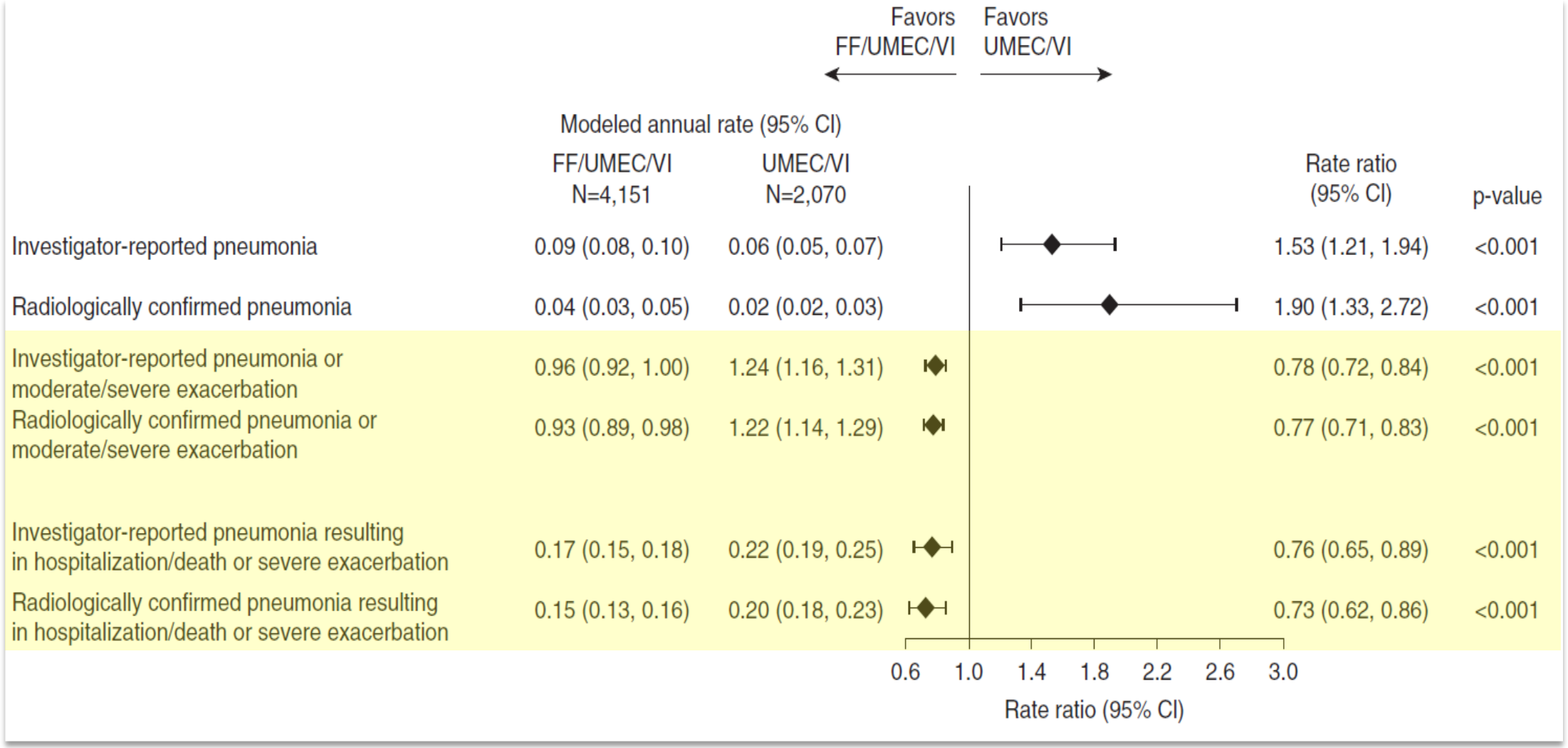
Risk of Exacerbation and Pneumonia
Triple vs FF/VI

	Modeled annual rate (95% CI) FF/UMEC/VI N=4,151	FF/VI N=4,134	Rate ratio (95% CI)	p-value
Investigator-reported pneumonia	0.09 (0.08, 0.10)	0.09 (0.08, 0.10)	0.99 (0.84, 1.17)	0.937
Radiologically confirmed pneumonia	0.04 (0.03, 0.05)	0.04 (0.03, 0.05)	1.00 (0.80, 1.26)	0.993
Investigator-reported pneumonia or moderate/severe exacerbation	0.96 (0.92, 1.00)	1.12 (1.07, 1.17)	0.86 (0.81, 0.91)	<0.001
Radiologically confirmed pneumonia or moderate/severe exacerbation	0.93 (0.89, 0.98)	1.10 (1.05, 1.14)	0.85 (0.80, 0.91)	<0.001
Investigator-reported pneumonia resulting in hospitalization/death or severe exacerbation	0.17 (0.15, 0.18)	0.18 (0.16, 0.20)	0.93 (0.82, 1.06)	0.289
Radiologically confirmed pneumonia resulting in hospitalization/death or severe exacerbation	0.15 (0.13, 0.16)	0.16 (0.15, 0.18)	0.91 (0.79, 1.04)	0.152



Dransfield et al. Ann ATS 2021

Risk of Exacerbation and Pneumonia
Triple vs UMEC/VI



Dransfield et al. Ann ATS 2021

An Analysis of the IMPACT Trial Assessing Single-Inhaler Therapy With Fluticasone Furoate/Umeclidinium/Vilanterol (FF/UMEC/VI) Versus FF/VI and UMEC/VI Using a Composite Adverse Event Outcome in Patients With COPD

Wells JM[1], Bhatt SP[1], Carr TF[2], Criner GJ[3], Halpin DMG[4], Han MK[5], Jain RG[6], Kaye MG[7], Kraft M[2], Lipson DA[8,9], Mapel D[10], Mammen MJ[11], McEvoy C[12], Midwinter D[13], Singh D[14], Wise R[15], Dransfield MT[1]

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Recording by J Michael Wells

IMPACT

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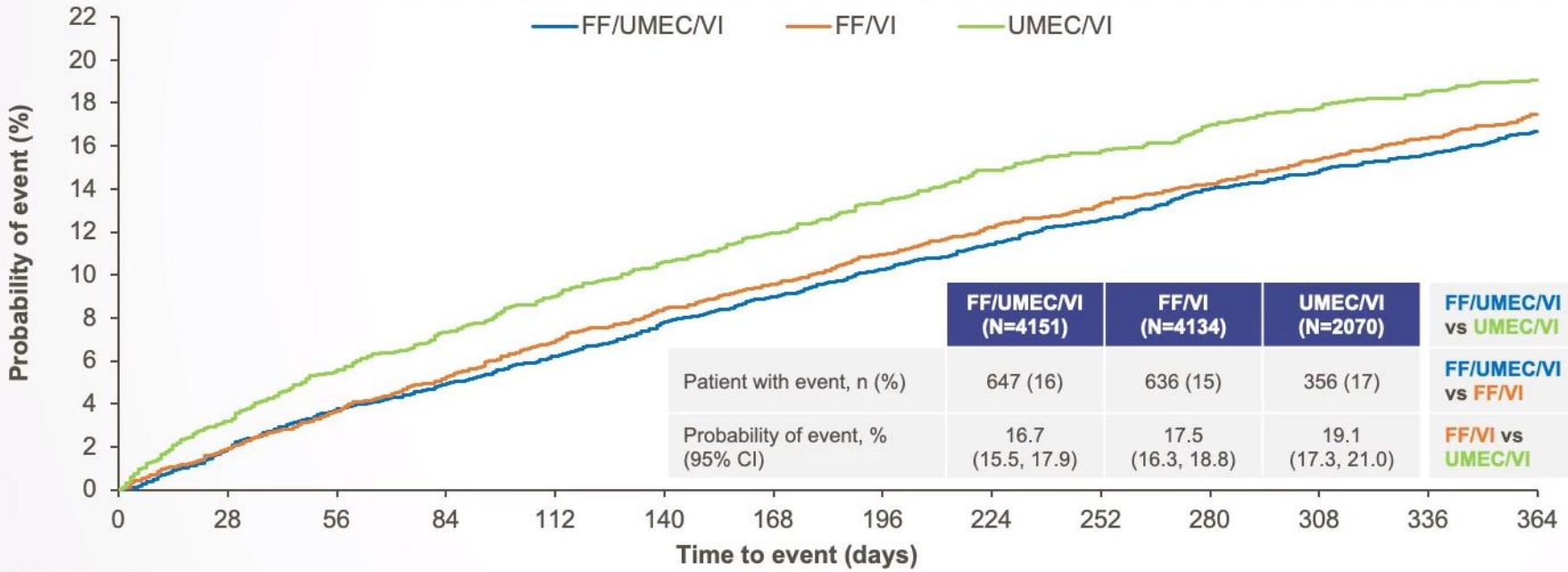
- This post hoc analysis aims to evaluate the benefit–risk profile of FF/UMEC/VI versus FF/VI and UMEC/VI in the IMPACT population by means of a cardiopulmonary composite endpoint including on-treatment exacerbations, pneumonia, CV events, and death

FF/UMEC/VI significantly reduced the risk of an on-treatment composite adverse event versus UMEC/VI

IMPACT TRIAL

TIME-TO-FIRST ON-TREATMENT SEVERE EXACERBATION OR SERIOUS PNEUMONIA OR SERIOUS CVAESI OR ACM

- FF/UMEC/VI significantly reduced composite event risk by 16.5% versus UMEC/VI. The point estimates for the reduction in the risk of a composite event favored FF/UMEC/VI over FF/VI and FF/VI over UMEC/VI but were not statistically significant.



	FF/UMEC/VI (N=4151)	FF/VI (N=4134)	UMEC/VI (N=2070)
Patient with event, n (%)	647 (16)	636 (15)	356 (17)
Probability of event, % (95% CI)	16.7 (15.5, 17.9)	17.5 (16.3, 18.8)	19.1 (17.3, 21.0)

	HR (95% CI)	Risk reduction, % (95% CI)	*P*-value
FF/UMEC/VI vs UMEC/VI	0.83 (0.73, 0.95)	16.5 (5.0, 26.7)	**0.006**
FF/UMEC/VI vs FF/VI	0.94 (0.84, 1.05)	6.2 (-4.7, 15.9)	0.255
FF/VI vs UMEC/VI	0.89 (0.78, 1.01)	11.1 (-1.3, 21.9)	0.077

Number of patients at risk

FF/UMEC/VI	4151	4014	3850	3746	3652	3529	3460	3398	3301	3238	3165	3101	3053	2930
FF/VI	4134	3924	3689	3552	3434	3284	3208	3124	3015	2959	2911	2841	2796	2672
UMEC/VI	2070	1948	1818	1740	1676	1607	1564	1526	1467	1441	1412	1378	1356	1309

ACM, all-cause mortality; CI, confidence interval; CVAESI, cardiovascular event of special interest; FF, fluticasone furoate; HR, hazard ratio; UMEC, umeclidinium; VI, vilanterol

Wells JM, et al. An Analysis of the IMPACT Trial Assessing Single-Inhaler Therapy With Fluticasone Furoate/Umeclidinium/Vilanterol (FF/UMEC/VI) Versus FF/VI and UMEC/VI Using a Composite Adverse Event Outcome in Patients With COPD.

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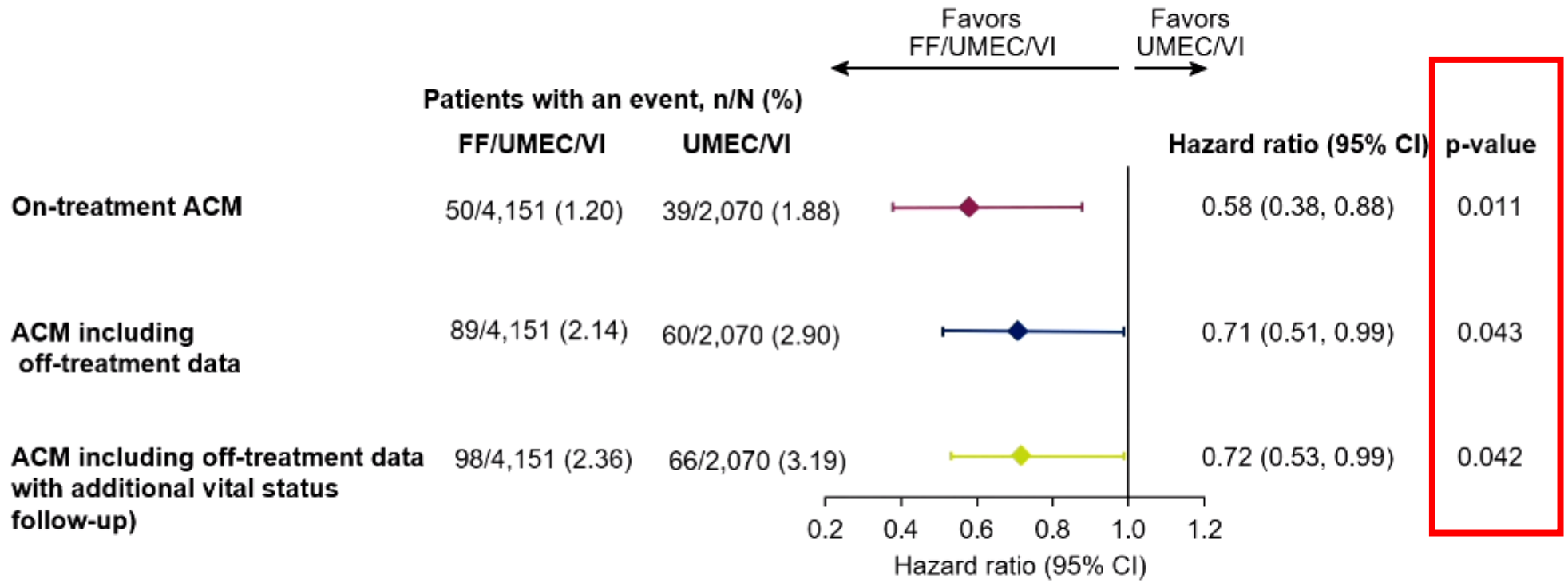
- Real world evidence (INTREPID study)

All cause mortality (ACM) in the IMPACT study



Forest plot of ACM analyses and hazard ratios FF/UMEC/VI versus UMEC/VI.
ACM: all-cause mortality; CI: confidence interval; FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol.

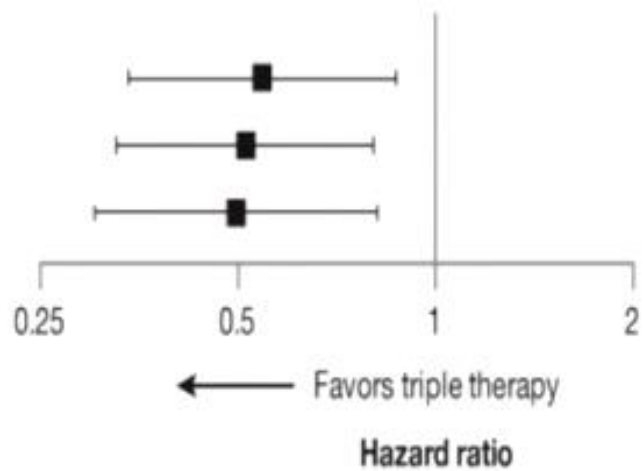
Lipson et al. Am J Respir Crit Care Med. 2020 Jun 15;201(12):1508-1516.

All cause mortality (ACM) in the ETHOS study

A

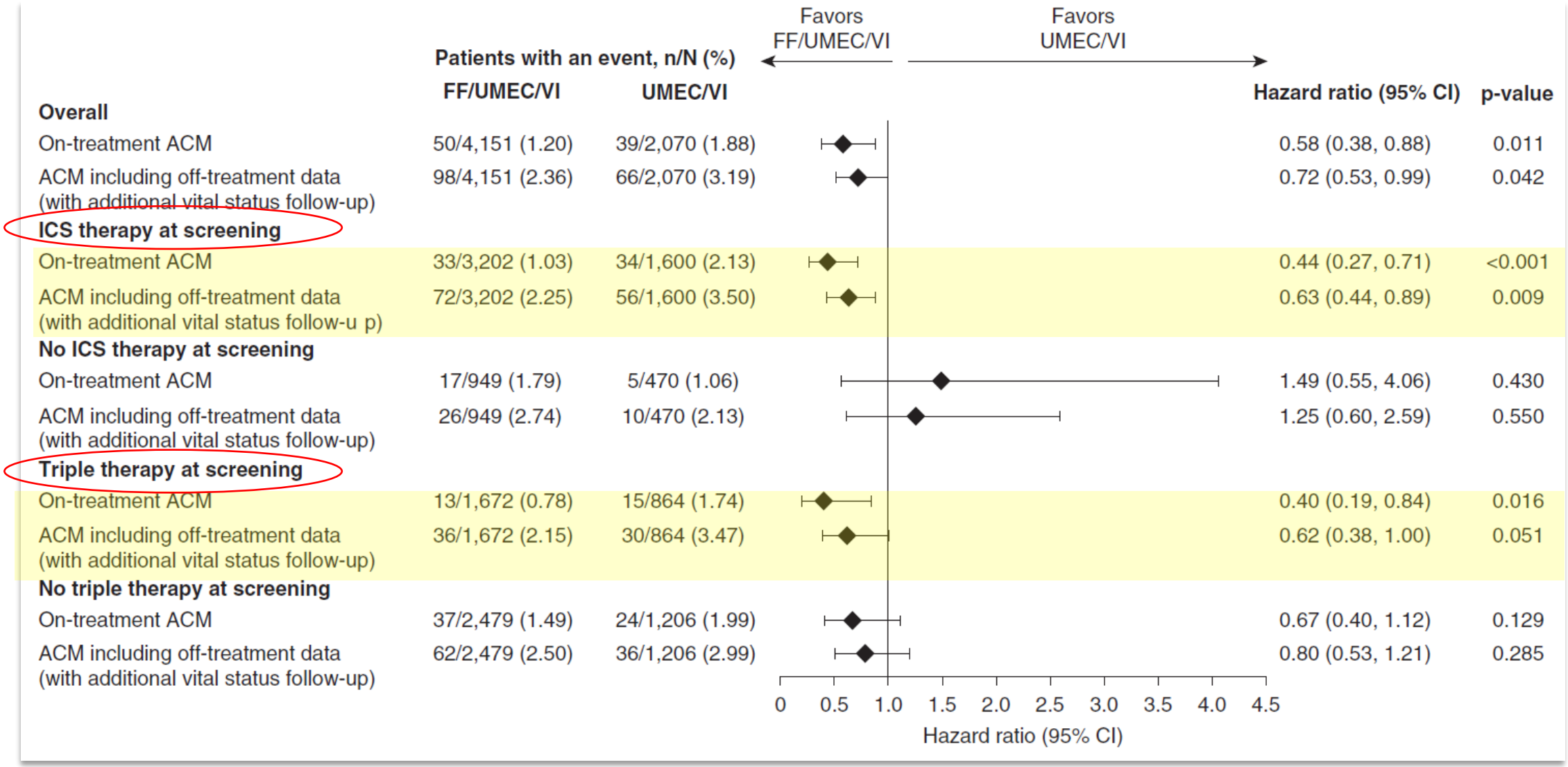
BGF 320/18/9.6 µg vs GFF

	Patients with an event, n (%)		HR (95% CI)	P-value
	BGF 320/18/9.6 µg (N=2137)	GFF 18/9.6 µg (N=2120)		
On- and off-treatment (original dataset)	28 (1.3)	49 (2.3)	0.54 (0.34, 0.87)	0.0111
On- and off-treatment (final retrieved dataset)	30 (1.4)	56 (2.6)	0.51 (0.33, 0.80)	0.0035
On-treatment (final retrieved dataset)	25 (1.2)	45 (2.1)	0.50 (0.30, 0.81)	0.0056



Martinez FJ et al. Article and supplement online ahead of print. *Am J Crit Care Med*. 2020.

All cause mortality by triple therapy or ICS use at screening



Reference : Lipson DA;American Journal of Respiratory and Critical Care Medicine;2020;201;1508-1516

Risk of All-cause Mortality During and After Severe Exacerbations in Patients With Chronic Obstructive Pulmonary Disease (COPD): Post Hoc Analysis of the IMPACT Trial

Mammen MJ[1], Carr TF[2], Criner GJ[3], Dransfield MT[4], Halpin DMG[5], Han MK[6], Hartley B[7], Jain RG[8], Kaul V[9,10], Kaye MG[11], Kraft M[2], Mapel D[12], Midwinter D[13], Scanlon PD[14], Singh D[15], Wells JM[4], Wise R[16], Lipson DA[17,18]

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Recording by Manoj J Mammen

IMPACT

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- This post hoc analysis investigated the risk of ACM during and following a moderate or severe exacerbation in patients enrolled in the IMPACT trial.

Summary of adjudicated primary causes of death during and following exacerbations

IMPACT TRIAL

- Overall, 4401 (42.5%) patients experienced on-treatment moderate exacerbations and 1180 (11.4%) patients experienced on-treatment severe exacerbations.
- The most common cause of death was cardiovascular in the exacerbation-free period and respiratory during the exacerbation.

Periods	Causes of death, n (%)					
	Cardiovascular	Respiratory	Cancer	Unknown	Other	Total
Exacerbation-free	36 (51)	6 (9)	6 (9)	16 (23)	6 (9)	70 (100)
Moderate exacerbation						
During	1 (25)	2 (50)	0	1 (25)	0	4 (100)
1–90 days post exacerbation	9 (56)	1 (6)	1 (6)	4 (25)	1 (6)	16 (100)
91–365 days post exacerbation	2 (22)	0	3 (33)	1 (11)	3 (33)	9 (100)
Severe exacerbation						
During	1 (3)	26 (81)	0	5 (16)	0	32 (100)
1–90 days post exacerbation	1 (20)	1 (20)	0	3 (60)	0	5 (100)
91–365 days post exacerbation	2 (100)	0	0	0	0	2 (100)

Moderate exacerbation, any exacerbation requiring antibiotics and/or oral/systemic corticosteroids, severe exacerbation, any exacerbation leading to hospitalization or death. Deaths were independently adjudicated by a clinical endpoint committee to determine the primary cause of death. Percentage are presented as percent of the total number of events in each period.

Mammen MJ, et al. Risk of All-cause Mortality During and After Severe Exacerbations in Patients With Chronic Obstructive Pulmonary Disease (COPD): Post Hoc Analysis of the IMPACT Trial.

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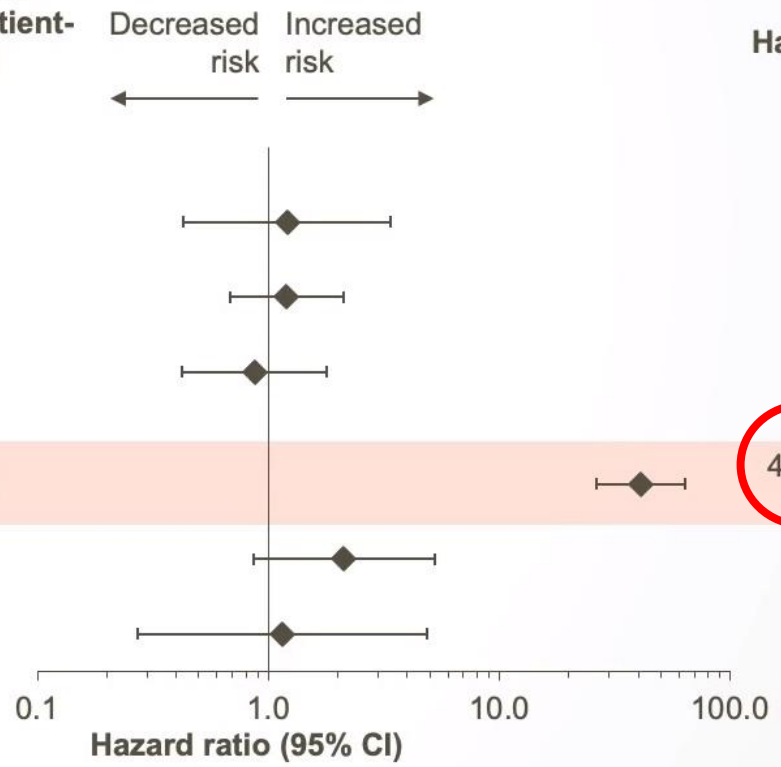
The risk of ACM significantly increased during a severe exacerbation

IMPACT TRIAL

- The risk of ACM significantly increased by 41-fold during a severe exacerbation event compared with the exacerbation-free period, and decreased thereafter with neither post-exacerbation periods showing a significant difference in risk compared with the baseline period.
- As expected, there was no statistically significant increase in the risk of ACM during a moderate exacerbation.

	n*	Patients with events (ACM), n (%)†	Duration at risk (patient-years)	Event rate (per 100 patient-years)	Hazard ratio (95% CI), *P*-value
Exacerbation-free period	10,330	70 (0.7)	6280	1.11	
Moderate exacerbation					
During	4397	4 (0.1)	295	1.36	1.21 (0.43, 3.37), *P*=0.717
1–90 days post exacerbation	4201	16 (0.4)	1192	1.34	1.20 (0.68, 2.12), *P*=0.530
91–365 days post exacerbation	2805	9 (0.3)	881	1.02	0.87 (0.42, 1.79), *P*=0.707
Severe exacerbation					
During	1180	32 (2.7)	65	49.45	41.22 (26.49, 64.15), *P*<0.001
1–90 days post exacerbation	980	5 (0.5)	190	2.63	2.13 (0.86, 5.29), *P*=0.102
91–365 days post exacerbation	474	2 (0.4)	133	1.51	1.15 (0.27, 4.84), *P*=0.852



Moderate exacerbation, any exacerbation requiring antibiotics and/or oral/systemic corticosteroids, severe exacerbation, any exacerbation leading to hospitalization or death. *n is the total number of patients who spent time in each period; †percent calculated as number of patients with events divided by the total number of patients who spent time in the period.
ACM, all-cause mortality; CI, confidence interval; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol
Mammen MJ, et al. Risk of All-cause Mortality During and After Severe Exacerbations in Patients With Chronic Obstructive Pulmonary Disease (COPD): Post Hoc Analysis of the IMPACT Trial.

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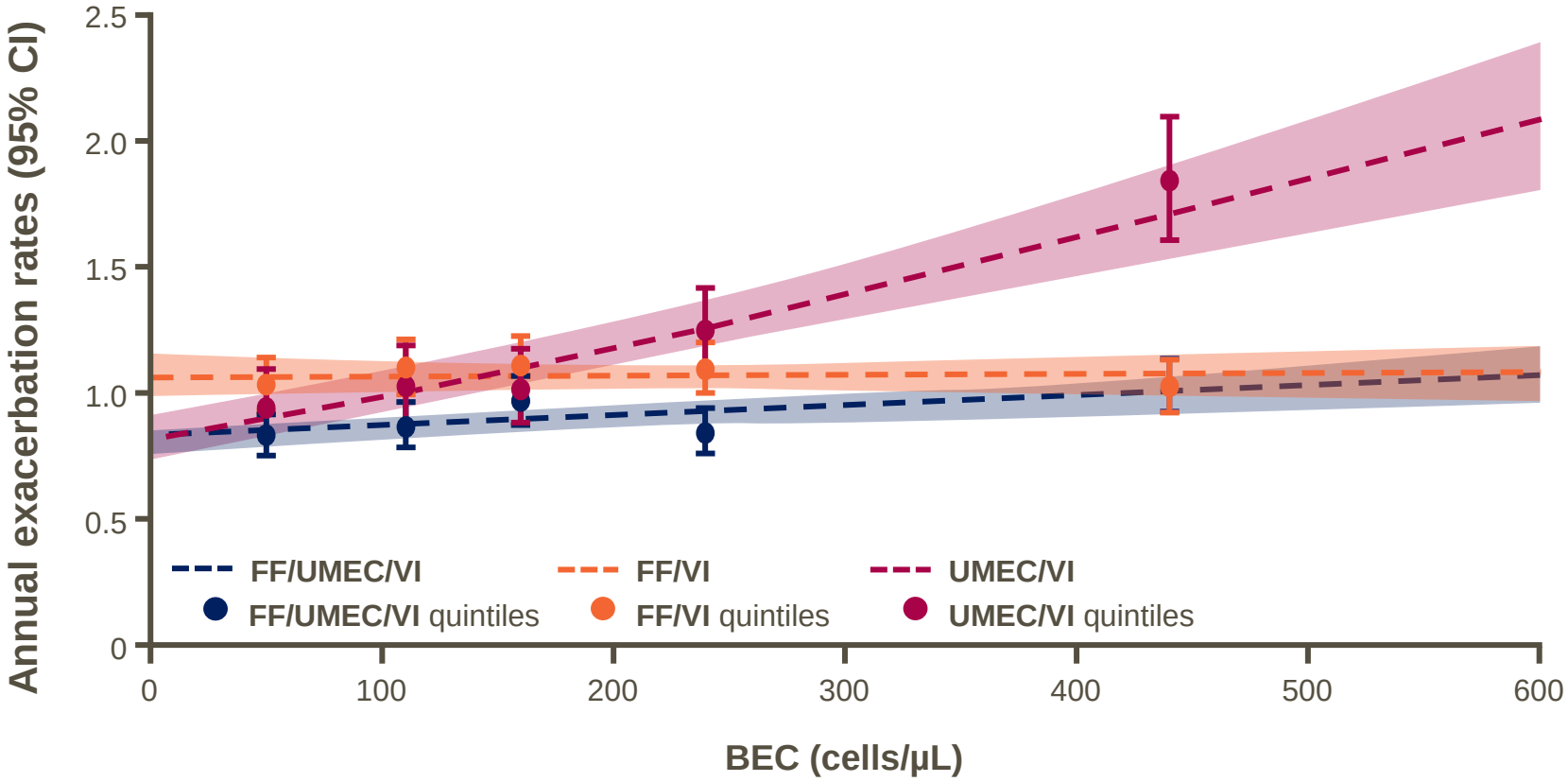
How can eosinophils guide the use of Triple Therapy?

Prospective analysis of IMPACT: Annual exacerbation rates by BEC

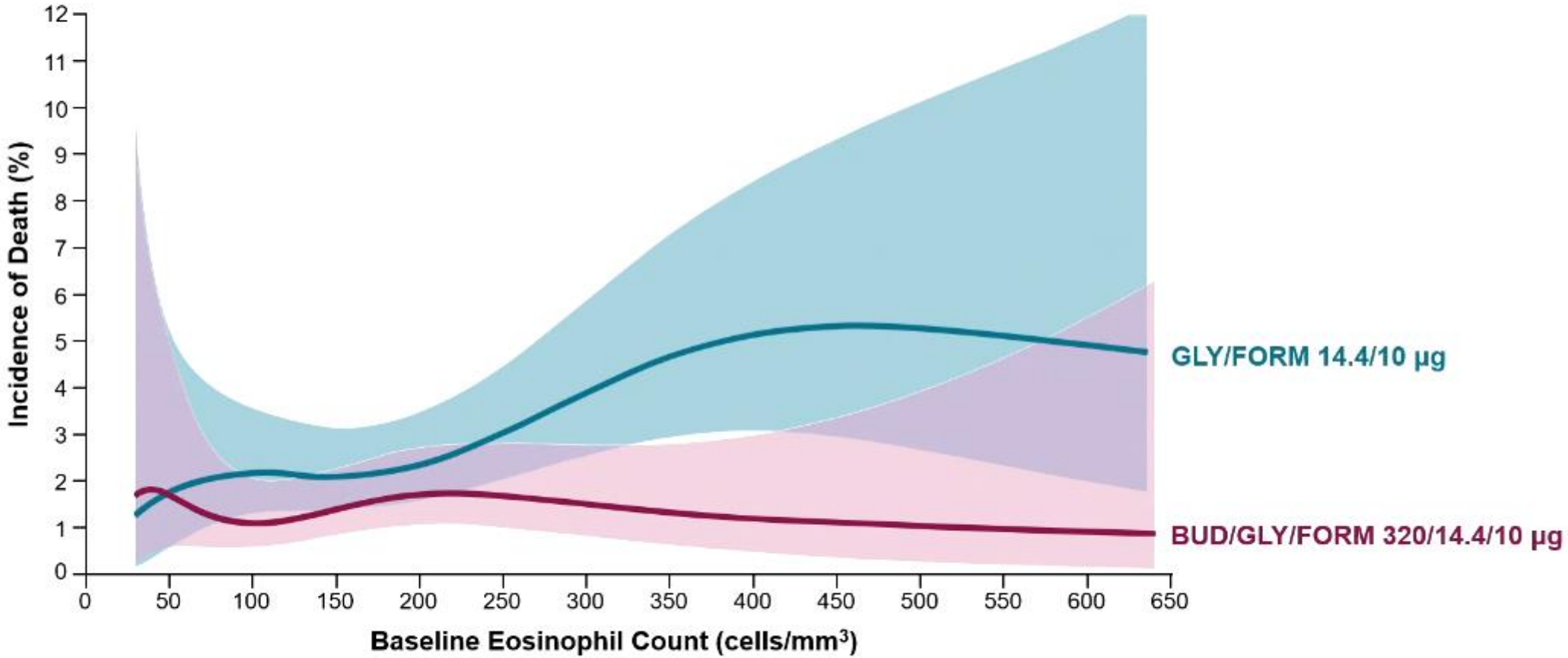


FF/UMEC/VI benefit is observed at EOS level ≥100 cells/µL

- **The greater the eosinophil level the greater the benefit from an ICS-containing medication**
- **At an EOS level of <100 cells/µL, patients are less likely to benefit from an ICS-containing medication***

Pascoe S, et al. *Lancet Respir Med*. 2019;7:745–756 (including Supplementary Appendix).

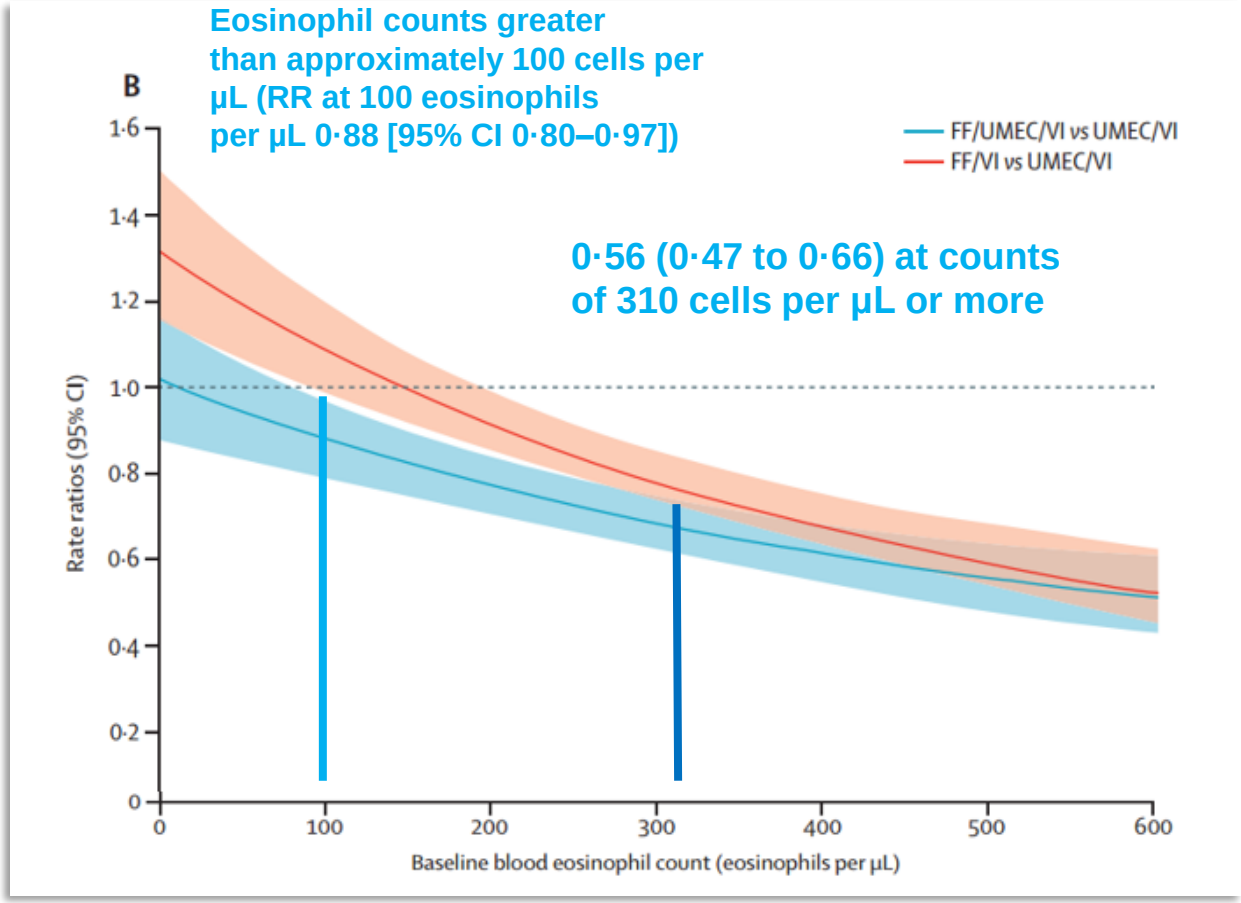
The Benefit of BUD 320/GLY/FORM vs. LAMA/LABA in Reducing Mortality Increased With Eosinophil Count



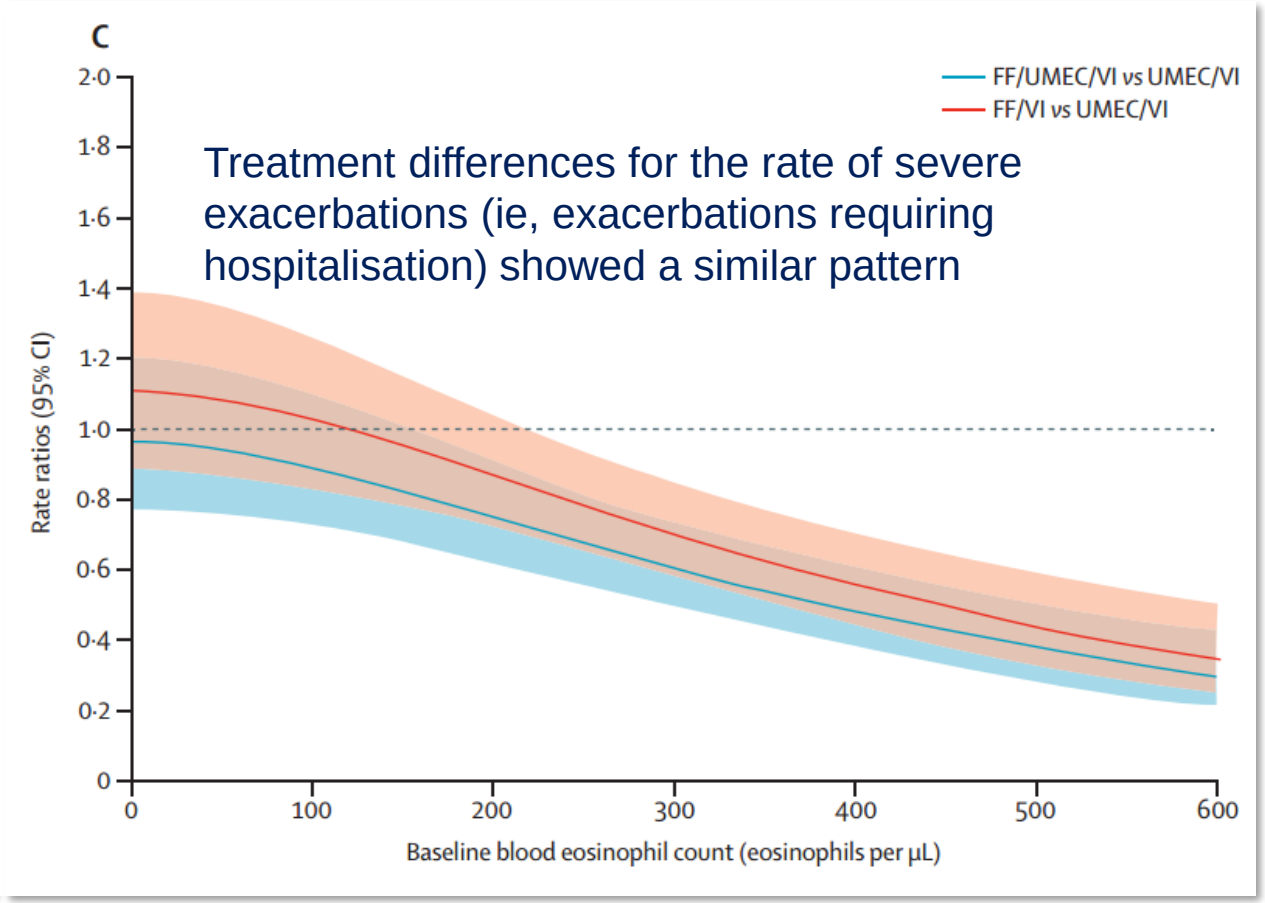
Notes: ITT population. All treatments were administered BID. Data from generalized additive model. Banded areas indicate 95% CI.

Martinez FJ et al. Article and supplement online ahead of print. *Am J Crit Care Med*. 2020.

Moderate or severe exacerbations (B)

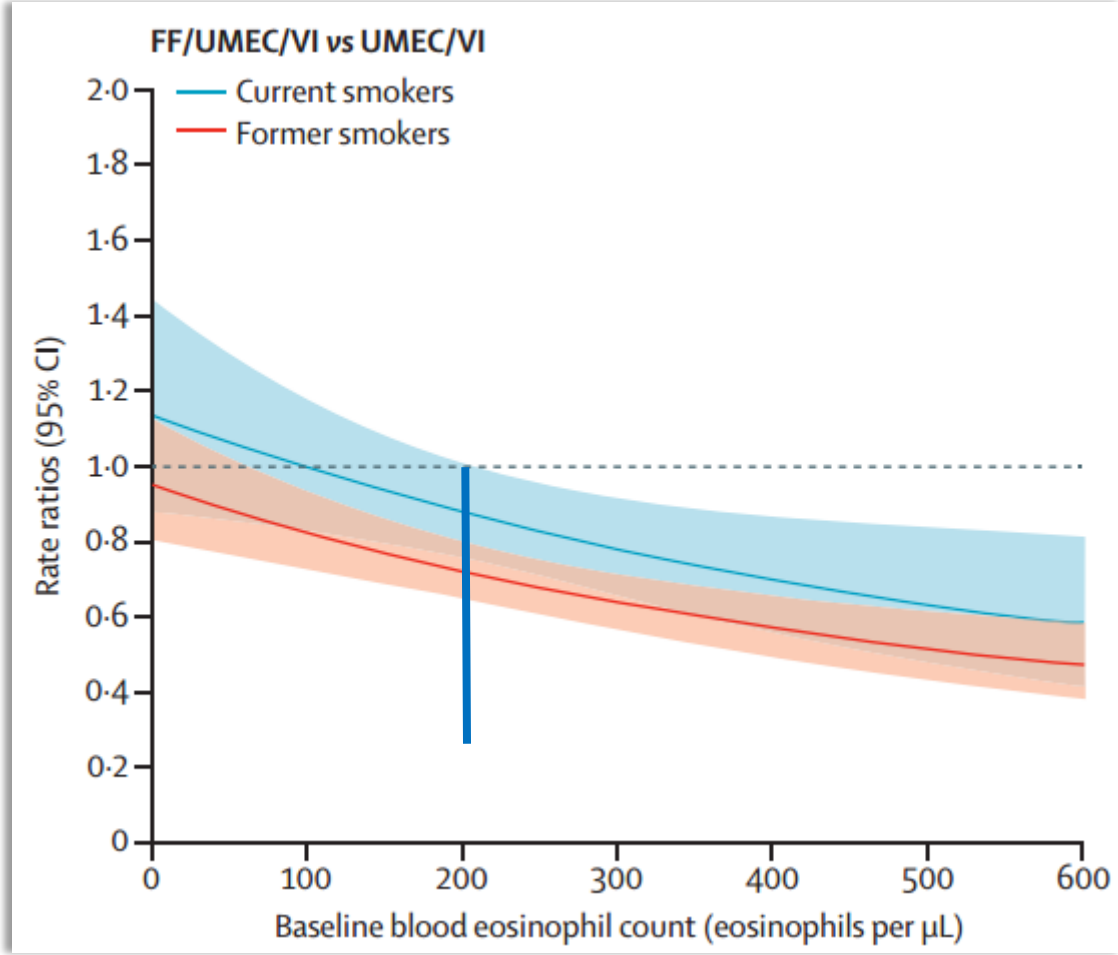


Severe exacerbations (C)

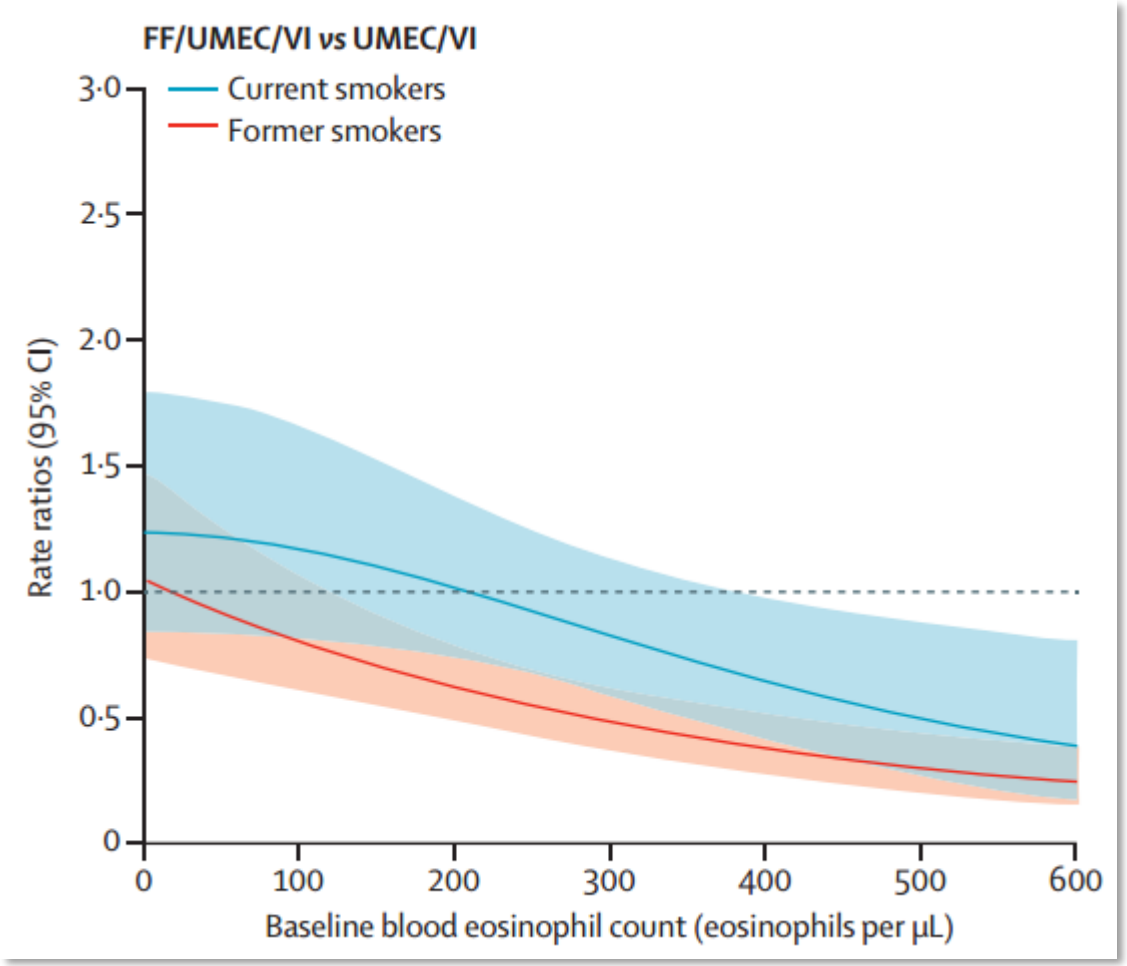


Pascoe S, et al. *Lancet Respir Med*. 2019;7:745–756 (including Supplementary Appendix).

Moderate or severe exacerbations (B)



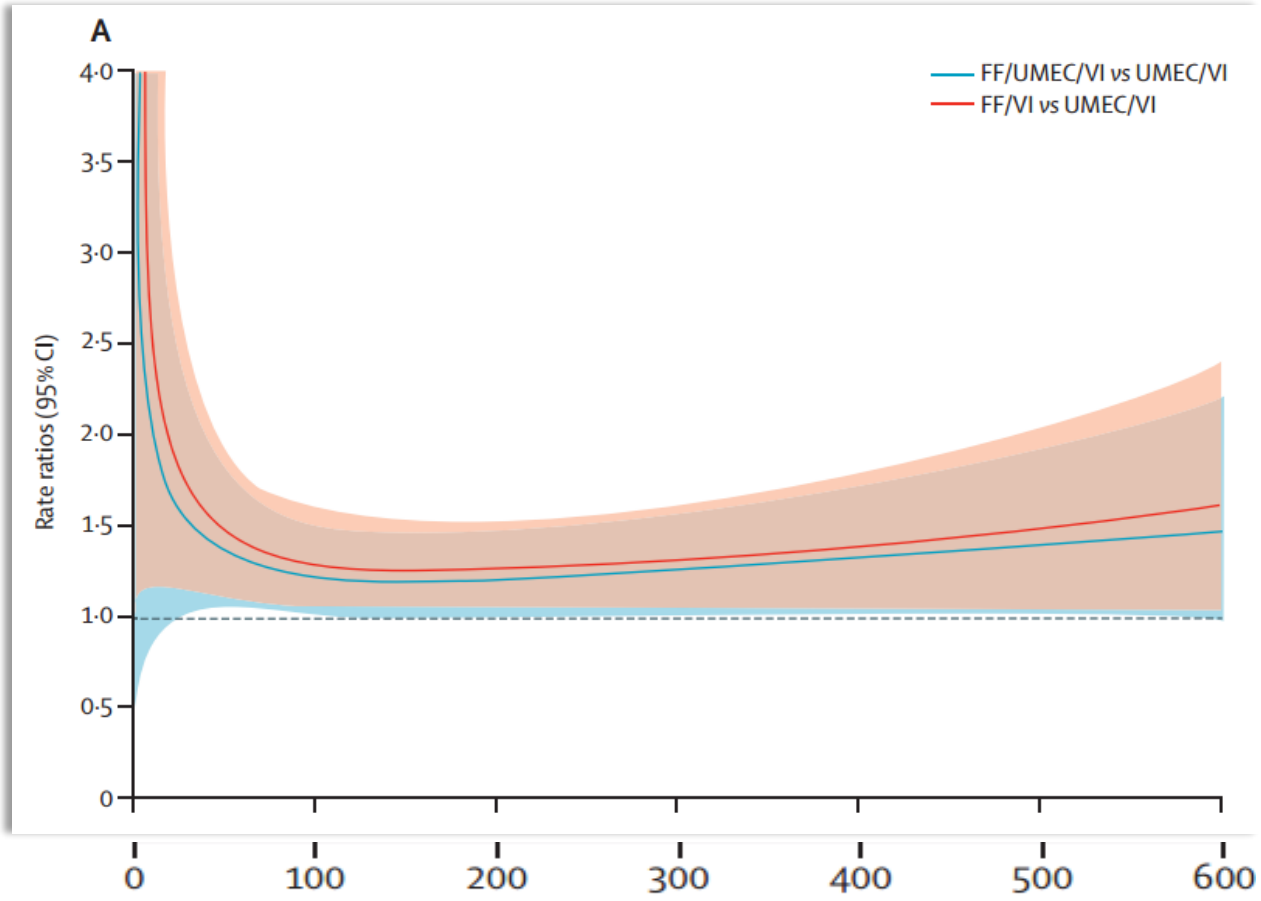
Severe exacerbations (C)

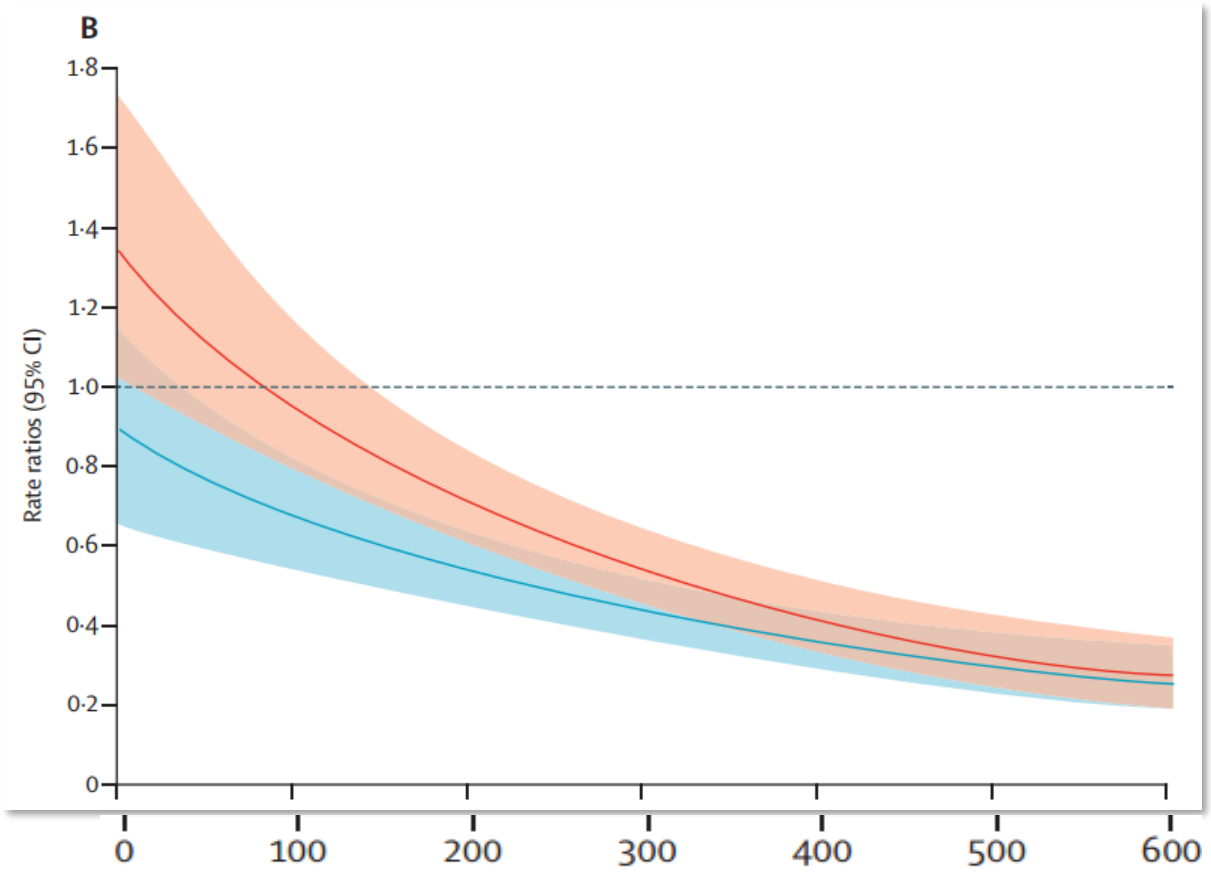


In former smokers, ICS benefits were observed at all blood eosinophil counts when comparing triple therapy with umeclidinium–vilanterol, whereas in current smokers no ICS benefit was observed at lower eosinophil counts, less than approximately 200 eosinophils per µL

Pascoe S, et al. *Lancet Respir Med*. 2019;7:745–756 (including Supplementary Appendix).

Between-treatment differences in moderate or severe exacerbations requiring only antibiotics (A), only oral corticosteroids (B)

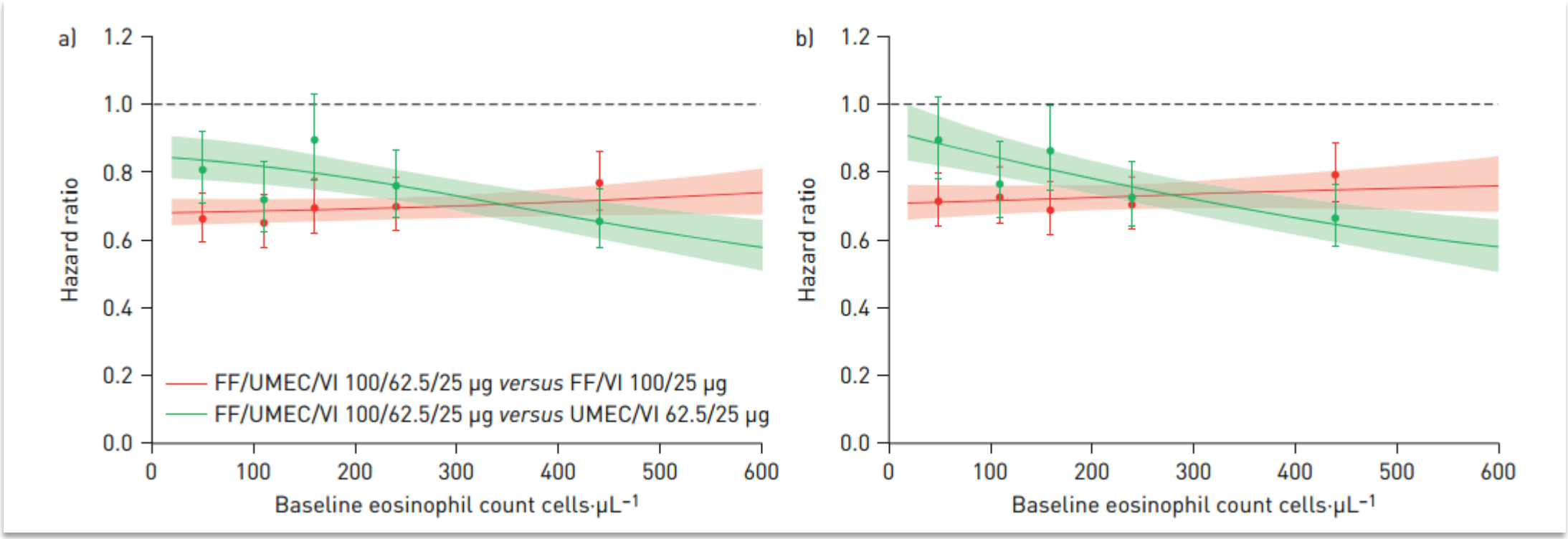




Pascoe S, et al. *Lancet Respir Med*. 2019;7:745–756 (including Supplementary Appendix).

Reprinted from *Lancet Respir Med*., vol. 7, Pascoe S, et al. Blood eosinophils and treatment response with triple and dual combination therapy in chronic obstructive pulmonary disease: analysis of the IMPACT trial, 745–756, 2019, with permission from Elsevier.

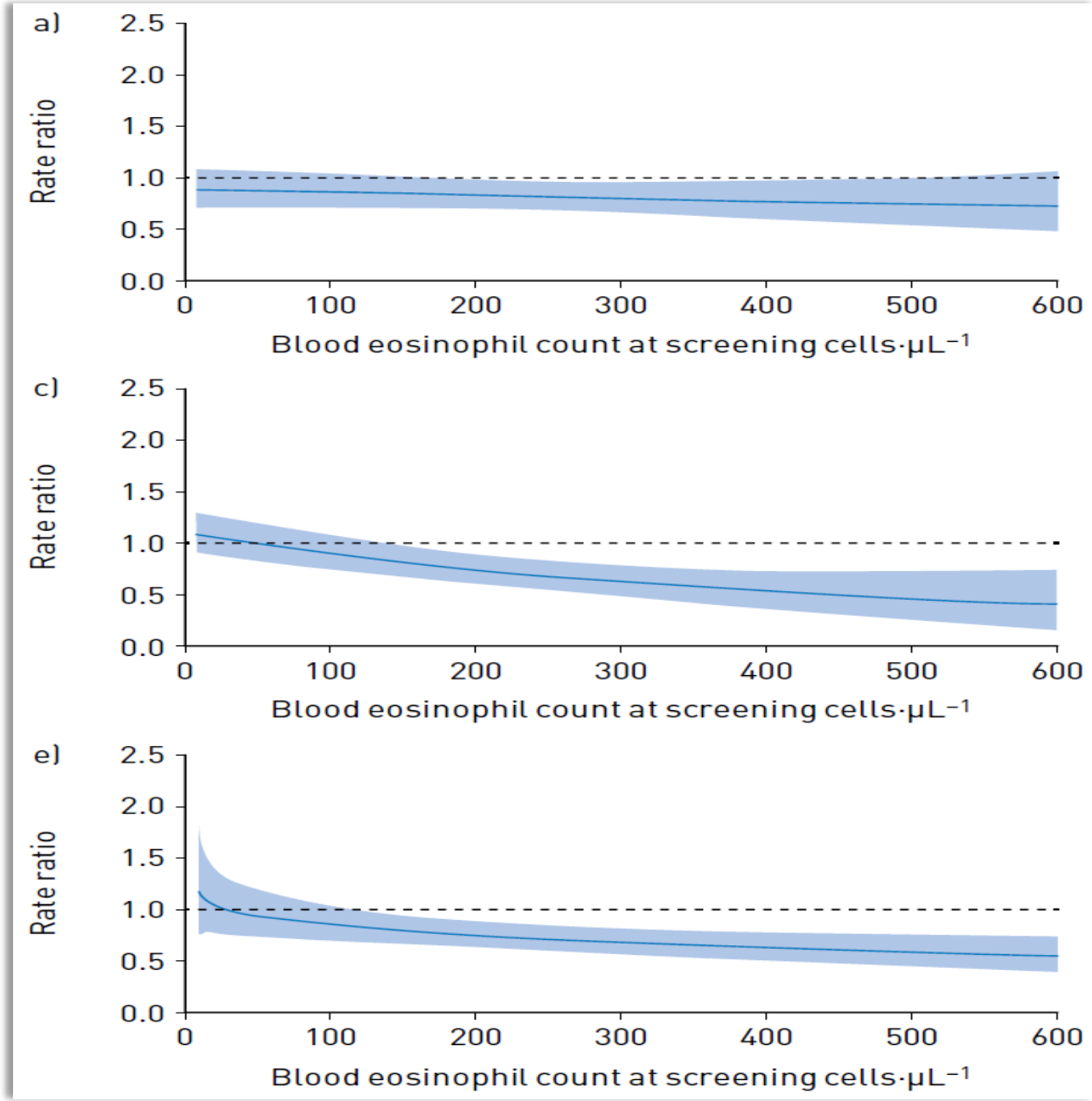
Hazard ratio (95% CI) for a first CID up to week 52 according to baseline blood eosinophil count assessed as a continuous variable using a) the three-component definition using the SGRQ (CID^{SGRQ}) and b) the three-component definition using the CAT (CID^{CAT})



This relationship was driven by **increased reduction in risk of moderate/severe exacerbation** events with FF/UMEC/VI versus UMEC/VI at higher blood eosinophil counts, as there was no detectable relationship between blood eosinophil counts and reduction in the risk of lung function or health status deterioration with FF/UMEC/VI versus UMEC/VI

Han MK, et al ERJ open research ;2021;7;00663-2020

Effects of Prior Exacerbation history and Eosinophil Count on Efficacy



Single moderate

Frequent moderate

Severe

FF/UMEC/VI reduce mod/severe Exacerbation

vs

UMEC/VI

- **single moderate 18%**
- **frequent moderate 29%**
- **severe 26%**

Halpin DMG;Eur Respir J;2020;55;1-12

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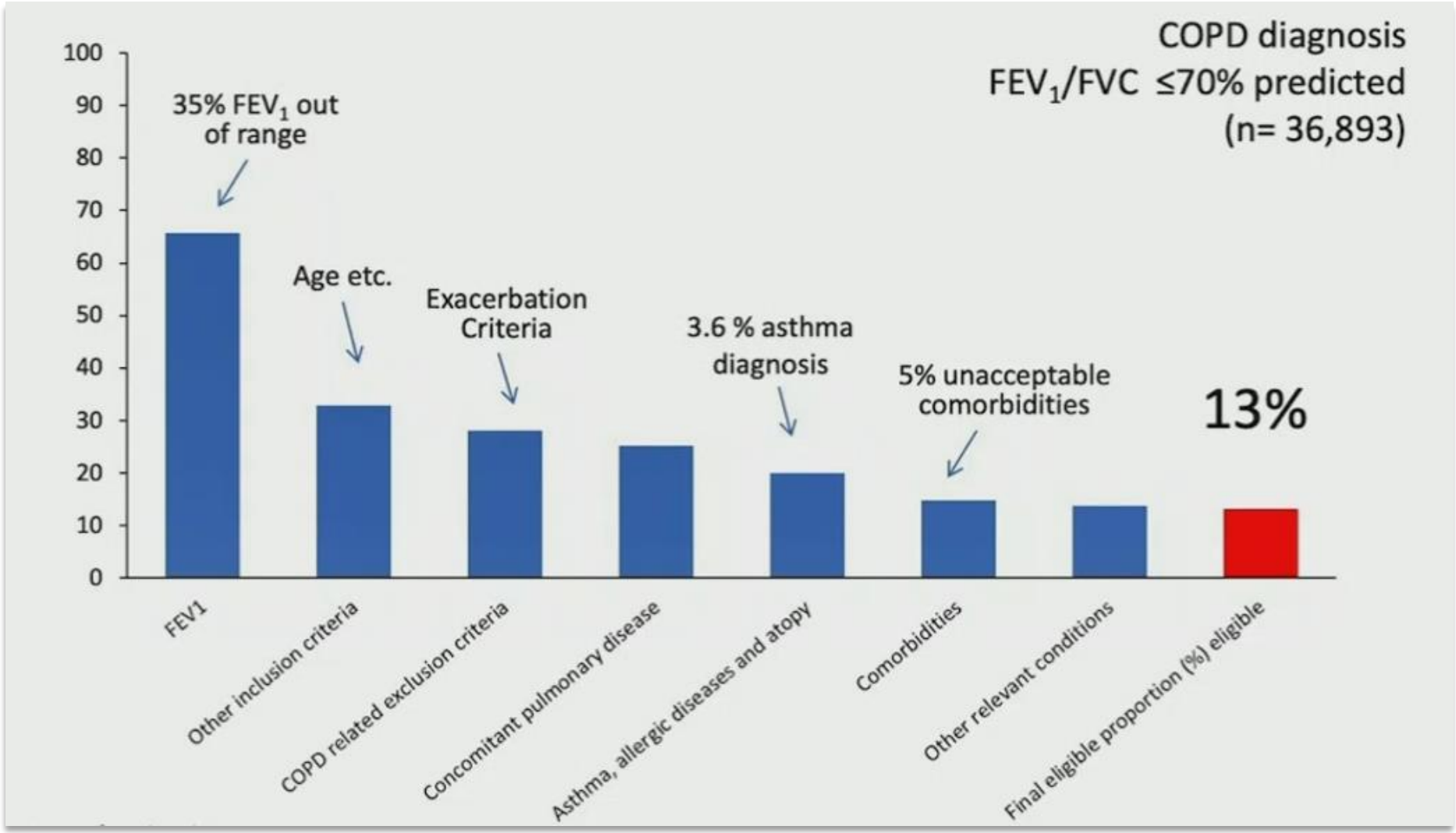
Patients in UK Primary Care of Dual Bronchodilator RCT Inclusion and Exclusion Criteria



Halpin et al. Resp Res 2016;17:120

Relationships among the explanatory clinical trials, observational study, and pragmatic clinical trials

Randomization
Comparability between patient groups

Continuum

Real-world evidence
Relative effectiveness of treatment in the real world

Prospective, blinded explanatory clinical trial

Pragmatic randomized clinical trial

Retrospective observational study

Reference: NY Jeong et, al. Cardiovasc Prev Pharmacother. 2020 Jul;2(3):85-98

Table 1. Comparison of the attributes that distinguish ECTs and PCTs

Feature	ECTs	PCTs
Question	Efficacy: does the intervention work under ideal setting?	Effectiveness: does the intervention benefit when used in routine practice?
Inclusion criteria of participants	Strict criteria to exclude high-risk or poorly adherent participants	Broader criteria to include various participants
Setting	Highly controlled experimental setting	Normal practice setting
Intervention	Thorough delivery and monitoring of intervention	Flexible delivery and monitoring of intervention
Comparator	Generally placebo control	Routine clinical treatment, mostly not placebo control
Outcomes	A restricted set of events or surrogated outcomes	A broad set of events or determined in the routine course of clinical practice
Sample size	Comparatively small	Comparatively large
Relevance to practice	Low relevance to practice	High relevance to practice
Follow-up period	Relatively short-term follow-up	Relatively long-term follow-up

ECT = explanatory clinical trial; PCT = pragmatic clinical trial.

The Clinical Effectiveness of Fluticasone Furoate/Umeclidinium Bromide/Vilanterol in a **Single** Inhaler (ELLIPTA)* when Compared with Non-ELLIPTA **Multiple** Inhaler Triple Therapies (MITT) in COPD Patients Within a Usual Care Setting

INTREPID

INVESTIGATION OF
TRELEGY
EFFECTIVENESS USUAL
PRACT**I**CE
DESIGN

- Sweden
- United Kingdom
- Netherlands
- Germany
- Spain

Reference: Halpin DMG;ERJ Open Research;2021;1-46

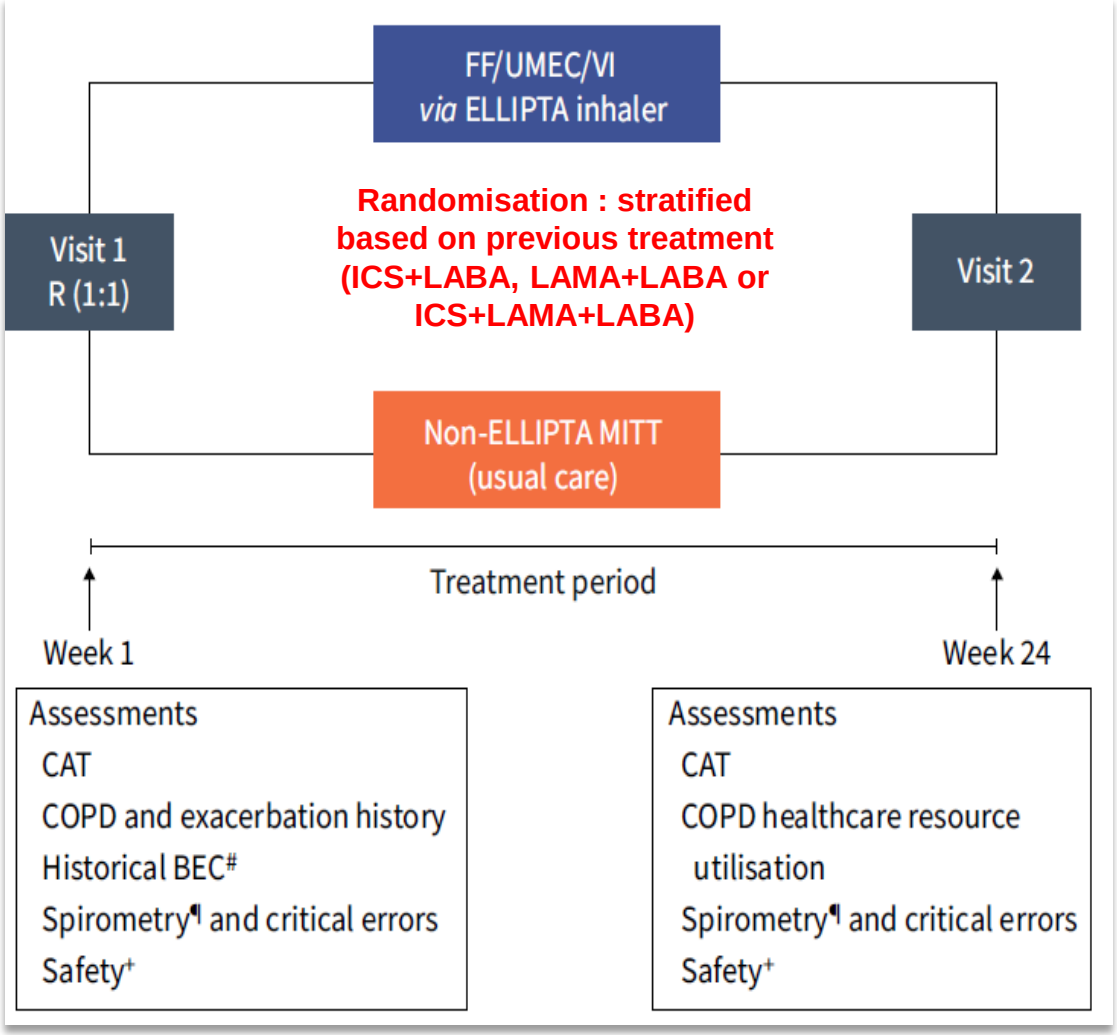
Study design

Randomised, open-label, parallel-group, multicentre, effectiveness Phase IV study of 24-weeks duration stratified by prior medication group

Patient population	
≥40 years of age and documented physician diagnosis of COPD	Patients receiving at least 60 days in the 16 weeks prior to randomisation non-Ellipta MITT or LAMA+LABA or ICS+LABA
At least one moderate/severe COPD exacerbation in the 3 years prior to randomisation	CAT ≥10

Limited exclusion criteria

- Recent history of life-threatening conditions
- Patients with resolution of an exacerbation <2 weeks prior to first visit
- Long-term use of oral corticosteroids



1. Halpin DMG;ERJ Open Research;2021;1-46
2. Worsley S;ERJ Open Research;2019;5;1-9

Study design: Endpoints

Primary endpoint

Proportion of responders based on the CAT at Week 24. Response defined as reduction from baseline of ≥2 points in CAT score at 24 weeks

Secondary endpoints

- **Change from baseline in FEV_1** at 24 weeks (in a subset of participants)
- Percentage of participants making at least **1 critical error** in inhalation technique at 24 weeks (in a subset of participants)

Safety

Examination of all SAEs, treatment-related AEs and AEs that lead to withdrawal from study or study treatment

- Other non-SAEs were not collected

Other endpoints

- Proportion of responders who experience a CID
- Annualised rate of moderate/severe exacerbations
- Time to first moderate/severe exacerbation

A&E, accident and emergency; AE, adverse event; CAT, COPD Assessment Test; CID, clinically important deterioration; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; HCRU, healthcare resource utilisation; SAE, serious adverse event

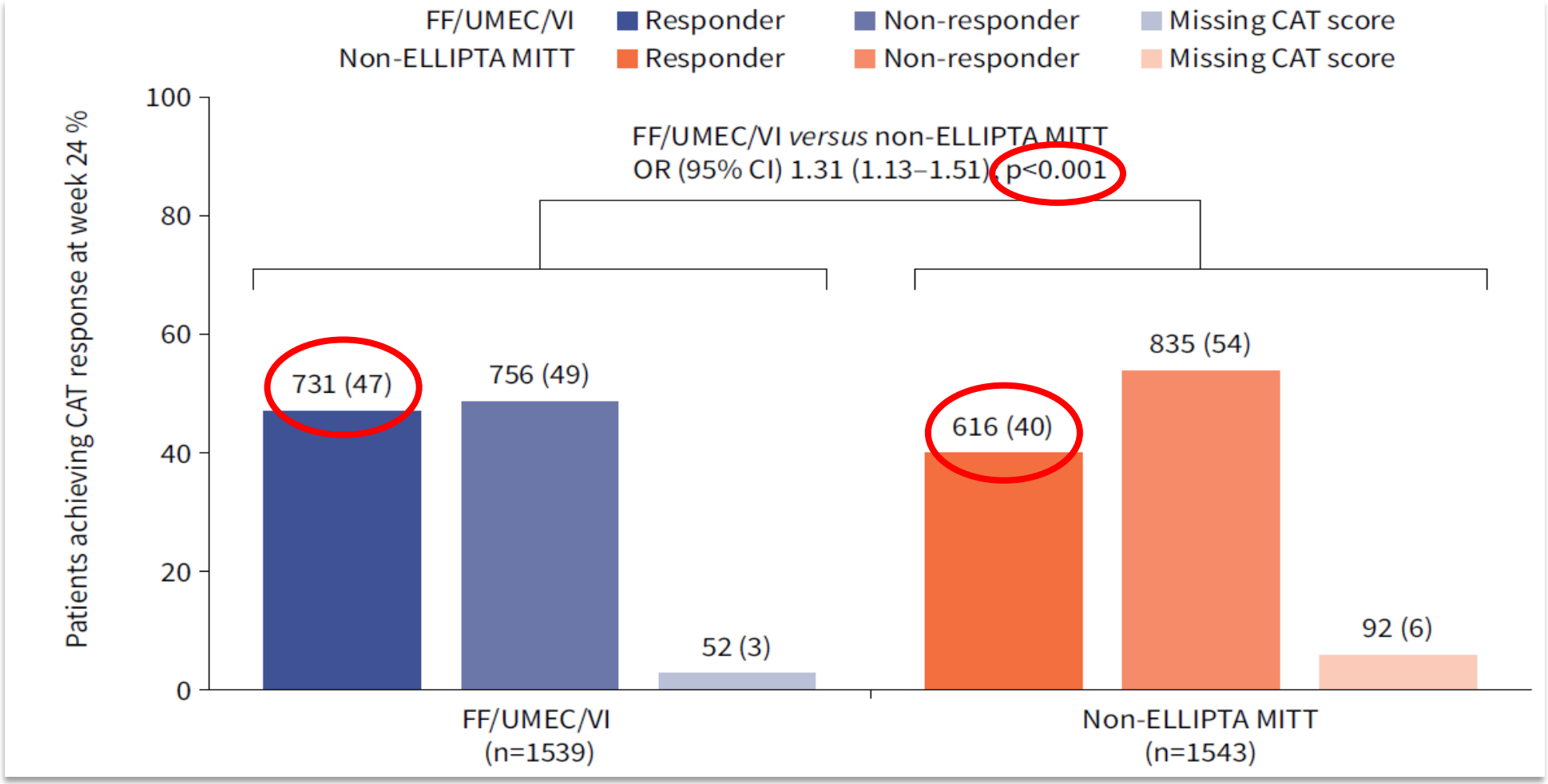
1. Halpin DMG;ERJ Open Research;2021;1-46
2. Worsley S;ERJ Open Research;2019;5;1-9

Summary of baseline demographics and disease characteristics

ITT population	FF/UMEC/VI (N=1545)	Non-Ellipta MITT (N=1547)	Total (N=3092)
Age (years), mean (SD)	67.8 (8.78)	67.8 (8.59)	67.8 (8.68)
Sex (% male)	837 (54%)	818 (53%)	1655 (54%)
Post-bronchodilator FEV_1 (L) (FEV_1 population)			
n	825	827	1652
Mean (SD)	1.474 (0.5653)	1.462 (0.5840)	1.468 (0.5746)
Post-bronchodilator percent predicted FEV_1, mean (SD) %	54.1 (18.49)	54.1 (18.58)	54.1 (18.53)
Reversibility to salbutamol, n (%)	174 (22)	186 (24)	360 (23)
Patients with moderate/severe COPD exacerbations in the prior 12 months			
0	363 (23%)	361 (23%)	724 (23%)
1	**615 (40%)**	**610 (39%)**	**1225 (40%)**
≥2	**567 (37%)**	**576 (37%)**	**1143 (37%)**
CAT score at screening			
n, mean (SD)	1543, 20.8 (6.76)	1547, 20.5 (6.62)	3090, 20.7 (6.69)
Prior medication use (Actual strata)			
ICS+LAMA+LABA	1226 (79%)	1235 (80%)	2461 (80%)
ICS+LABA	126 (8%)	126 (8%)	252 (8%)
LABA+LAMA	192 (12%)	183 (12%)	375 (12%)
Missing	1 (<1%)	3 (<1%)	4 (<1%)

Reference: Halpin DMG;ERJ Open Research;2021;1-46

Primary effectiveness endpoint % CAT responders at week 24: Primary endpoint (ITT population)



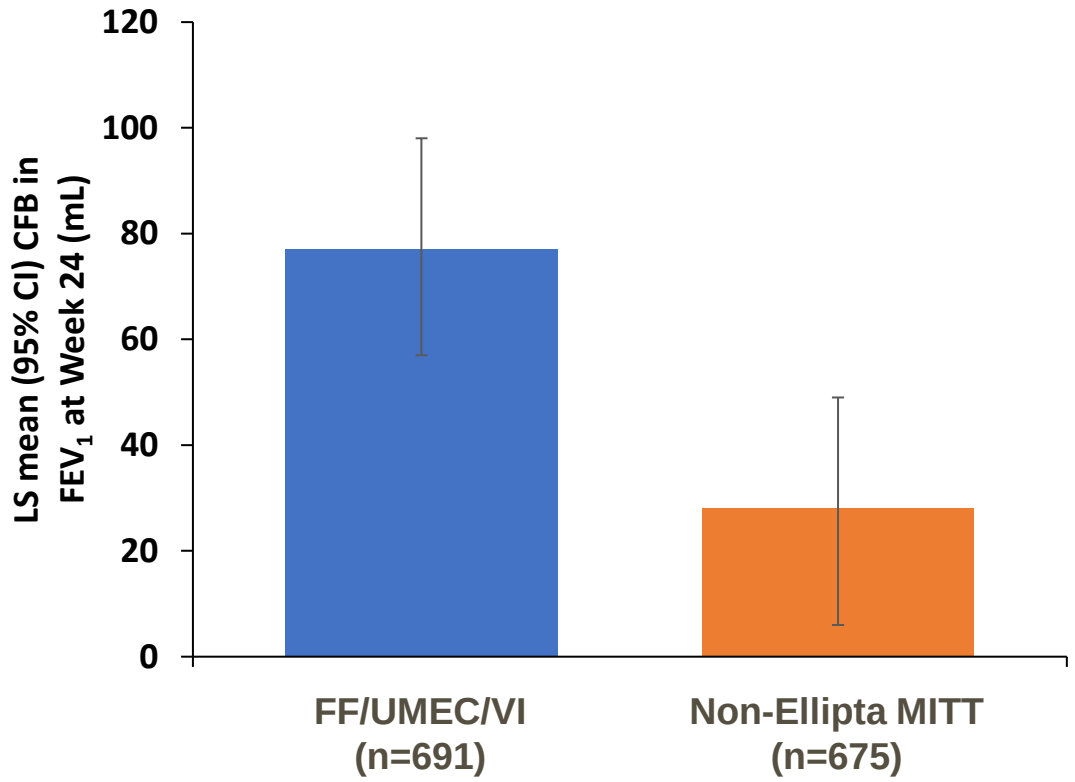
Reference: Halpin DMG;ERJ Open Research;2021;1-46

*Response defined as a CAT score of 2 units below baseline or lower.

FF/UMEC/VI significantly improved lung function versus non-ELLIPTA MITT at Week 24

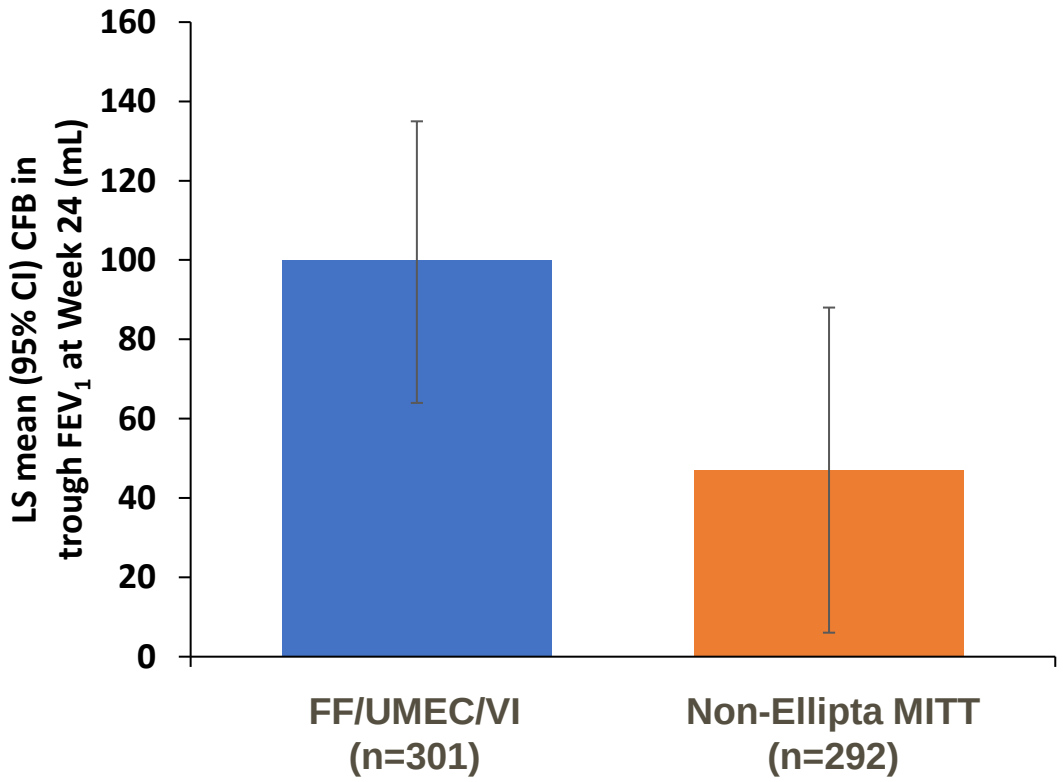
FEV_1

Difference (95% CI): 50 mL (26, 73); **P<0.001**



Trough FEV_1

Difference (95% CI): 53 mL (9, 96); **P=0.017**

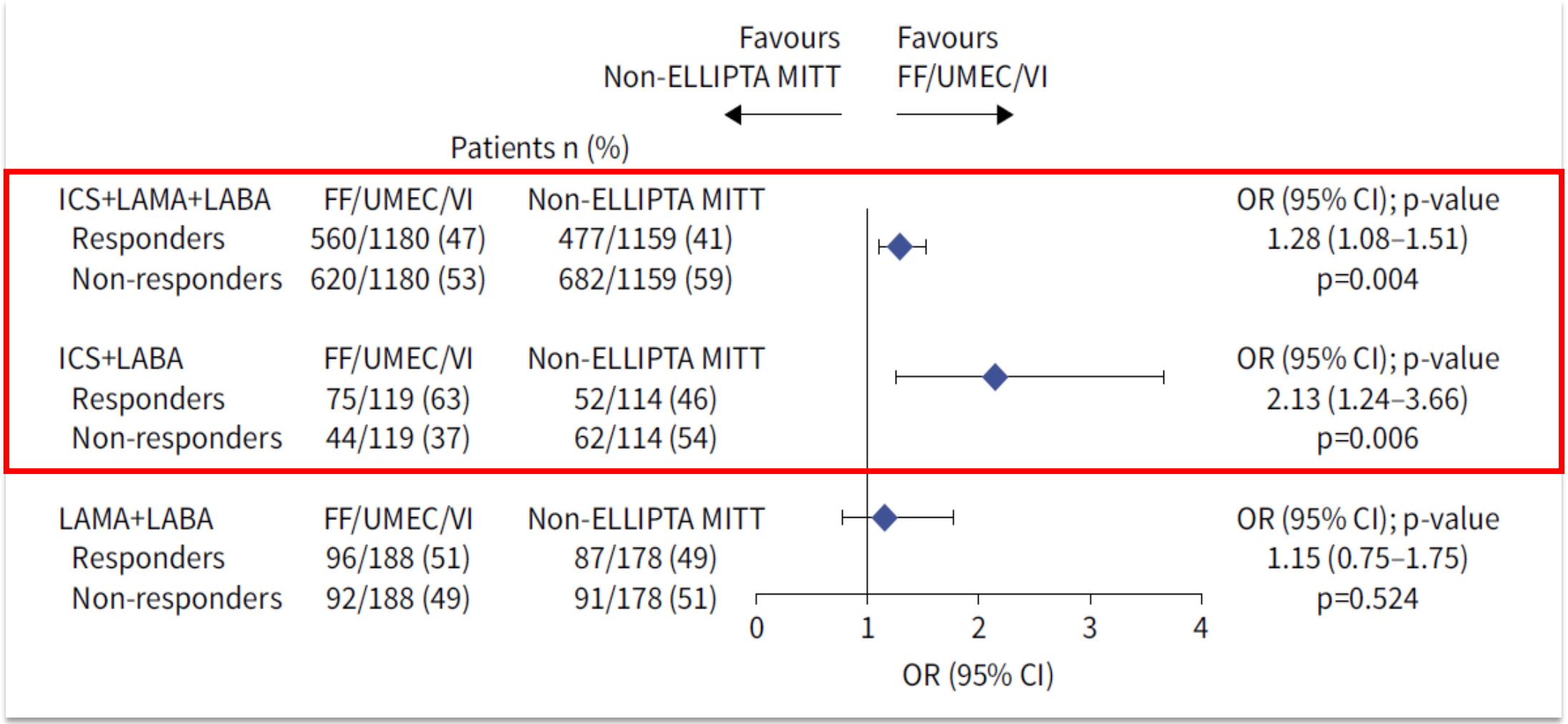


Reference: Halpin DMG;ERJ Open Research;2021;1-46

CFB, change from baseline; CI, confidence interval; FEV1, forced expiratory volume in 1 second; FF, fluticasone furoate; LS, least square; MITT, multiple-inhaler triple therapy; UMEC, umeclidinium; VI, vilanterol.

Consistent treatment effect across prior medication strata

CAT responders at Week 24 by actual prior medication strata



Reference: Halpin DMG;ERJ Open Research;2021;1-46

Critical Error secondary endpoint result % of patients with ≥1 critical error at Week 24 (critical error population)

No statistical difference between FF/UMEC/VI and usual care (p-value = 0.103)

There were unexpected low critical errors across inhalers, especially for non-Ellipta MITT arm

	FF/UMEC/VI (N=691)	Non-Ellipta MITT (N=267)
n	653	230
Patients with at least one critical error	38 (6%)	7 (3%)
Patients with no critical error	615 (94%)	223 (97%)
FF/UMEC/VI vs non-Ellipta MITT		
Odds ratio	1.99	
95% CI	(0.87, 4.53)	
p-value	0.103	

Reference: Halpin DMG;ERJ Open Research;2021;1-46

Estimand uses a hypothetical strategy. For patients who modified their randomised treatment and did not use the same devices as their randomised treatment we ignore any error assessment data recorded for that patient, and treat as missing data. If they are using the same devices then we are able to use their data. Missing data were not imputed

Incidence of on-randomized-treatment adverse events

FF/UMEC/VI showed a similar safety profile compared with non-Ellipta MITT regarding SAEs, including pneumonia

	FF/UMEC/VI		Non-ELLIPTA MITT	
	Patients n (%)	Events rate¶ (n)	Patients n (%)	Events rate¶ (n)
Patients n	1545		1547	
Total duration at risk patient-years	636.7		685.8	
Any adverse event	250 (16)	590.6 (376)	151 (10)	322.2 (221)
Any treatment-related adverse event	145 (9)	329.8 (210)	44 (3)	77.3 (53)
Any adverse event leading to study withdrawal	115 (7)	279.6 (178)	32 (2)	70.0 (48)
Any SAE	114 (7)	257.6 (164)	114 (7)	255.2 (175)
Any treatment-related SAE	13 (<1)	20.4 (13)	6 (<1)	10.2 (7)
Any fatal SAE	8 (<1)	20.4 (13)	8 (<1)	23.3 (16)
Any treatment-related fatal SAE	0	0	0	0
Serious AESIs				
Cardiovascular effects	29 (2)	55.0 (35)	23 (1)	39.4 (27)
Decreased BMD and associated fractures	6 (<1)	9.4 (6)	4 (<1)	7.3 (5)
Infective pneumonia	27 (2)	44.0 (28)	32 (2)	46.7 (32)
LRTI excluding infective pneumonia	7 (<1)	11.0 (7)	10 (<1)	14.6 (10)

Reference: Halpin DMG;ERJ Open Research;2021;1-46

Note: n=number of patients, #=number of events
Note: Rate is event rate per 1000 patient-years, calculated as the number of events x 1000, divided by the total duration at risk

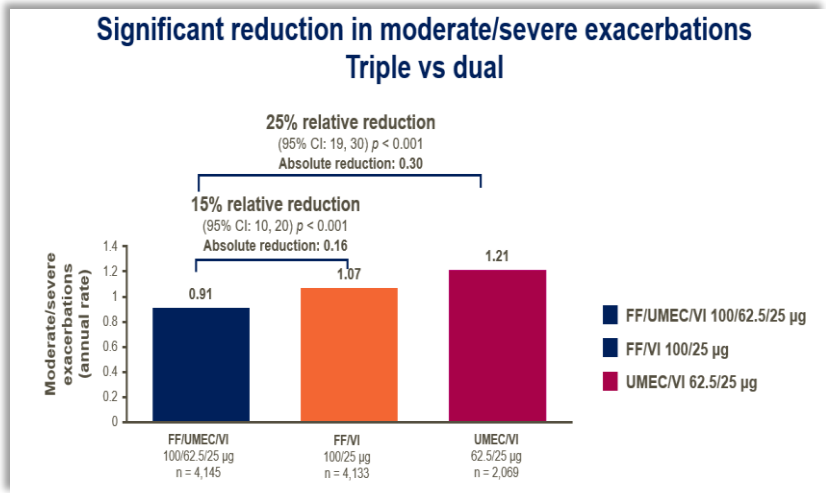
INTREPID : Conclusions

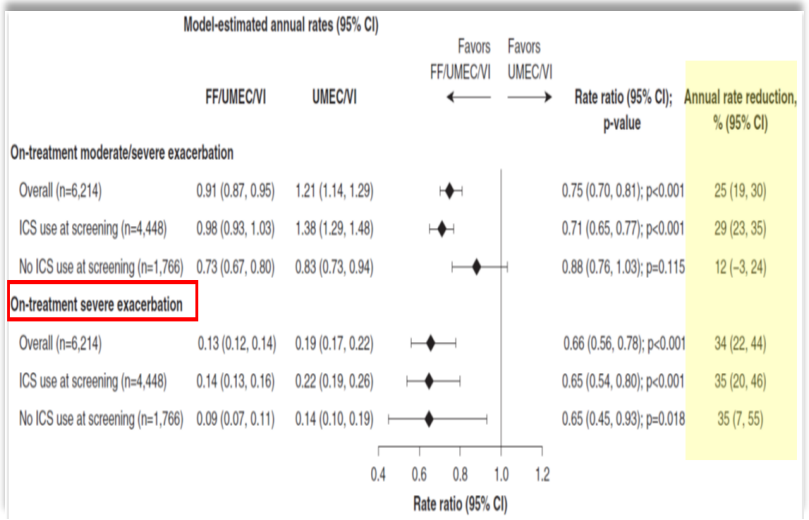
In the usual clinical care setting, treatment with single-inhaler FF/UMEC/VI resulted in significantly more patients achieving **health status improvement and greater lung function** benefit versus non-ELLIPTA MITT, with a similar safety profile

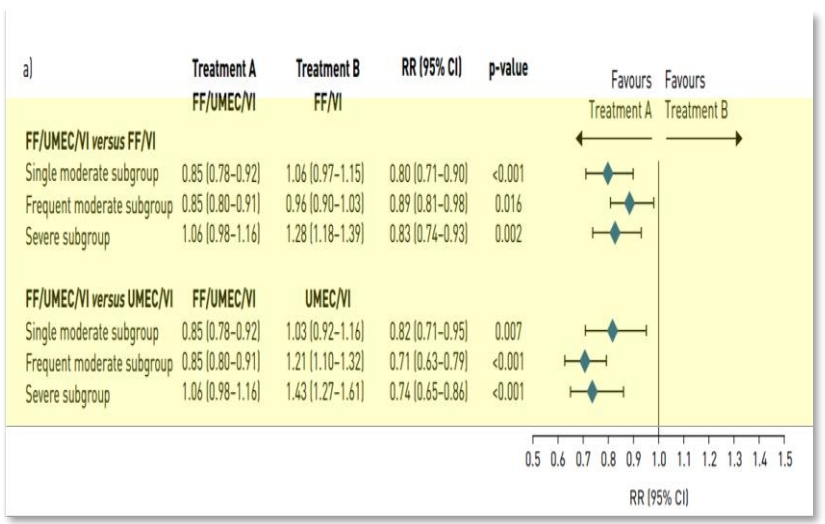
This pragmatic study broadens the understanding of the effectiveness of FF/UMEC/VI beyond the traditional RCT setting, into real-world clinical practice

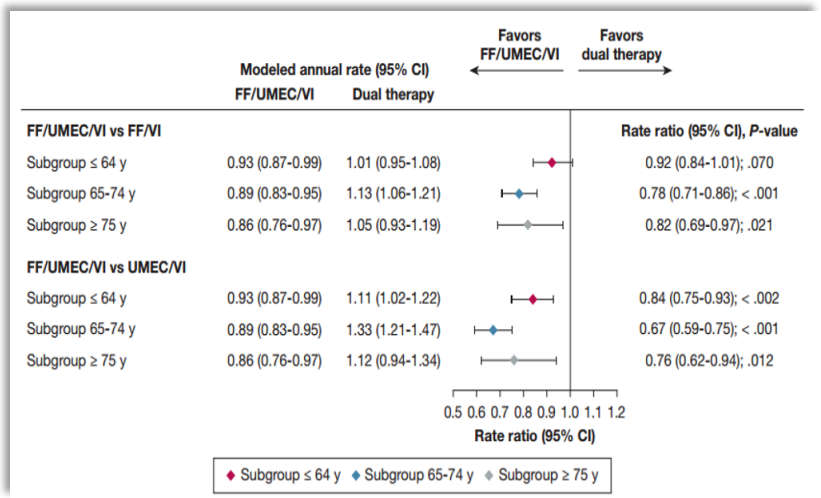
Reference: Halpin DMG;ERJ Open Research;2021;1-46

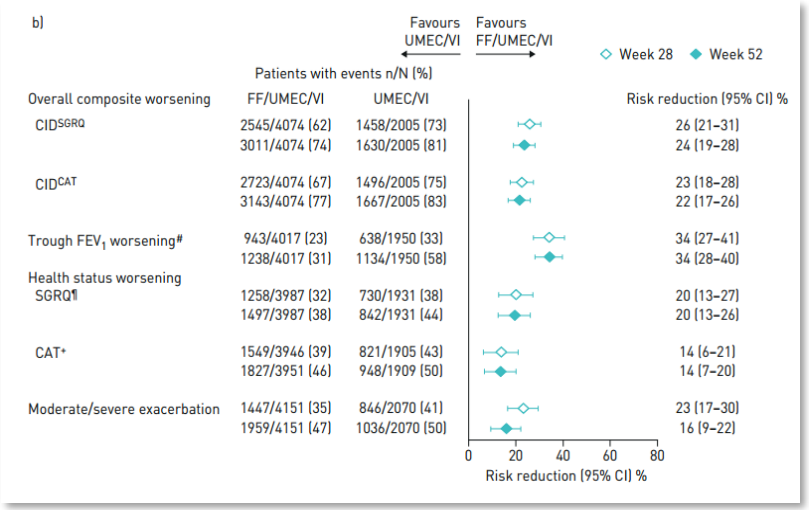
Summary: Role of Triple Therapy in COPD treatment

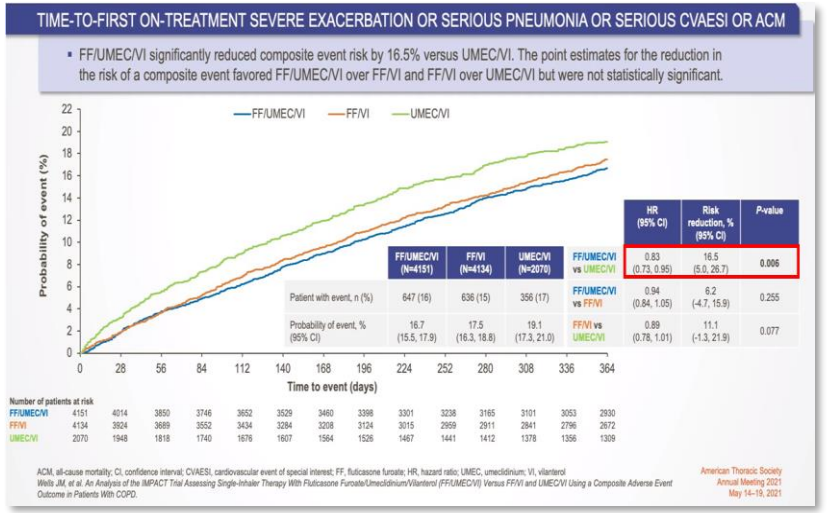






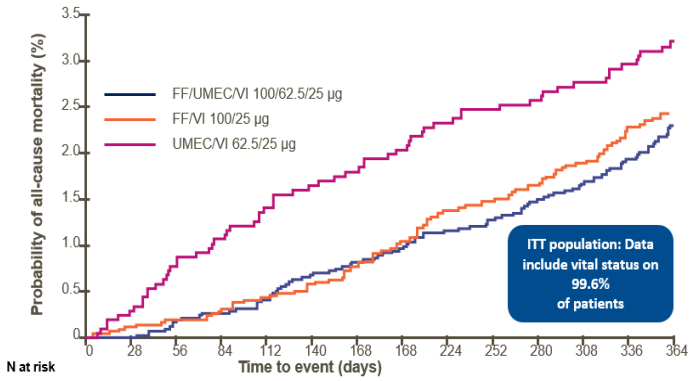


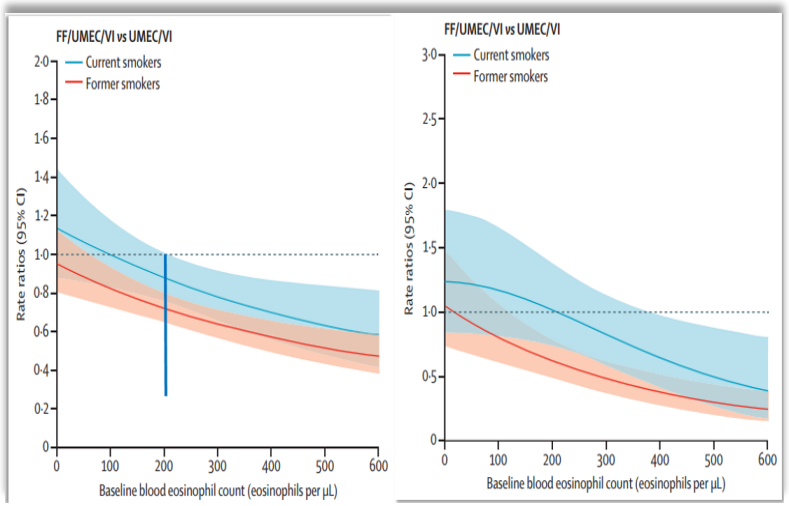


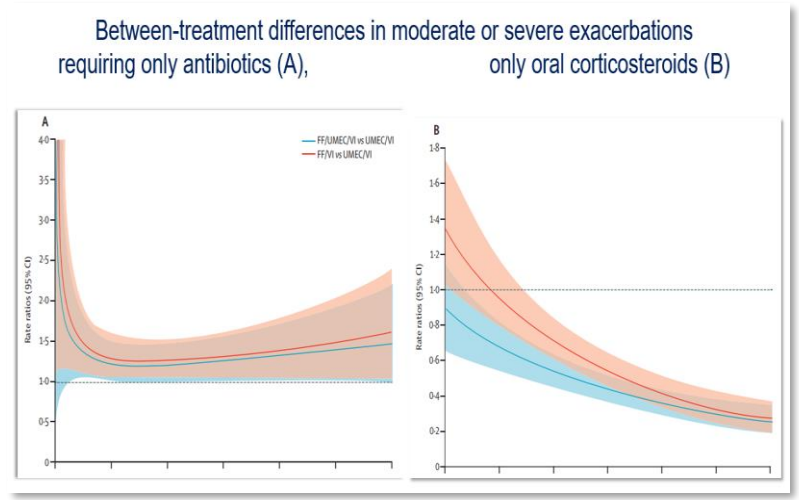


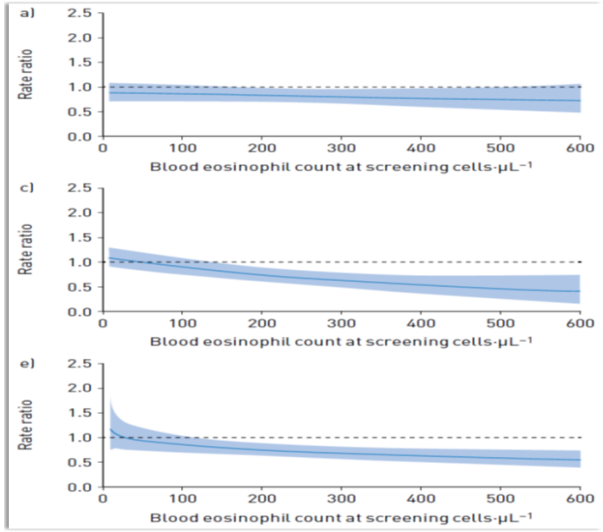
Summary: Role of Triple Therapy in COPD treatment

Post hoc analysis on/off-treatment All-cause mortality









Single moderate

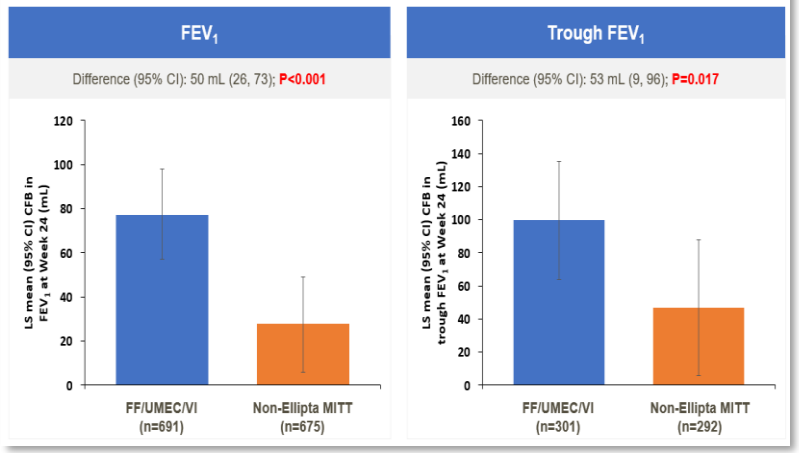
Frequent moderate

Severe

Primary effectiveness endpoint % CAT responders at week 24: Primary endpoint (ITT population)

	FF/UMEC/VI (N=1545)	Non-Ellipta MITT (N=1547)
n	1539	1543
CAT score at week 24 (Mean ± SD)	18.0 ± 8.0	19.1 ± 7.9
Change from baseline in CAT score at Week 24	-2.8 ± 6.3	-1.3 ± 6.0
Responder*	731 (47%)	616 (40%)
FF/UMEC/VI vs non-Ellipta MITT in CAT responders		
Odds ratio	1.31	
95% CI	(1.13, 1.51)	
p-value	<0.001	

FF/UMEC/VI significantly improved lung function versus non-ELLIPTA MITT at Week 24



THANK YOU FOR YOUR ATTENTION !