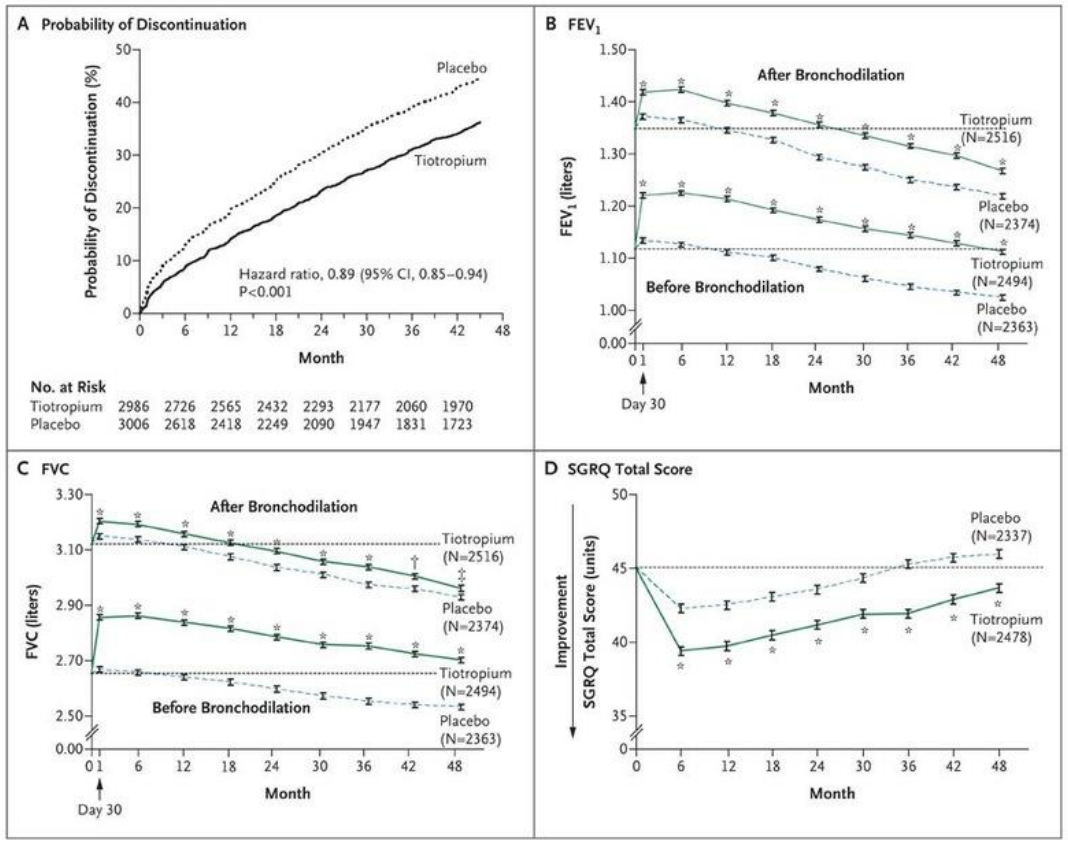
Triple therapy in COPD

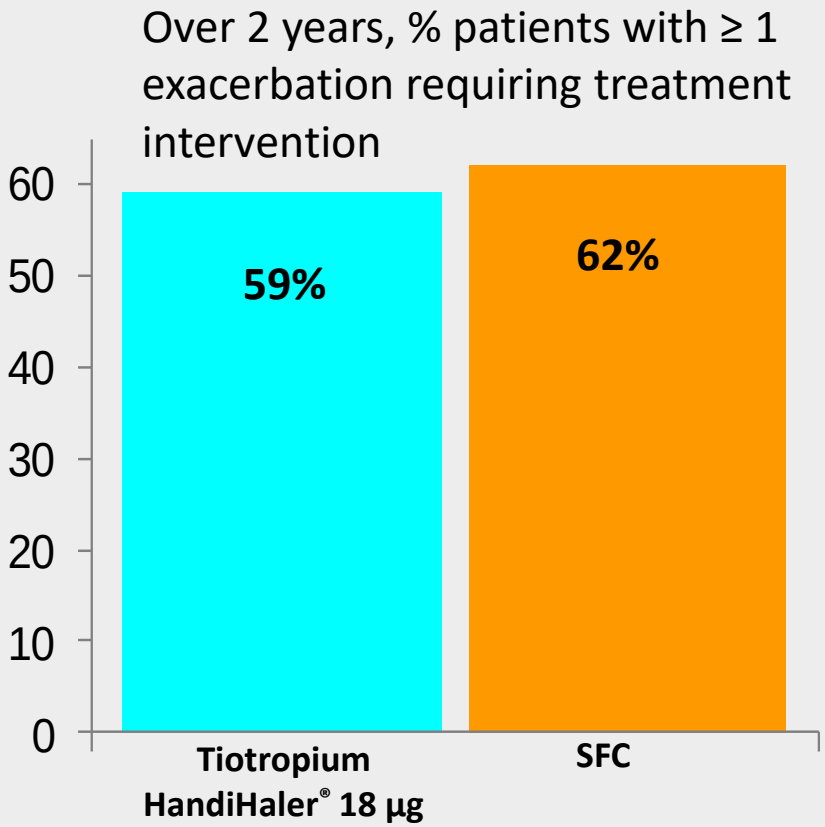
서울의대 윤호일

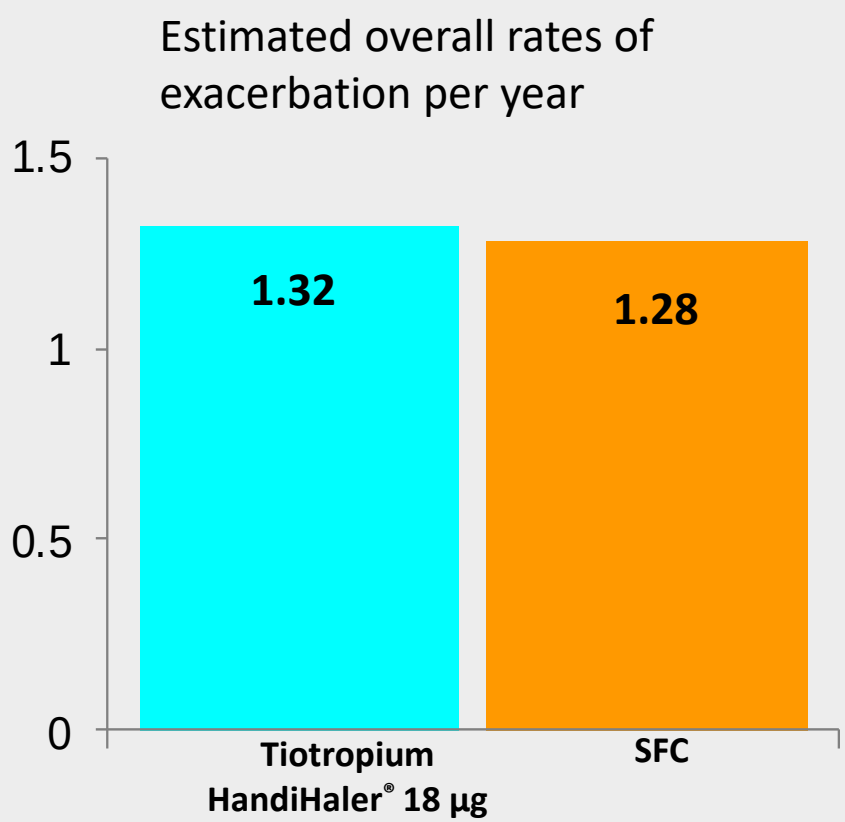
TORCH (ICS/LABA VS. ICS or LABA)



	Placebo	Salmeterol	Fluticasone	Salm + Flut
Moderate or severe exacerbations (no./pt./year)	1.13	0.97	0.93	0.85
Rate ratio		0.85	0.82	0.75
(95% CI)		(0.78-0.93)	(0.76-0.89)	(0.69-0.81)
Versus placebo				
Severe requiring hospitalization (no./pt./year)	0.19	0.16	0.17	0.16
Rate ratio		0.82	0.88	0.83
(95% CI)		(0.69-0.96)	(0.74-1.03)	(0.71-0.98)
Versus placebo				

INSPIRE (LABA VS LABA+ICS) :EXACERBATION RATES

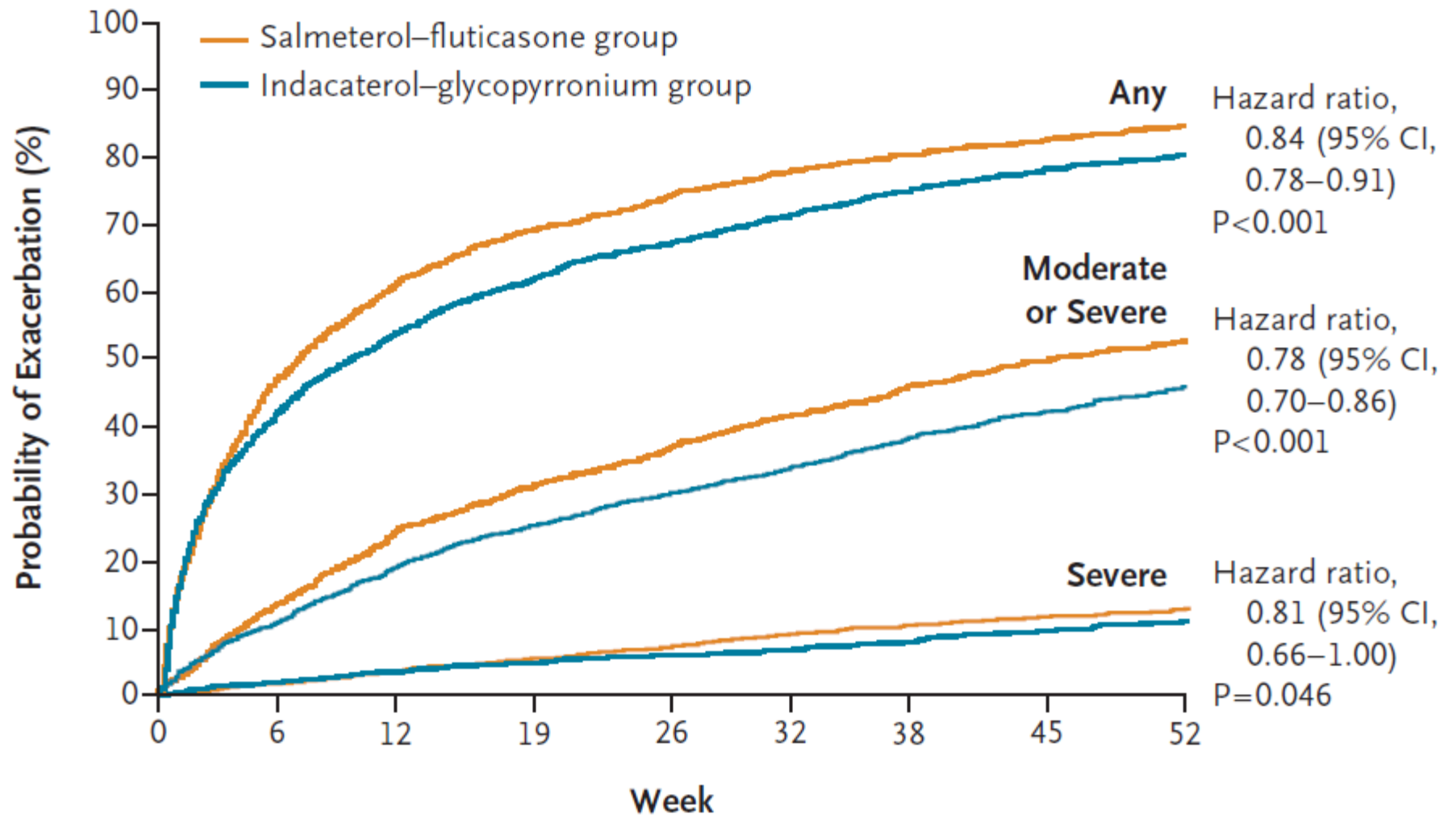




Ratio rates 0.967, (95% CI, 0.836-1.119), P=0.656
No difference between exacerbation rates/year

Wedzicha JA, et al. *Am J Respir Crit Care Med.* 2008;177:19-26.

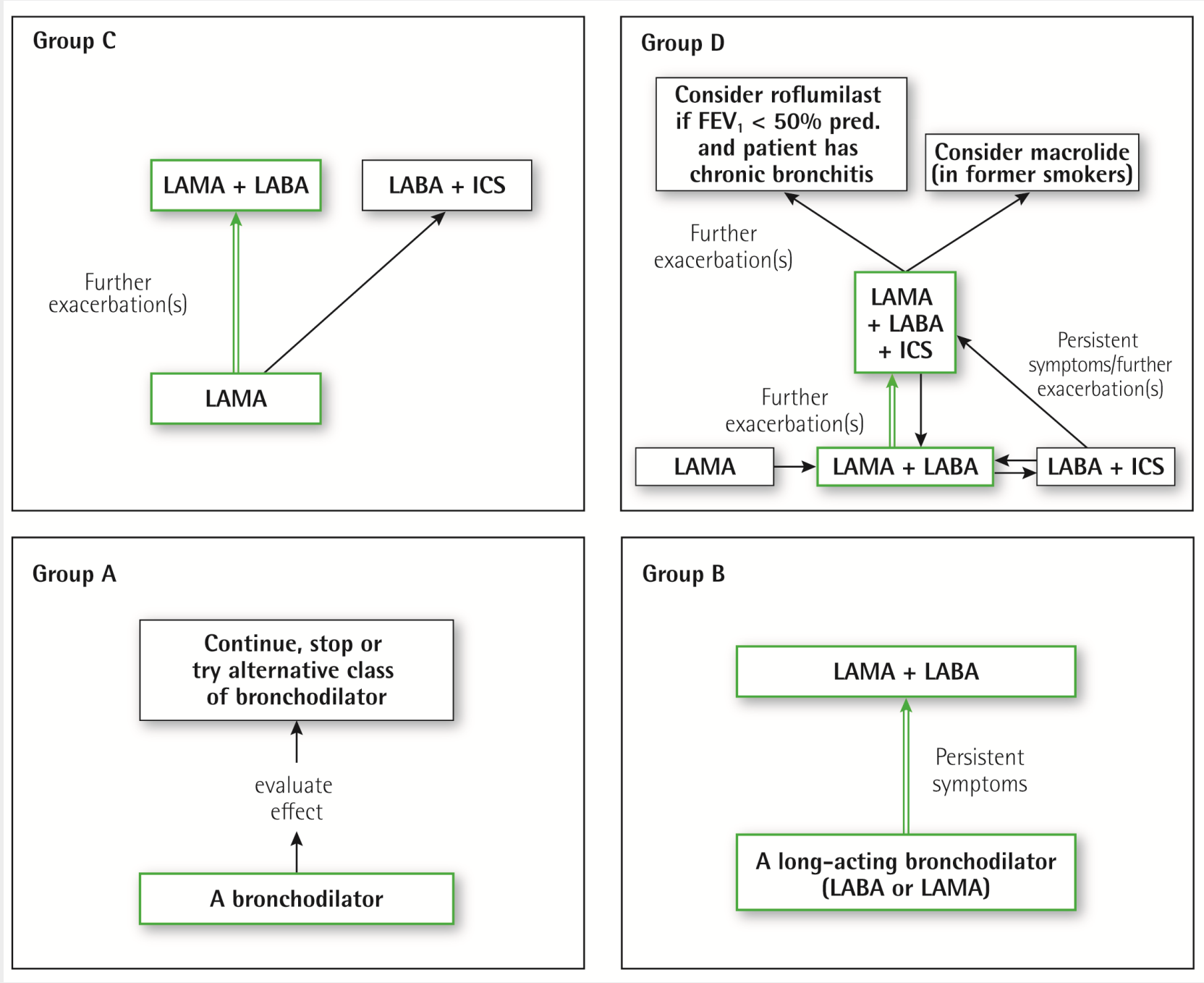
FLAME : LAMA/LABA VS. ICS/LABA



Wedzicha et al NEJM 2016

Reducing exacerbation

- ICS/LABA > LABA or ICS (TORCH)
- ICS/LABA = LAMA (INSPIRE)
- LAMA/LABA > ICS/LABA (FLAME)


Group C
LAMA + LABA
LABA + ICS
Further exacerbation(s)
LAMA
Group D
Consider roflumilast if FEV1 < 50% pred. and patient has chronic bronchitis
Consider macrolide (in former smokers)
Further exacerbation(s)
LAMA + LABA + ICS
Persistent symptoms/further exacerbation(s)
Further exacerbation(s)
LAMA
LAMA + LABA
LABA + ICS
Group A
Continue, stop or try alternative class of bronchodilator
evaluate effect
A bronchodilator
Group B
LAMA + LABA
Persistent symptoms
A long-acting bronchodilator (LABA or LAMA)

Reducing exacerbation

- ICS/LABA > LABA or ICS (TORCH)
- ICS/LABA = LAMA (INSPIRE)
- LAMA/LABA > ICS/LABA (FLAME)
- ICS/LAMA/LABA ? LAMA/LABA or ICS/LABA

TRILOGY, TRINITY, TRIBUTE

Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β_2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial

Dave Singh, Alberto Papi, Massimo Corradi, Ilona Pavlišová, Isabella Montagna, Catherine Francisco, Géraldine Cohuet, Stefano Vezzoli, Mario Scuri, Jørgen Vestbo

Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial

Jørgen Vestbo, Alberto Papi, Massimo Corradi, Viktor Blazhko, Isabella Montagna, Catherine Francisco, Géraldine Cohuet, Stefano Vezzoli, Mario Scuri, Dave Singh

Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial

Alberto Papi, Jørgen Vestbo, Leonardo Fabbri, Massimo Corradi, Hélène Prunier, Géraldine Cohuet, Alessandro Guasconi, Isabella Montagna, Stefano Vezzoli, Stefano Petruzzelli, Mario Scuri, Nicolas Roche, Dave Singh**

TRILOGY, TRINITY, TRIBUTE

	TRILOGY	TRINITY	TRIBUTE
Study	BDP/FF/GB	BDP/FF/GB	BDP/FF/GB
Control	BDP/FF	TIO BDP/FF+TIO	IND/GLY
n	1360	2600	1600
duration	52w	52w	52w
Primary outcome	FEV1	exacerbation	exacerbation

TRILOGY, TRINITY, TRIBUTE

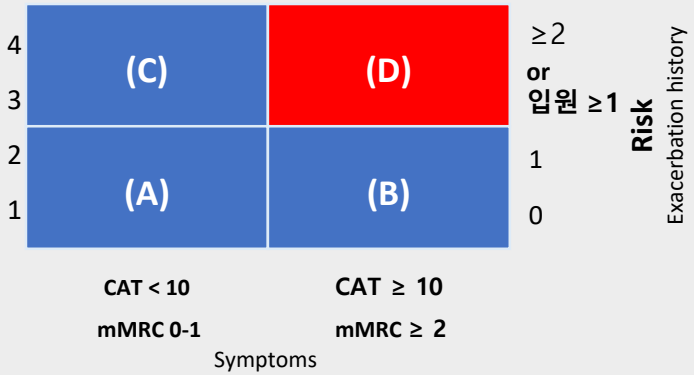
Inclusion criteria

- Age 40+ and COPD diagnosis
- FEV_1 < 50% + ≥1 moderate or severe exacerbations in the 12 months
- Patients under double therapy for at least 2 months prior to screening
- Symptomatic patients at screening with a CAT score ≥10

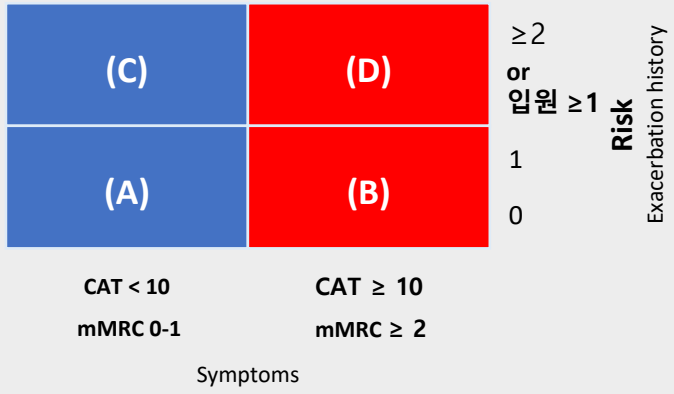
Exclusion criteria

- Already on triple therapy (ICS/LABA/LAMA)
- Diagnosis of asthma or history of allergic rhinitis or atopy
- COPD exacerbation in the 4 weeks before screening or during the run-in period
- Clinically significant CV conditions or laboratory abnormalities

2016 GOLD



2017 GOLD



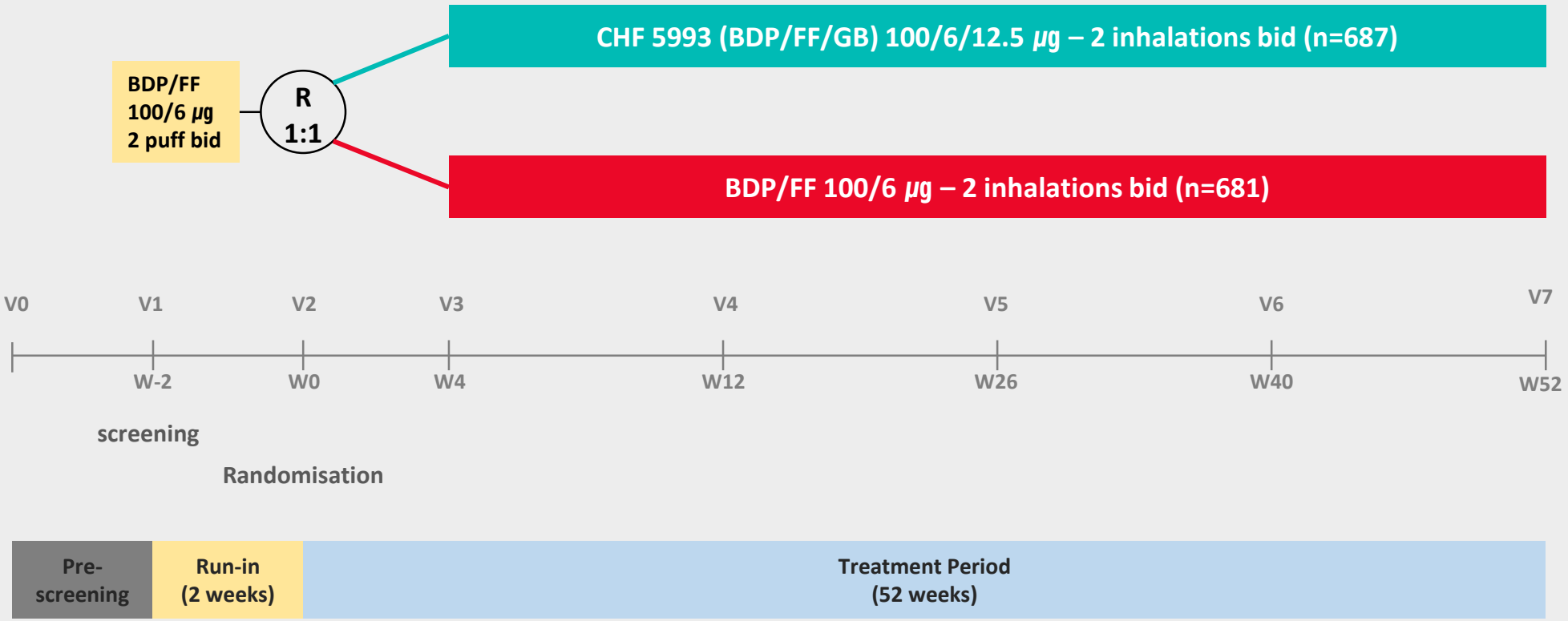
Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β_2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial

Dave Singh, Alberto Papi, Massimo Corradi, Ilona Pavlišová, Isabella Montagna, Catherine Francisco, Géraldine Cohuet, Stefano Vezzoli, Mario Scuri, Jørgen Vestbo

Singh et al. Lancet 2016; 388: 963–73

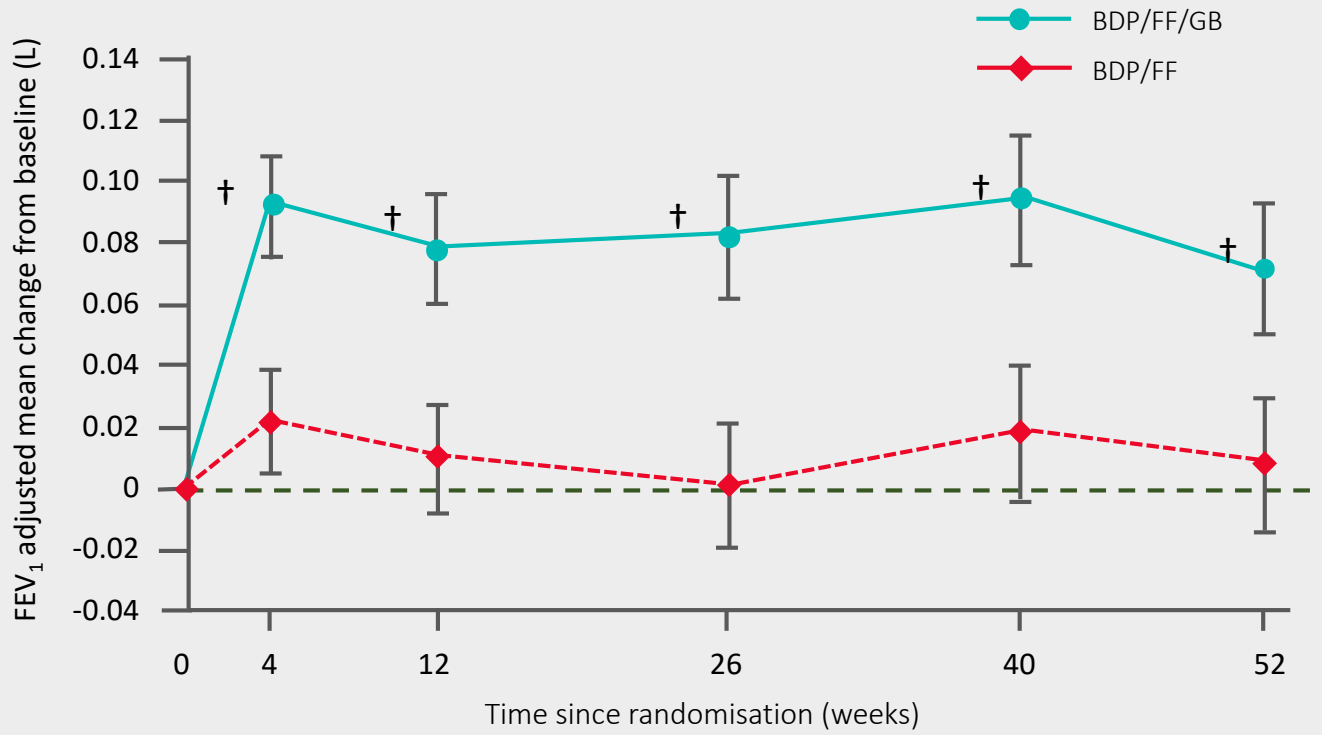
TRILOGY

Double-blind, randomized, multinational, multicentre, 2-arm parallel-group, active-controlled study



Primary endpoint: Lung Function

Pre-dose FEV_1



Number with available measurements

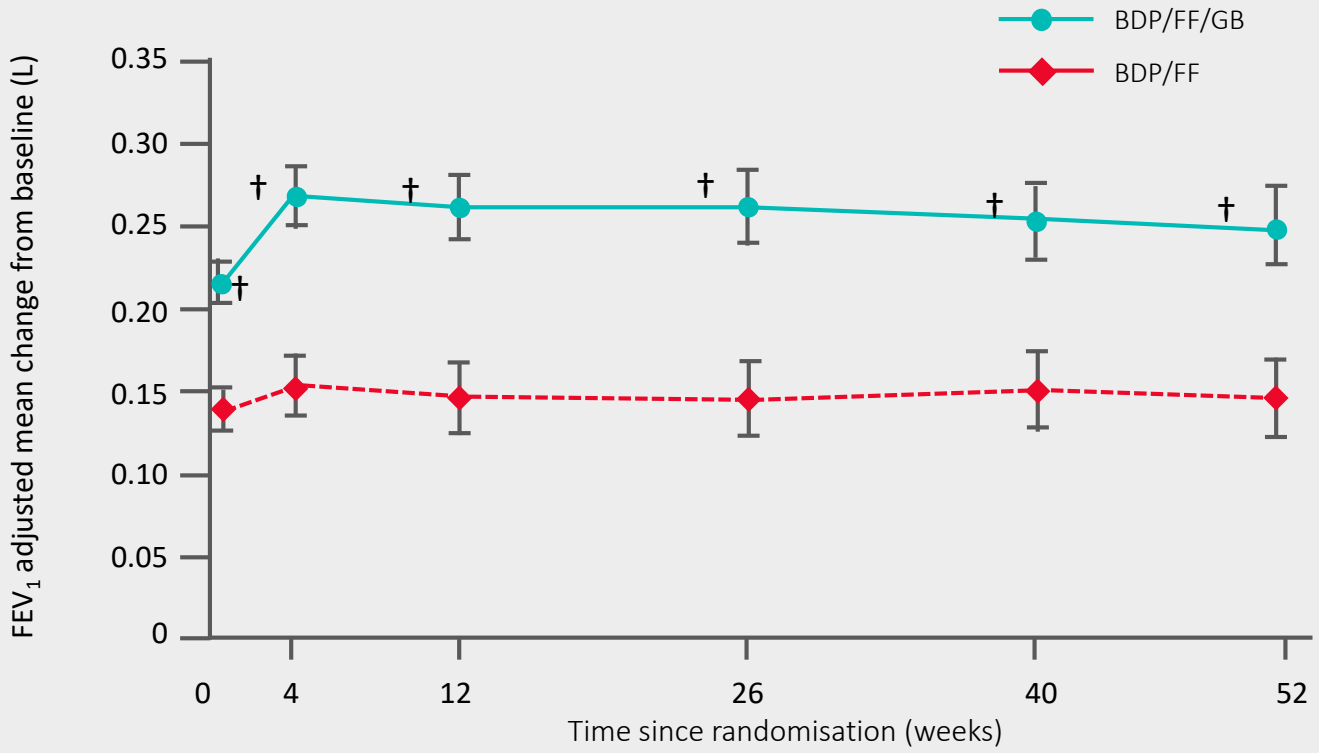
BDP/FF/GB	686	679	660	642	622	606
BDP/FF	679	669	654	616	597	578

	BDP/FF/GB	BDP/FF	Adjusted mean difference between treatments	P value
Baseline	1.096 (0.381)	1.094 (0.393)	-	-
Week 26	0.082 (0.062 to 0.102)	0.001 (-0.019 to 0.021)	**0.081** (0.052 to 0.109)	P<0.001
Week 52	0.071 (0.050 to 0.093)	0.008 (-0.014 to 0.030)	0.063 (0.032 to 0.094)	P<0.001

†p<0·001 for the difference between BDP/FF/GB and BDP/FF

Primary endpoint: Lung Function

2-h post-dose FEV_1



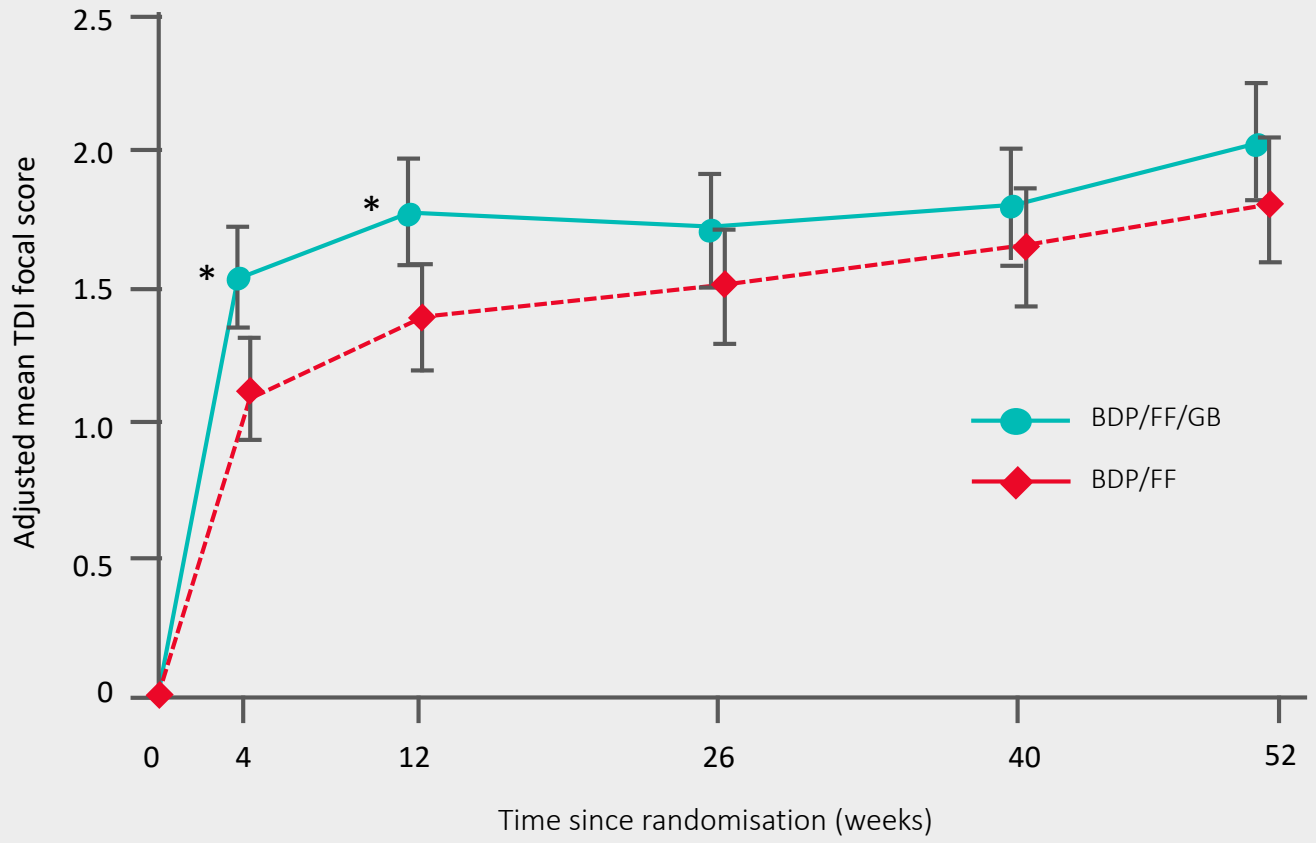
Number with available measurements

BDP/FF/GB	683	675	657	631	615	598
BDP/FF	674	660	648	609	590	575

	BDP/FF/GB	BDP/FF	Adjusted mean difference between treatments	P value
Week 26	0.26 (0.240 to 0.283)	0.145 (0.123 to 0.166)	0.117 (0.086 to 0.147)	P<0.001
Week 52	0.249 (0.226 to 0.273)	0.146 (0.122 to 0.170)	0.103 (0.069 to 0.137)	P<0.001

†p<0·001 for the difference between BDP/FF/GB and BDP/FF

Primary endpoint: TDI focal score



Number with available measurements

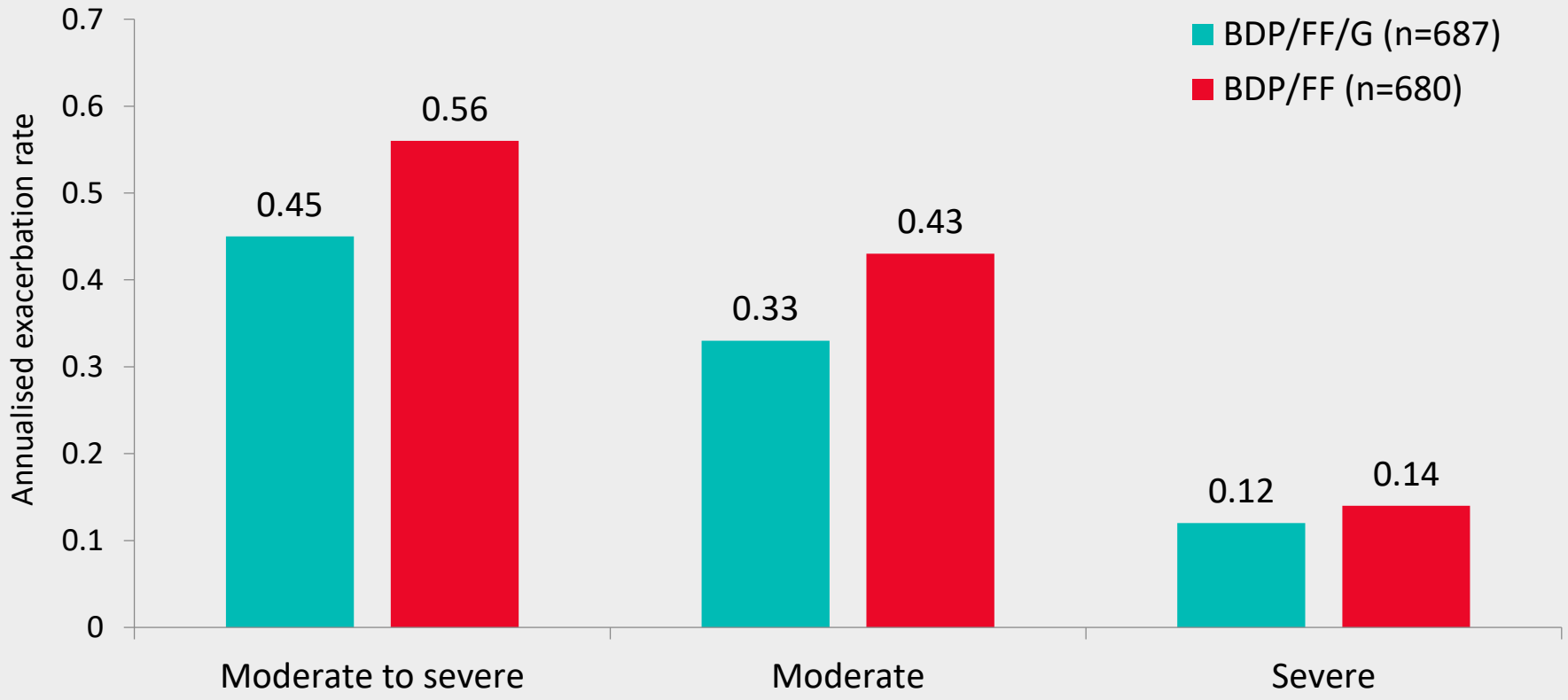
BDP/FF/GB	687	680	661	642	622	608
BDP/FF	680	672	651	619	596	579

	BDP/FF/GB	BDP/FF	Adjusted mean difference between treatments	P value
BDI# focal score	5.27 (1.81)	5.45 (1.82)	-	-
TDI focal score at week 26	1.71 (1.50 to 1.92)	1.50 (1.2 to 1.71)	**0.21** (-0.08 to 0.51)	P=0.160
TDI focal score at week 52	2.03 (1.81 to 2.25)	1.81 (1.59 to 2.04)	0.21 (-0.10 to 0.53)	P=0.186

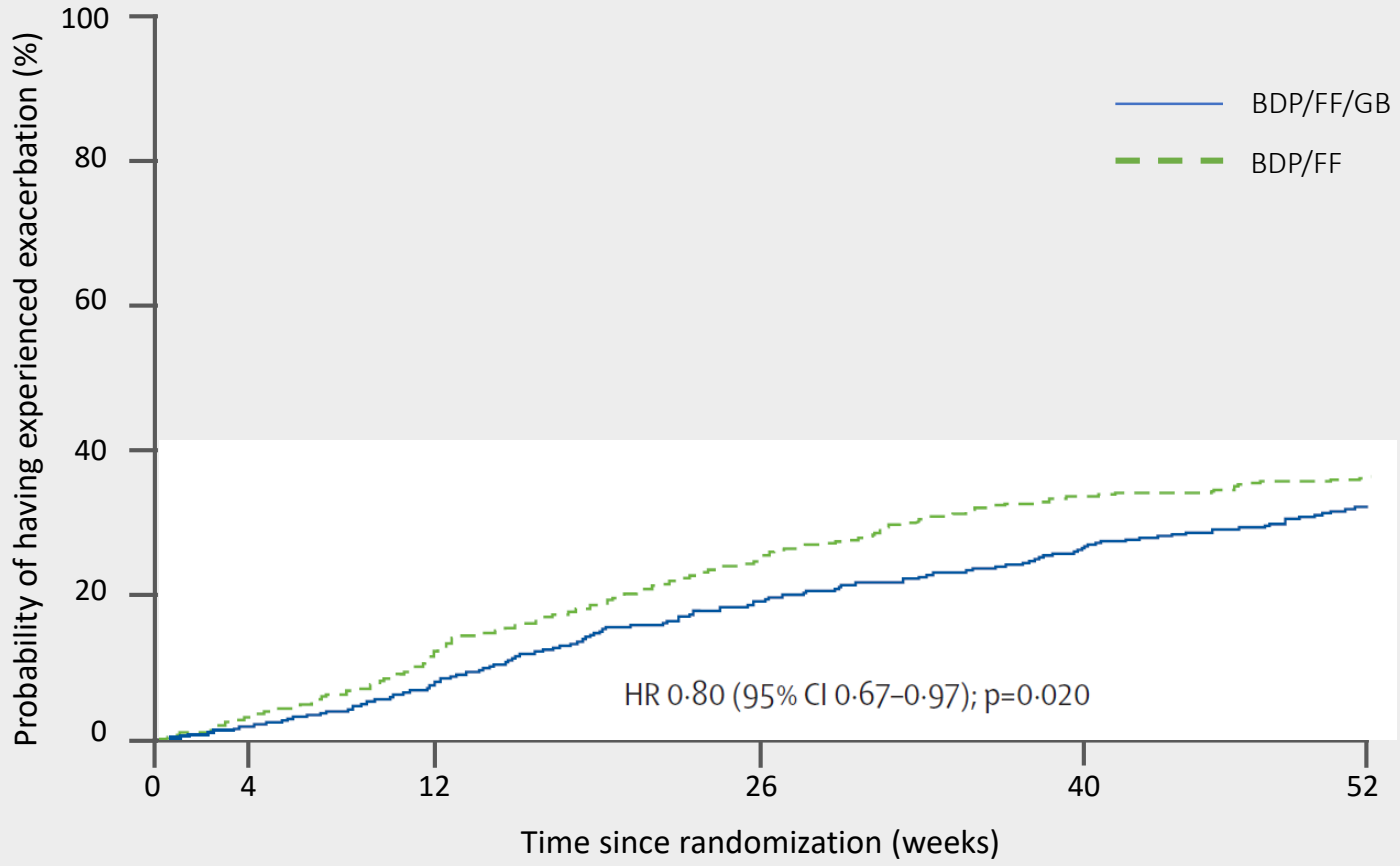
*p<0·01 for the difference between BDP/FF/GB and BDP/FF

#BDI focal score is the baselie value from which TDI focal score is assessed

Secondary endpoint: Moderate/severe COPD exacerbation rate

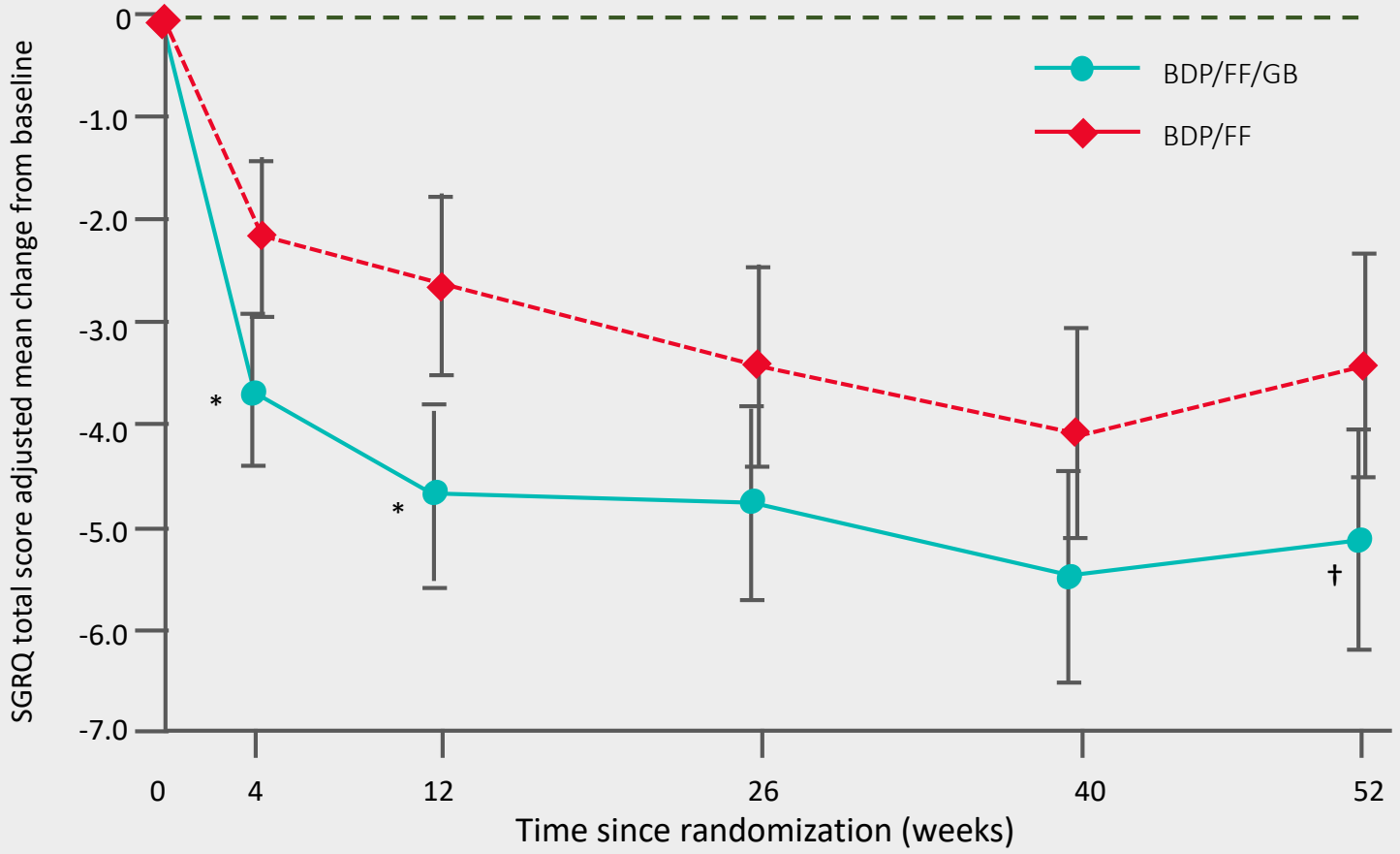


Secondary endpoint: Time to first moderate/severe exacerbation



Number with available measurements						
BDP/FF/GB	687	669	620	528	465	292
BDP/FF	680	649	588	483	414	265

Secondary endpoint: adjusted mean change from baseline in SGRQ total score



Number with available measurements

BDP/FF/GB	658	628	601	594	572	559
BDP/FF	644	607	597	558	545	532

*p<0·01 for the difference between BDP/FF/GB and BDP/FF
†p<0·05 for the difference between BDP/FF/GB and BDP/FF

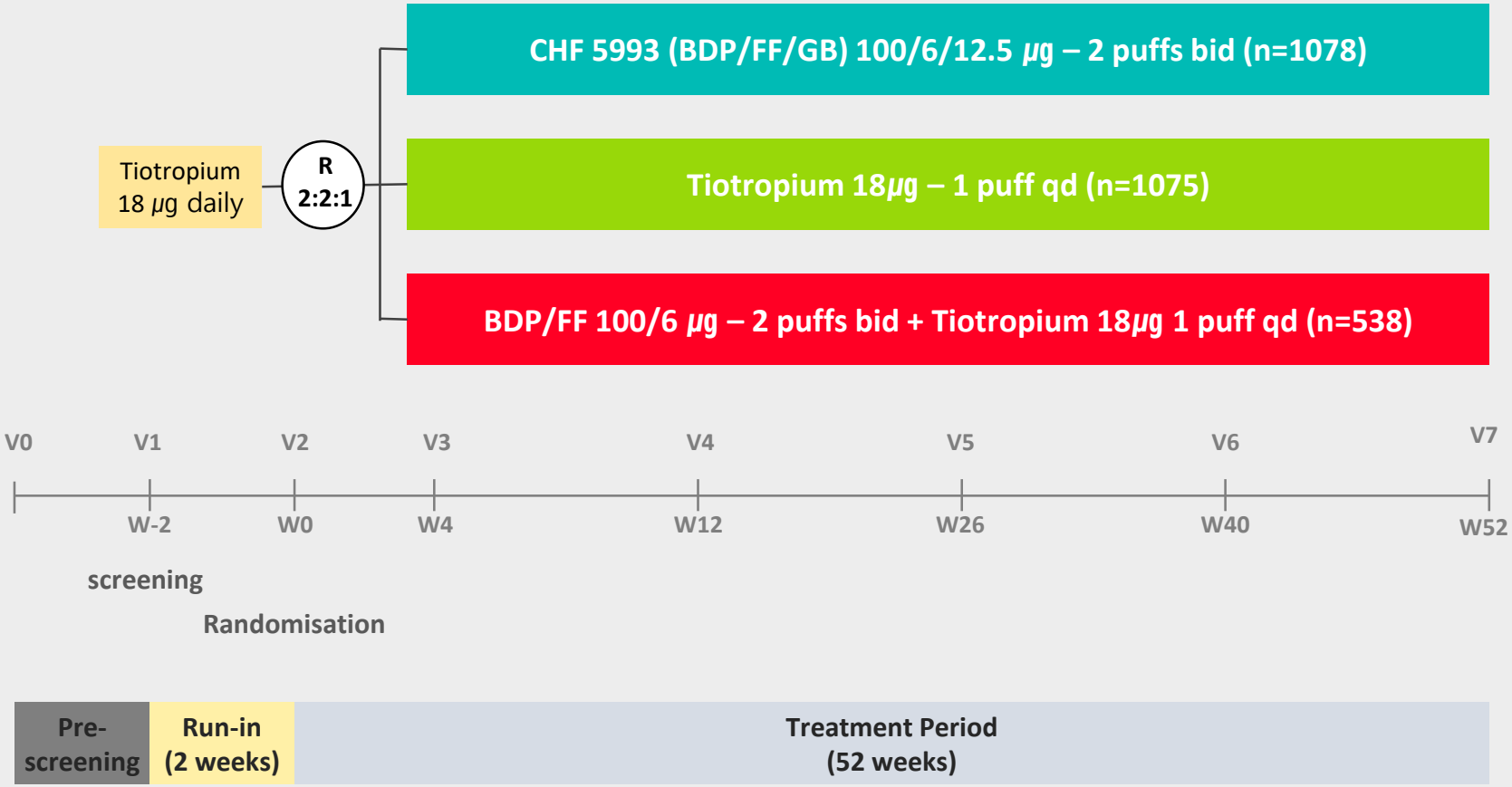
Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial

Jørgen Vestbo, Alberto Papi, Massimo Corradi, Viktor Blazhko, Isabella Montagna, Catherine Francisco, Géraldine Cohuet, Stefano Vezzoli, Mario Scuri, Dave Singh

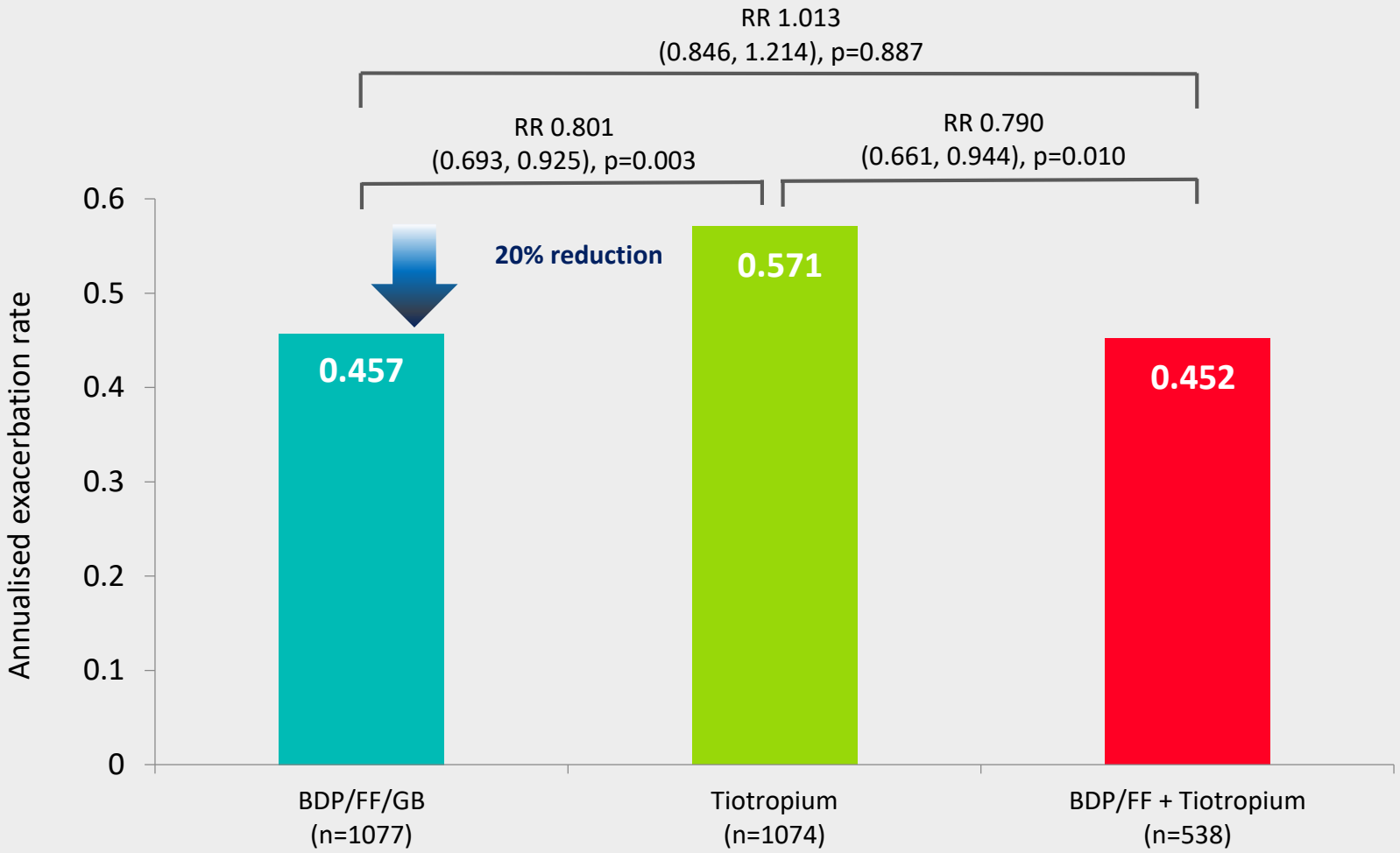
Vestbo et al, Lancet 2017; 389: 1919–29

TRINITY

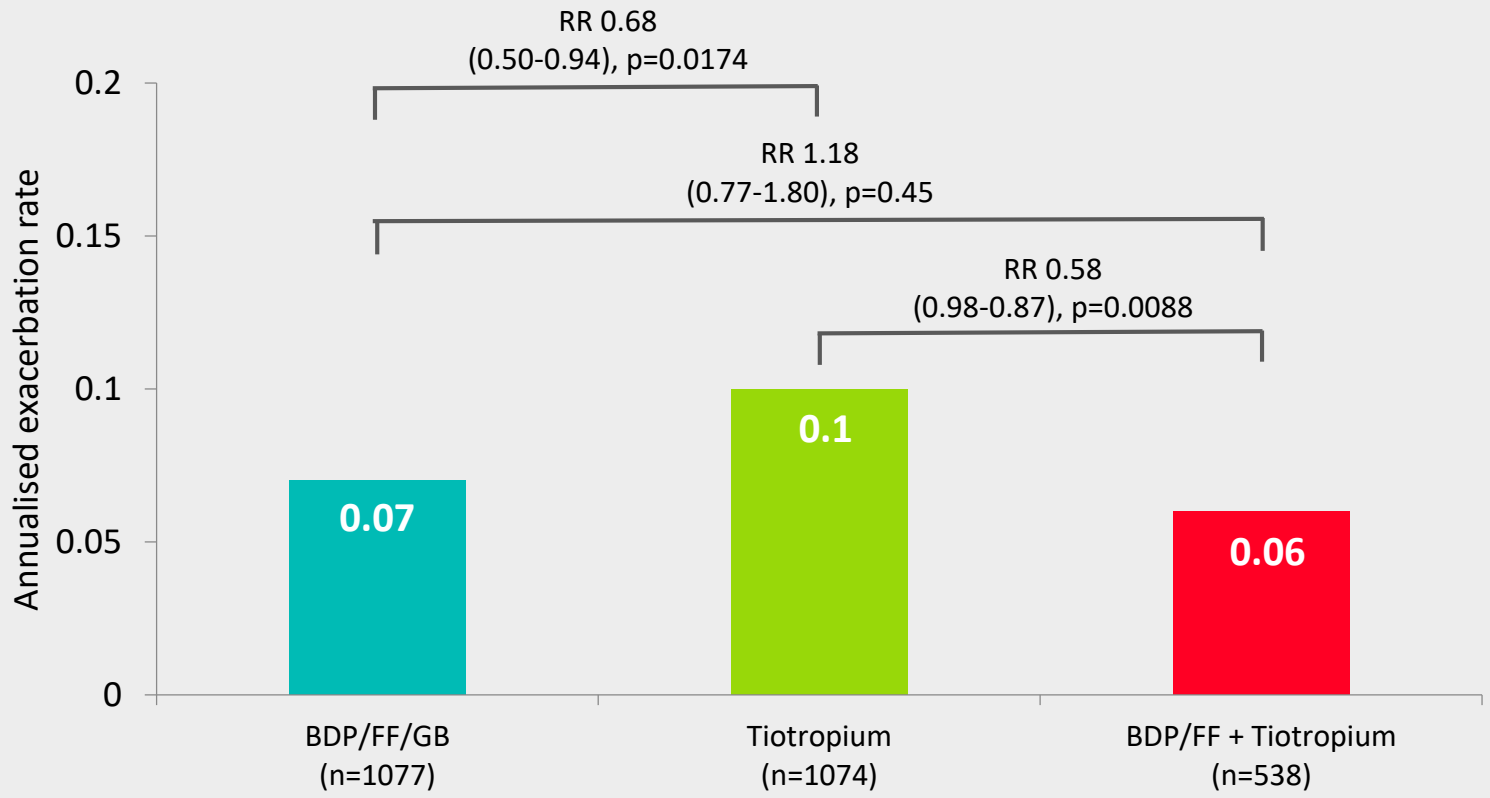
Double-blind, double dummy, randomized, multinational, multicentre, 3-arm parallel-group, active-controlled study



Moderate/severe COPD exacerbation rate

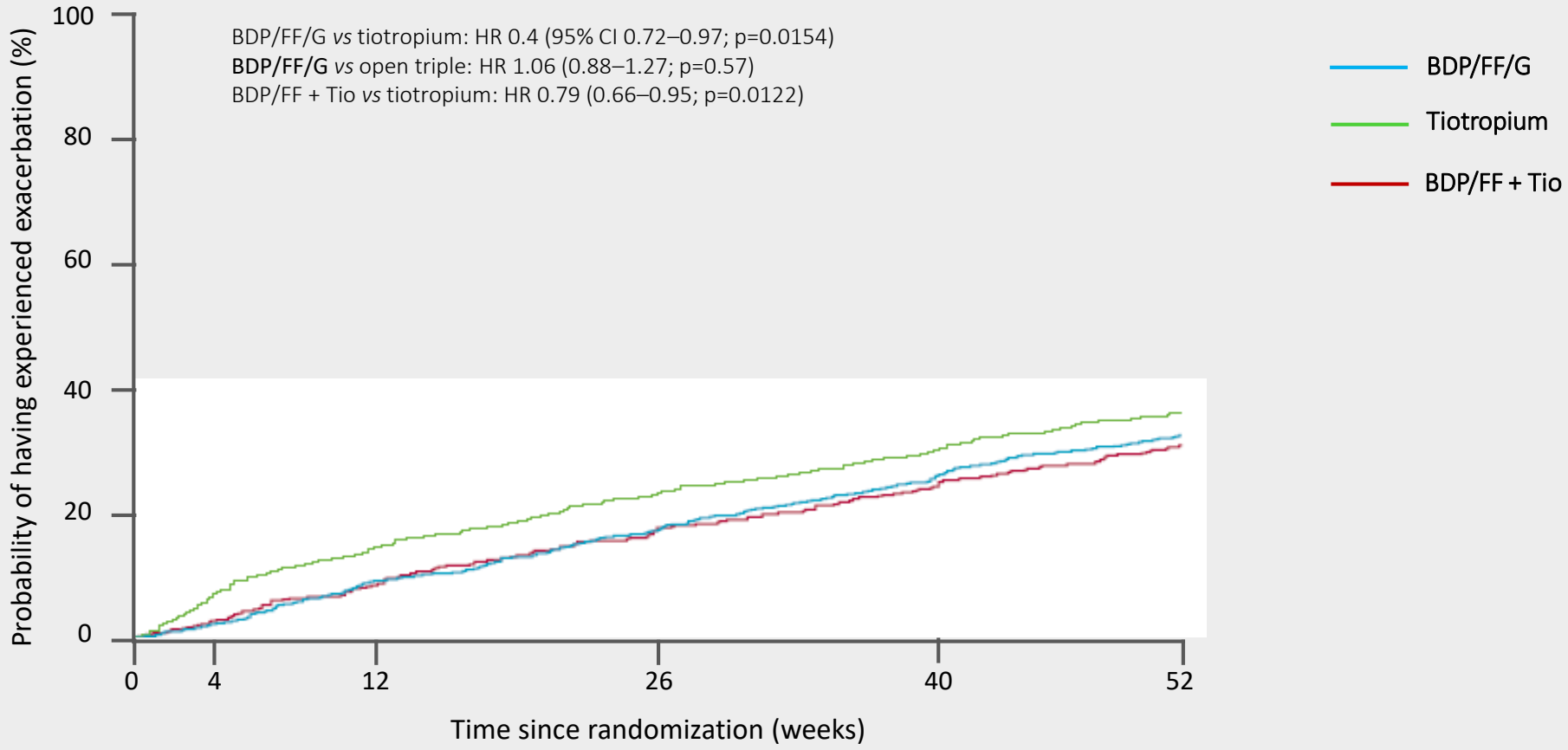


Severe COPD exacerbation rate



	BDP/FF/G	Tiotropium	BDP/FF + Tiotropium
No. of exacerbations	88	120	39
No.(%) of patients with exacerbations	75 (7.0%)	99 (9.2%)	35 (6.5%)
Adjusted rate (per pts/year)	0.067	0.098	0.057
Adjusted rate ratio vs. Tio	0.68 (0.49, 0.93) p=0.017		0.58 (0.38, 0.87) p=0.009
Adjusted rate ratio vs. BDP/FF + Tio	1.18 (0.77, 1.80) p=0.447		

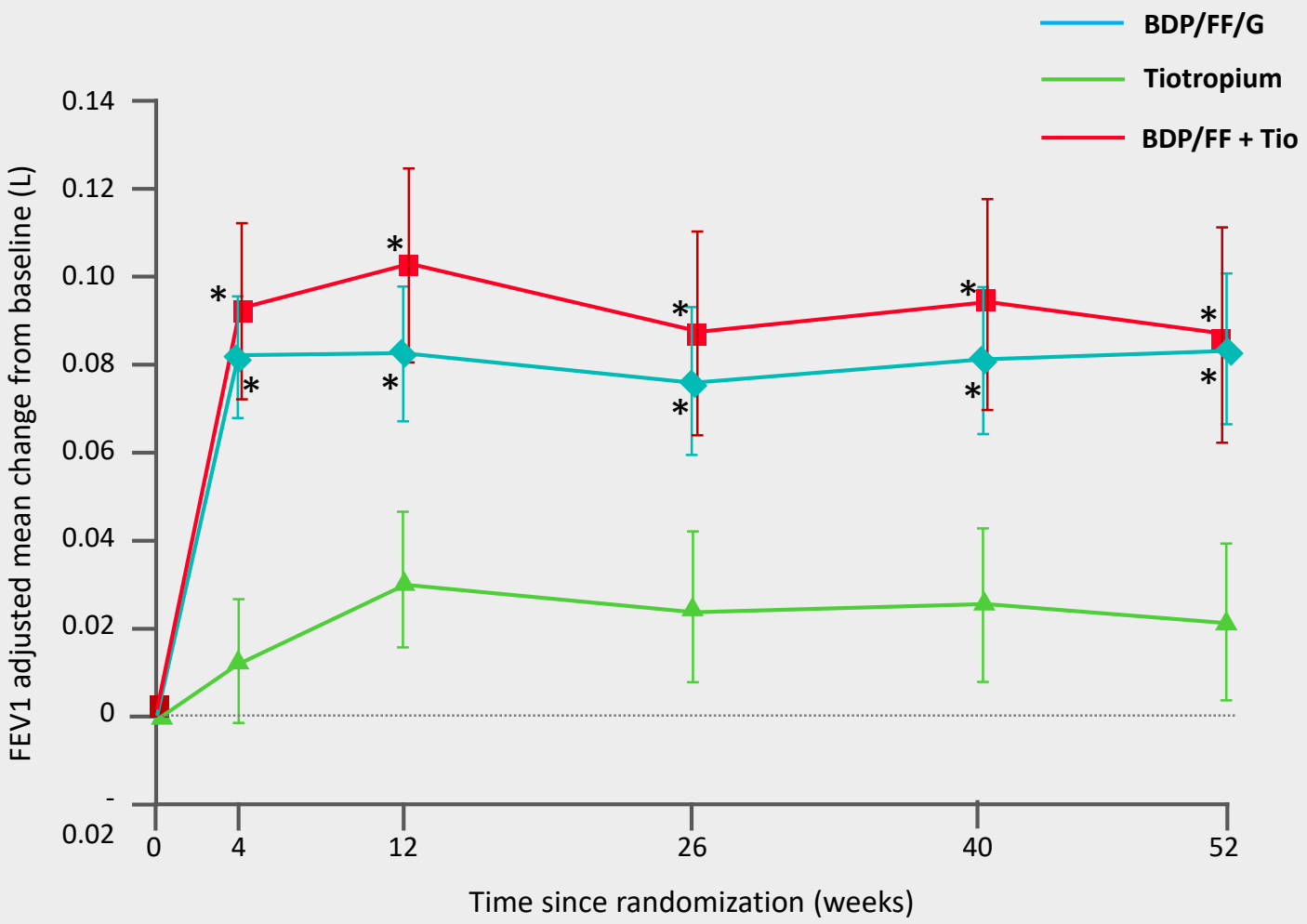
Time to first moderate/severe COPD exacerbation



Number at risk

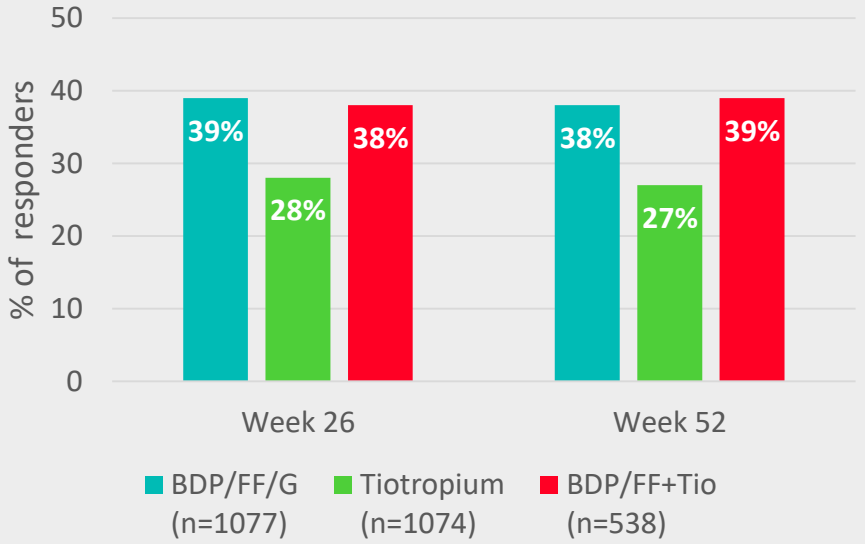
BDP/FF/G	1077	1044	955	851	748	426
Tiotropium	1074	986	875	766	675	374
BDP/FF + Tio	538	520	484	426	381	223

Pre-dose morning FEV_1 (L)



*p<0.001 vs Tiotropium

Responder Analysis
(≥ 100 mL increase from baseline)



Odds Ratio

	Week 26	Week 52
BDP/FF/G vs Tiotropium	1.61 (1.34–1.93); p<0.0001	1.62 (1.35–1.95); p<0.0001
BDP/FF/G vs BDP/FF+Tio	1.04 (0.84–1.30); p=0.69	0.95 (0.76–1.18); p=0.63
BDP/FF+Tio vs Tiotropium	1.54 (1.23–1.92); p=0.0001	1.71 (1.37–2.13); p<0.0001

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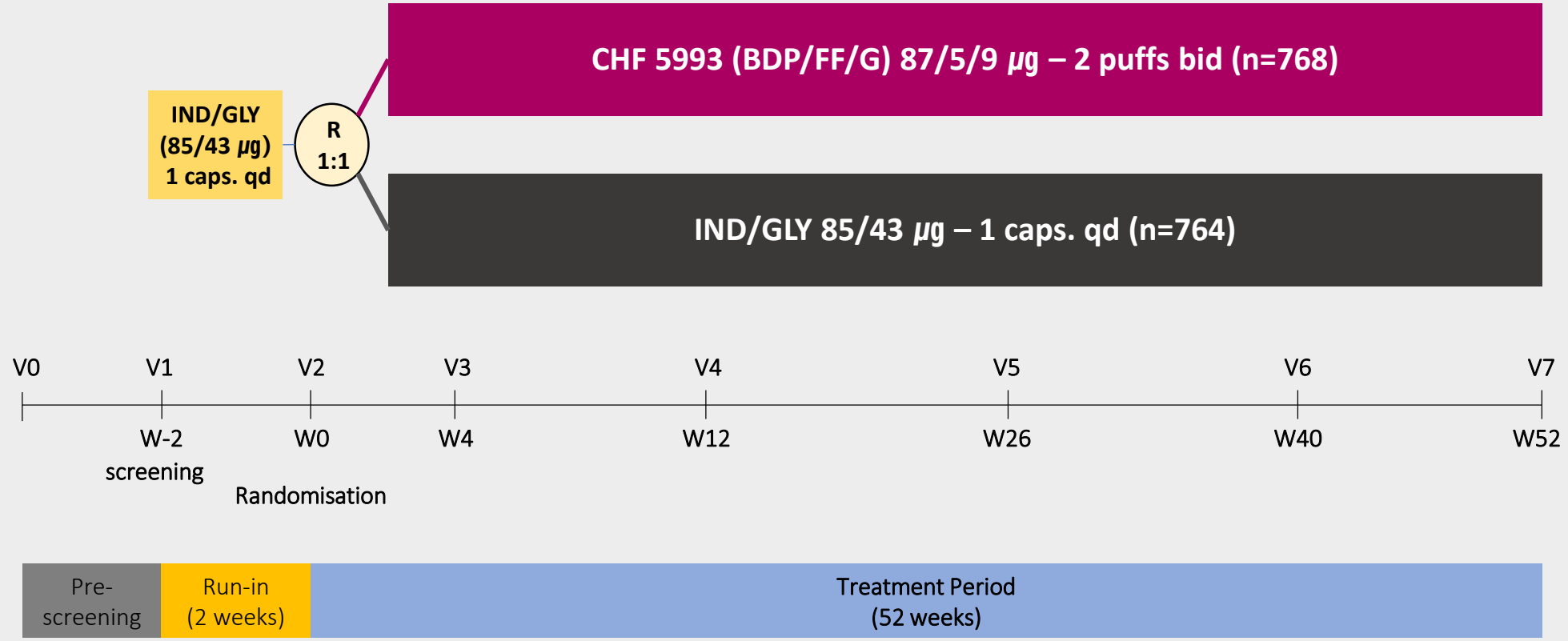
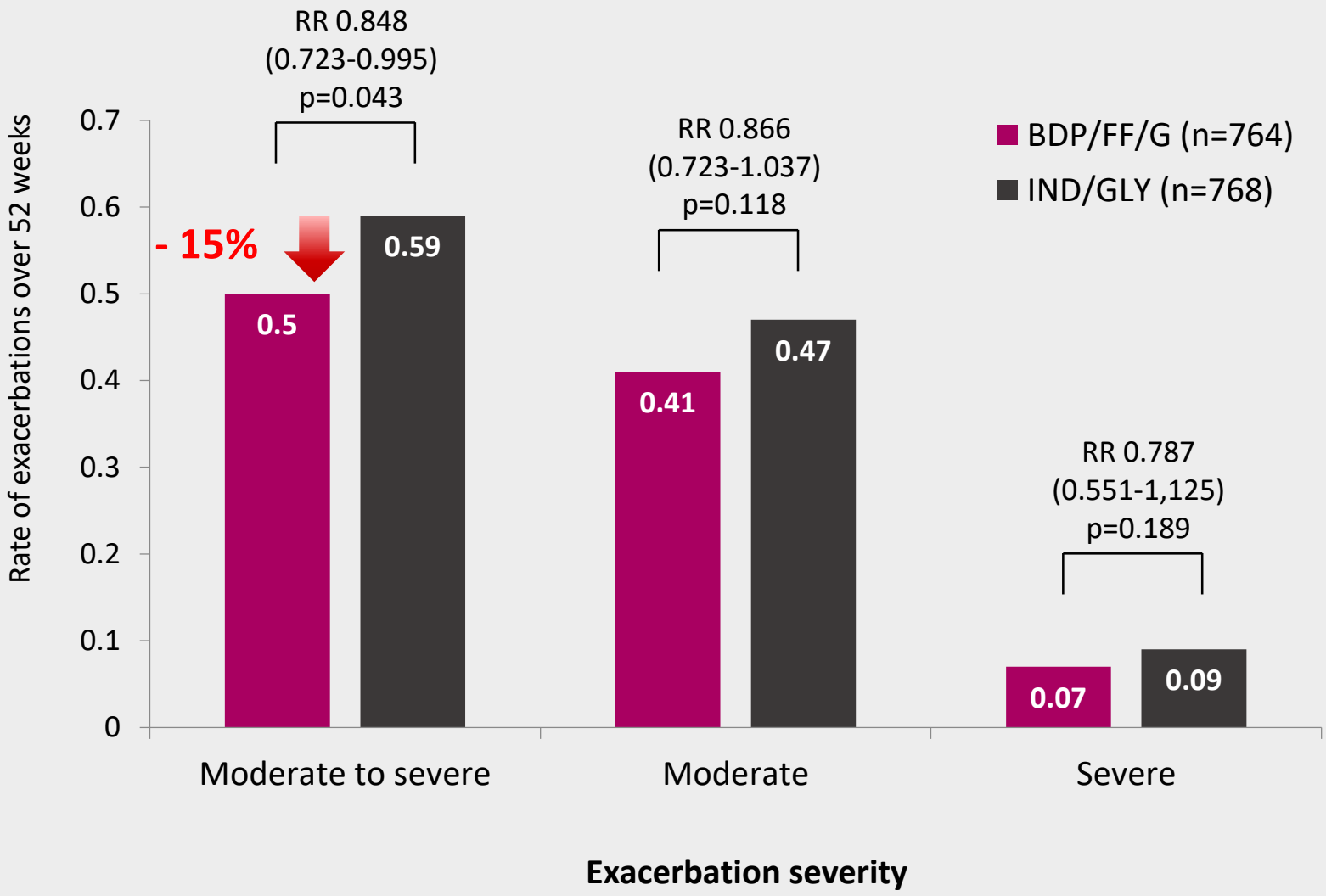
Papi A et al. Lancet 2018;391:1076-1084

TRIBUTE

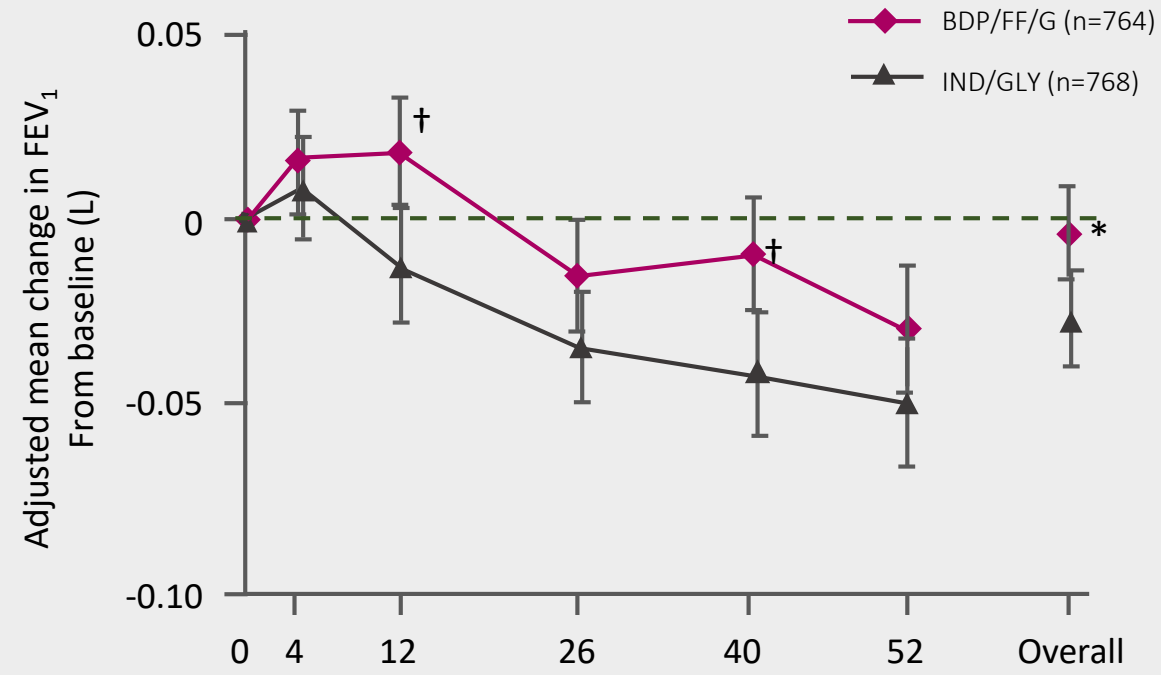
Double-blind, Double-dummy, Randomized, Multinational, multicentre, 2-arm parallel group, Active-controlled



Moderate to severe exacerbation



Secondary Endpoint: Lung Function



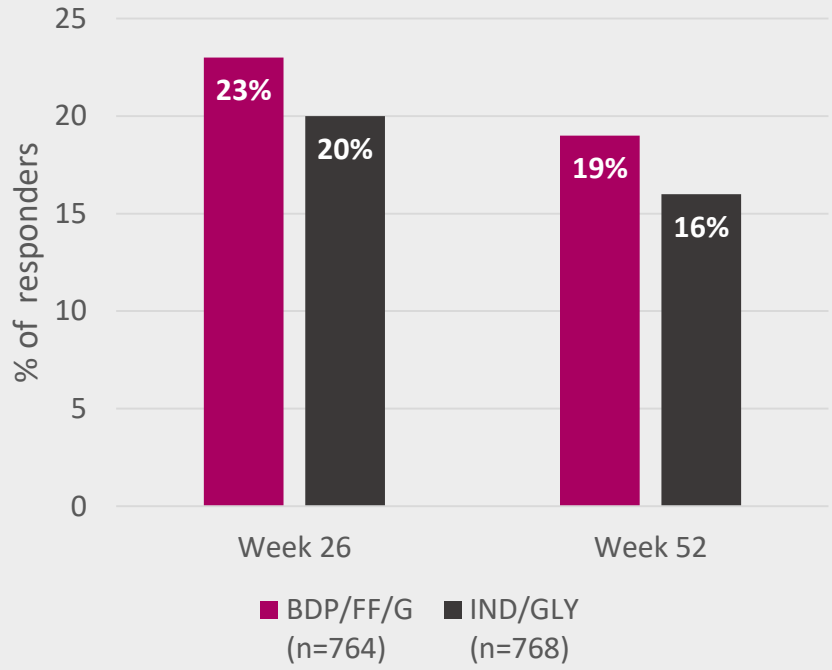
Adjusted mean difference between treatments (mL)						
	8	32	20	32	19	22
Number with available measurements						
BDP/FF/G 761	754	737	718	694	988	757
IND/GLY 767	758	742	712	677	652	760

*p<0·05 *vs* IND/GLY.
†p<0·01 *vs* IND/GLY.

Responder* Analysis

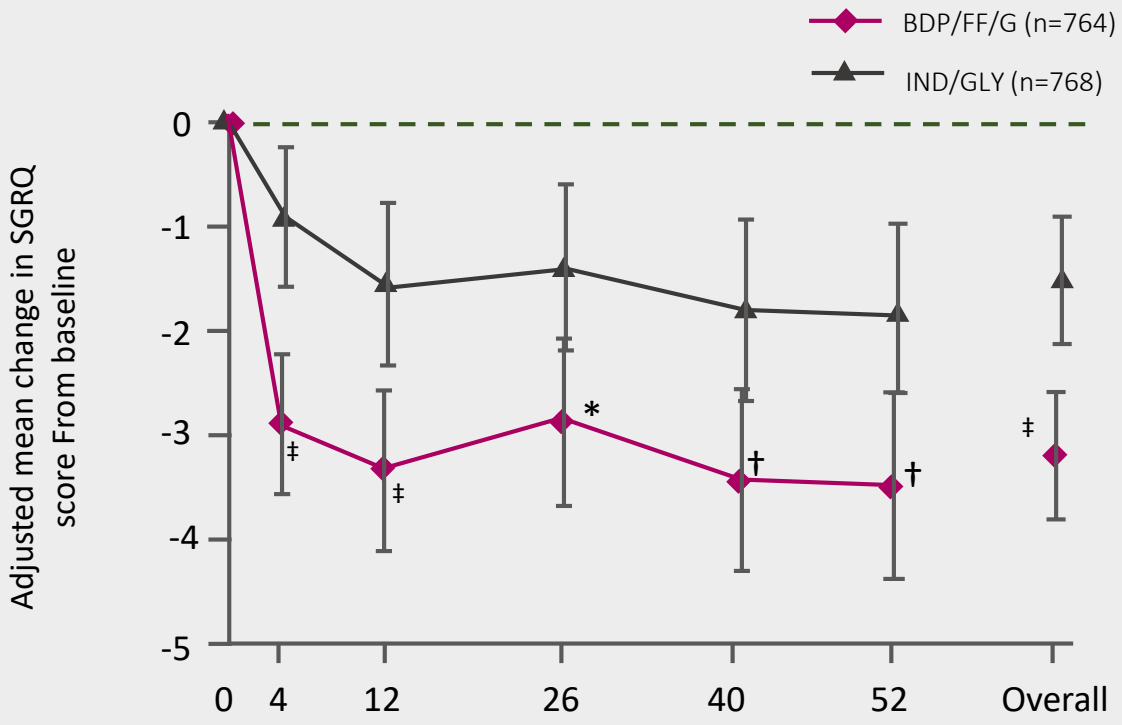
OR 1.18
(95% CI: 0.92, 1.50)
P=0.194

OR 1.19
(95% CI: 0.91, 1.55)
P=0.198



*Response defined as ≥100 mL increase from baseline

Secondary Endpoint: SGRQ



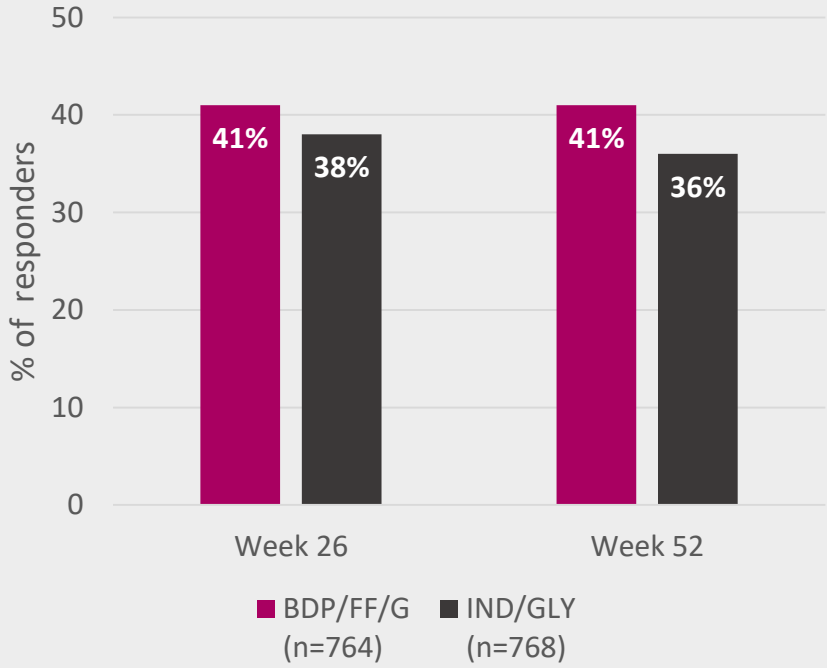
Adjusted mean difference between treatments		-1.96	-1.75	-1.43	-1.62	-1.64	-1.68
Number with available measurements							
BDP/FF/G	763	757	740	722	695	667	760
IND/GLY	768	762	744	716	679	654	763

*p<0·05 *vs* IND/GLY.
†p<0·01 *vs* IND/GLY. ‡p≤0·001 *vs* IND/GL

Responder# Analysis

OR 1.13
(95% CI: 0.92, 1.40)
P=0.255

OR 1.22
(95% CI: 0.99, 1.51)
P=0.068



#Response defined as ≥4 unit decrease from baseline

The NEW ENGLAND JOURNAL of MEDICINE

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Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD

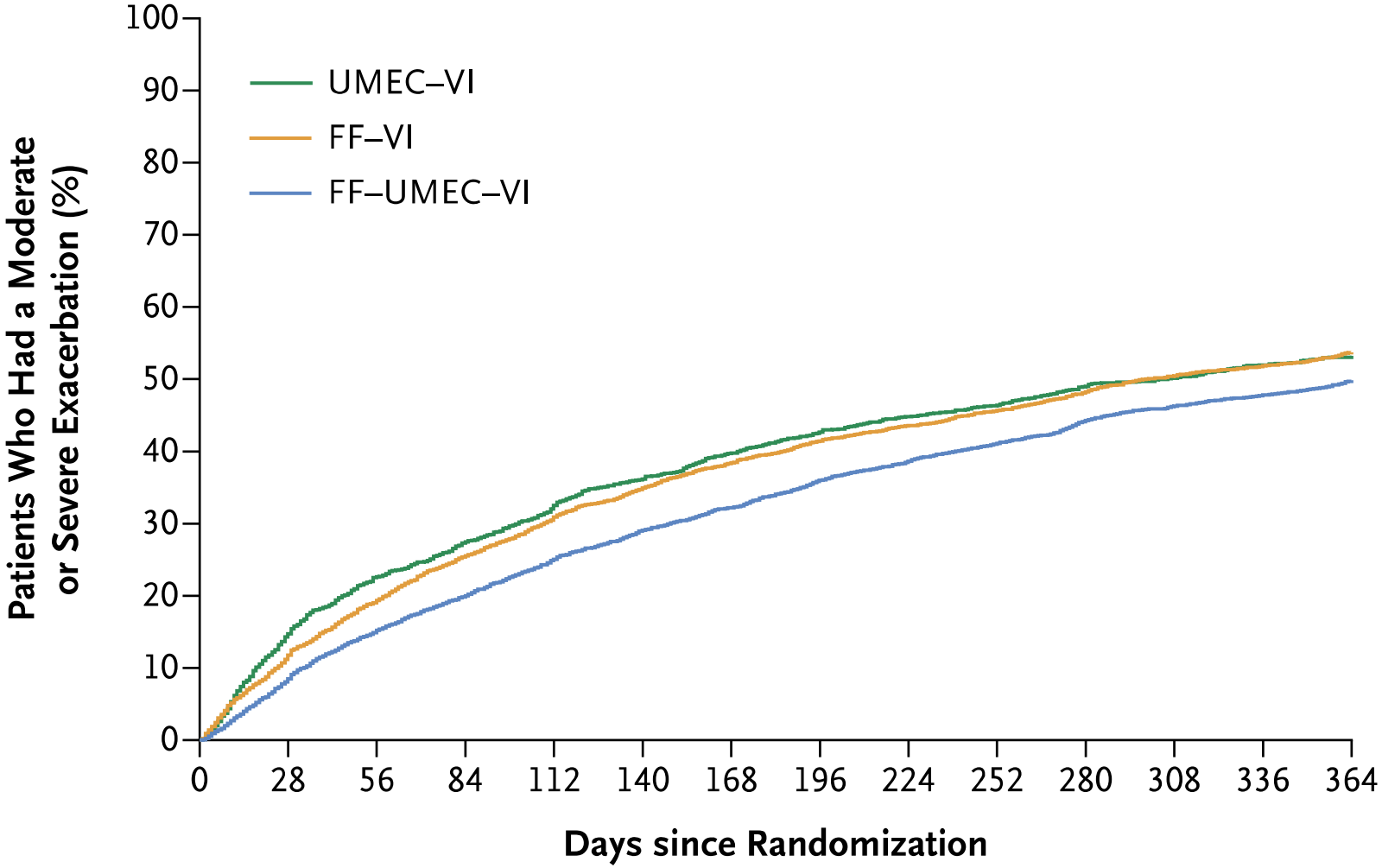
David A. Lipson, M.D., Frank Barnhart, D.V.M., Noushin Brealey, M.D., Jean Brooks, M.Sc., Gerard J. Criner, M.D., Nicola C. Day, Ph.D., Mark T. Dransfield, M.D., David M.G. Halpin, M.D., MeiLan K. Han, M.D., C. Elaine Jones, Ph.D., Sally Kilbride, M.Sc., Peter Lange, M.D., David A. Lomas, M.D., Ph.D., Fernando J. Martinez, M.D., Dave Singh, M.D., Maggie Tabberer, M.Sc., Robert A. Wise, M.D., and Steven J. Pascoe, M.B., B.S., for the IMPACT Investigators

IMPACT trial

- N=10,355 patients
- Symptomatic COPD with high exacerbation risk
- ICS/LAMA/LABA vs. ICS/LABA vs. LAMA/LABA
- 1yr (52w)
- Rate of mod/severe exacerbations

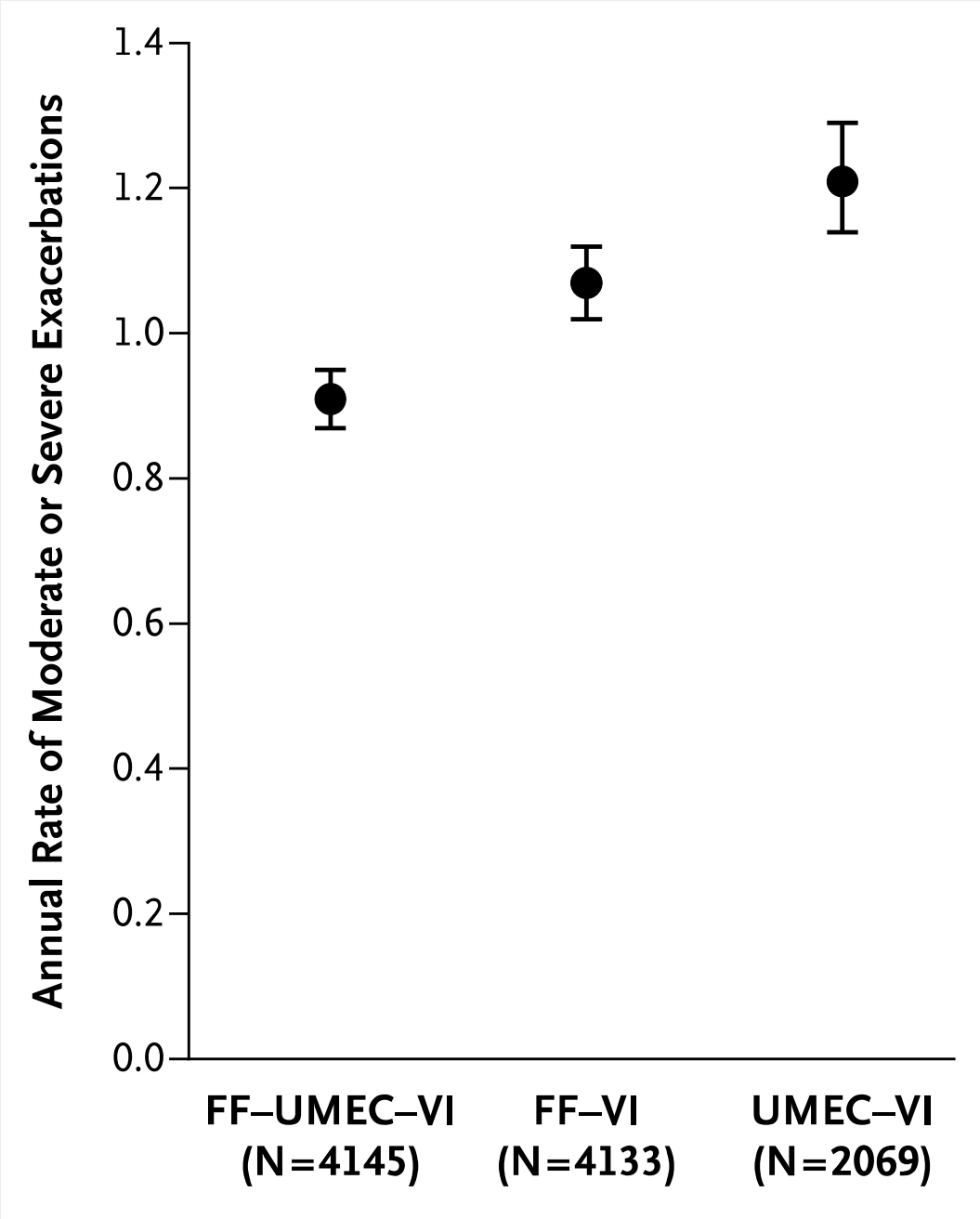
IMPACT trial: inclusion

- Age ≥ 40
- CAT ≥ 10
- FEV1<50% AND ≥1 m/s exacerbation
- FEV1 50%-80% AND (≥ 2 m. exacerbation or ≥ 1 s. exacerbation)
- Prev. medication (inc. ICS) allowed during run-in period

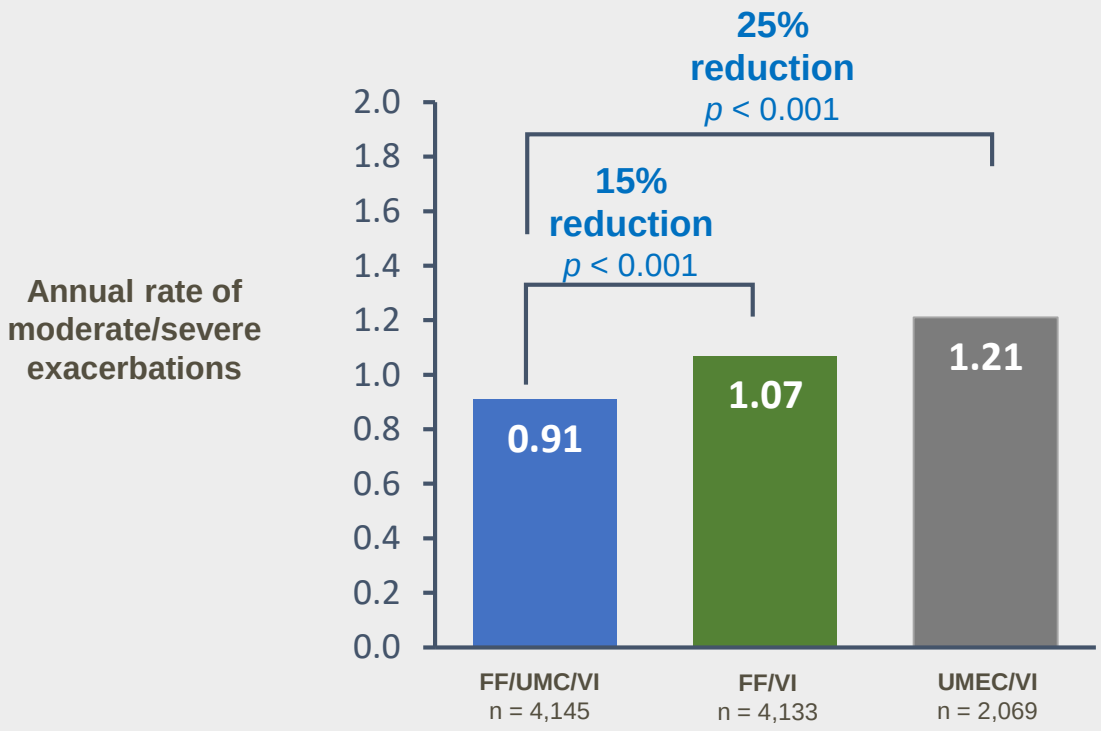


No. at Risk

UMEC–VI	2070	1721	1516	1406	1301	1201	1123	1059	1001	971	917	884	851	642
FF–VI	4134	3554	3133	2838	2620	2410	2250	2120	2004	1823	1823	1729	1671	1228
FF–UMEC–VI	4151	3758	3408	3186	2954	2752	2614	2457	2324	2216	2085	1988	1919	1419


Annual Rate of Moderate or Severe Exacerbations
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
FF–UMEC–VI (N=4145)
FF–VI (N=4133)
UMEC–VI (N=2069)

IMPACT: Reduction in m/s exacerbations



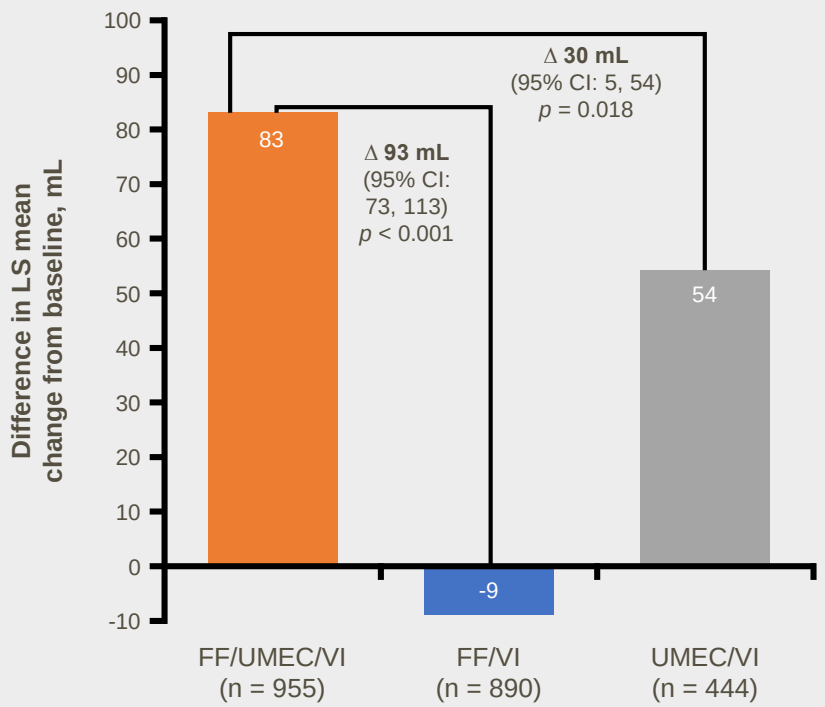
Adapted from Lipson DA, et al. *N Engl J Med.* 2018;378:1671–1680.

IMPACT TRIAL

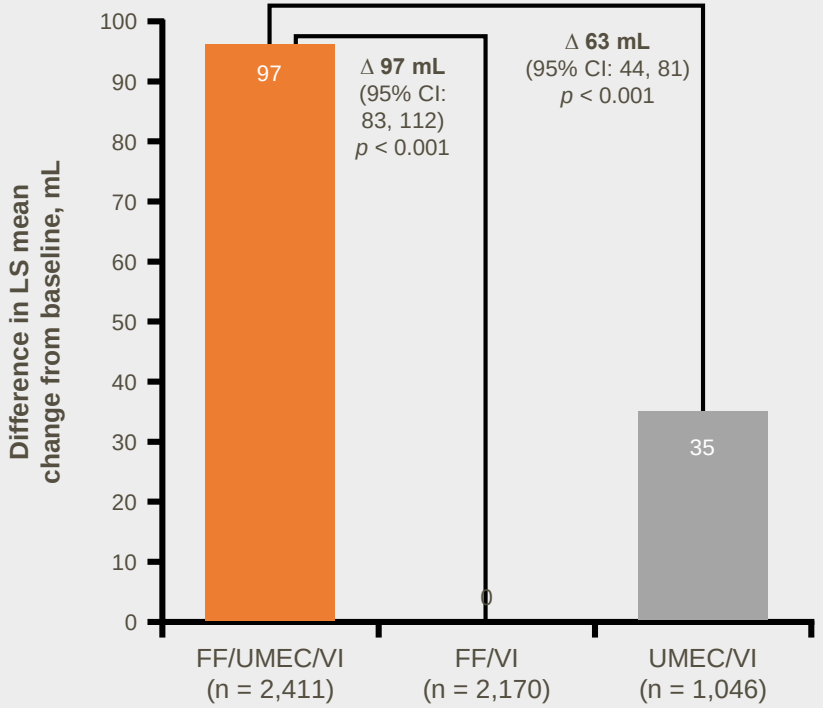
IMPACT – FEV1 and SGRQ

Outcome	Triple Therapy (N = 4151)	Fluticasone Furoate–Vilanterol (N = 4134)	Umeclidinium–Vilanterol (N = 2070)
Trough FEV_1			
No. of patients evaluated	3366	3060	1490
Mean at wk 52 (95% CI) — ml	1274 (1265 to 1282)	1177 (1168 to 1185)	1220 (1208 to 1232)
Mean change from baseline (95% CI) — ml	94 (86 to 102)	–3 (–12 to 6)	40 (28 to 52)
Difference between triple therapy and dual-therapy comparator (95% CI) — ml	—	97 (85 to 109)†	54 (39 to 69)†
SGRQ total score‡			
No. of patients evaluated	3318	3026	1470
Mean at wk 52 (95% CI)	45.0 (44.5 to 45.4)	46.8 (46.3 to 47.2)	46.8 (46.1 to 47.4)
Mean change from baseline (95% CI)	–5.5 (–5.9 to –5.0)	–3.7 (–4.2 to –3.2)	–3.7 (–4.4 to –3.0)
Difference between triple therapy and dual-therapy comparator (95% CI)	—	–1.8 (–2.4 to –1.1)†	–1.8 (–2.6 to –1.0)†
Response according to SGRQ total score at wk 52 — no. (%)§	1723 (42)	1390 (34)	696 (34)
Odds ratio for triple therapy vs. dual-therapy comparator (95% CI)	—	1.41 (1.29 to 1.55)†	1.41 (1.26 to 1.57)†

- **1 moderate and 0 severe exacerbations**



- **≥2 moderate and/or ≥1 severe exacerbations**



Reducing exacerbation

- ICS/LABA > LABA or ICS (TORCH)
- ICS/LABA = LAMA (INSPIRE)
- LAMA/LABA > ICS/LABA (FLAME)
- ICS/LAMA/LABA > LAMA/LABA or ICS/LABA (IMPACT)

IMPACT – Adverse Events

Event	Triple Therapy (N = 4151)		Fluticasone Furoate–Vilanterol (N = 4134)		Umeclidinium–Vilanterol (N = 2070)	
	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)
Anticholinergic syndrome	184 (4)	60.8 (226)	140 (3)	47.1 (163)	70 (3)	47.7 (81)
Asthma or bronchospasm	27 (<1)	7.5 (28)	34 (<1)	10.1 (35)	16 (<1)	9.4 (16)
Cardiovascular effects	450 (11)	167.2 (621)	430 (10)	157.0 (543)	224 (11)	166.6 (283)
Cardiac arrhythmia	153 (4)	50.9 (189)	161 (4)	51.5 (178)	81 (4)	51.2 (87)
Cardiac failure	138 (3)	42.5 (158)	126 (3)	42.8 (148)	68 (3)	44.8 (76)
CNS hemorrhages and cerebrovascular conditions	41 (<1)	12.1 (45)	28 (<1)	9.3 (32)	11 (<1)	6.5 (11)
Hypertension	113 (3)	35.5 (132)	115 (3)	35.0 (121)	54 (3)	34.2 (58)
Ischemic heart disease	80 (2)	26.1 (97)	57 (1)	18.5 (64)	47 (2)	30.6 (52)
Lower respiratory tract infection, excluding pneumonia	200 (5)	63.0 (234)	199 (5)	69.7 (241)	108 (5)	76.0 (129)
Pneumonia	317 (8)	95.8 (356)	292 (7)	96.6 (334)	97 (5)	61.2 (104)
Urinary retention	8 (<1)	2.7 (10)	12 (<1)	3.5 (12)	9 (<1)	5.3 (9)

TRINITY: Safety

	BDP/FF/GB N=1077	Tiotropium N=1076	BDP/FF+Tio N=537
Deaths	20 (1.9%)	29 (2.7%)	8 (1.5%)
Serious AEs	140 (13%)	164 (15%)	68 (13%)
COPD exacerbations	76 (7.1%)	100 (9.3%)	35 (6.5%)
Pneumonia	21 (1.9%)	14 (1.3%)	9 (1.7%)
AEs	594 (55%)	622 (58%)	309 (58%)
COPD exacerbations	351 (33%)	383 (36%)	167 (31%)
Nasopharyngitis	57 (5.3%)	66 (6.1%)	20 (3.7%)
Headache	43 (4.0%)	41 (3.8%)	18 (3.4%)
Dypnoea	23 (2.1%)	37 (3.4%)	8 (1.5%)
Pneumonia	28 (2.6%)	19 (1.8%)	12 (2.2%)
Cough	18 (1.7%)	23 (2.1%)	9 (1.7%)
Viral RTI	15 (1.4%)	15 (1.4%)	13 (2.4%)

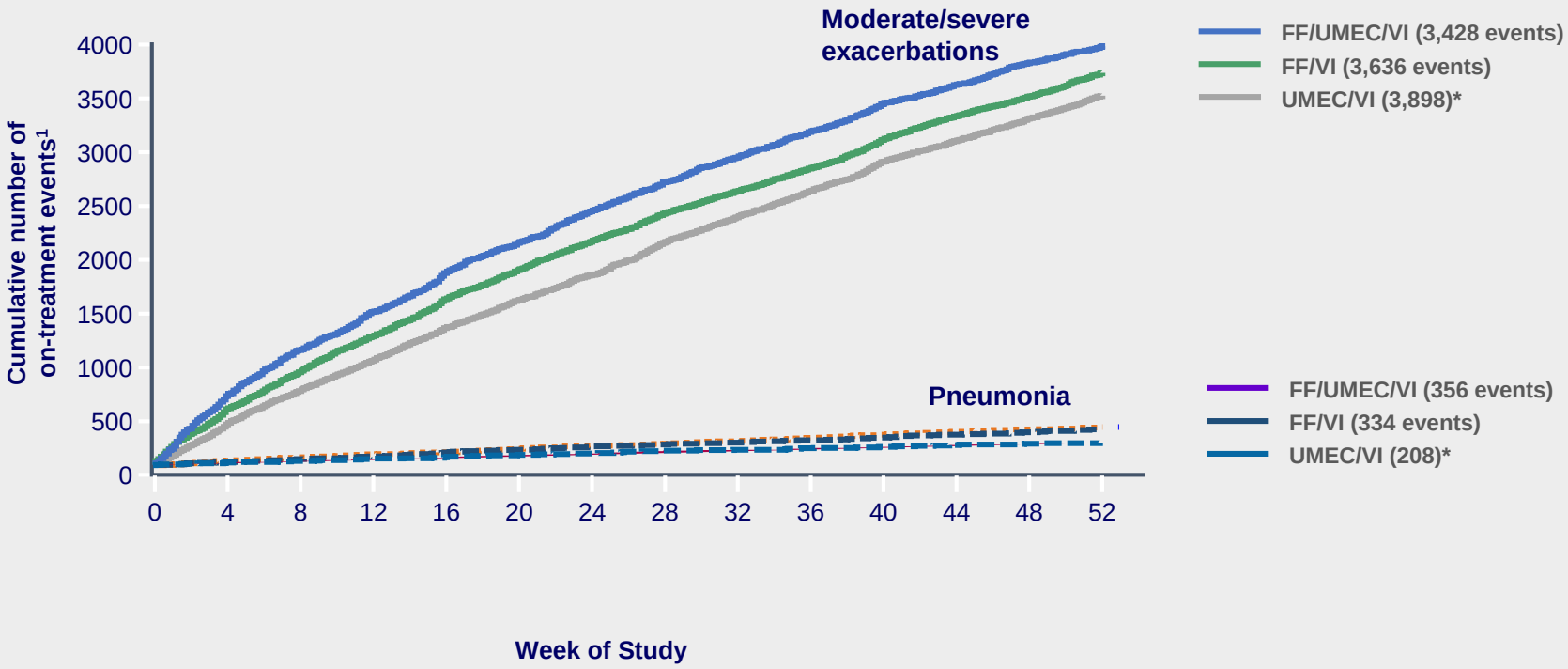
TRIBUTE: Safety

	BDP/FF/G (n=764)	IND/GLY (n=768)
Adverse events	490 (64%)	516 (67%)
COPD	273 (36%)	288 (38%)
Nasopharyngitis	43 (6%)	37 (5%)
Headache	44 (6%)	35 (5%)
Pneumonia	28 (4%)	27 (4%)
Respiratory tract infection	22 (3%)	28 (4%)
Dyspnoea	23 (3%)	24 (3%)
Back pain	21 (3%)	23 (3%)
Hypertension	15 (2%)	26 (3%)
Cough	13 (2%)	25 (3%)
Cardiac failure	15 (2%)	16 (2%)
Ischaemic heart disease	8 (1%)	16 (2%)
Myocardial infarction	1 (<1%)	8 (1%)
Angina pectoris	5 (1%)	1 (<1%)
Coronary artery disease	2 (<1%)	4 (1%)
Myocardial ischaemia	2 (<1%)	4 (1%)

Serious adverse events	117 (15%)	130 (17%)
COPD	61 (8%)	69 (9%)
Pneumonia	18 (2%)	17 (2%)
Cardiac failure	6 (1%)	7 (1%)
Death	3 (<1%)	8 (1%)
Ischaemic heart disease	2 (<1%)	11 (1%)
Myocardial infarction	1 (<1%)	8 (1%)
Coronary artery disease	1 (<1%)	2 (<1%)
Myocardial ischaemia	0	1 (<1%)
Atrial fibrillation	0	7 (1%)
Respiratory failure	3 (<1%)	4 (1%)
Lung neoplasm	4 (1%)	2 (<1%)
Treatment-related adverse events	43 (6%)	37 (5%)
Oral candidiasis	12 (2%)	6 (1%)
Dry mouth	3 (<1%)	6 (1%)
Cough	1 (<1%)	7 (1%)
Treatment-related serious adverse events	1 (<1%)	1 (<1%)
Severe adverse events	86 (11%)	87 (11%)
Adverse events leading to study drug discontinuation	37 (5%)	47 (6%)
Adverse events leading to death	16 (2%)	21 (3%)

80% of pneumonia were confirmed by imaging

IMPACT: Cumulative number of pneumonias and moderate/severe exacerbations[1-3]



1. Lipson DA, et al. ATS 2018 (oral primary presentation) #A1014; 2. GlaxoSmithKline. Data on file. RF/TLY/0053/18(1); 3. Lipson DA, et al. *N Engl J Med.* 2018;378:1671–1680; 4. Kew KM & Seniukovich A. *Cochrane Database Syst Rev*. 2014;3:CD010115; 5. European Medicines Agency. PRAC reviews known risk of pneumonia with inhaled corticosteroids for chronic obstructive pulmonary disease. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2016/03/WC500203476.pdf. (accessed August 2018); 6. Suissa S, et al. *Thorax*. 2012;67:957–963.

FULFIL trial

- ICS/LABA/LAMA (FF/UMEC/VI) vs. ICS/LABA (BUD/FOR)
- 24w
- 1,810
- Co-primary
  - FEV1
  - SGRQ

ORIGINAL ARTICLE

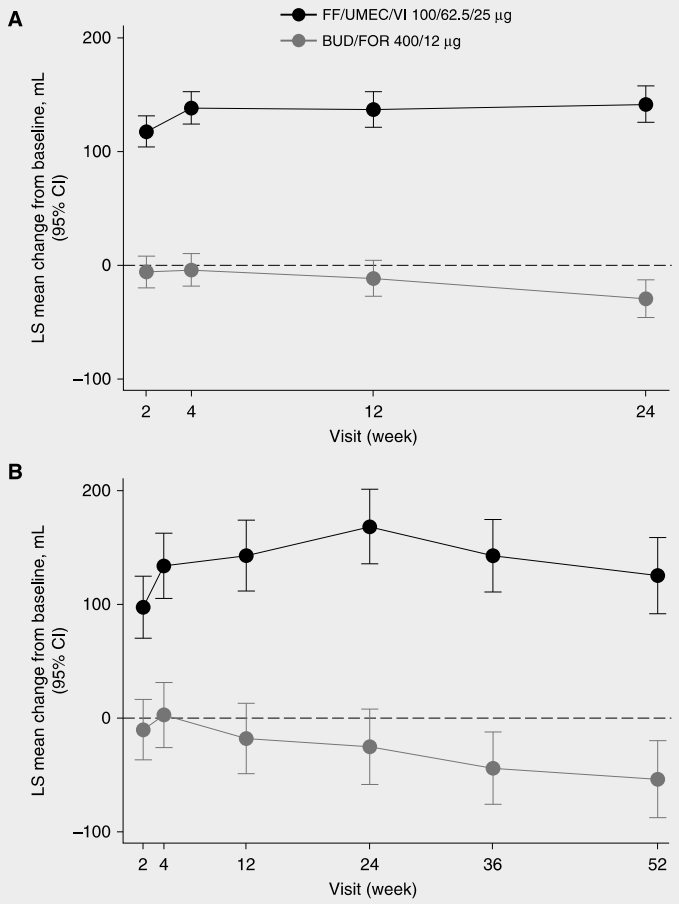
FULFIL Trial: Once-Daily Triple Therapy for Patients with Chronic Obstructive Pulmonary Disease

David A. Lipson[1,2], Helen Barnacle[3], Ruby Birk[3], Noushin Brealey[3], Nicholas Locantore[1], David A. Lomas[4], Andrea Ludwig-Sengpiel[5], Rajat Mohindra[3]*, Maggie Tabberer[3], Chang-Qing Zhu[3], and Steven J. Pascoe[1]

[1]GlaxoSmithKline, King of Prussia, Pennsylvania; [2]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; [3]GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex, United Kingdom; [4]UCL Respiratory, University College London, London, United Kingdom; and [5]KLB Health Research, Lübeck, Germany

AJRCCM 2017;196(4):438

Change from baseline, trough FEV1



Annual COPD exacerbation rates

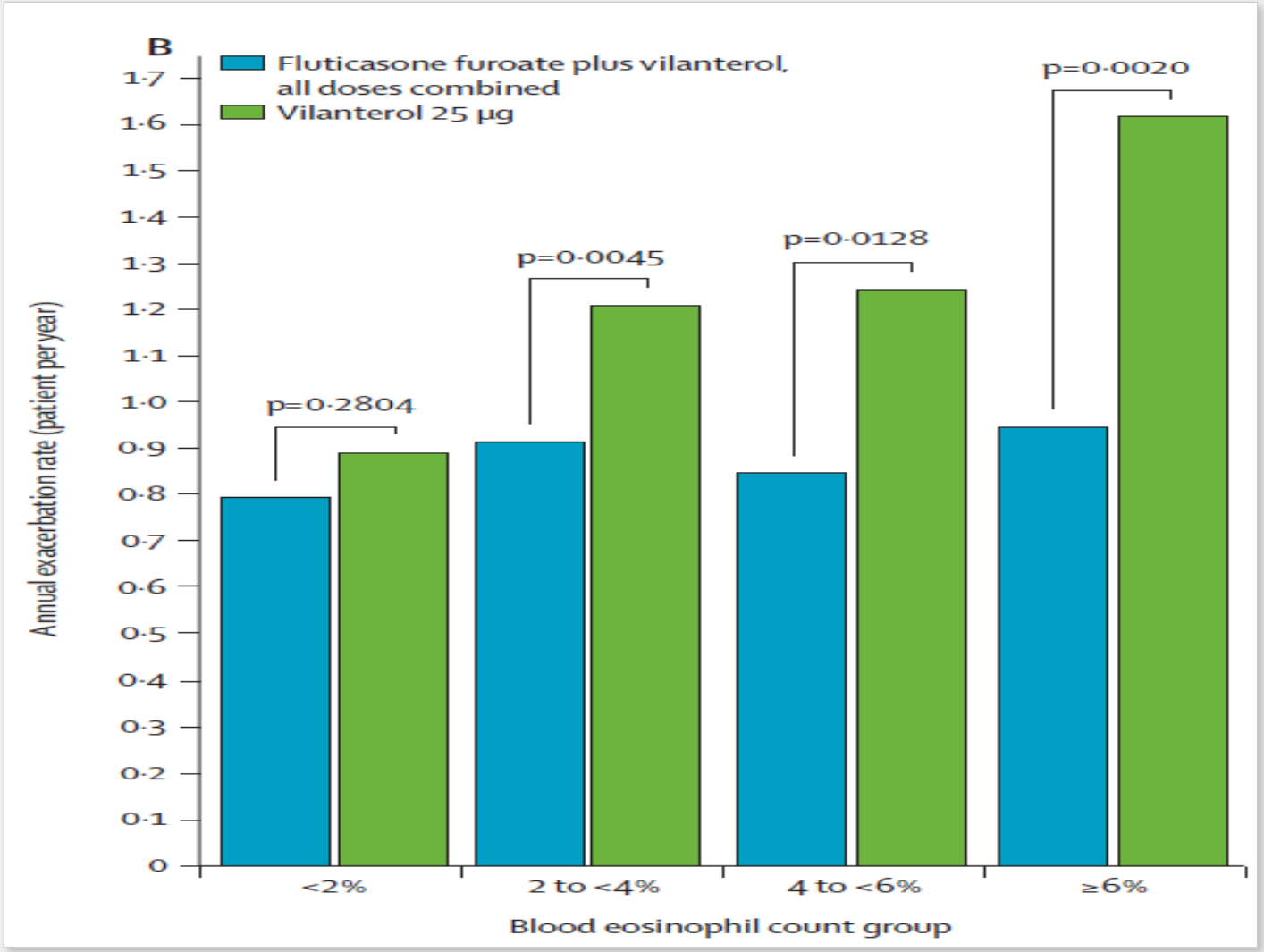
	Up to 24 wk (ITT Population)		Up to 52 wk (EXT Population)	
	FF/UMEC/VI 100/62.5/25 μg (*n* = *911*)	**BUD/FOR 400/12 μg (*n* = *899*)**	**FF/UMEC/VI 100/62.5/25 μg (*n* = *210*)**	**BUD/FOR 400/12 μg (*n* = *220*)**
Population, n	907	892	210	219
Moderate and severe exacerbations				
Mean rate	0.22	0.34	0.20	0.36
Ratio (95% CI); *P* value	0.65 (0.49–0.86); 0.002		0.56 (0.37–0.85); 0.006	
Reduction in rate, % (95% CI)	35 (14–51)		44 (15–63)	
Mild, moderate, and severe exacerbations				
Mean rate	0.25	0.39	0.22	0.40
Ratio (95% CI); *P* value	0.65 (0.50–0.84); <0.001		0.55 (0.37–0.81); 0.003	
Reduction in rate, % (95% CI)	35 (16–50)		45 (19–63)	

Definition of abbreviations: BUD = budesonide; CI = confidence interval; COPD = chronic obstructive pulmonary disease; EXT = extension; FF = fluticasone furoate; FOR = formoterol; ITT = intent-to-treat; UMEC = umeclidinium; VI = vilanterol.
Ratios and *P* values are calculated for FF/UMEC/VI versus BUD/FOR.

Side effects (FF/UMEC/VI vs. BUD/FOR)

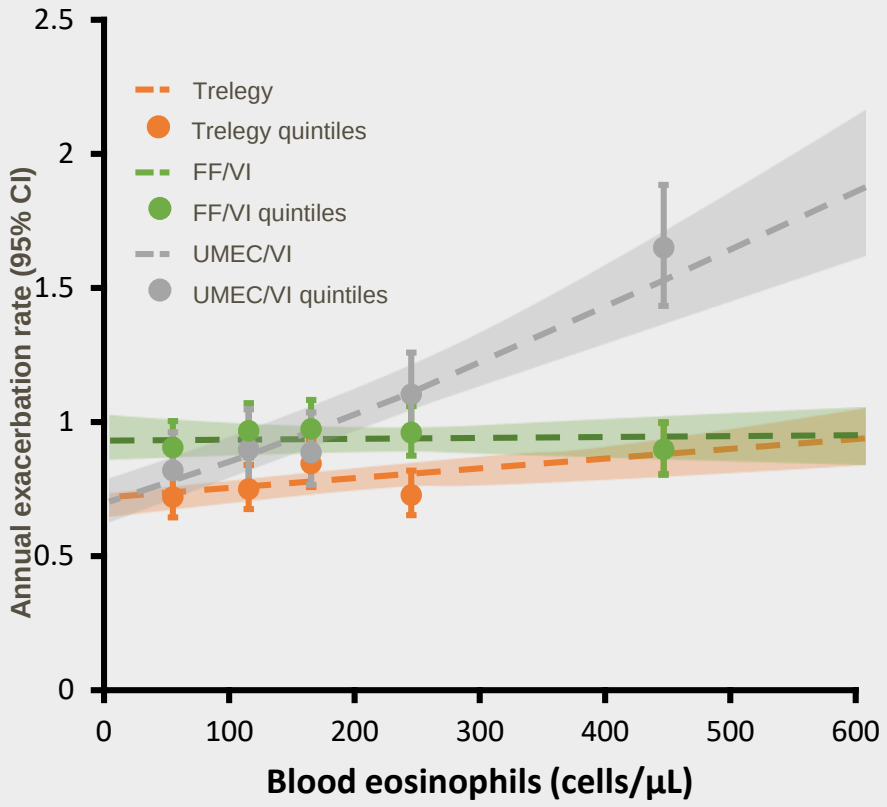
	ITT Population (24 wk)		EXT Population (52 wk)	
	FF/UMEC/VI 100/62.5/25 μg (*n* = *911*)	BUD/FOR 400/12 μg (*n* = *899*)	FF/UMEC/VI 100/62.5/25 μg (*n* = *210*)	BUD/FOR 400/12 μg (*n* = *220*)
Adverse events occurring in ⩾2% of patients in either population				
Nasopharyngitis	64 (7)	43 (5)	23 (11)	22 (10)
Headache	44 (5)	53 (6)	17 (8)	22 (10)
URTI	20 (2)	19 (2)	6 (3)	10 (5)
COPD	15 (2)	23 (3)	5 (2)	22 (10)
Back pain	19 (2)	18 (2)	4 (2)	5 (2)
Arthralgia	17 (2)	13 (1)	5 (2)	6 (3)
Pneumonia	19 (2)	7 (<1)	4 (2)	4 (2)
Pharyngitis	15 (2)	9 (1)	5 (2)	1 (<1)
Oropharyngeal pain	9 (<1)	10 (1)	6 (3)	1 (<1)
Dizziness	—	—	1 (<1)	6 (3)
Blood pressure increased	4 (<1)	8 (<1)	0	4 (2)
Dyspnea	—	—	0	4 (2)
Vertigo	—	—	0	4 (2)
Adverse events of special interest				
Cardiovascular effects	39 (4.3)	47 (5.2)	18 (8.6)	22 (10.0)
Pneumonia	20 (2.2)	7 (0.8)	4 (1.9)	4 (1.8)
Local steroid effects*	19 (2.1)	24 (2.7)	8 (3.8)	7 (3.2)
Anticholinergic syndrome*	16 (1.8)	17 (1.9)	4 (1.9)	12 (5.5)
Hypersensitivity	10 (1.1)	10 (1.1)	3 (1.4)	1 (0.5)
Hyperglycemia/diabetes†	5 (0.5)	4 (0.4)	0	4 (1.8)
Decreased bone mineral density	4 (0.4)	6 (0.7)	1 (0.5)	1 (0.5)
LRTI (excluding pneumonia)	3 (0.3)	4 (0.4)	1 (0.5)	0
Ocular effects*	1 (0.1)	4 (0.4)	—	—
Urinary retention	1 (0.1)	0	—	—
Asthma/bronchospasm	0	1 (0.1)	—	—

BLOOD EOSINOPHILS AS A BIOMARKER FOR ICS RESPONSE



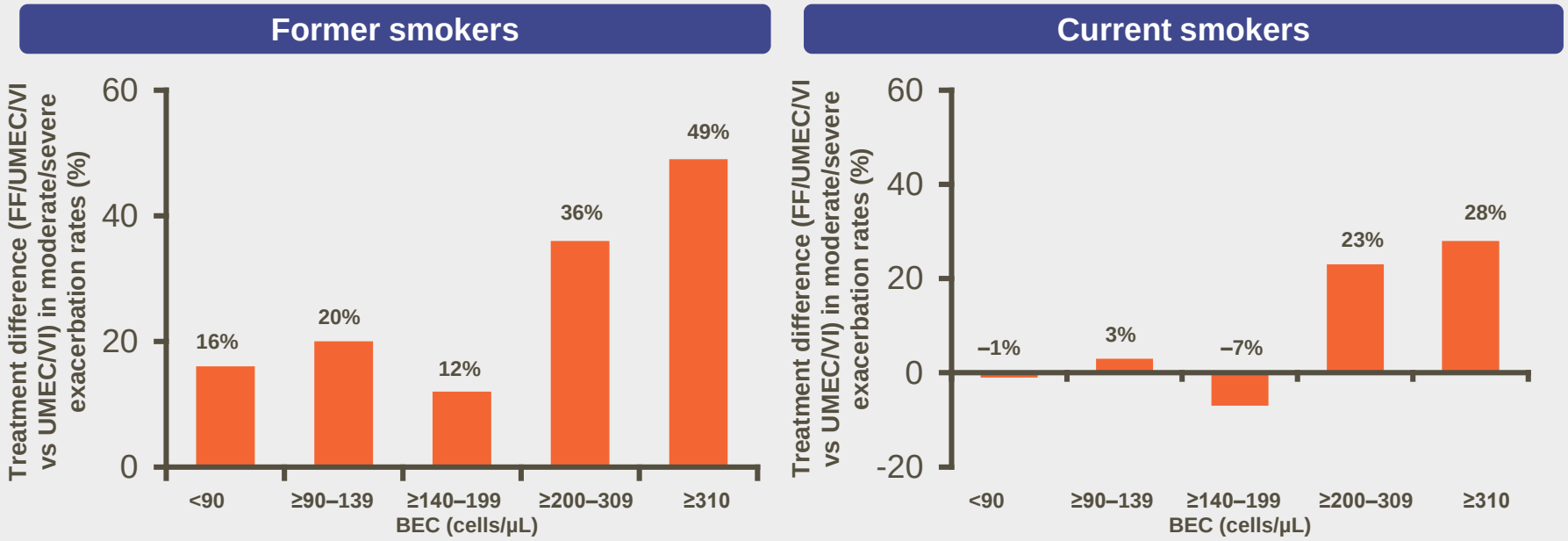
Pascoe S et al. Lancet Respir Med 2015;3:435-42

IMPACT: exacerbation frequency and blood eosinophils



Pascoe S, et al. ERS 2018. #OA2127.

Smoking status and blood eosinophils on difference in m/s exacerbations (FF/UMEC/VI vs. UMEC/VI)



Pascoe S, et al. ERS 2018. #OA2127

Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial

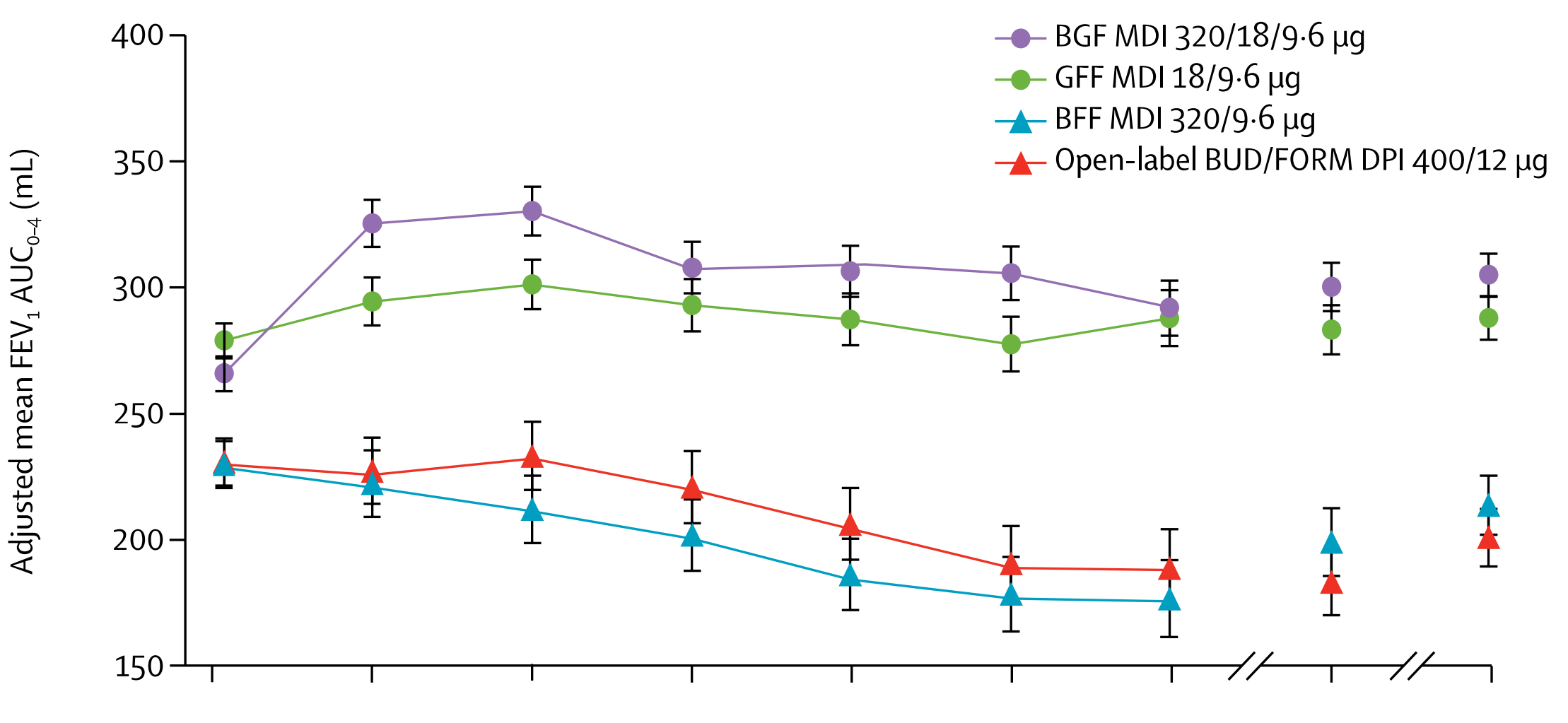
Gary T Ferguson, Klaus F Rabe, Fernando J Martinez, Leonardo M Fabbri, Chen Wang, Masakazu Ichinose, Eric Bourne, Shaila Ballal, Patrick Darken, Kiernan DeAngelis, Magnus Aurivillius, Paul Dorinsky, Colin Reisner

Lancet Respir Med 2018:6;747

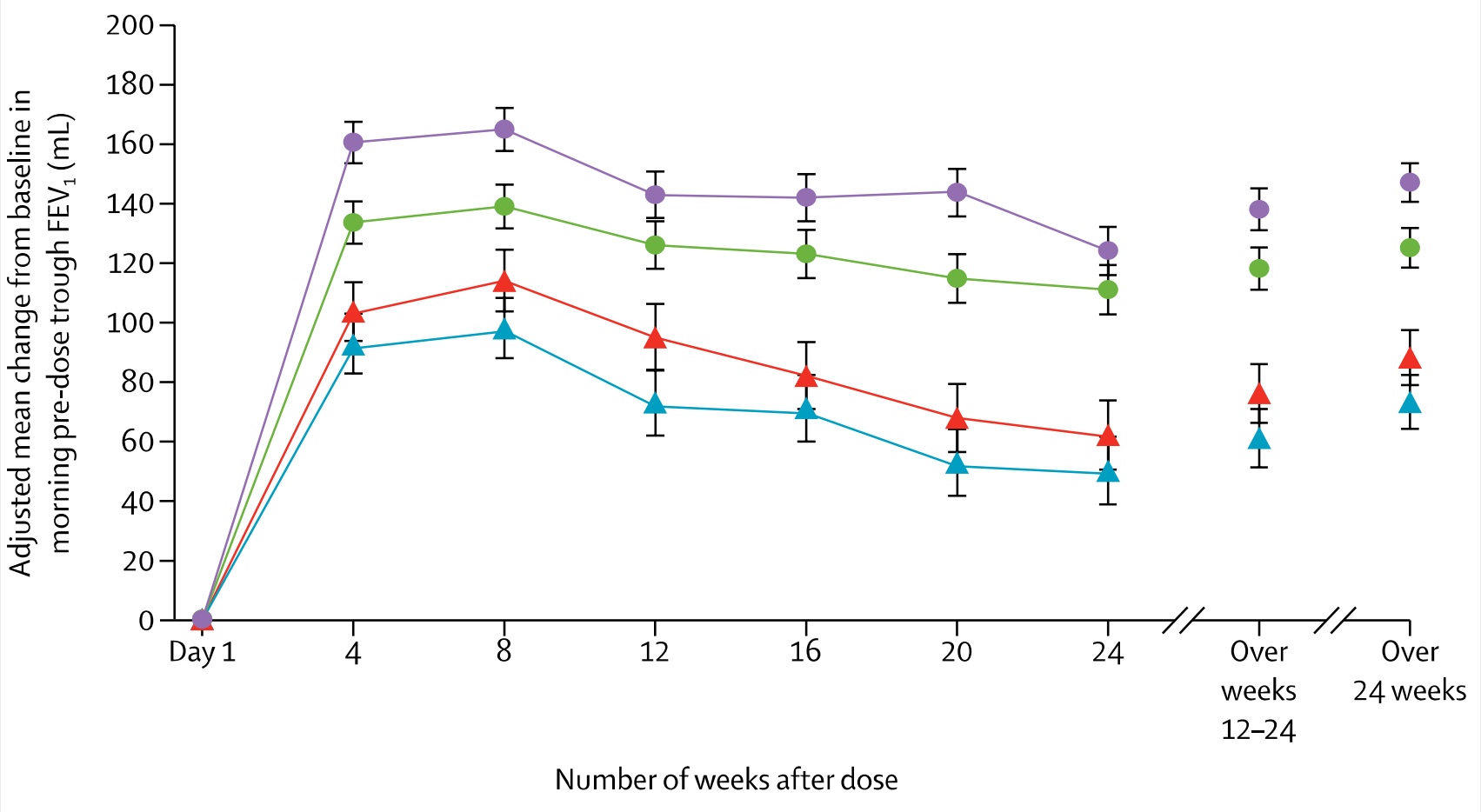
KRONOS study

- N=3,047 patients
- Symptomatic COPD with low exacerbation risk
- ICS/LAMA/LABA(MDI) vs. LAMA/LABA(MDI) vs. ICS/LABA (MDI) vs. ICS/LABA (DPI)
- 6 mon
- FEV1

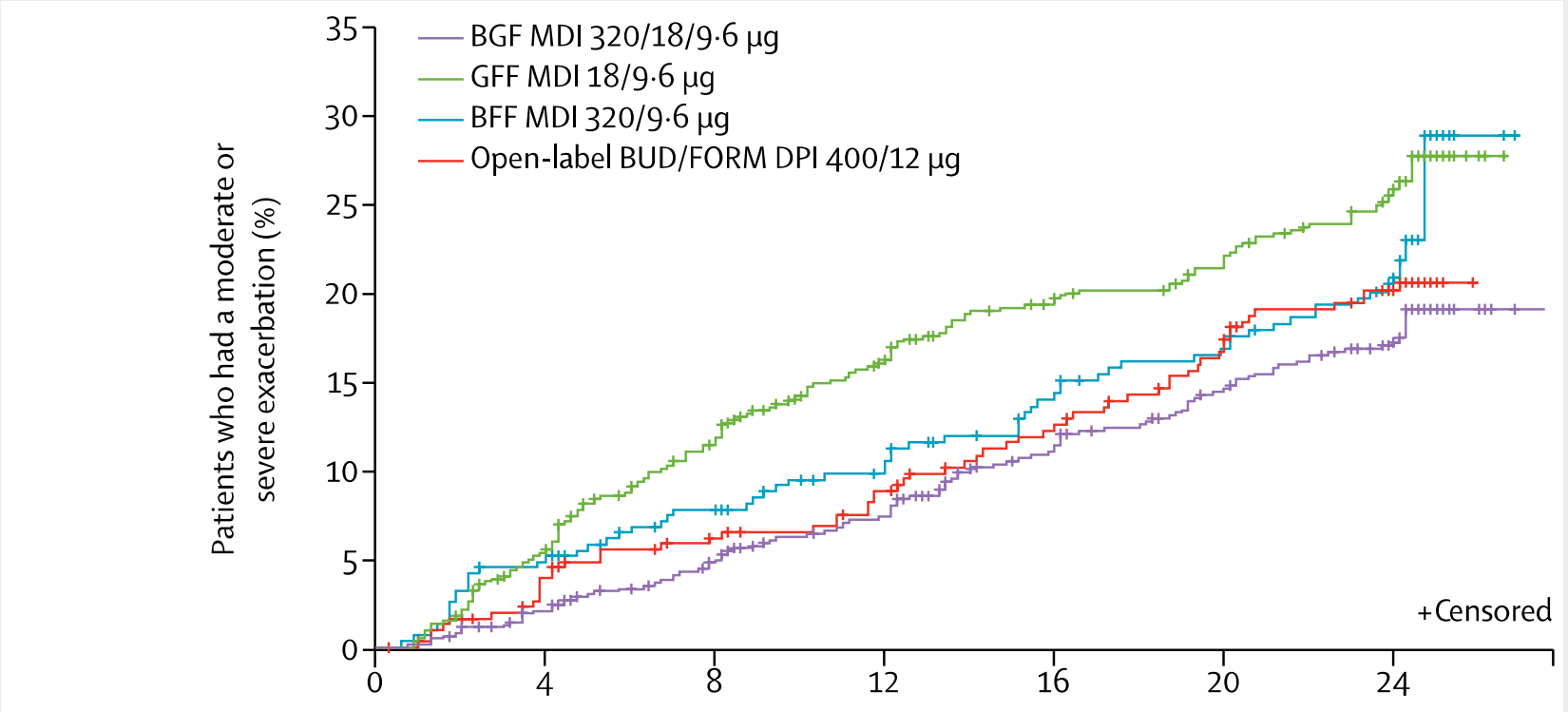
FEV1 AUC


BGF MDI 320/18/9·6 µg
GFF MDI 18/9·6 µg
BFF MDI 320/9·6 µg
Open-label BUD/FORM DPI 400/12 µg
Adjusted mean FEV1 AUC0–4 (mL)
400
350
300
250
200
150

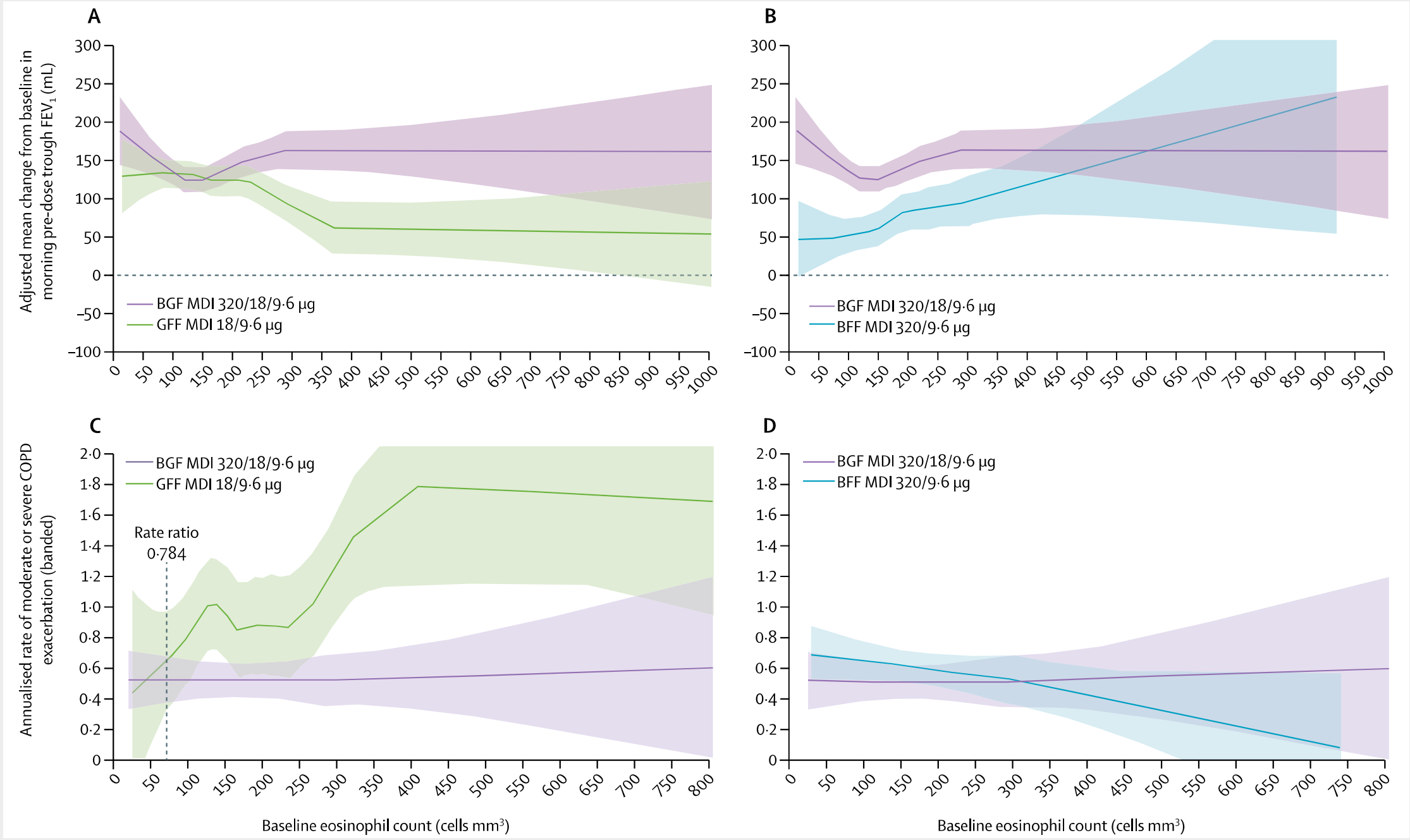
Δ trough FEV1



Time to 1st exacerbation

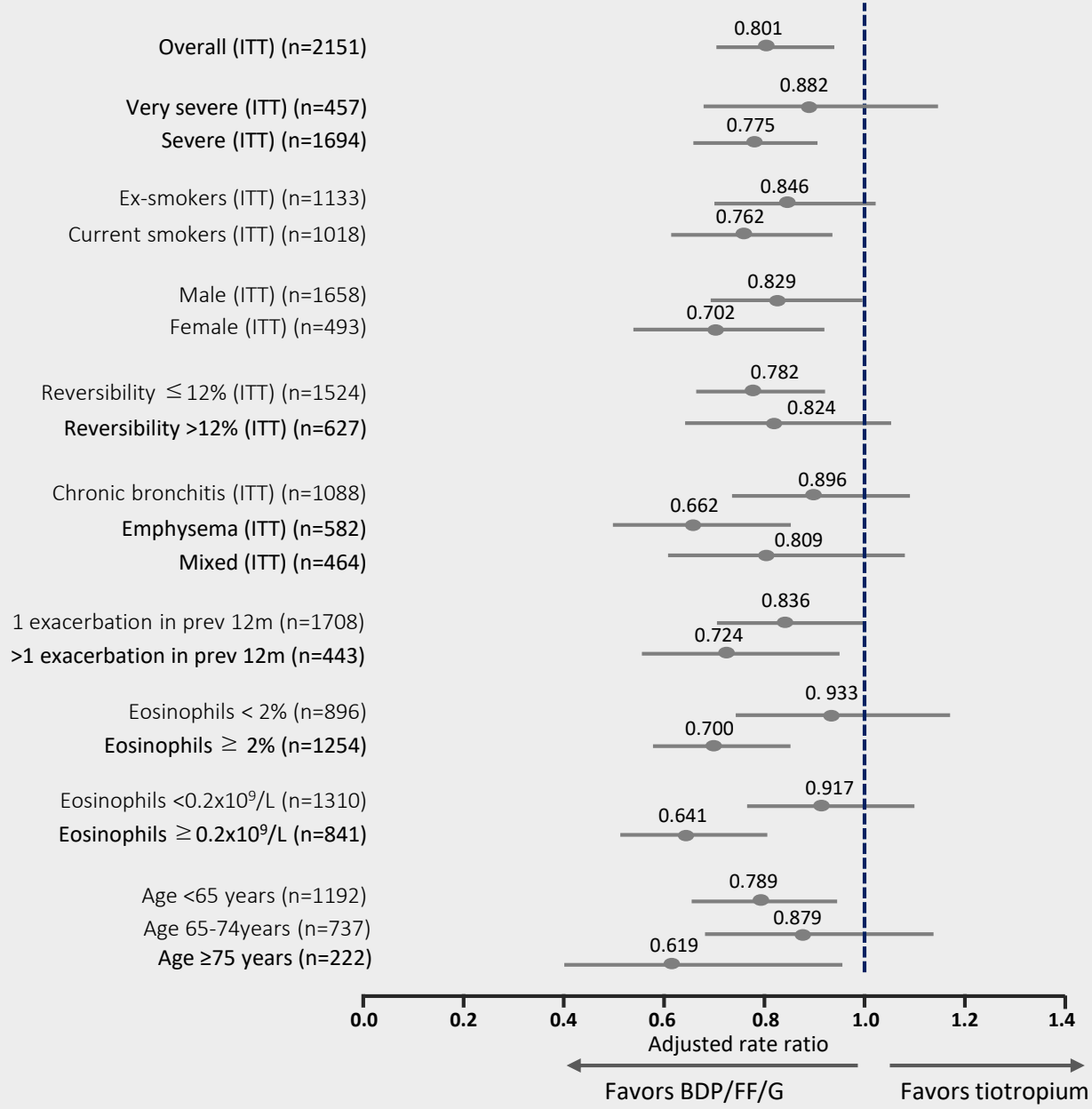


Number at risk							
BGF MDI 320/18/9·6 µg	639	620	590	561	526	498	428
GFF MDI 18/9·6 µg	625	585	532	492	463	446	371
BFF MDI 320/9·6 µg	314	295	277	260	242	233	196
Open-label BUD/FORM DPI 400/12 µg	318	297	282	271	257	241	203


A
Adjusted mean change from baseline in morning pre-dose trough FEV1 (mL)
300
250
200
150
100
50
0
−50
−100
BGF MDI 320/18/9·6 µg
GFF MDI 18/9·6 µg
0 50 100 150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950 1000
B
300
250
200
150
100
50
0
−50
−100
BGF MDI 320/18/9·6 µg
BFF MDI 320/9·6 µg
0 50 100 150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950 1000
C
Annualised rate of moderate or severe COPD exacerbation (banded)
2·0
1·8
1·6
1·4
1·2
1·0
0·8
0·6
0·4
0·2
0
BGF MDI 320/18/9·6 µg
GFF MDI 18/9·6 µg
Rate ratio
0·784
0 50 100 150 200 250 300 350 400 450 500 550 600 650 700 750 800
Baseline eosinophil count (cells mm3)
D
2·0
1·8
1·6
1·4
1·2
1·0
0·8
0·6
0·4
0·2
0
BGF MDI 320/18/9·6 µg
BFF MDI 320/9·6 µg
0 50 100 150 200 250 300 350 400 450 500 550 600 650 700 750 800
Baseline eosinophil count (cells mm3)

TRINITY: Subgroup analysis (mod./severe exacerbation)

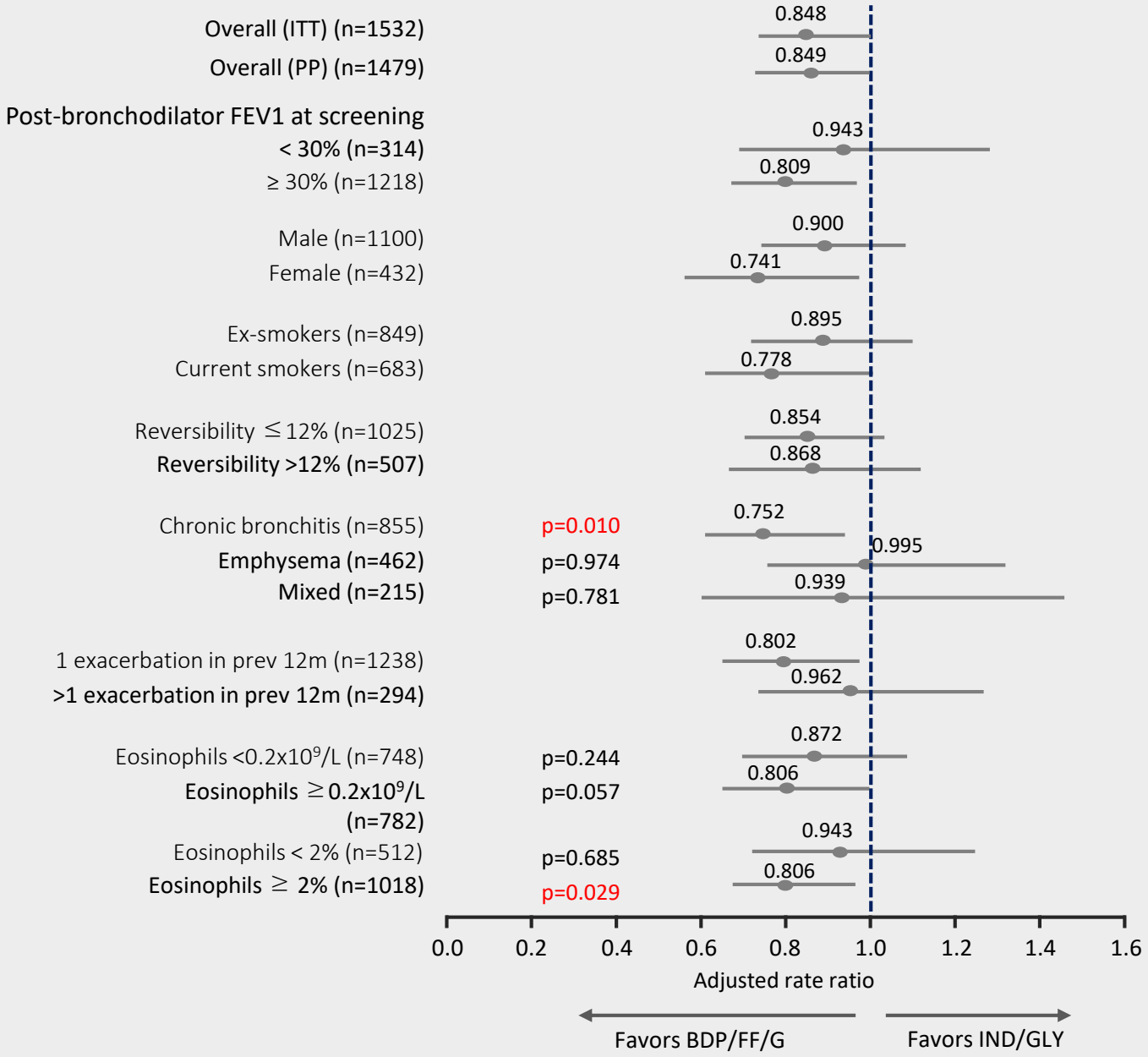
BDP/FF/G vs tiotropium



Ref. TRINITY_Supplementary appendix

TRIBUTE: Subgroup analysis (mod./severe exacerbation)

BDP/FF/G vs IND/GLY



Ref. TRIBUTE_Supplementary appendix

Conclusion

- Triple therapy can reduce exacerbations in COPD patients with high risk of exacerbation compared to ICS/LABA, LABA/LAMA
- ICS (esp. fluticasone) is associated with increased pneumonia
- ICS response is associated blood eosinophil