2022.04.08 KATRD 2022년도 제2차 Interactive Learning

Landmark Studies in Respiratory Disease - COPD

Randomized Controlled Trial vs. Real World Data – LAMA/LABA –

민 경 훈 / 문 지 용

국내 흡입제 출시 현황

고려대학교 KOREA UNIVERSITY

1981년
벤톨린

1994년
풀미코트

1996년
후릭소타이드

2000년
세레타이드

2001년
심비코트

2005년
스피리바핸디헬러

2008년
알베스코

2009년
포스터

2010년
온브리즈

2011년
스피리바레스피맷

2014년
플루티폼

2015년
아노로

에어플루잘

에클리라

플루테롤

듀어클리어

2016년
심비코트 라피헬러

인크루즈

바헬바 레스피맷

2017년
포스터 넥스트할러

2021년
트렐리지

에너제어, 어택트라

조터나

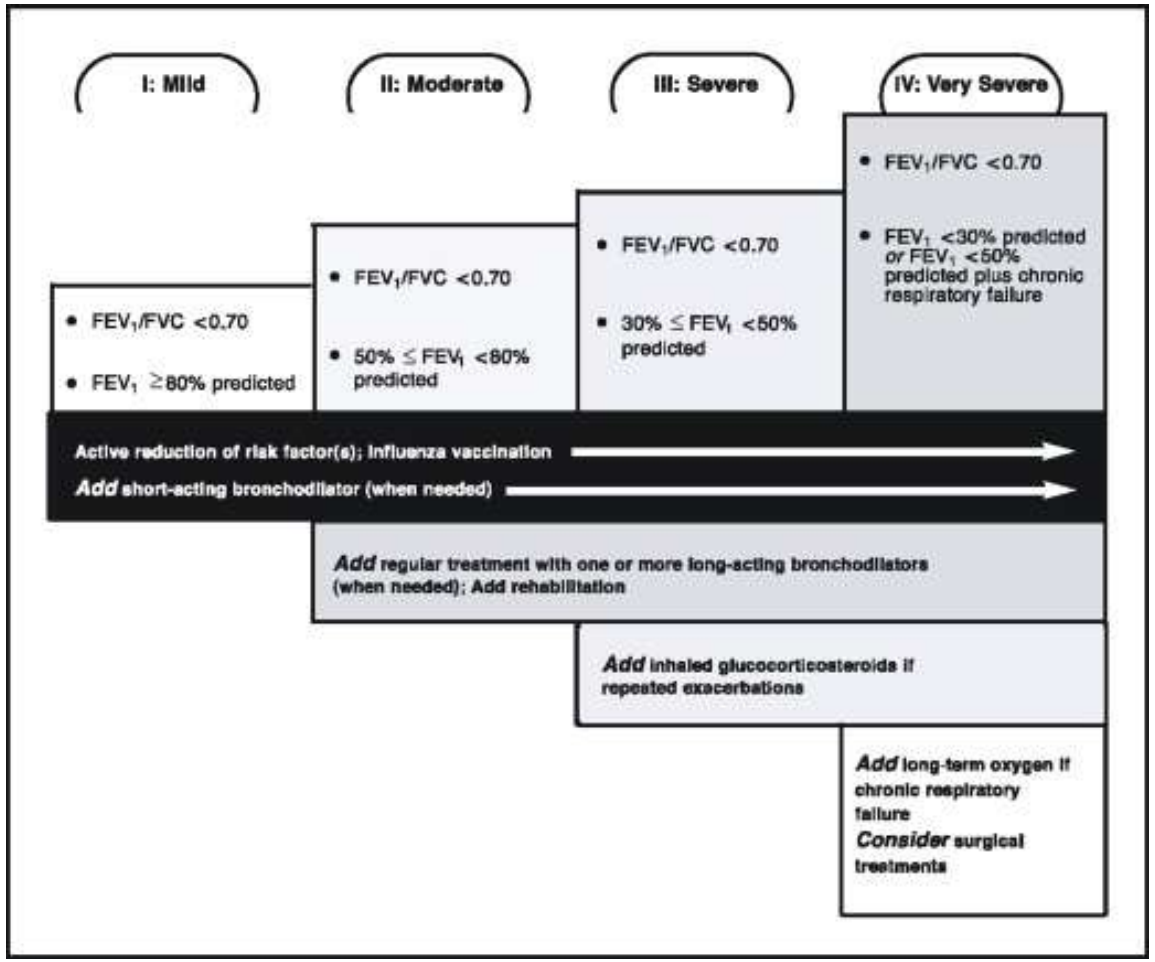
렐바

출시 대기
트림보우

LABA and LAMA Position in Previous COPD Guideline

고려대학교 KOREA UNIVERSITY

2010년

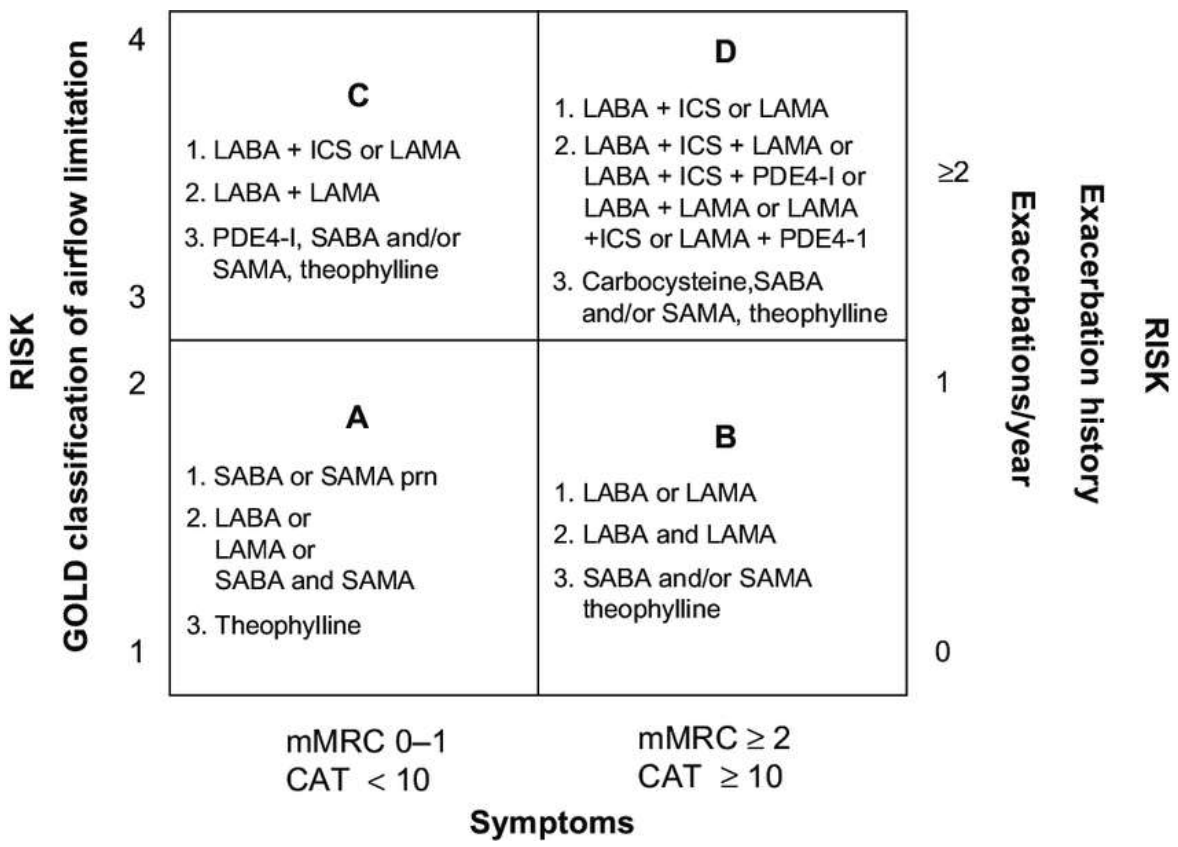


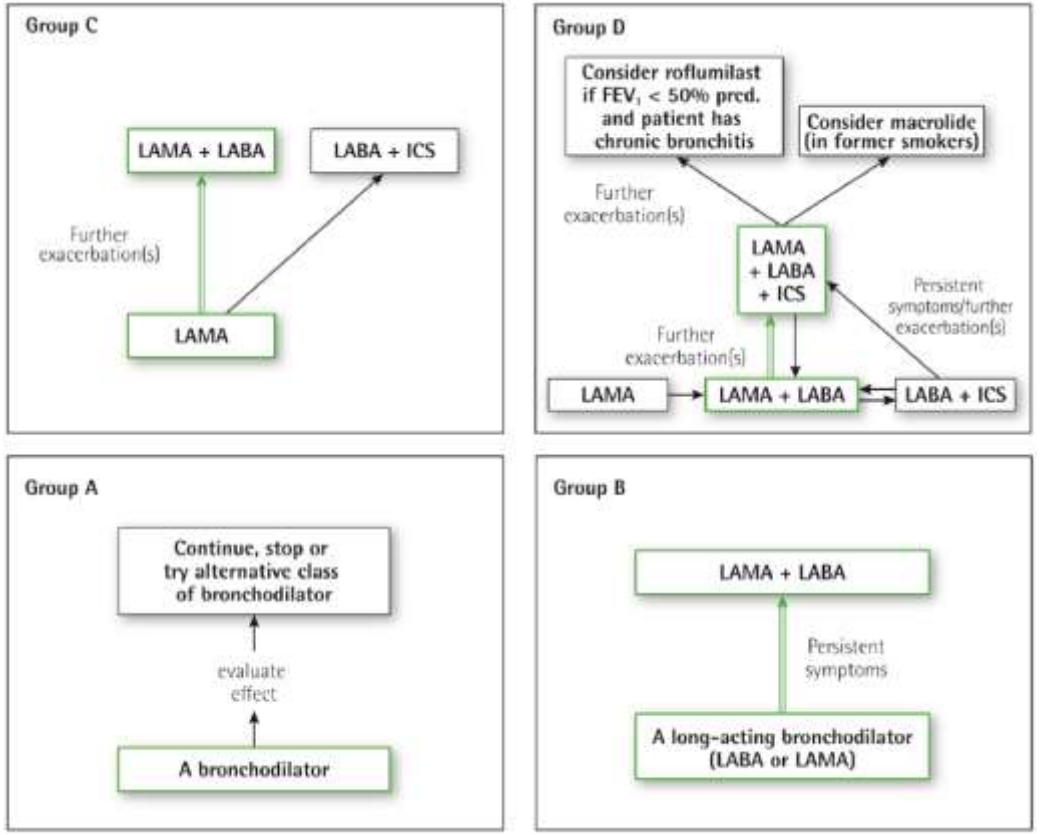
2005년

중증도	제0기	제1기	제2기	제3기	제4기
	위험시기	경증	중등증	중증	고도중증
특징	만성증상 위험인자에 노출 정상 폐기능	$FEV_1/FVC<70\%$ $FEV_1 \geq 80\%$ 증상 있거나 없음	$FEV_1/FVC<70\%$ $50\% \leq FEV_1<80\%$ 증상 있거나 없음	$FEV_1/FVC<70\%$ $30\% \leq FEV_1<50\%$ 증상 있거나 없음	$FEV_1/FVC<70\%$ $FEV_1<30\%$ 혹은 $FEV_1<50\%$이면서 만성호흡부전 동반
	위험인자 회피: 인플루엔자 백신				
		필요 시 속효성 기관지확장제 추가			
			한 가지 이상의 지속성 기관지확장제 정규치료 추가 호흡재활 추가		
				반복 악화 시엔 흡입 부신피질호르몬제 추가	
					만성호흡부전 시엔 장기산소요법 추가 외과적 치료 고려

GOLD Report 2010
COPD 진료지침 2005 대한결핵 및 호흡기학회

LABA and LAMA Position in Previous COPD Guideline





GOLD Report 2011
GOLD Report 2017

LABA and LAMA Position in Previous COPD Guideline

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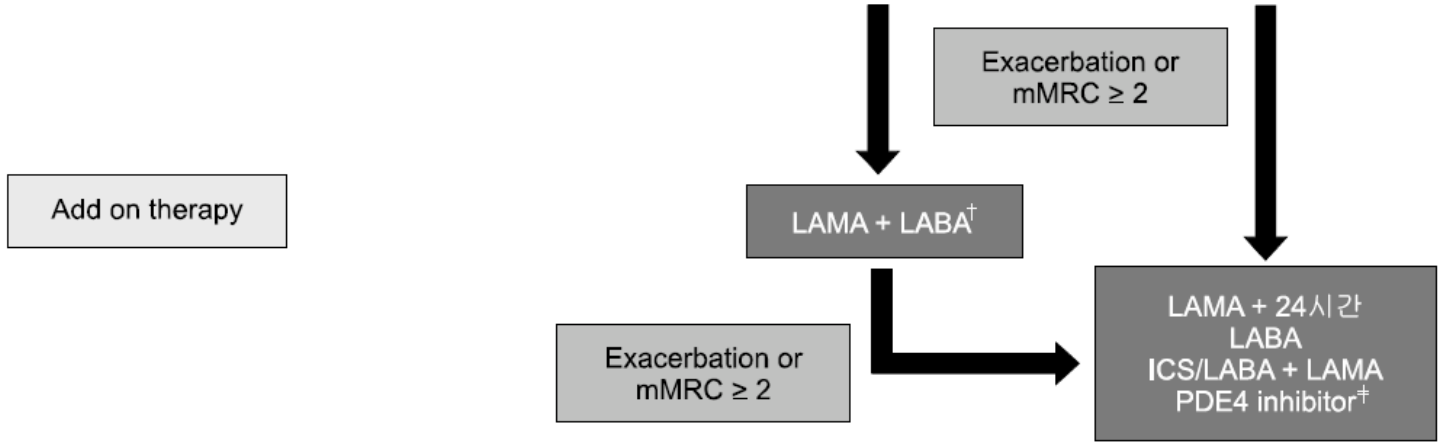
• 안정 시 COPD의 약물 단계치료

	$FEV_1 \geq 60\%$ pred. and 0~1 exacerbation/year		$FEV_1 < 60\%$ pred. or ≥ 2 exacerbation/year or history of AE COPD* related admission (다군)
	mMRC 0~1 or CAT < 10 (가군)	mMRC ≥ 2 or CAT ≥ 10 (나군)	
	Short-acting beta2-agnoist as required		
First choice	Short-acting beta2-agnoist as required	LAMA or LABA†	LAMA or 24시간 LABA or ICS/LABA or LABA + LAMA



COPD 진료지침 2014 대한결핵 및 호흡기학회

Initiation of Pharmacological Treatment of Stable COPD

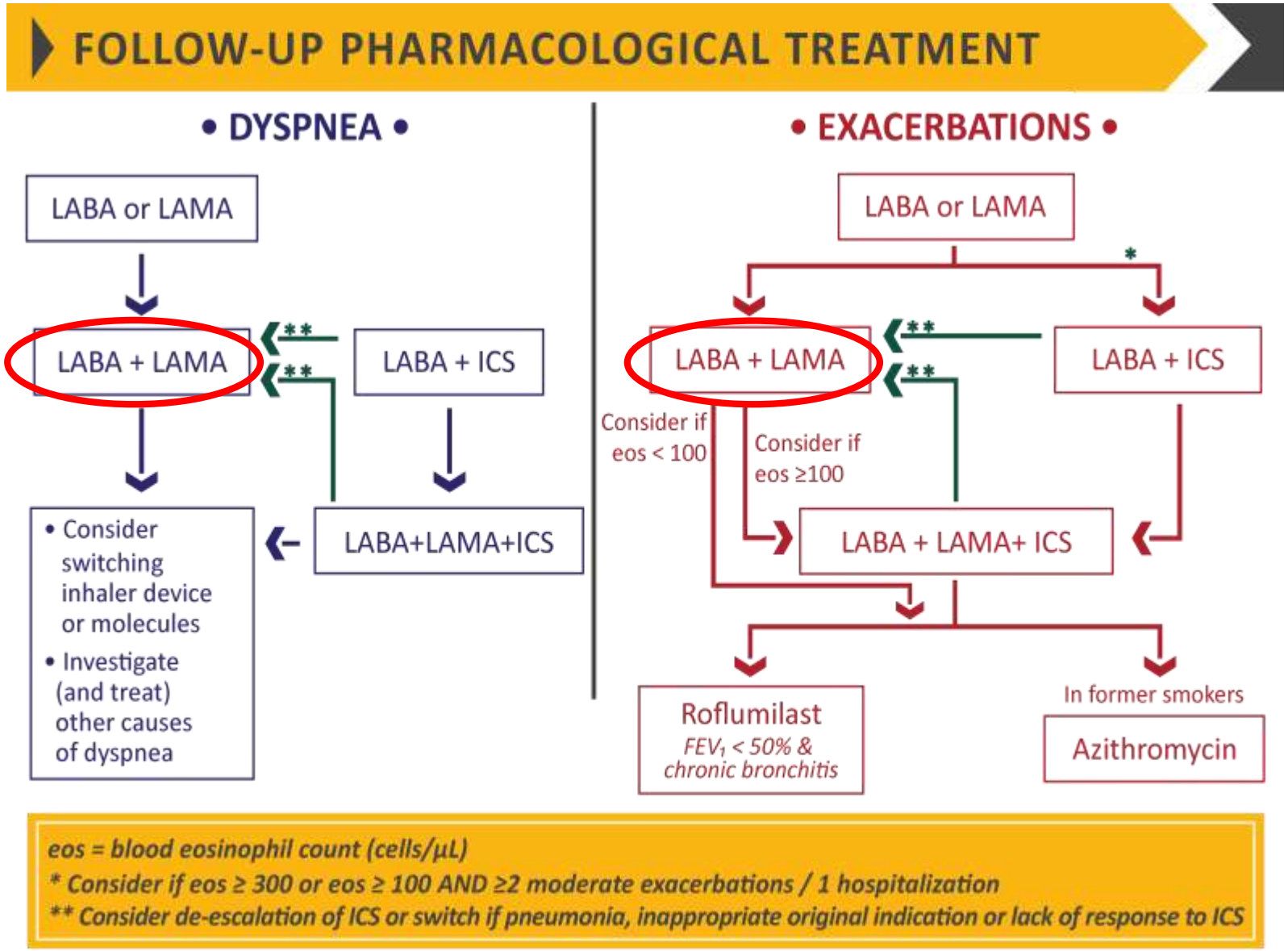
고려대학교 KOREA UNIVERSITY

INITIAL PHARMACOLOGICAL TREATMENT

≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization	**Group C** LAMA	**Group D** LAMA or LAMA + LABA* or ICS + LABA** *Consider if highly symptomatic (e.g. CAT > 20) **Consider if eos ≥ 300
0 or 1 moderate exacerbations (not leading to hospital admission)	**Group A** A Bronchodilator	**Group B** A Long Acting Bronchodilator (LABA or LAMA)
	mMRC 0-1 CAT < 10	mMRC ≥ 2 CAT ≥ 10

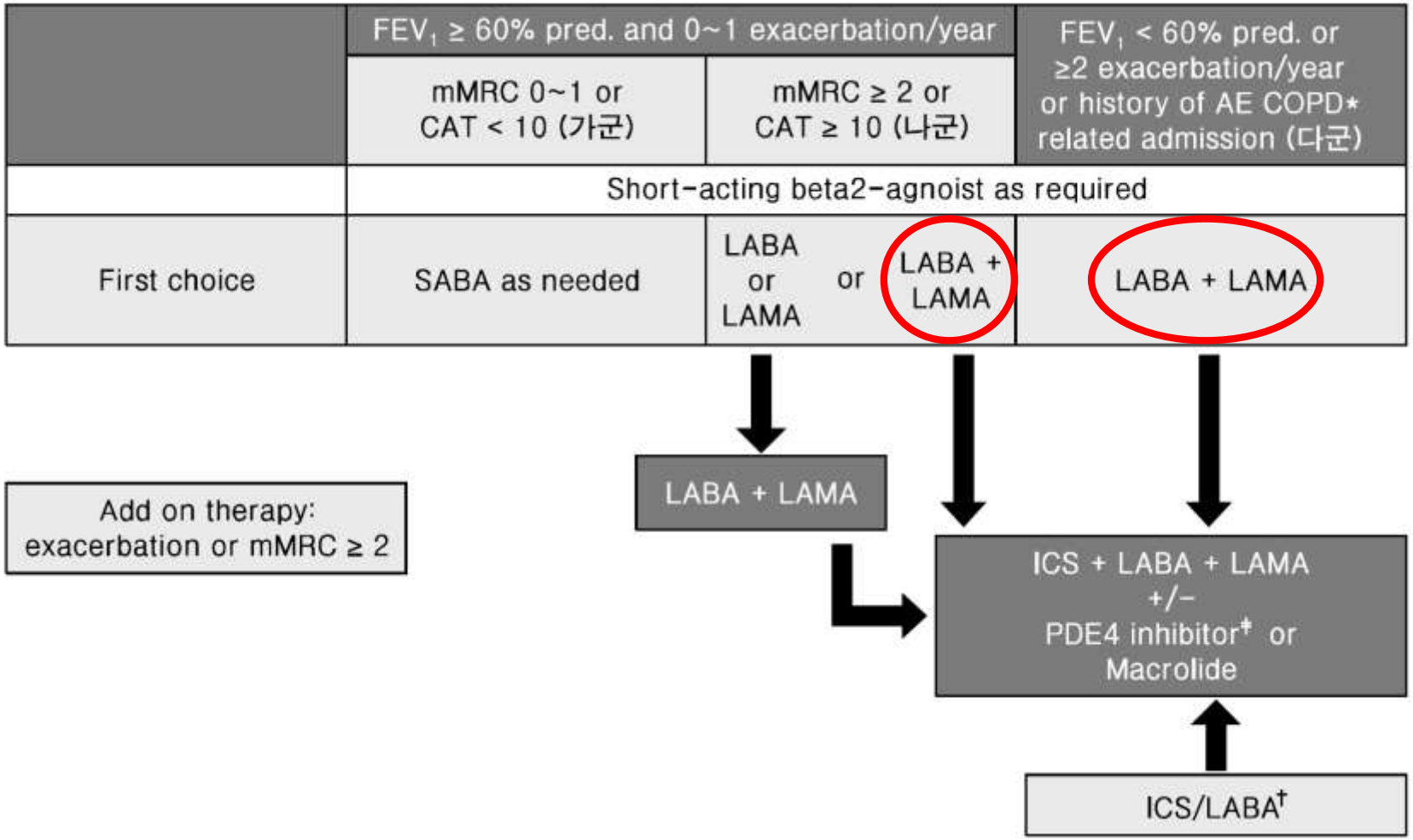
GOLD Report 2022

Follow-up Pharmacological Treatment of Stable COPD



GOLD Report 2022

안정 시 COPD의 약물 단계 치료



COPD 진료지침 2018개정, 대한결핵 및 호흡기학회

LABA+LAMA and LABA/LAMA

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LABA

온브리즈
(Indacaterol)

LAMA

스피리바
(Tiotropium)

인크루즈
(Umeclidinium)

애클리라
(Aclidinium)

LAMA/LABA

바헬바
(Olodaterol + Tiotropium)

아노로
(Vilanterol / Umeclidinium)

조터나
(Indacaterol + Glycopyrronium)

듀어클리어
(Formoterol + Aclidinium)

Trends in the Utilization of COPD Therapeutic Regimen

고려대학교 KOREA UNIVERSITY

Trends in the utilisation of COPD therapeutic regimens before and after the introduction of LAMA/LABA combination products: A population-based study

Lianne Parkin[a], Wayne Khuu[b], Matthew B. Stanbrook[b,c,d], Mina Tadrous[b,e,f], Diana Martins[e], Tara Gomes[b,d,e,f,*]

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[b] The Institute for Clinical Evaluative Sciences, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada
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[e] Li Ka Shing Knowledge Institute, 30 Bond St, Toronto, Ontario M5B 1W8, Canada
[f] The Leslie Dan Faculty of Pharmacy, University of Toronto, 144 College Street, Toronto, Ontario M5S 3M2, Canada

- **Administrative healthcare data from Ontrario, Canada**
- **≥ 65 years old with COPD**
- **January 2010 ~ May 2016**
- **N: 567,324**

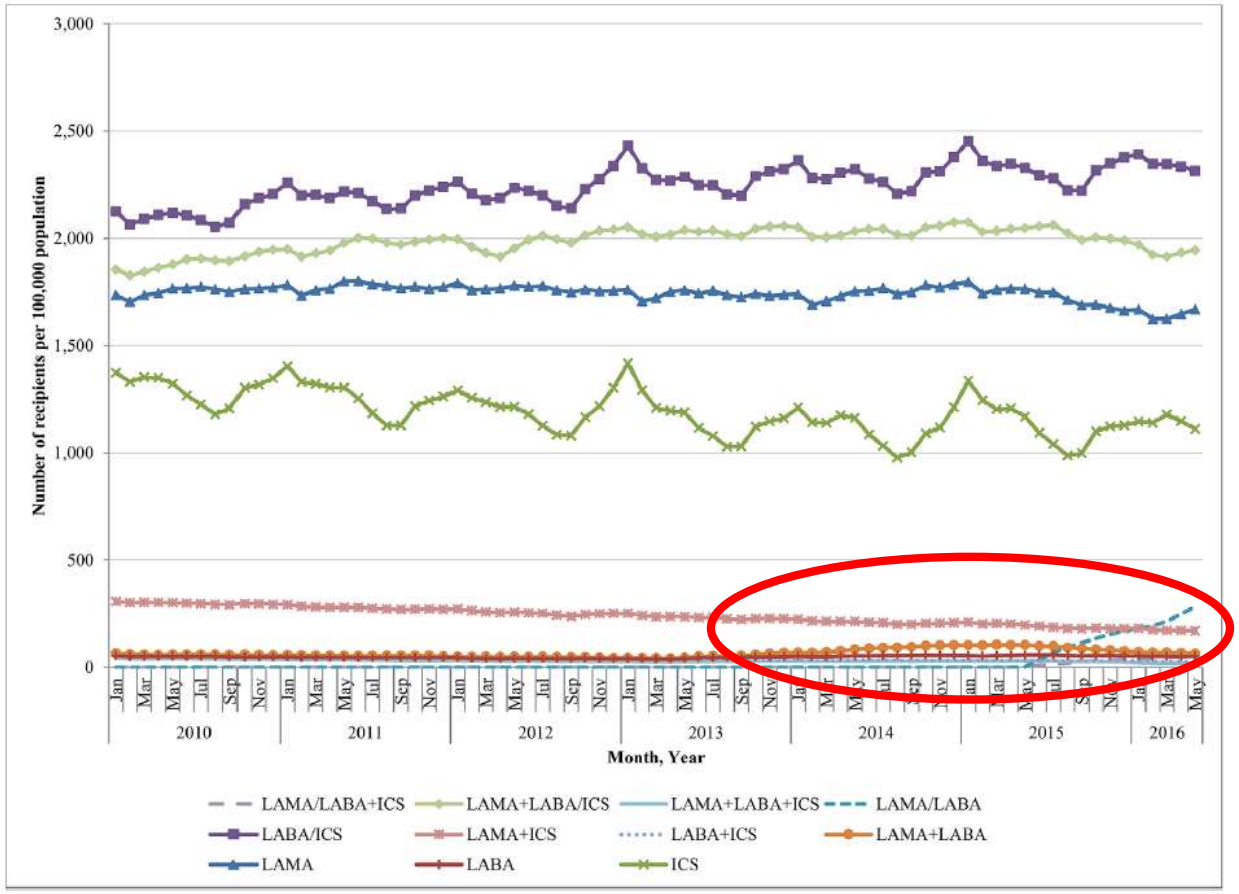

Fig. 1. Number of recipients (per 100,000 population) in each COPD therapy group by month, 2010–2016 (2-column fitting image).

Parkin L, et al. Respiratory Research 2018;143:1-7

Trends in the Utilization of COPD Therapeutic Regimen

고려대학교 KOREA UNIVERSITY

ORIGINAL RESEARCH

Relationship Between Changes in Inhalation Treatment Level and Exacerbation of Chronic Obstructive Pulmonary Disease: Nationwide the Health Insurance and Assessment Service Database

- **Health Insurance Review and Assessment Service (HIRA)**
- **May 2014 ~ April 2017**
- **Total of 68,942 COPD patients were included for 3 years of longitudinal analyses**

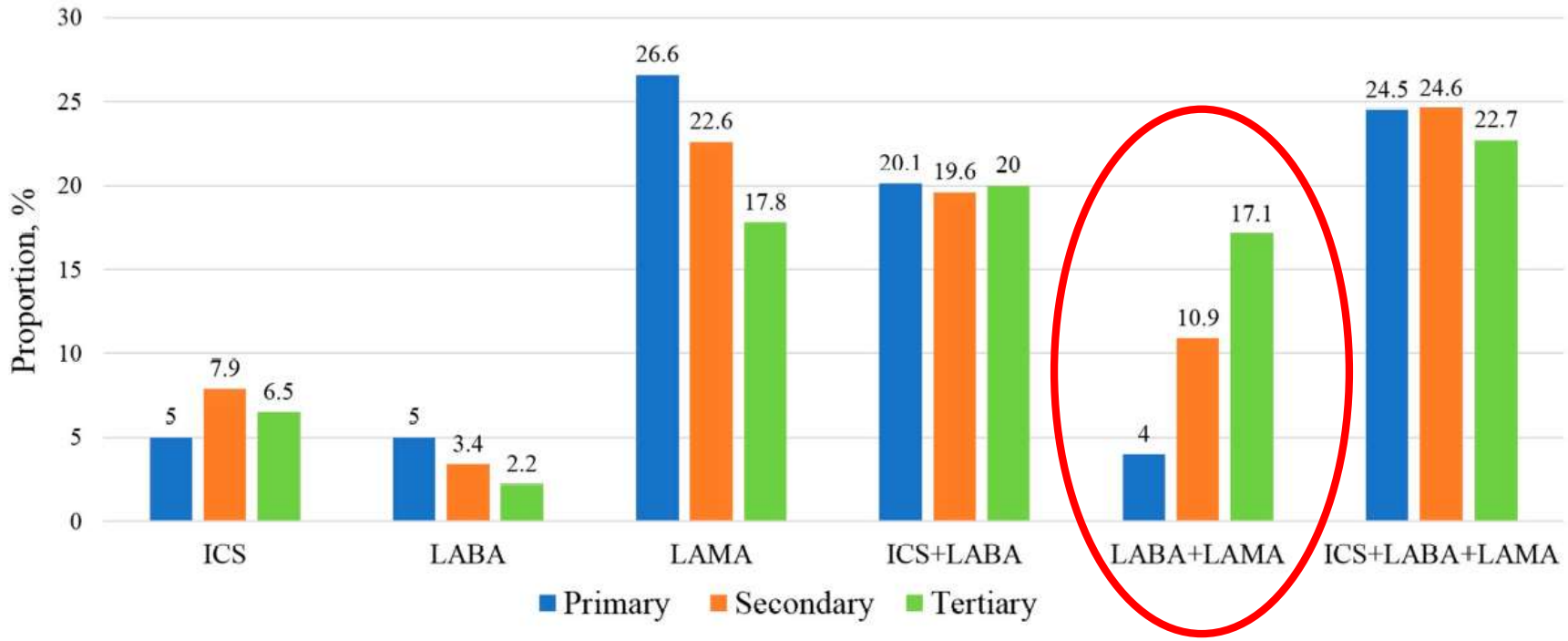

Figure 1 Proportion of COPD medication in each assessment.

Jo YS, et al. Int J Chron Obstruct Pulmon Dis 2020;15:1367-1375.

Trends in the Utilization of COPD Therapeutic Regimen

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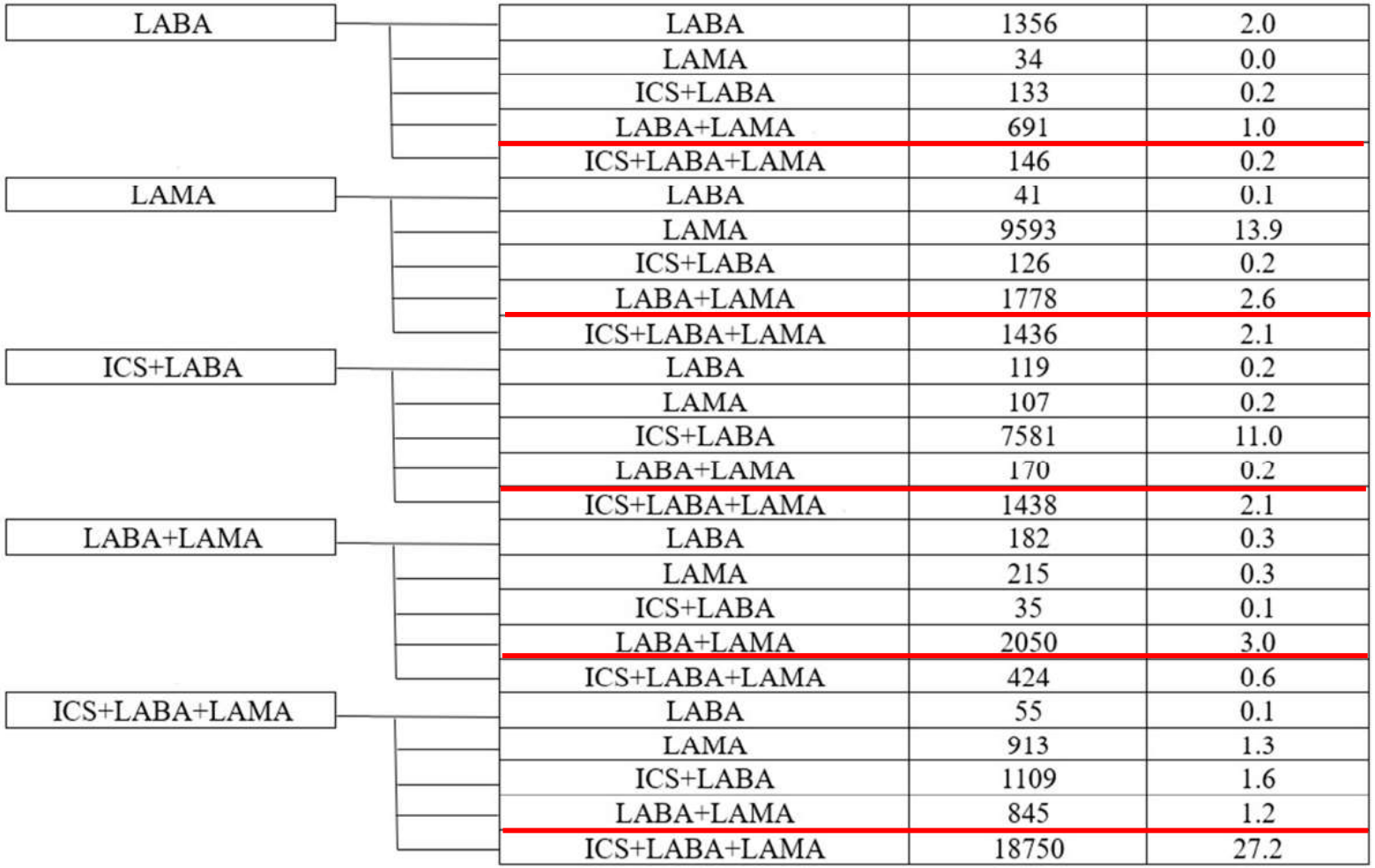


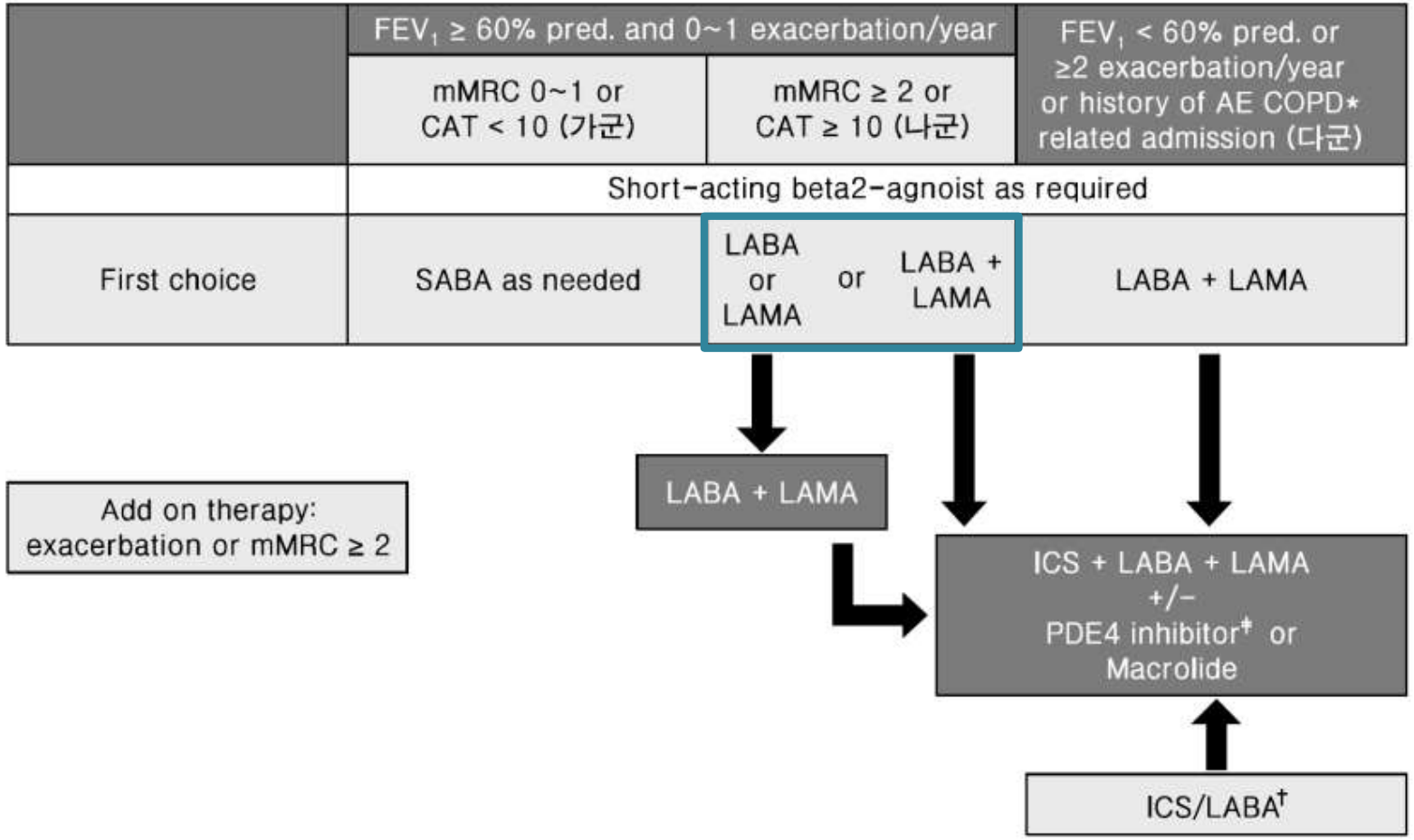
First	Second	N	%
LABA	LABA	1356	2.0
	LAMA	34	0.0
	ICS+LABA	133	0.2
	LABA+LAMA	691	1.0
	ICS+LABA+LAMA	146	0.2
LAMA	LABA	41	0.1
	LAMA	9593	13.9
	ICS+LABA	126	0.2
	LABA+LAMA	1778	2.6
	ICS+LABA+LAMA	1436	2.1
ICS+LABA	LABA	119	0.2
	LAMA	107	0.2
	ICS+LABA	7581	11.0
	LABA+LAMA	170	0.2
	ICS+LABA+LAMA	1438	2.1
LABA+LAMA	LABA	182	0.3
	LAMA	215	0.3
	ICS+LABA	35	0.1
	LABA+LAMA	2050	3.0
	ICS+LABA+LAMA	424	0.6
ICS+LABA+LAMA	LABA	55	0.1
	LAMA	913	1.3
	ICS+LABA	1109	1.6
	LABA+LAMA	845	1.2
	ICS+LABA+LAMA	18750	27.2

Figure 3 Changes of inhaler treatment between first and second assessment.

Ji YS, et al. Int J Chron Obstruct Pulmon Dis 2020;15:1367-1375.

Voting#1

"나"군에서 첫 흡입제로 무엇을 처방하는 것이 좋을까?



1. LAMA
2. LABA
3. LAMA-LABA

Voting#2

LAMA-LABA로 기대되는 효과는?

고려대학교 KOREA UNIVERSITY

1. 폐기능 개선

2. 호흡곤란 개선

3. 운동능력 향상

4. 삶의 질 향상

5. 급성악화 예방

LAMA-LABA Fixed Dose Combinations

Brand Name	LAMA	LABA	LAMA/LABA	Availability in Korea
Xoterna Breezehaler (Korea), Utibro Breezehaler (Europe & Canada) Ultibron Neohaler (USA)	Glycopyrrolate 50 μg 15.6 μg BID	Indacaterol 110 μg 27.5 μg BID	GLY/IND or **IND/GLY**	O
Vahelva Respimat (Korea) Stiolto Respimat (USA) Inspiolto Respimat (Canada)	Tiotropium 2.5 μg	Olodaterol 2.5 μg	**TIO/OLO**	O
Bevespi Aeroshere	Glycopyrrolate	Formoterol	GLY/FOR (GFF)	X
Anoro Ellipta Laventair Ellipta	Umeclidinium 62.5 μg	Vilanterol 25 μg	**UMEC/VIL**	O
DuaKlir Genuair	Aclidinium 340 μg	Formoterol 12 μg	ACL/FOR	O

Selected Outcomes and Definition of Significant Differences

Outcome	MCID	Comments
Trough FEV_1	**100** mL	No MCID established for AUC, FVC
Health-related quality of life	**SGRQ**: 4 units	**Higher** score indicate **poorer** health status
Dyspnea	**TDI** ≥1 unit	–
Rescue medication use	No validated MCID	–
Exacerbations	1 exacerbation/year, 22% reduction	**Definition** of AECOPD **varies**. **Seasonal variation** in frequency impacts studies <12 months
Daily respiratory symptoms	**e-RS** total >-2	Suggested responder definition
Exercise Tolerance	**6MWT**: 25 – 80 m	
Safety		Major adverse cardiovascular events (**MACE**)

Modified from Cohen JS et al. Int J Chron Obstruct Pulmon Dis 2016;11:785-97. [PMID: 27143870]

Contents

Lung Function (Trough FEV1, FEV1 AUC)

- IND/GLY: SHINE, ENLIGHTEN, BEACON, ILLUMINATE, LANTERN
- TIO/OLO: TONADO, VIVACITO, OTEMTO
- UMEC/VIL: DB2113373, DB2113360, DB2113361, ZEP177155, EMAX

Symptom (Dyspnea Index) & Health-related quality of life (SGRQ)

- IND/GLY: BRIGHT, BLAZE, ILLUMINATE, LANTERN
- TIO/OLO: OTEMTO
- UMEC/VIL: DB2113361, ZEP177155, EMAX

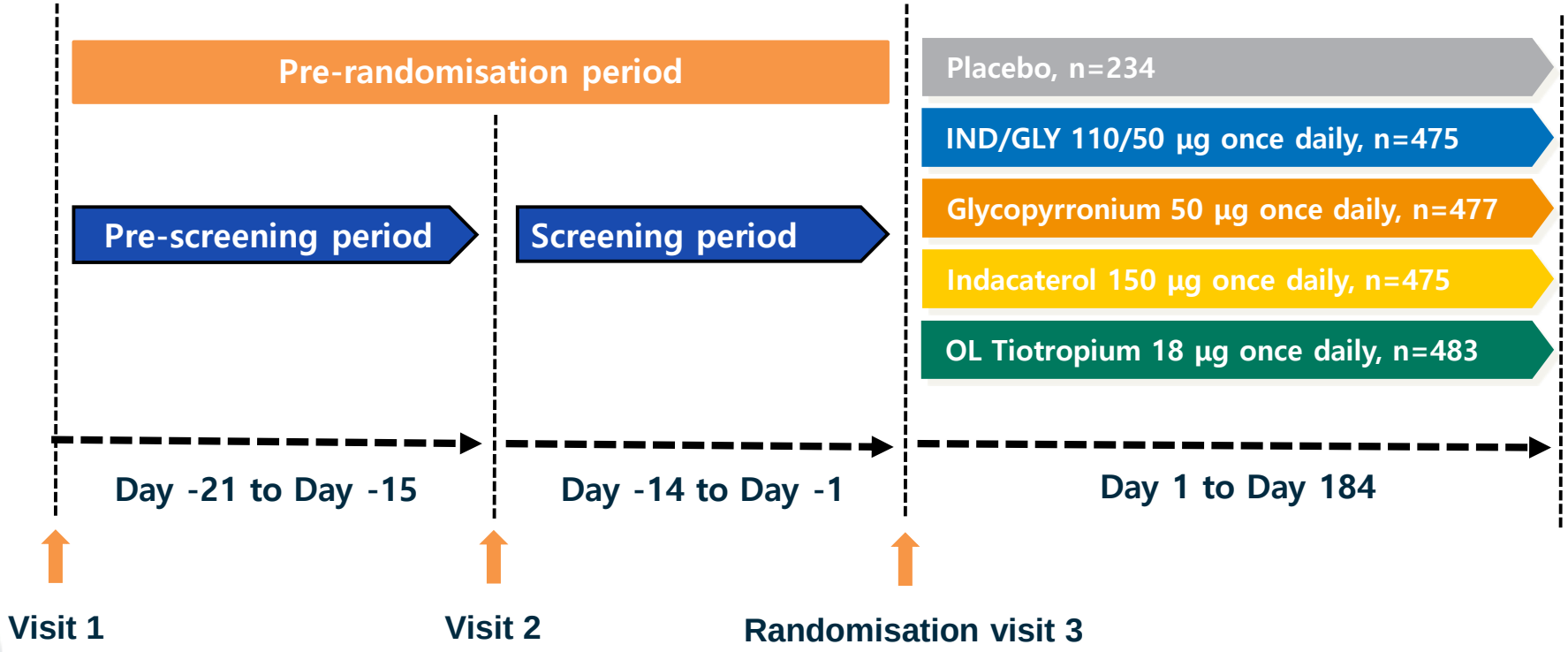
Acute Exacerbation (Annual Rate of Exacerbation)

- IND/GLY: SPARK, FLAME
- TIO/OLO: DYNAGITO
- (UMEC/VIL: DB2113373, DB2113361, ZEP177155, EMAX)

Lung Function

LABA/LAMA (Ind/Gly) vs. LABA (Ind) vs. LAMA (Gly) vs. LAMA (Tio)
– SHINE (Design) –

- **2144** patients with moderate-to-severe COPD (GOLD II or III)
- **no AE** in 1 year (74.6%)
- Ind/Gly (110/50) : Ind (150) : Gly (50) : Tio (18, open label) : placebo = 2:2:2:2:1
- The primary end-point: **trough FEV1** at week 26



Bateman ED et al. Eur Respir J 2013;42:1484-94. [PMID: 23722616]

LABA/LAMA (Ind/Gly) vs. LABA (Ind) vs. LAMA (Gly) vs. LAMA (Tio)
– SHINE (FEV_1) –

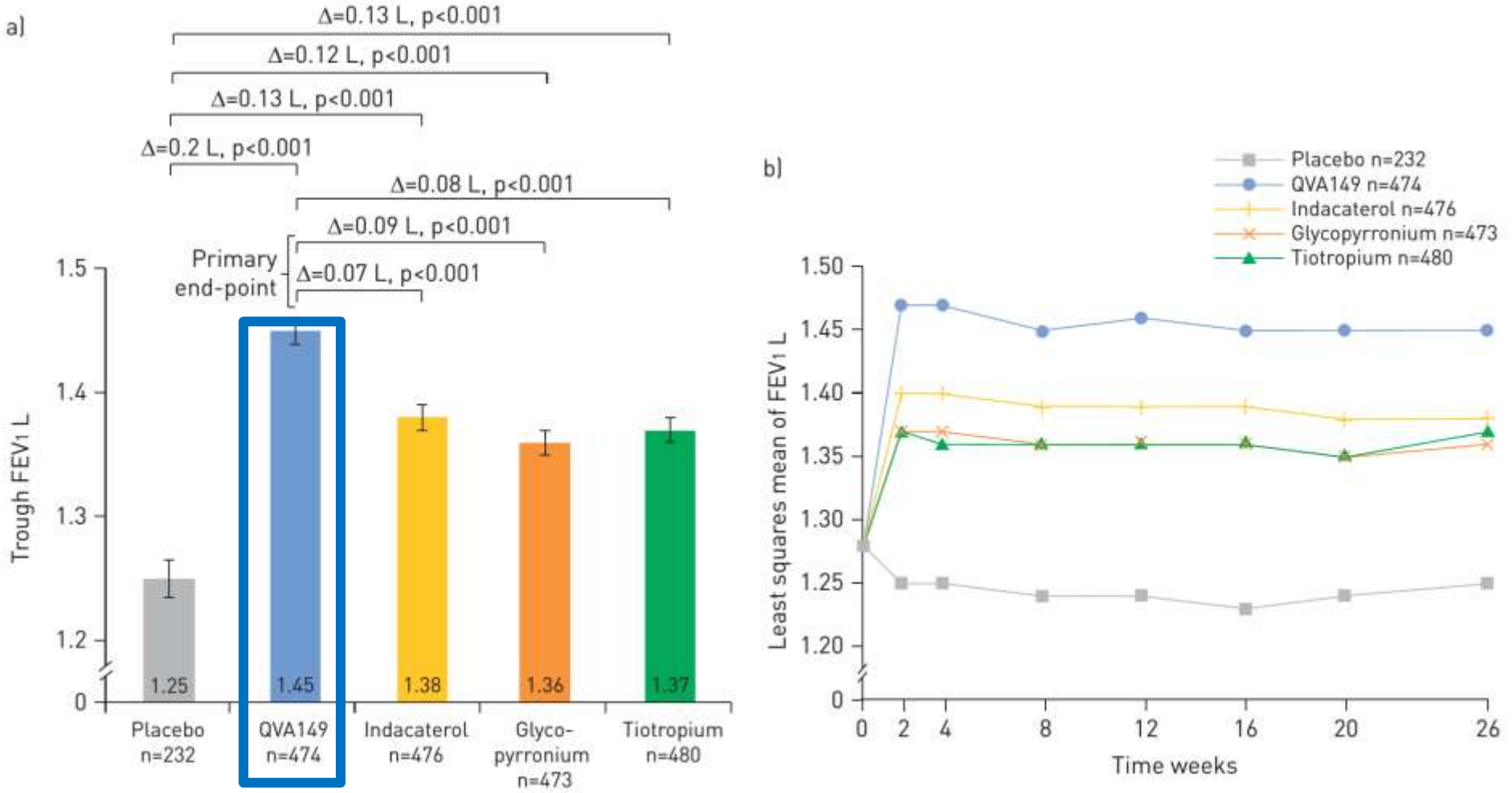
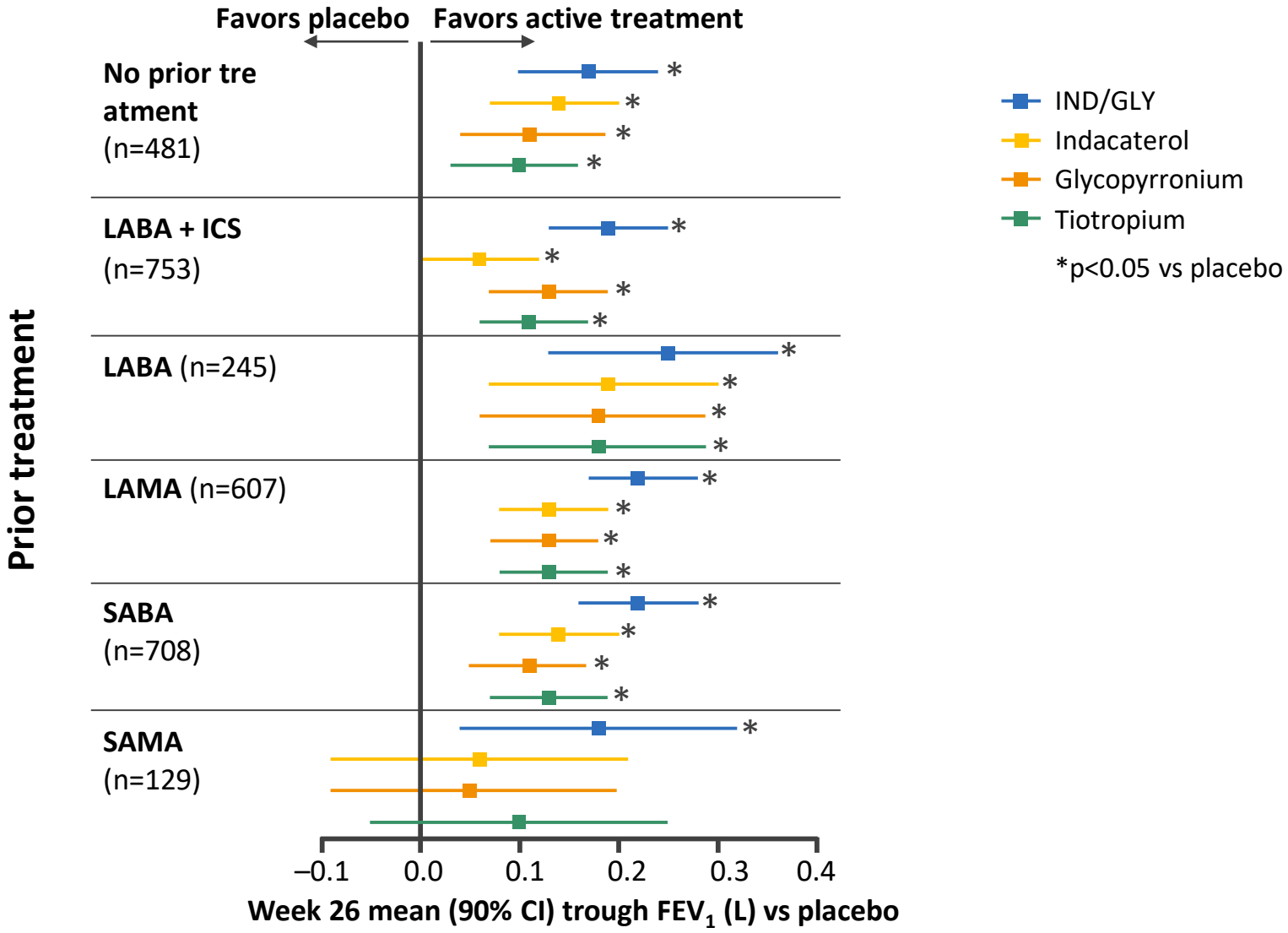


FIGURE 3 Trough forced expiratory volume in 1 s (FEV_1) a) at week 26 and b) over the entire 26-week treatment period. a) Data are presented as least squares mean ± SE. One-sided adjusted p-values are presented for comparisons in the statistical gatekeeping procedure and two-sided p-values are presented for all other comparisons. b) QVA149 was superior to all active treatments and placebo at all timepoints (all $p<0.001$). n: number per treatment group in the full analysis set.

Bateman ED et al. Eur Respir J 2013;42:1484-94. [PMID: 23722616]

IND/GLY also provided benefits in trough FEV_1 regardless of prior treatment



Bateman ED et al. Eur Respir J 2013;42:1484-94. [PMID: 23722616]

LABA/LAMA (Ind/Gly) vs. Placebo
– ENLIGHTEN (Design) –

- 52-week, multicenter, double-blind, parallel-group, placebo-controlled study
- moderate-to-severe COPD (FEV1 of **≥ 30% and < 80%**; n=339; **no AE in the 6** weeks)
- Primary endpoint: **safety & tolerability** for treatment-emergent adverse events (AEs)

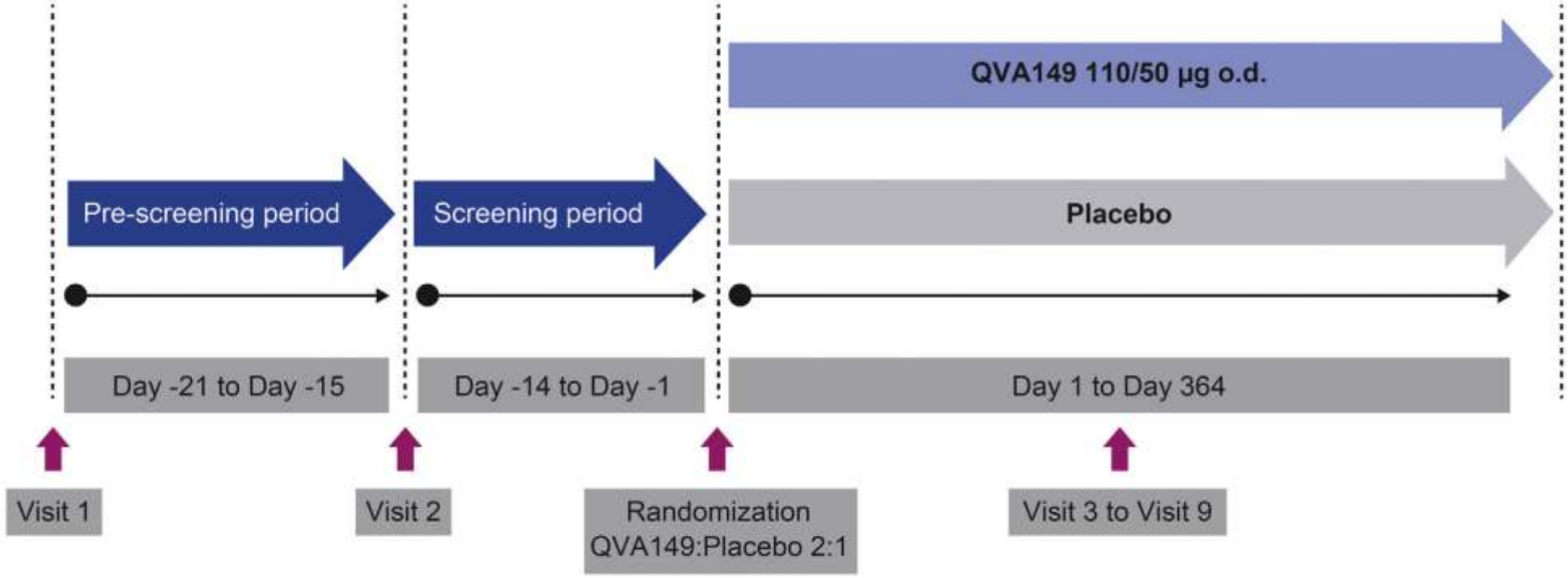
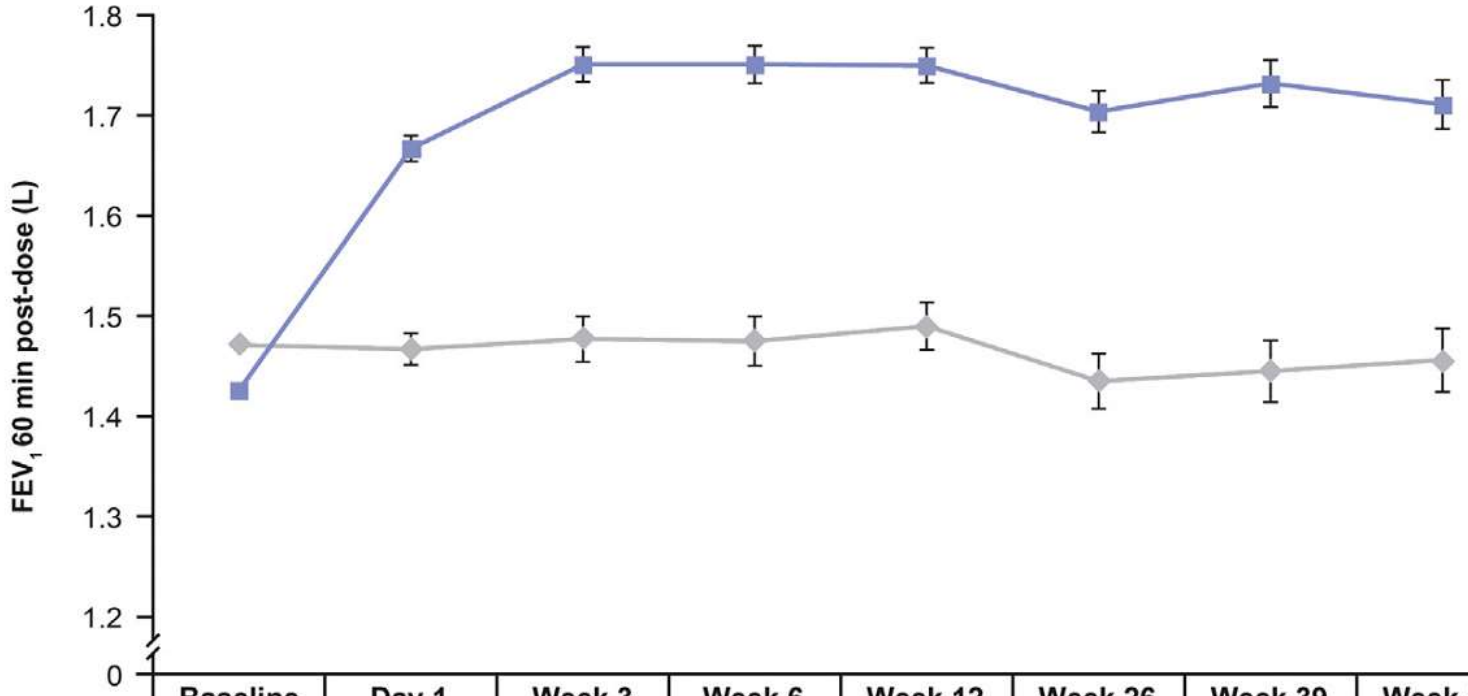


Figure 1 Study design.

Dahl R et al. Respir Med 2013;107:1558-67. [PMID: 23867808]

LABA/LAMA (Ind/Gly) vs. Placebo – ENLIGHTEN (postBD FEV1) –



	Baseline	Day 1	Week 3	Week 6	Week 12	Week 26	Week 39	Week 52
Placebo	1.471	1.467	1.477	1.475	1.490	1.435	1.445	1.456
QVA149	1.426	1.667	1.751	1.751	1.750	1.704	1.732	1.711

Baseline data collected pre-dose; Data are LS means ± SE; QVA149-placebo difference: $p < 0.001$ at all timepoints over 52 weeks

- QVA149 demonstrated a good safety and tolerability profile, providing rapid and sustained bronchodilation over 52 weeks in patients with moderate-to-severe COPD

Dahl R et al. Respir Med 2013;107:1558-67. [PMID: 23867808]

Open Access Full Text Article

ORIGINAL RESEARCH

Efficacy and safety of QVA149 compared to the concurrent administration of its monocomponents indacaterol and glycopyrronium: the BEACON study

Ronald Dahl[1]
Dalal Jadayel[2]
Vijay KT Alagappan[3]
Hungta Chen[3]
Donald Banerji[3]

[1]Department of Dermatology, Allergy Centre, Odense University Hospital, Odense, Denmark; [2]Novartis Horsham Research Centre, Horsham, UK; [3]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

- In this multicenter, double-blind, parallel group study, patients with stage II or stage III COPD
- The primary endpoint was to evaluate the **noninferiority** of QVA149 as compared with concurrent administration of **IND+GLY**, for **trough FEV1** after **4 weeks** of treatment.

BEACON

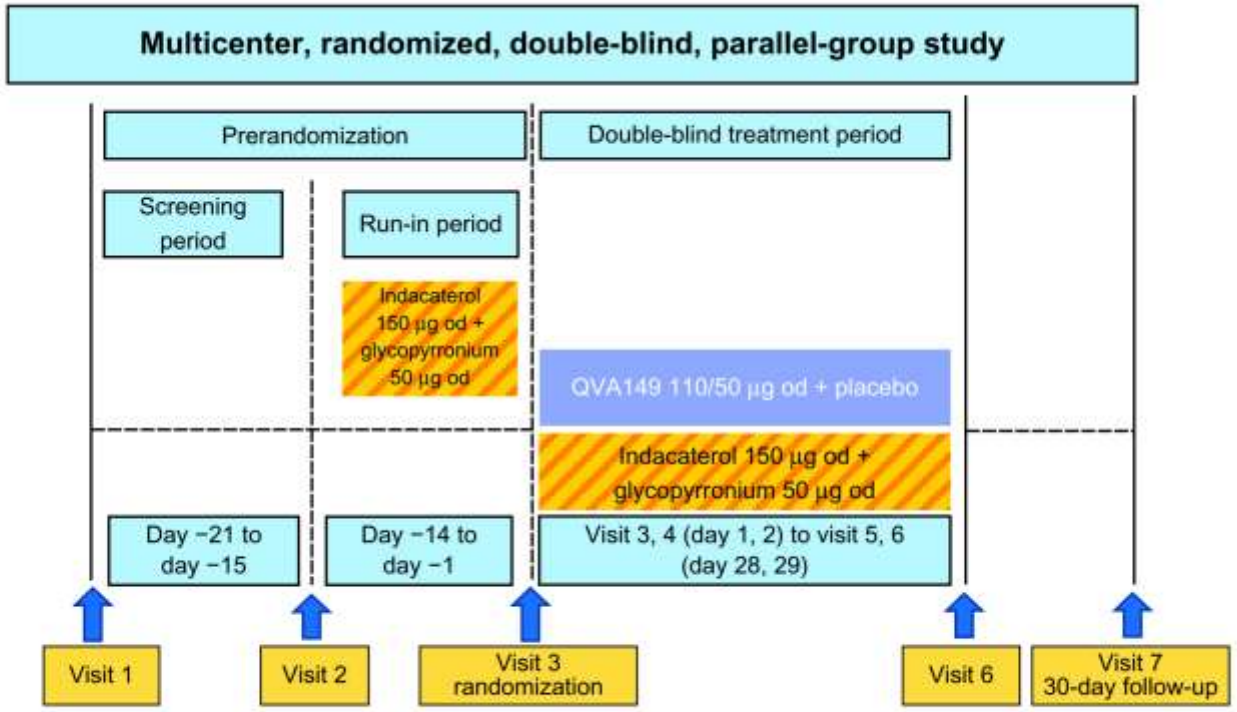
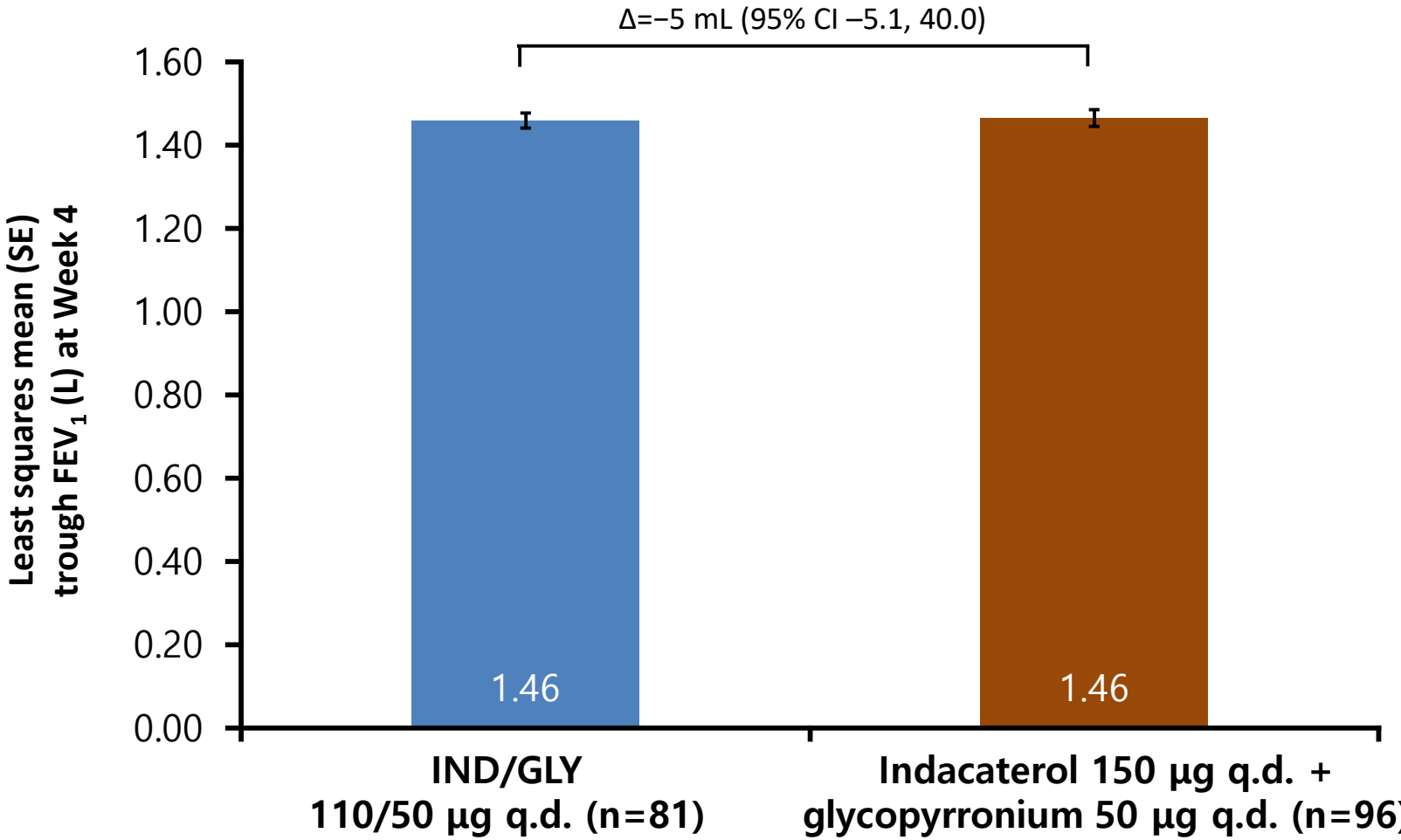


Figure 1 BEACON study design.
Abbreviation: od, once daily.

Dahl R et al. Int J Chron Obstruct Pulmon Dis 2013;8:501-8. [PMID: 24159259]

IND/GLY was non-inferior to the free combination of indacaterol + glycopyrronium for trough FEV_1 at Week 4



Dahl R et al. Int J Chron Obstruct Pulmon Dis 2013;8:501-8. [PMID: 24159259]

LABA/LAMA (Ind/Gly) vs. ICS/LABA (SFC) – ILLUMINATE (Design) –

- efficacy, safety, and tolerability of **IND/GLY** versus **salmeterol–fluticasone (SFC)**
- 523 patients with moderate-to-severe COPD (**without AE** in the previous year)
- The primary endpoint was to demonstrate **the superiority of IND/GLY** compared with **SFC** for the standardised area under the curve from 0 to 12 h post dose for forced expiratory volume in 1 second (**FEV1 AUC_{0-12h}**) after **26** weeks of treatment.

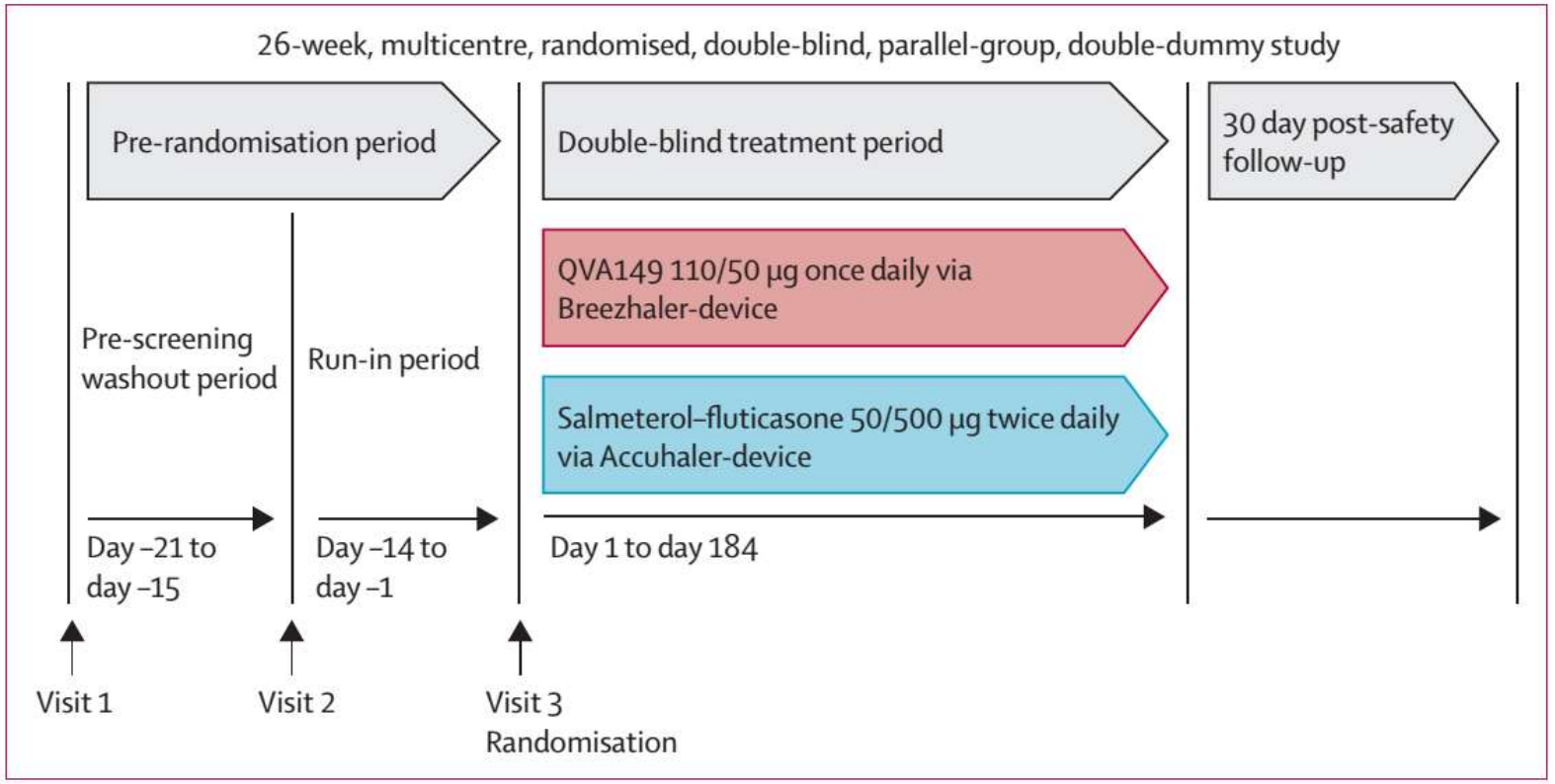
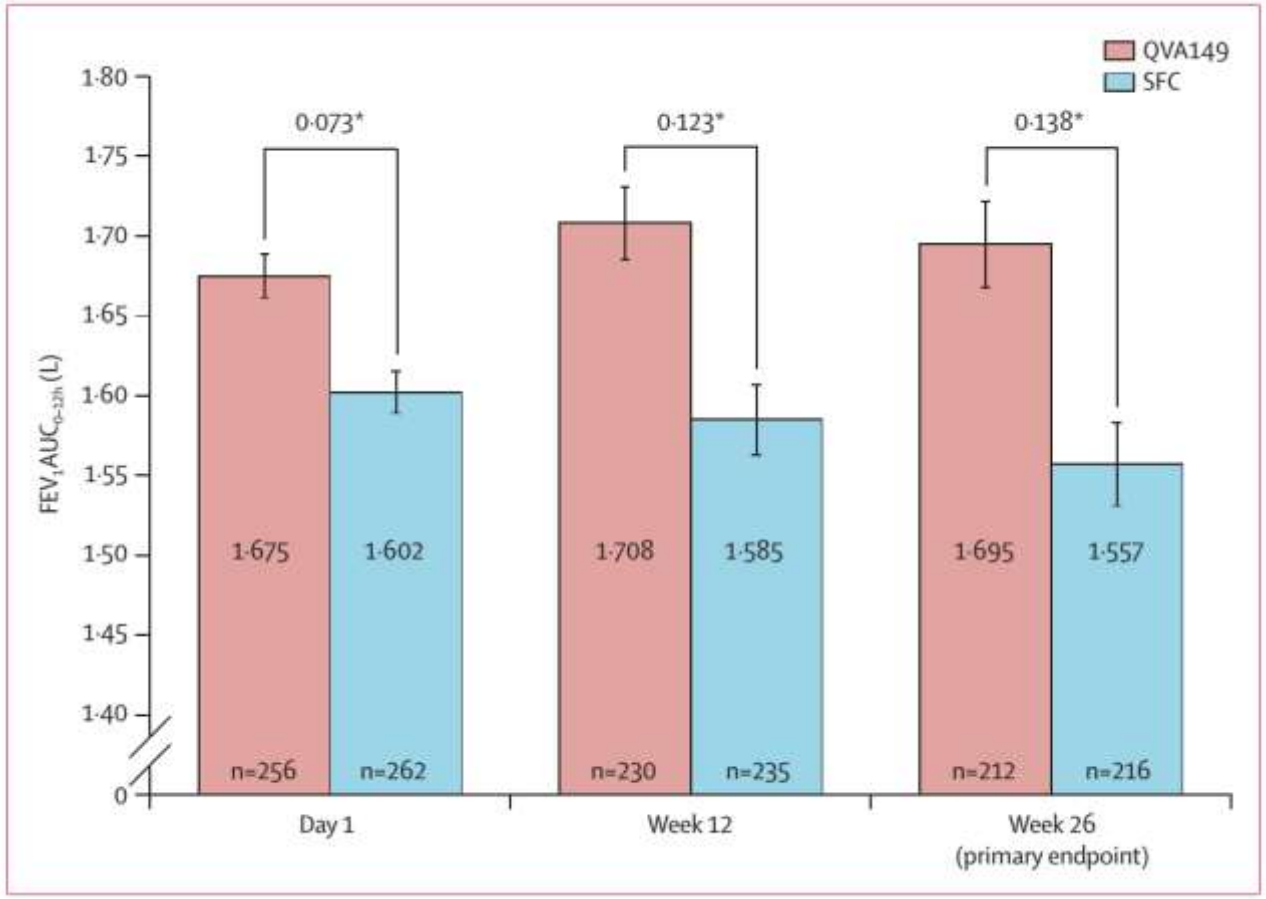


Figure 1: **ILLUMINATE study design**

Vogelmeier CF et al. Lancet Respir Med 2013;1:51-60. [PMID: 24321804]

LABA/LAMA (Ind/Gly) vs. ICS/LABA (SFC) – ILLUMINATE (FEV_1 AUC_{0-12h}) –

- patients with moderate-to-severe COPD (**without AE** in the previous year)
- The primary endpoint was to demonstrate the **superiority** of **IND/GLY** compared with SFC for postBD FEV1 $AUC_{0–12h}$ after **26** weeks of treatment.



Vogelmeier CF et al. Lancet Respir Med 2013;1:51-60. [PMID: 24321804]

LABA/LAMA (Ind/Gly) vs. ICS/LABA (SFC) – LANTERN (Design) –

- 676 moderate-to-severe COPD patients with **a history of AE ≤ 1** in the previous year
- Primary end point: **non-inferiority** for **trough FEV1** at week **26**

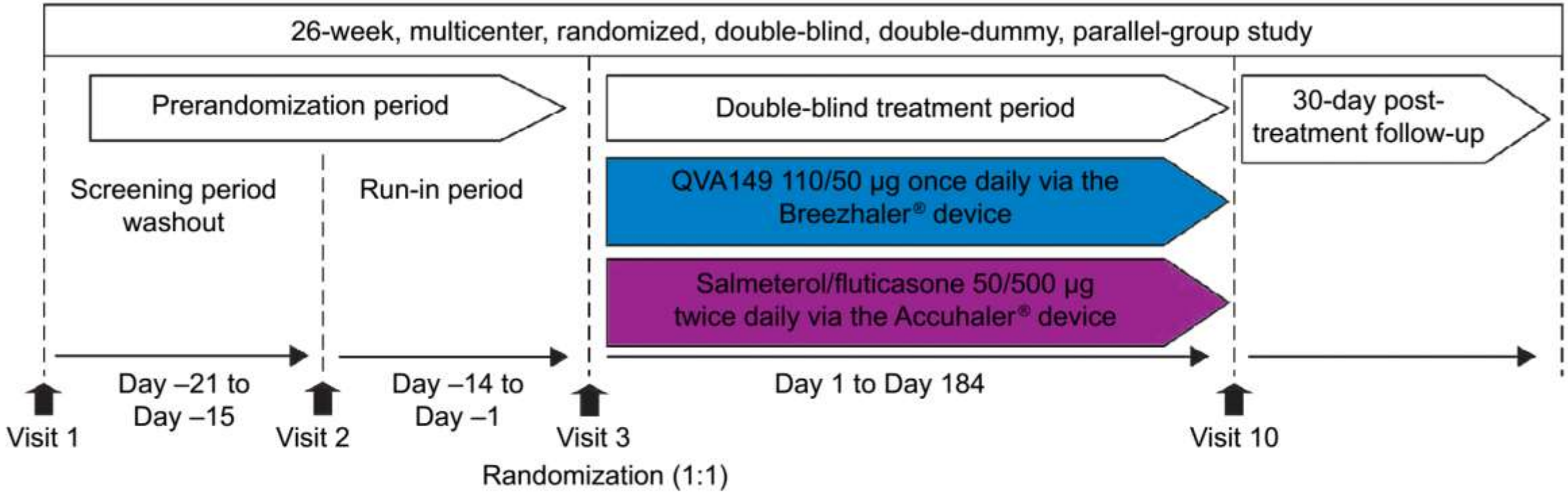
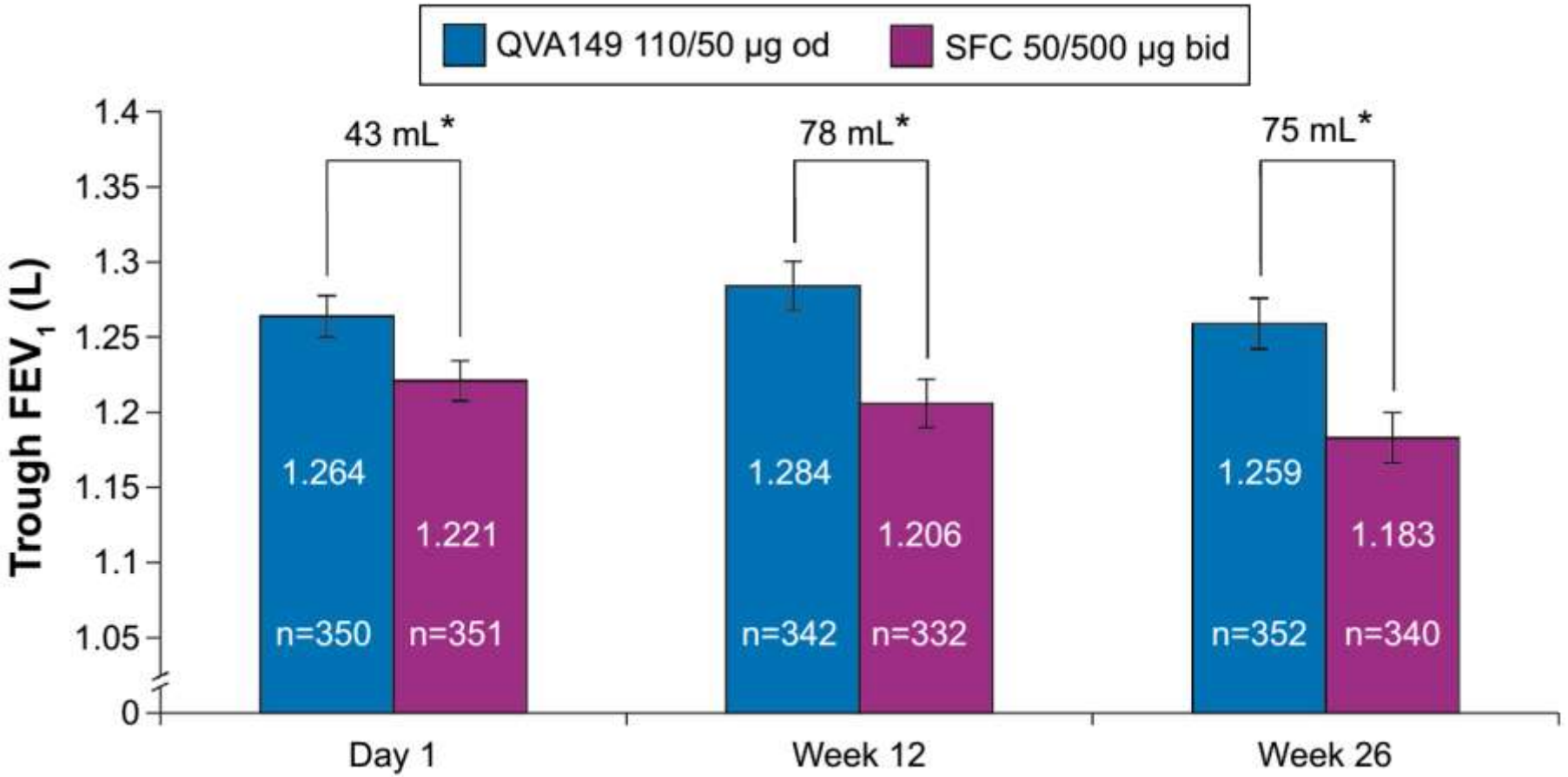


Figure 1 The LANTERN study design.

Zhong N et al. Int J Chron Obstruct Pulmon Dis 2015;10:1015-26. [PMID: 26082625]

LABA/LAMA (Ind/Gly) vs. ICS/LABA (SFC) – LANTERN (FEV_1) –

- 676 moderate-to-severe COPD patients with **a history of AE ≤ 1** in the previous year
- Primary end point: **non-inferiority** for **trough FEV1** at week **26**



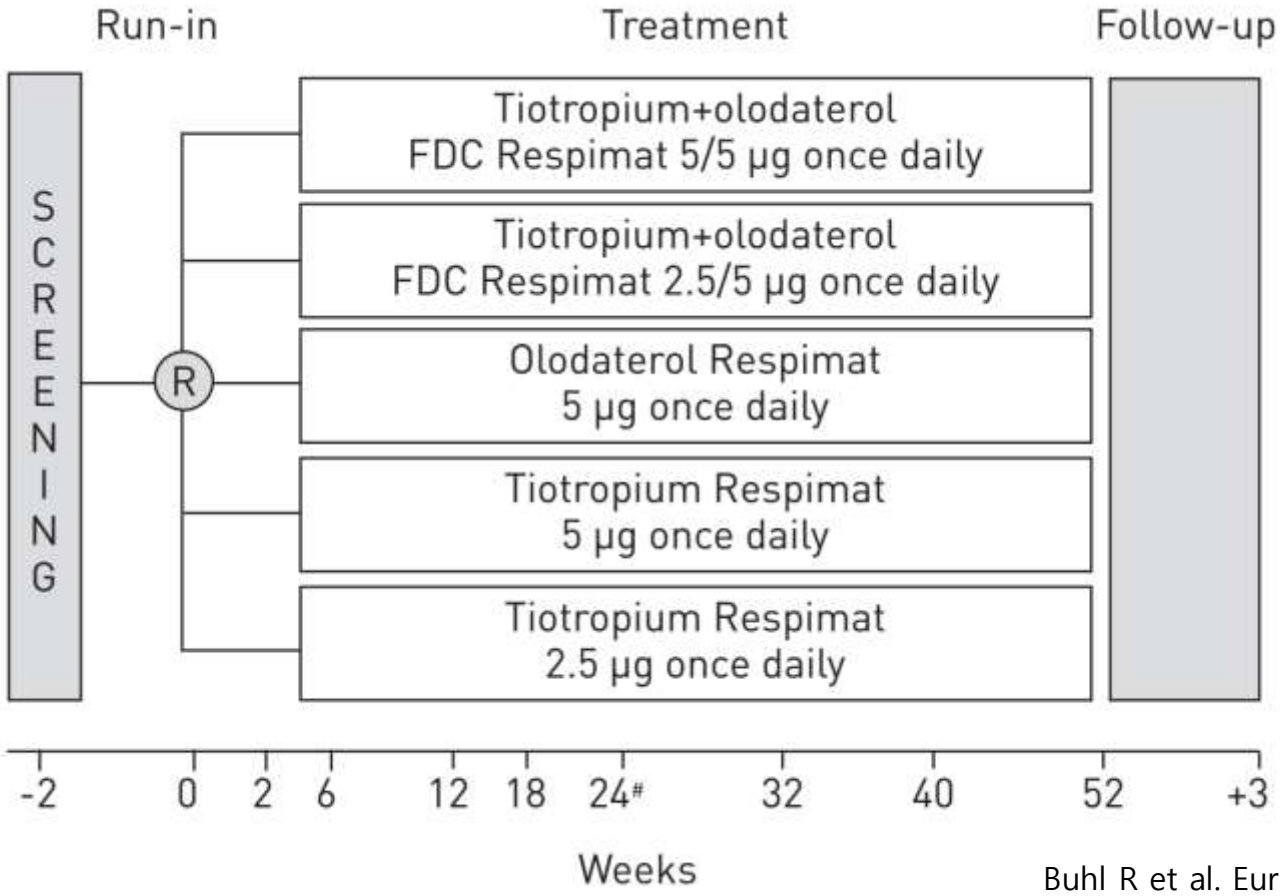
Zhong N et al. Int J Chron Obstruct Pulmon Dis 2015;10:1015-26. [PMID: 26082625]

Tiotropium and olodaterol fixed-dose combination *versus* mono-components in COPD (GOLD 2–4)

Roland Buhl[1], François Maltais[2], Roger Abrahams[3], Leif Bjermer[4], Eric Derom[5], Gary Ferguson[6], Matjaž Fležar[7], Jacques Hébert[8], Lorcan McGarvey[9], Emilio Pizzichini[10], Jim Reid[11], Antony Veale[12], Lars Grönke[13], Alan Hamilton[14], Lawrence Korducki[15], Kay Tetzlaff[13,16], Stella Waitere-Wijker[17], Henrik Watz[18] and Eric Bateman[19]

TONADO

- Tx
  - tiotropium+olodaterol FDC 2.5/5 μg or 5/5 μg
  - tiotropium 2.5 μg or 5 μg, or
  - Olodaterol 5 μg
    - Respimat inhaler over 52 weeks
- Primary end points (at **24** weeks.)
  - FEV1 AUC0–3 response
  - trough FEV1 response
  - SGRQ total score



Buhl R et al. Eur Respir J 2015;45:969-79. [PMID: 25573406]

Key inclusion and exclusion criteria – TONADO –

Key inclusion criteria	Key exclusion criteria
Male or female outpatients with a history of moderate to very severe COPD (GOLD 2–4)	History of asthma
Aged ≥40 years	Significant disease other than COPD
Current or ex-smokers with a smoking history of >10 pack-years	Myocardial infarction within 1 year of screening
Post-bronchodilator FEV_1 <80% of predicted normal	Unstable or life-threatening cardiac arrhythmia
Post-bronchodilator FEV_1/forced vital capacity <70%	Known active tuberculosis; clinically evident bronchiectasis; cystic fibrosis or life-threatening pulmonary obstruction
	Hospitalization for heart failure within the past year; diagnosed thyrotoxicosis or paroxysmal tachycardia
	Previous thoracotomy with pulmonary resection
	Regular use of daytime oxygen if patients were unable to abstain during clinic visits
	Current enrollment in a pulmonary rehabilitation program (or completed in prior 6 weeks)

Ferguson GT et al. Adv Ther 2015;32:523-36. [PMID: 26112656]

LABA/LAMA (TIO/OLO) vs. LAMA (TIO) vs LABA (OLO) – TONADO (Trough FEV1) –

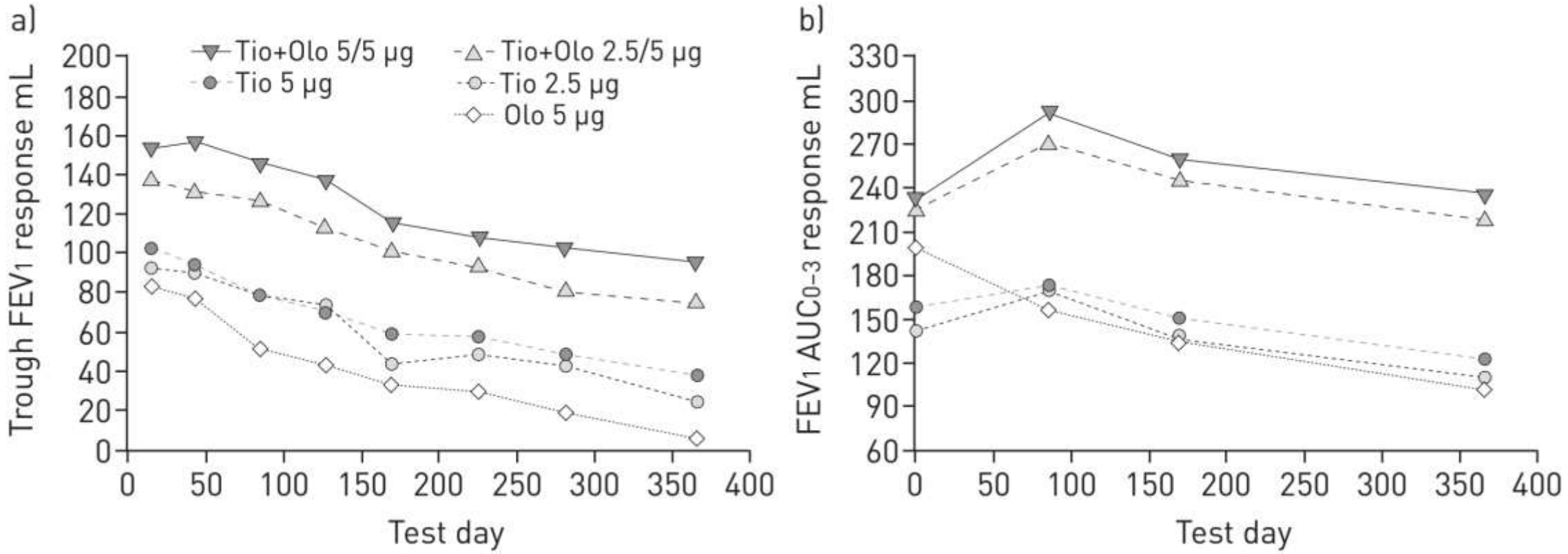


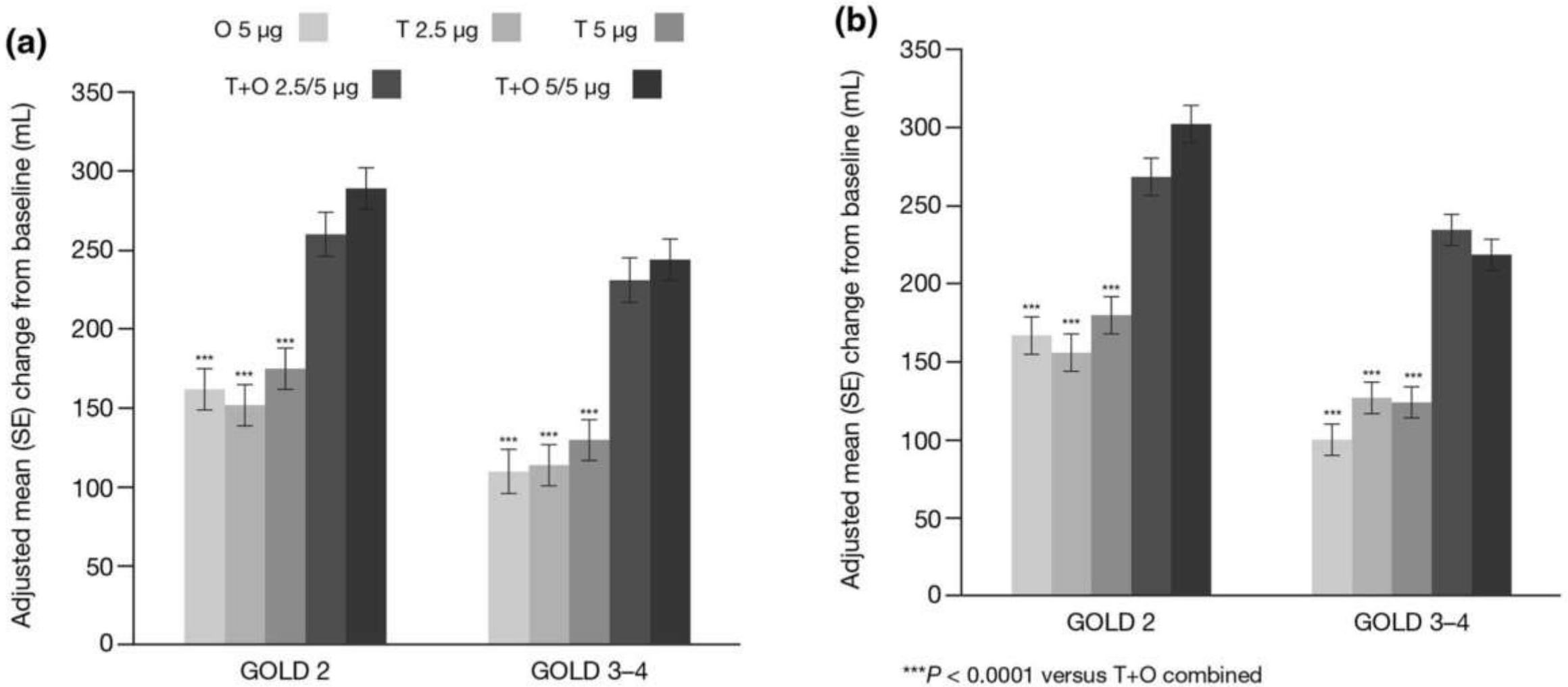
FIGURE 3 Lung function end points (combined data set) over 52 weeks: full analysis set. a) adjusted mean trough forced expiratory volume in 1 s (FEV_1); all comparisons of Tio+Olo 5/5 µg and 2.5/5 µg *versus* the monotherapies were statistically significant ($p<0.001$). b) FEV_1 area under the curve from 0 to 3 h (AUC_{0-3}); all comparisons of Tio+Olo 5/5 µg and 2.5/5 µg *versus* the monotherapies were statistically significant ($p<0.01$). Tio: tiotropium; Olo: olodaterol.

Buhl R et al. Eur Respir J 2015;45:969-79. [PMID: 25573406]

LABA/LAMA (TIO/OLO) vs. LAMA (TIO) vs LABA (OLO) – TONADO (FEV1 AUC0-3) –

(a) Patients without prior LAMA or LABA use

(b) Patients with prior LAMA or LABA use



Ferguson GT et al. Adv Ther 2015;32:523-36. [PMID: 26112656]

The 24-h lung-function profile of once-daily tiotropium and olodaterol fixed-dose combination in chronic obstructive pulmonary disease

VIVACITO

Kai-Michael Beeh [a,*], Jan Westerman [b], Anne-Marie Kirsten [c], Jacques Hébert [d], Lars Grönke [e], Alan Hamilton [f], Kay Tetzlaff [e,g], Eric Derom [h]

- a randomised, double-blind, placebo-controlled, Phase III trial with an incomplete crossover design
- Patients received four of the following six treatment options for 6 weeks each: placebo, olodaterol 5 mg, tiotropium 2.5 mg, tiotropium 5 mg, tiotropium þ olodaterol FDC 2.5/5 mg and tiotropium þ olodaterol FDC 5/5 mg, all delivered via the Respimat® inhaler
- The primary end point was forced expiratory volume in 1 s (**FEV1**) area under the curve from 0 to 24 h (**AUC0-24**) response after **6** weeks of treatment

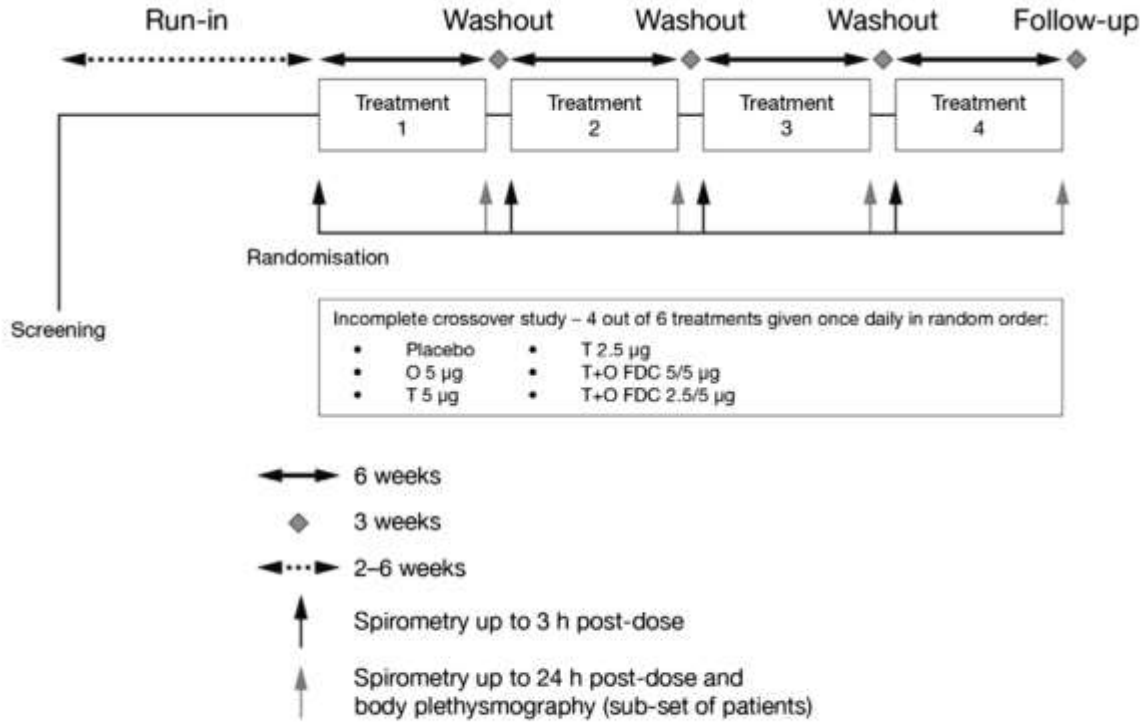


Fig. 1. Trial design. O, olodaterol; T, tiotropium; FDC, fixed-dose combination.

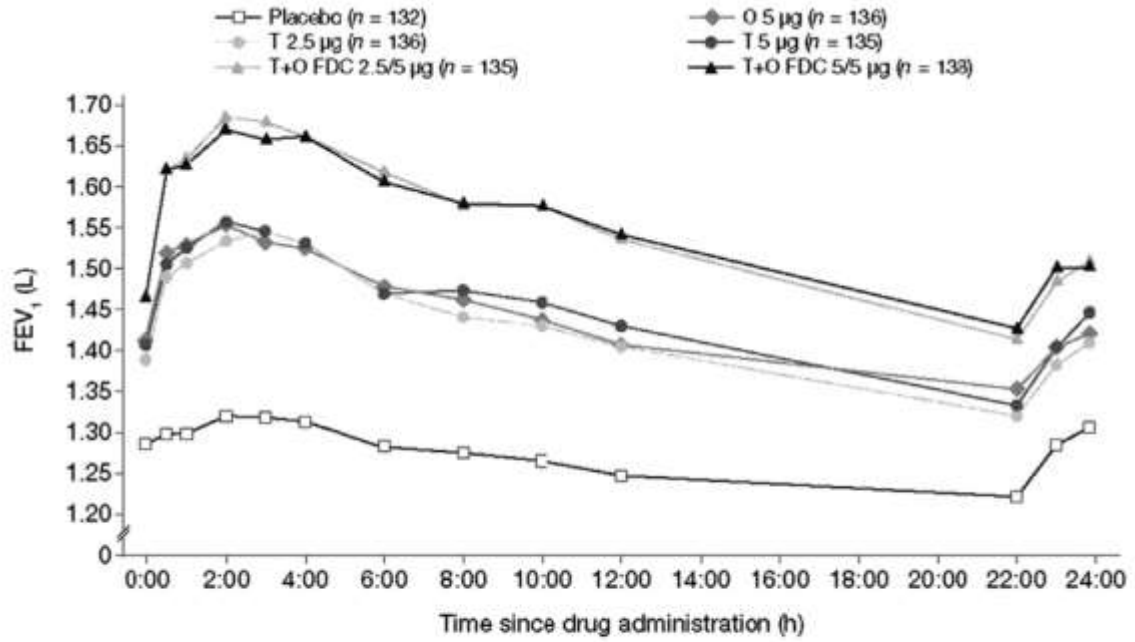


Fig. 3. Adjusted mean 24-h FEV_1 profile after 6 weeks of treatment (full analysis set). FEV_1, forced expiratory volume in 1 s; T, tiotropium; O, olodaterol; FDC, fixed-dose combination.

Singh D et al. Respir Med 2015;109:1312-9. [PMID: 26320402]

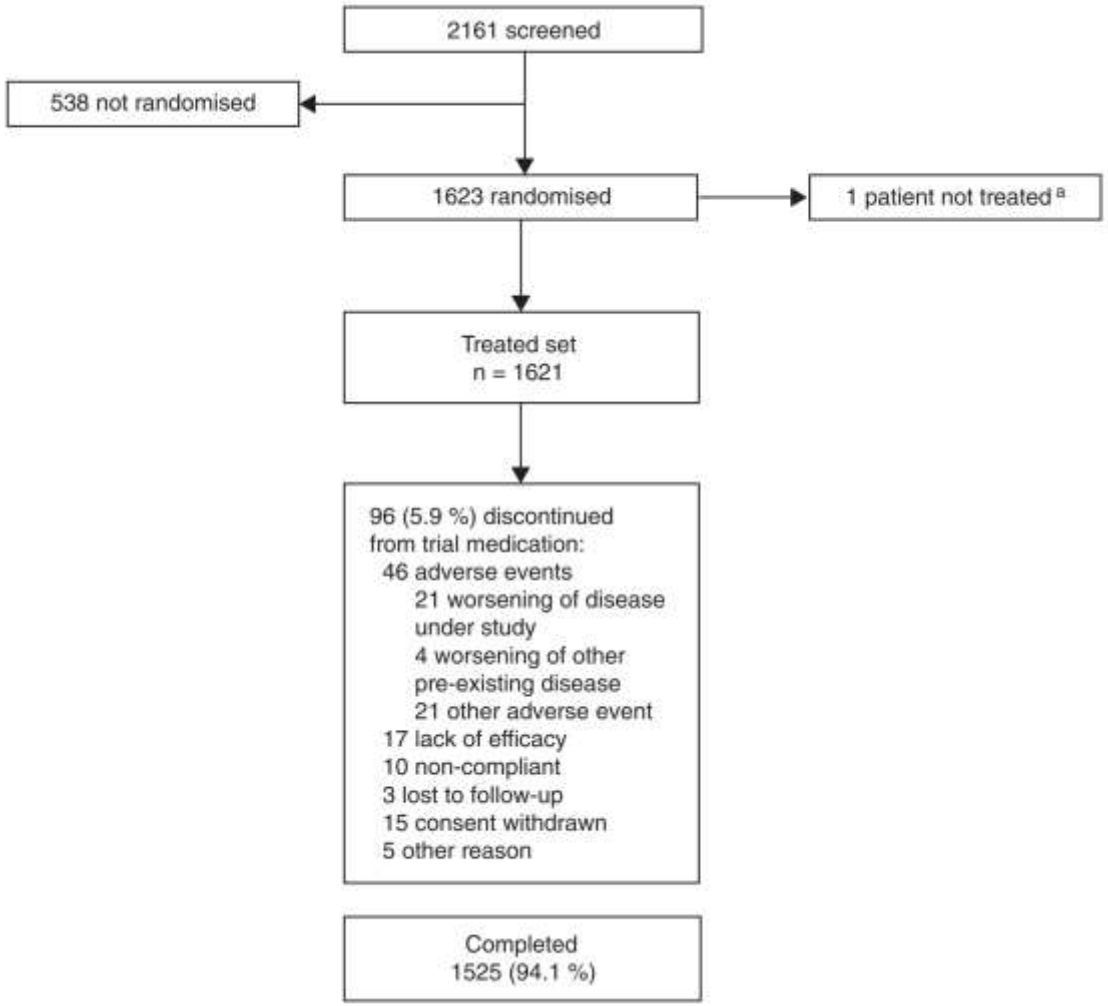
RESEARCH Open Access

Effects of tiotropium + olodaterol versus tiotropium or placebo by COPD disease severity and previous treatment history in the OTEMTO® studies

Dave Singh[1*], Mina Gaga[2], Olaf Schmidt[3], Leif Bjermer[4], Lars Grönke[5], Florian Voß[5] and Gary T. Ferguson[6]

OTEMTPTO

- a total of **1623** patients
- TIO/OLO, TIO or placebo
- 4 subgroups:
  - GOLD 2/3
  - GOLD A/B/C/D
  - treatment naïve vs. not treatment naive
  - receiving inhaled corticosteroids (ICS) at baseline vs. not receiving ICS at baseline
- Primary end points:
  - **FEV1 AUC from 0 to 3 h** response,
  - trough FEV1
  - SGRQ total score



Singh D et al. Respir Res 2016;17:73. [PMID: 27316465]

LAMA/LABA (TIO/OLO) vs. LAMA (TIO) vs. Placebo – OTEMPTO (trough FEV1) –

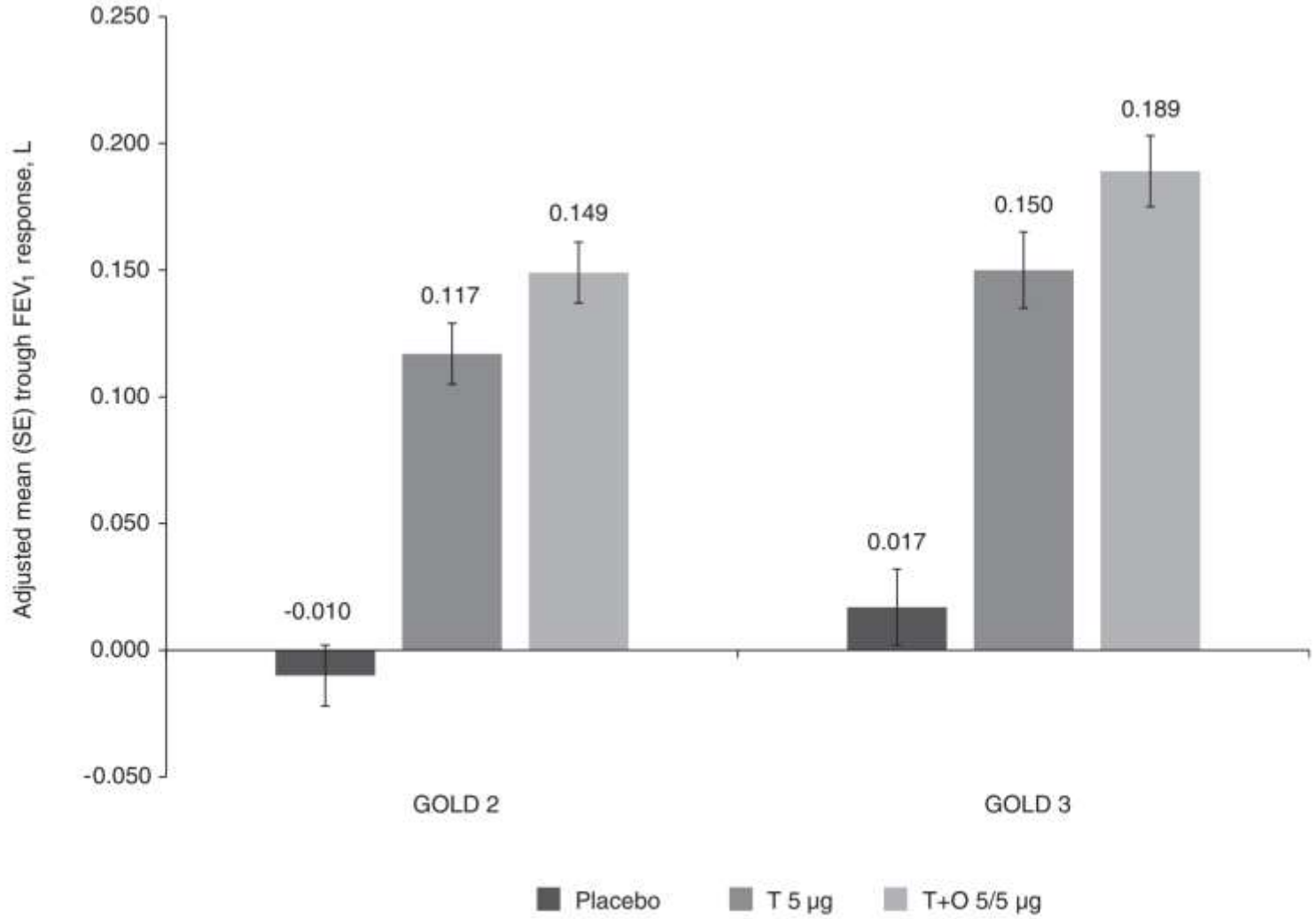
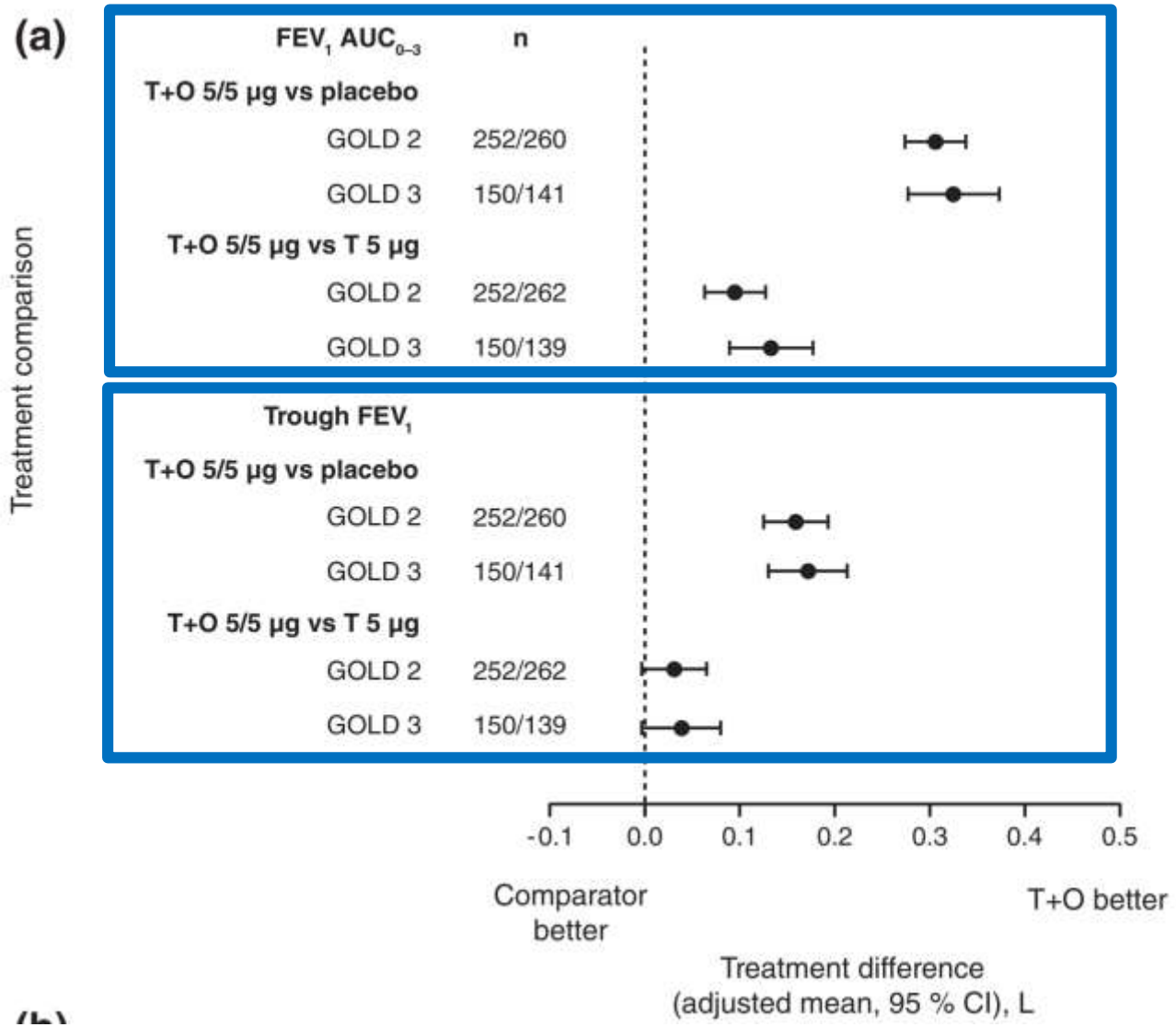


Fig. 2 Adjusted mean trough FEV_1 responses at 12 weeks in patients with GOLD 2 and 3 disease. FEV_1: forced expiratory volume in 1 s; GOLD: Global initiative for chronic Obstructive Lung Disease; SE: standard error; T: tiotropium; O: olodaterol

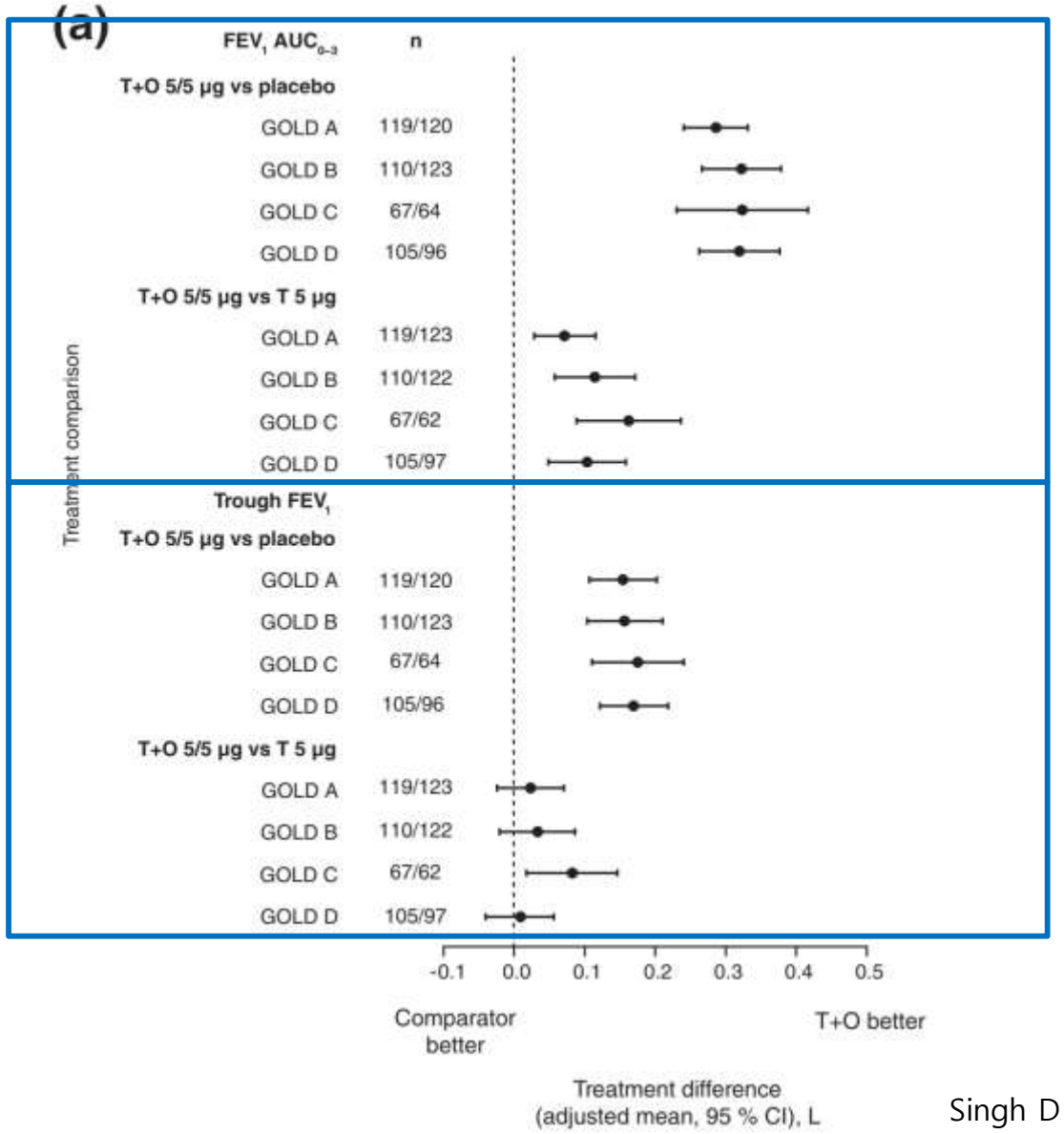
Singh D et al. Respir Res 2016;17:73. [PMID: 27316465]

LAMA/LABA (TIO/OLO) vs. LAMA (TIO) vs. Placebo – OTEMPTO (FEV1, subgroup: GOLD 2 & 3) –



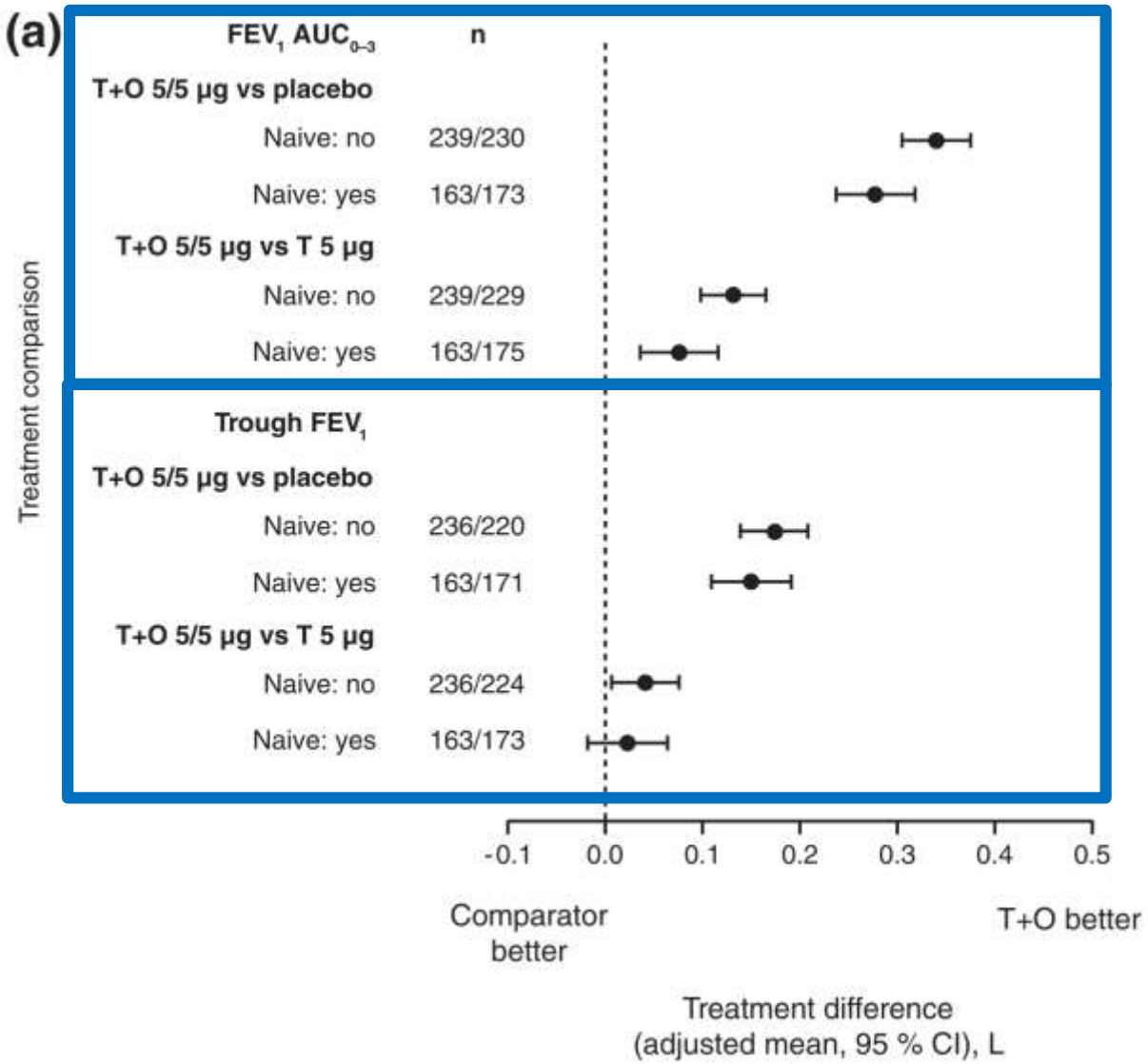
Singh D et al. Respir Res 2016;17:73. [PMID: 27316465]

LAMA/LABA (TIO/OLO) vs. LAMA (TIO) vs. Placebo – OTEMPTO (FEV1, subgroup: GOLD ABCD) –



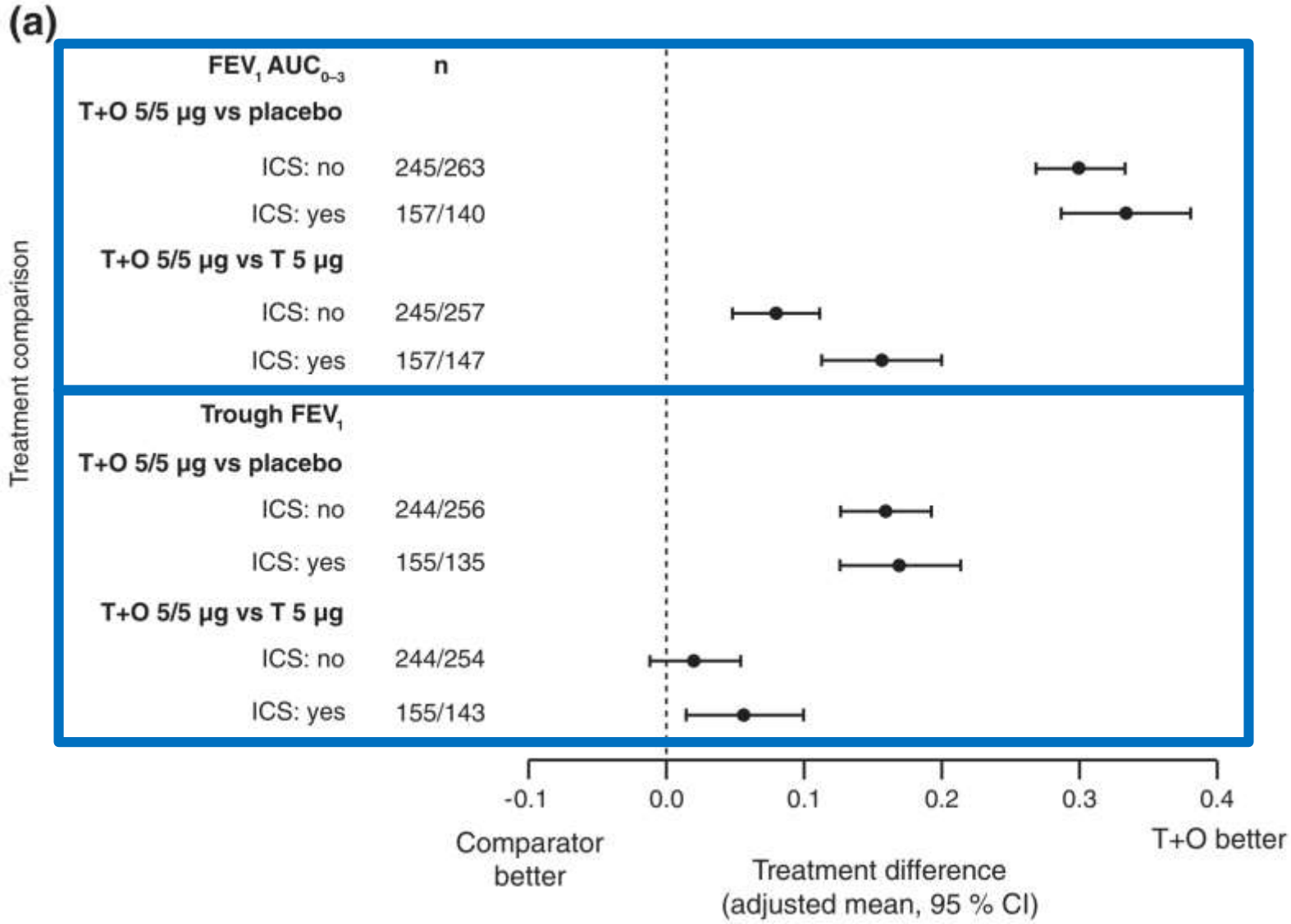
Singh D et al. Respir Res 2016;17:73. [PMID: 27316465]

LAMA/LABA (TIO/OLO) vs. LAMA (TIO) vs. Placebo – OTEMPTO (FEV1, subgroup: Tx-naive) –



Singh D et al. Respir Res 2016;17:73. [PMID: 27316465]

LAMA/LABA (TIO/OLO) vs. LAMA (TIO) vs. Placebo – OTEMPTO (FEV1, subgroup: ICS) –



Singh D et al. Respir Res 2016;17:73. [PMID: 27316465]

Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD

DB2113372

J.F. Donohue [a,*], M.R. Maleki-Yazdi [b], S. Kilbride [c], R. Mehta [d], C. Kalberg [d], A. Church [d]

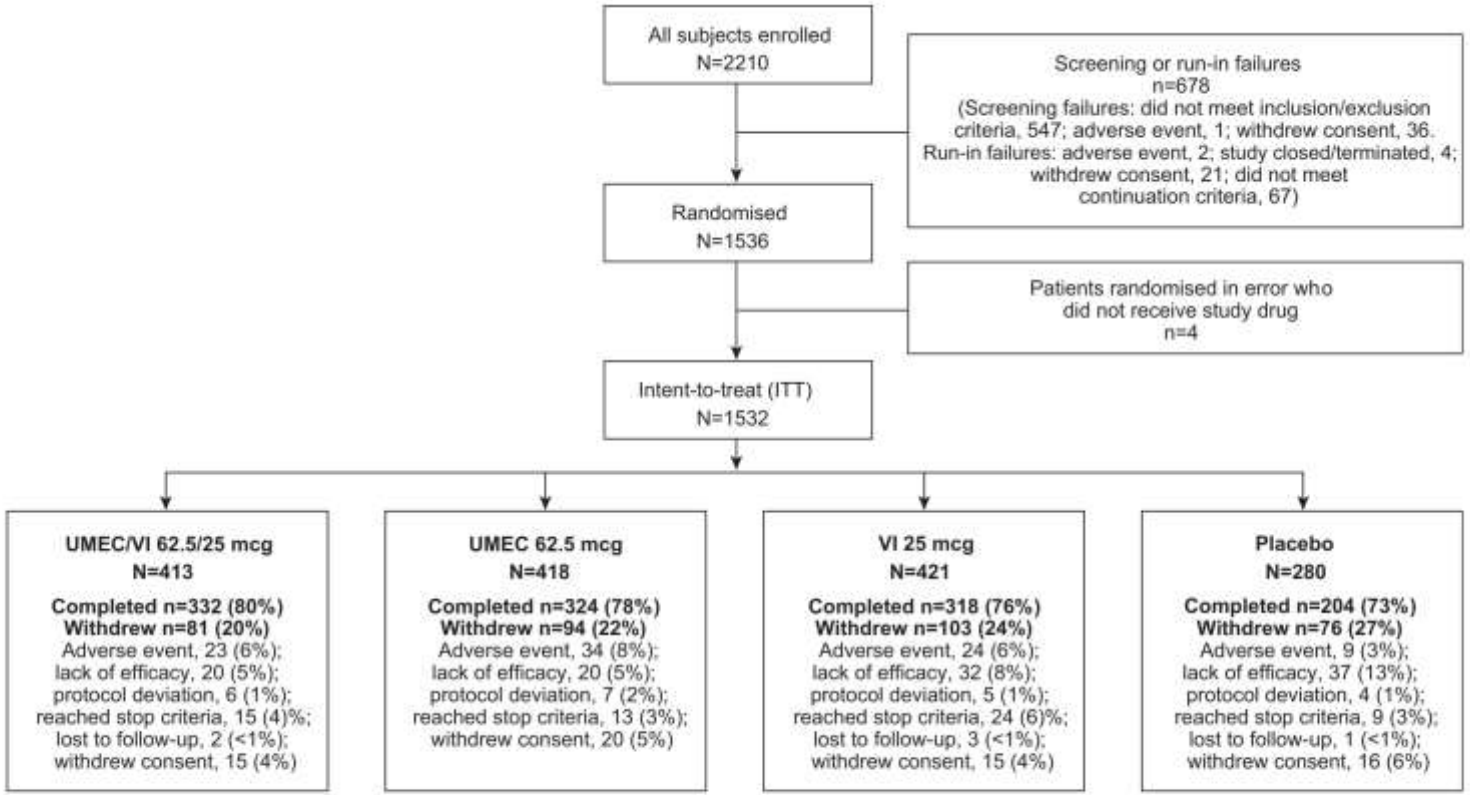


Figure 1 Patient disposition and flow diagram. Note: Some patients were classed by the reporting investigator as completers but did not have a Day 169 Visit or did not complete Day 169; others attended a Day 169 Visit or completed Day 169 assessments but were not classed as completers by the reporting investigator. Patients were considered to have completed if they completed the last clinic visit excluding follow-up (Visit 9) and did not withdraw at that visit.

- A **24-week**, randomised, double-blind, placebocontrolled, multicentre, parallel-group study
- Eligible patients
  - a history of cigarette smoking of ≥10 pack-years
  - FEV1/FVC <0.7
  - a postBD **FEV1 ≤70%** of predicted
  - Dyspnoea: **≥2 on the mMRC**
- Exclusion
  - **current diagnosis of asthma** or other known respiratory disorders
- Tx
  - **UMEC/VIL** 62.5/25
  - **UMEC** 62.5
  - **VIL** 25
  - **Placebo**
- Primary efficacy end point
  - **trough FEV1** on day 169 (23-24 h postdose)

Donohue JF et al. Respir Med 2013;107:1538-46 [PMID 23830094]

DB2113372

Table 1 Patient demographics and baseline characteristics (intent-to-treat population).

	Placebo (*N* = 280)	UMEC 62.5 (*N* = 418)	VI 25 (*N* = 421)	UMEC/VI 62.5/25 (*N* = 413)
Age (y)				
Mean (SD)	62.2 (9.04)	64.0 (9.16)	62.7 (8.52)	63.1 (8.71)
Sex				
Female *n* (%)	85 (30)	120 (29)	136 (32)	108 (26)
Male *n* (%)	195 (70)	298 (71)	285 (68)	305 (74)
Current smoker at screening[a]				
n (%)	150 (54)	207 (50)	199 (47)	203 (49)
Smoking pack-years				
Mean (SD)	47.2 (27.21)	46.8 (27.03)	44.7 (23.16)	46.5 (25.80)
ICS use at screening				
n (%)	137 (49)	219 (52)	212 (50)	212 (51)
Post-salbutamol % predicted FEV_1				
Mean (SD)	46.7 (12.71)	46.8 (13.39)	48.2 (13.27)	47.8 (13.19)
Post-salbutamol FEV_1/FVC				
Mean (SD)	47.1 (11.47)	46.8 (11.07)	47.4 (11.49)	48.0 (11.42)
GOLD stage				
n	280	417	420	412
II, *n* (%)	119 (43)	191 (46)	197 (47)	201 (49)
III, *n* (%)	133 (48)	172 (41)	179 (43)	166 (40)
IV, *n* (%)	28 (10)	54 (13)	44 (10)	45 (11)
% reversibility to salbutamol				
Mean (SD)	15.3 (15.54)	13.9 (14.92)	15.7 (15.57)	13.9 (15.06)
% reversibility to salbutamol and ipratropium[b]				
Mean (SD)	22.7 (19.61)	22.3 (18.51)	23.6 (19.42)	22.2 (18.82)
Reversible to salbutamol				
n (%)	91 (33)	121 (29)	155 (37)	129 (31)
Reversible to salbutamol and ipratropium				
n (%)	146 (54)	223 (54)	230 (56)	227 (56)

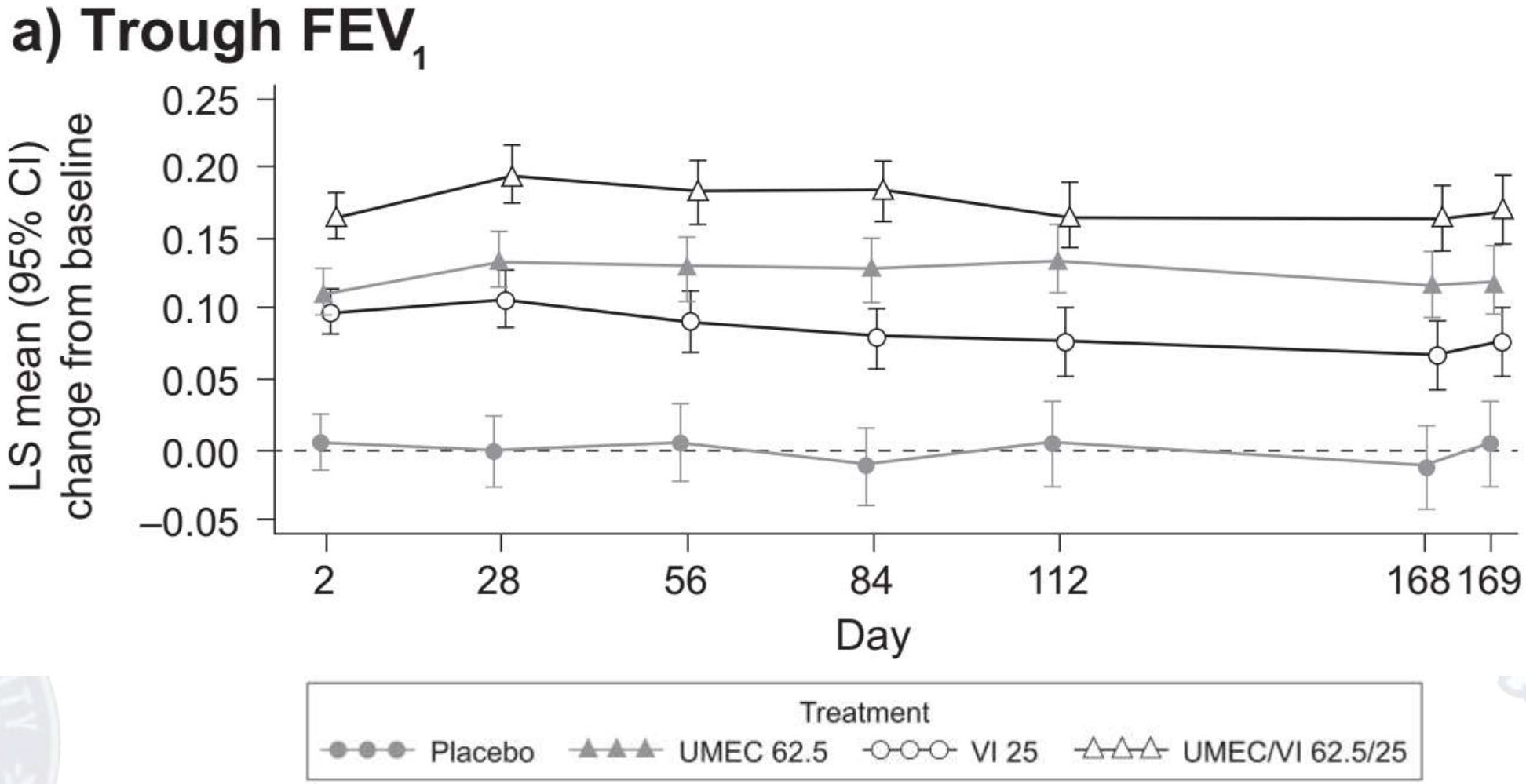
FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; SD, standard deviation.

[a] Reclassified: patient reclassified as current smoker if smoked within 6 months.

[b] Reversibility to salbutamol and ipratropium was defined as an increase in FEV_1 of ≥12% and ≥0.2 L following administration of both salbutamol and ipratropium.

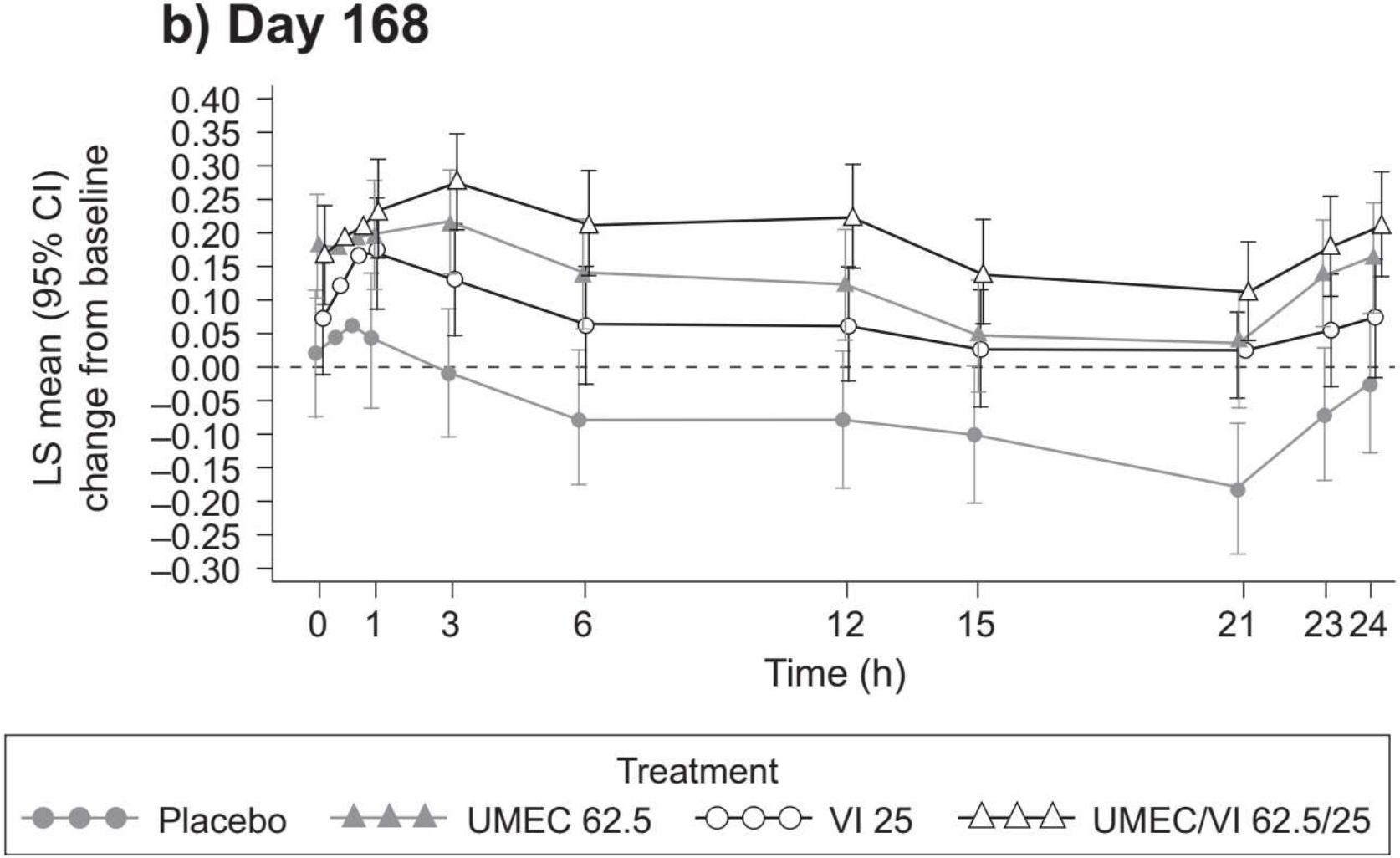
Donohue JF et al. Respir Med 2013;107:1538-46 [PMID 23830094]

LAMA/LABA (UMEC/VIL) vs. LAMA (UMEC) vs. LABA (VIL) vs. Placebo – DB2113373 (Trough FEV1) –



Donohue JF et al. Respir Med 2013;107:1538-46 [PMID 23830094]

LAMA/LABA (UMEC/VIL) vs. LAMA (UMEC) vs. LABA (VIL) vs. Placebo – DB2113373 (Serial FEV1) –



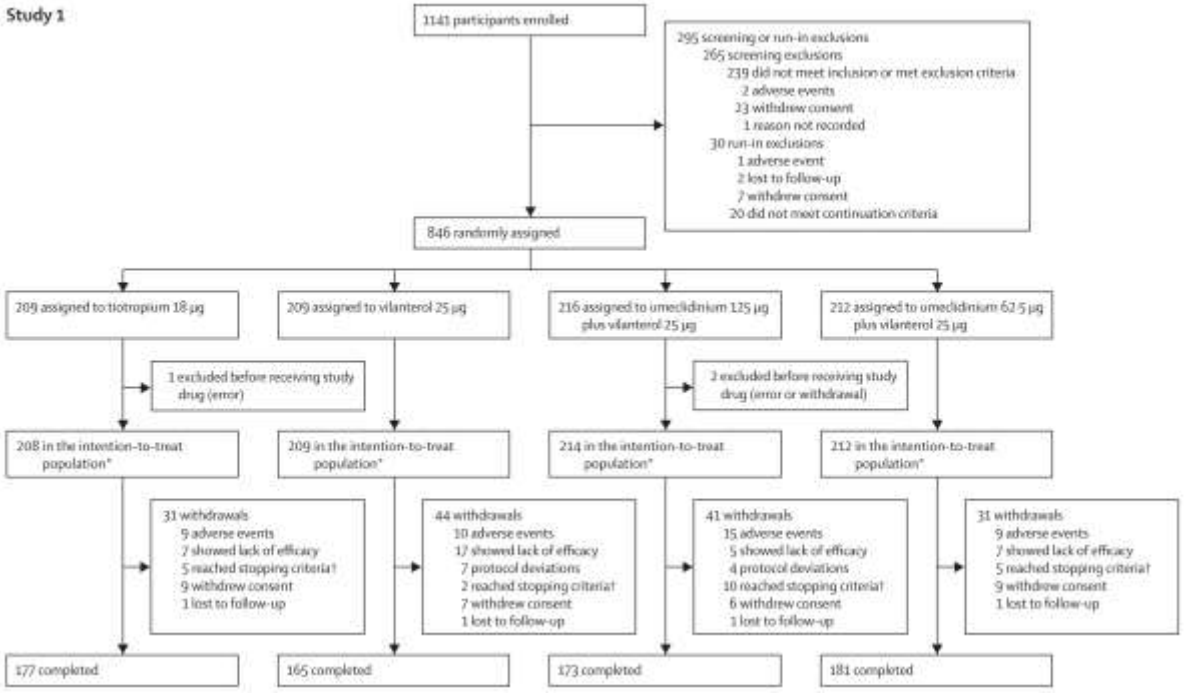
Donohue JF et al. Respir Med 2013;107:1538-46 [PMID 23830094]

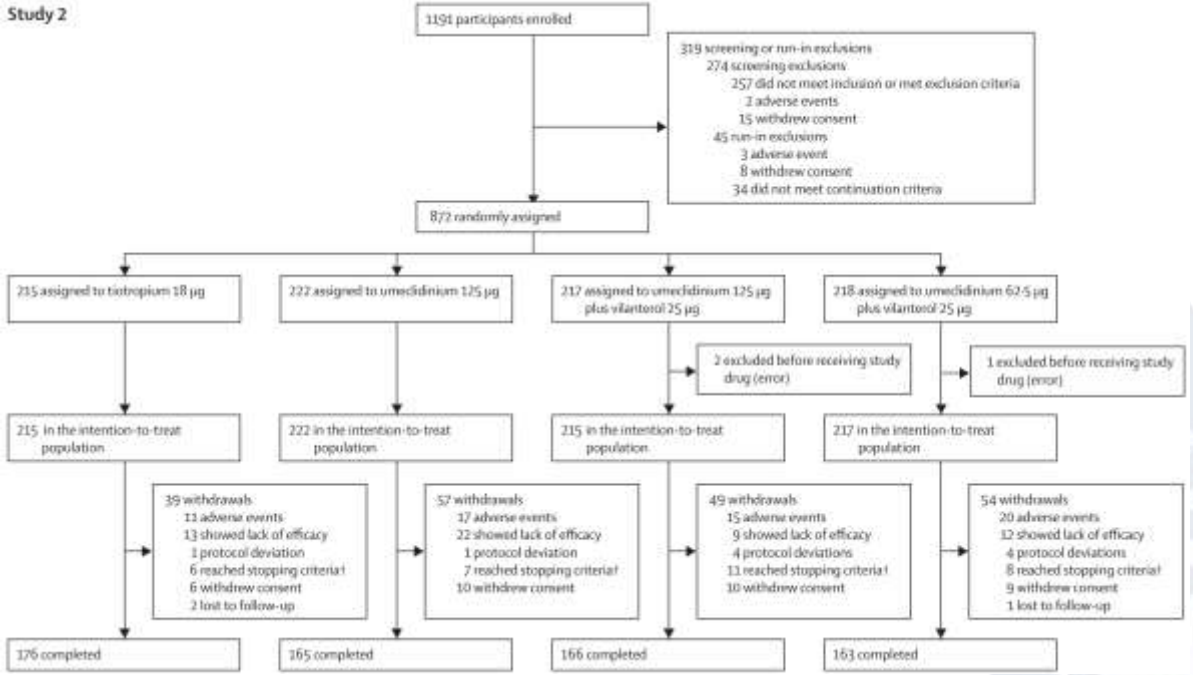
DB2113360

Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials

Marc Decramer, Antonio Anzueto, Edward Kerwin, Thomas Kaelin, Nathalie Richard, Glenn Crater, Maggie Tabberer, Stephanie Harris, Alison Church

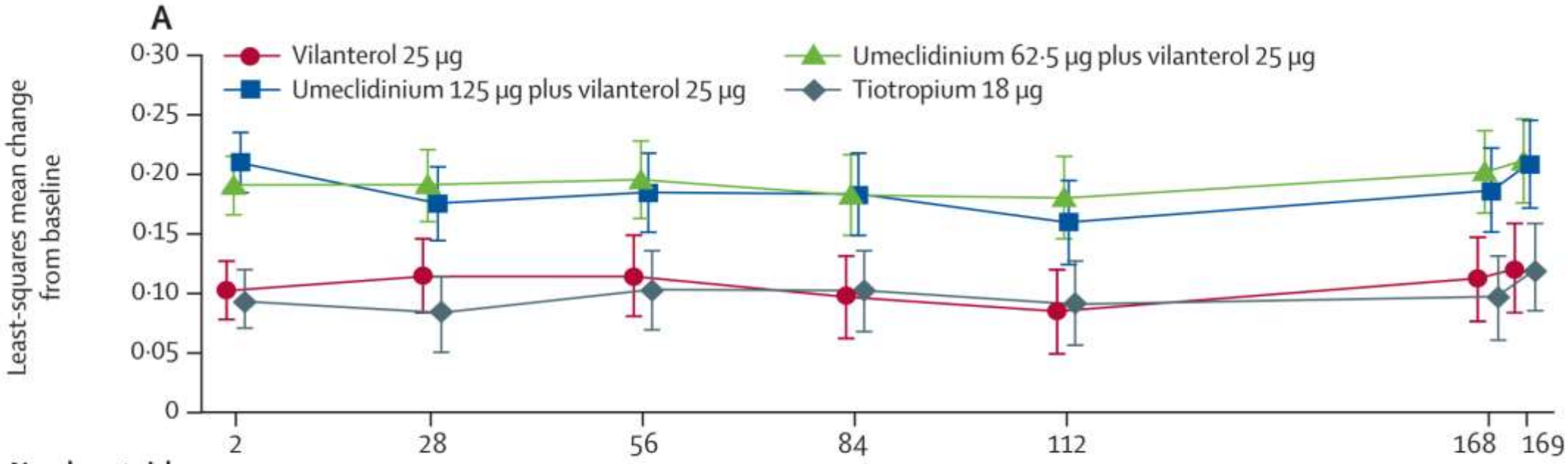
- two multicentre, randomised, blinded, double-dummy, parallel-group, active-controlled trials
- Eligible patients
  - a history of cigarette smoking of ≥10 pack-years
  - FEV1/FVC <0.7 & a **postBD FEV1 ≤70%** of predicted
  - Dyspnoea: A score of **≥2 on the mMRC**
- Exclusion
  - Asthma: **A current diagnosis of asthma**
- Tx: UMEC/VIL 125/25, 62.5/25, TIO, & UMEC 125 or VIL
- The primary outcome: **trough FEV1** on day 169





Decramer M et al. Lancet Respir Med 2014;2:472-86 [PMID 24835833]

LAMA/LABA (UMEC/VIL) vs. LAMA (TIO) vs. LABA (VIL) – DB2113360 (Trough FEV1, study 1) –

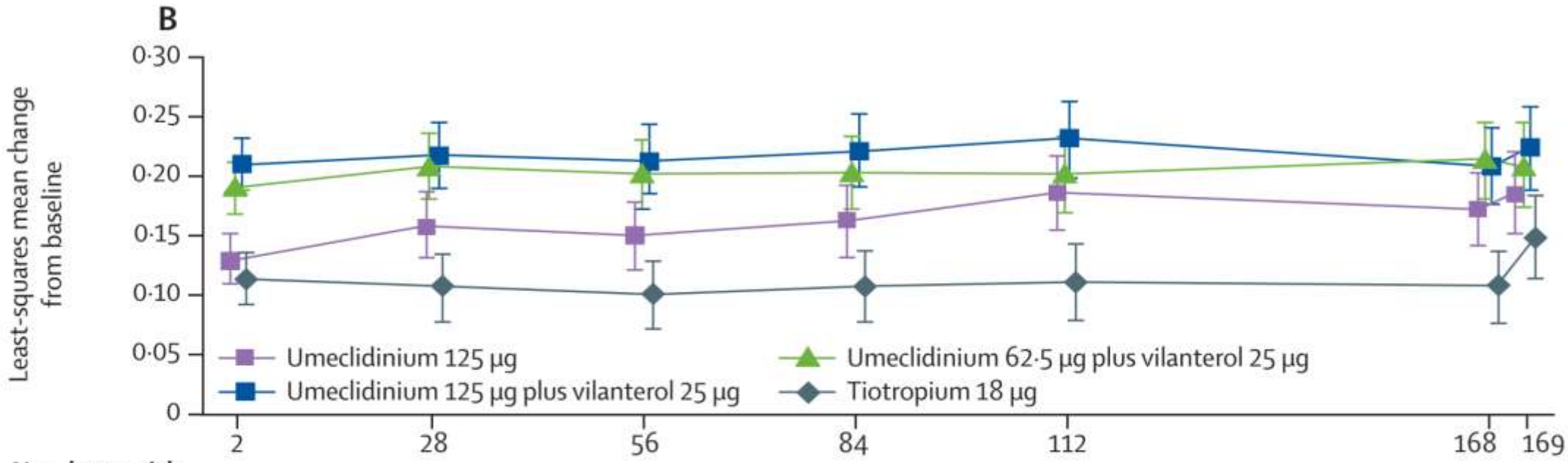


Number at risk

Vilanterol 25 µg	201	193	187	182	171	164	162
Umeclidinium 125 µg plus vilanterol 25 µg	204	194	189	184	176	167	167
Umeclidinium 62·5 µg plus vilanterol 25 µg	205	200	196	193	187	178	177
Tiotropium 18 µg	196	188	186	181	176	171	173

Decramer M et al. Lancet Respir Med 2014;2:472-86 [PMID 24835833]

LAMA/LABA (UMEC/VIL) vs. LAMA (TIO) vs. LAMA (UMEC) – DB2113360 (Trough FEV1, study 2) –



Number at risk							
Umeclidinium 125 µg	218	203	192	185	172	164	163
Umeclidinium 125 µg plus vilanterol 25 µg	211	199	187	181	174	168	164
Umeclidinium 62·5 µg plus vilanterol 25 µg	210	195	187	181	174	164	161
Tiotropium 18 µg	210	195	194	188	183	177	175

Decramer M et al. Lancet Respir Med 2014;2:472-86 [PMID 24835833]

Once-Daily Umeclidinium/Vilanterol 125/25 μg Therapy in COPD

A Randomized, Controlled Study

Bartolome Celli, MD, FCCP; Glenn Crater, MD, FCCP; Sally Kilbride, MSc; Rashmi Mehta, PhD; Maggie Tabberer, MSc; Chris J. Kalberg, PhD; and Alison Church, MD

DB2113361

- a double-blind, placebo-controlled, parallel-group study
- Primary efficacy end point: **trough FEV1** on day 169 (23-24 h postdose)

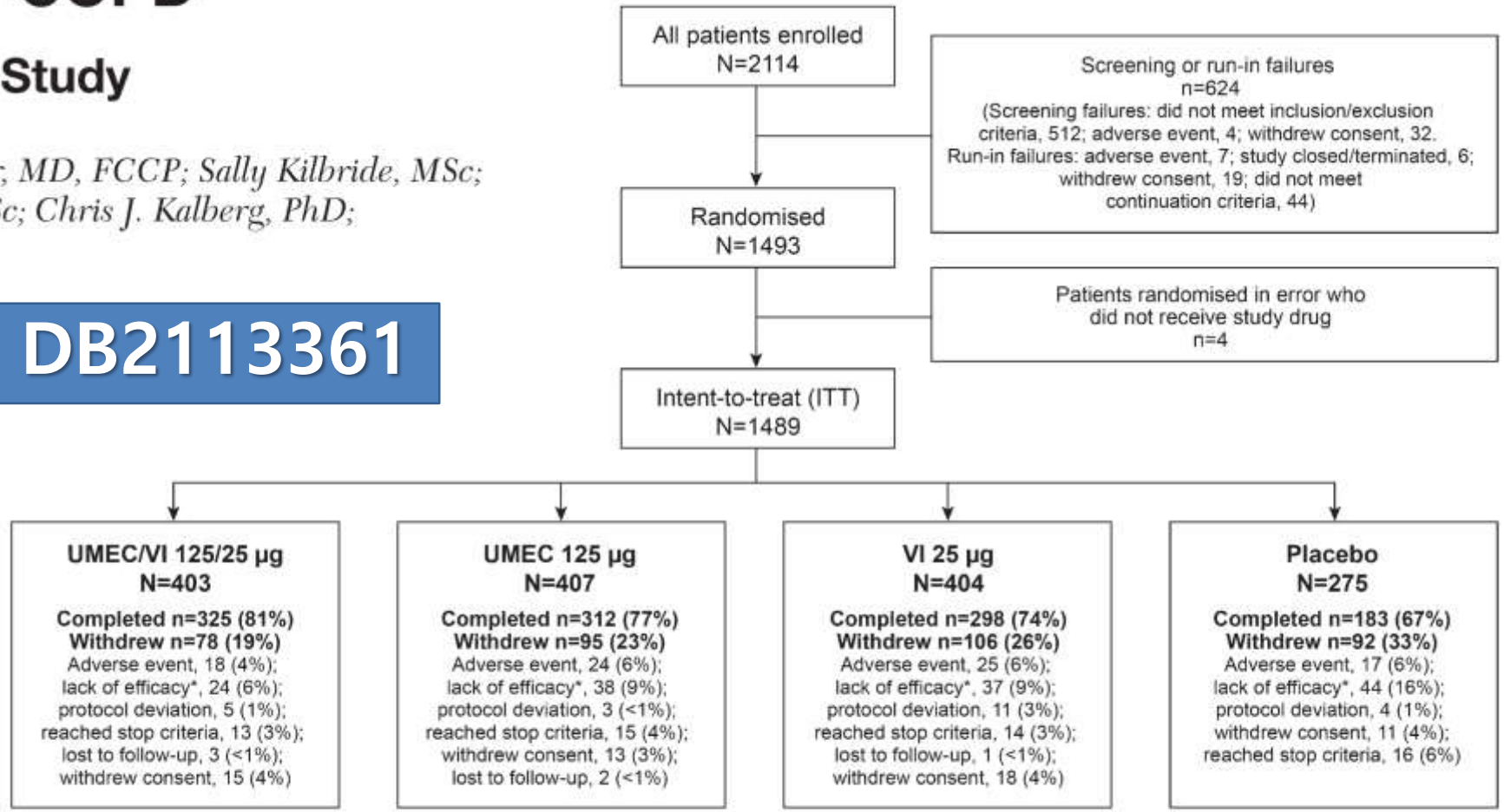
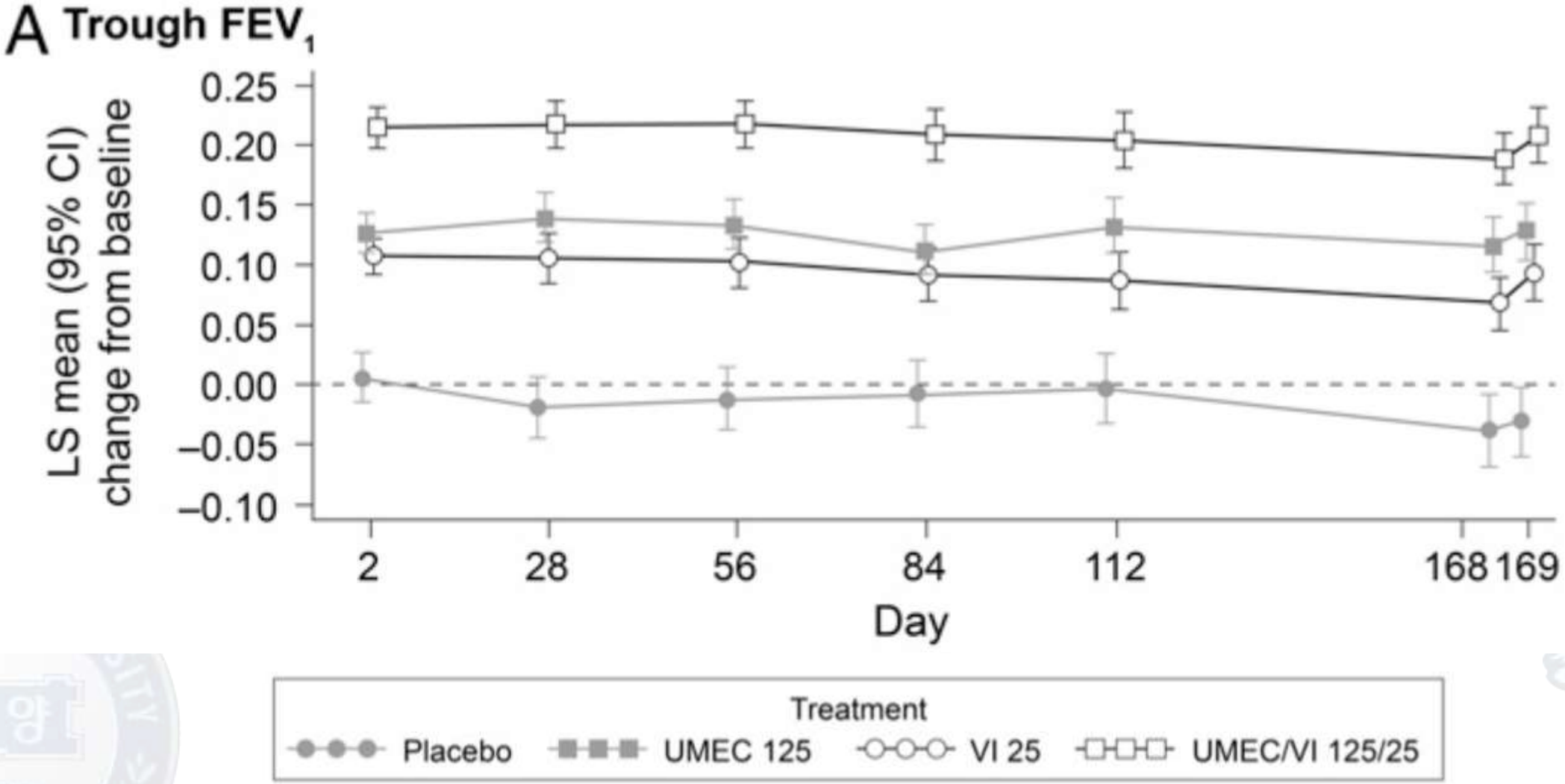


FIGURE 1. Study flow diagram. Note: Some patients were classed by the reporting investigator as completers but did not have a day 169 visit or did not complete day 169; others attended a day 169 visit or completed day 169 assessments but were not classed as completers by the reporting investigator. Patients were considered to have completed if they completed the last clinic visit excluding follow-up (visit 9) and did not withdraw at that visit. *Mainly due to COPD exacerbation. UMEC = umeclidinium bromide; VI = vilanterol.

Celli B et al. Chest 2014;145:981-91 [PMID 24385182]

LAMA/LABA (UMEC/VIL) vs. LAMA (UMEC) vs. LABA (VIL) – DB2113361 (Trough FEV1) –



Celli B et al. Chest 2014;145:981-91 [PMID 24385182]

Efficacy and safety of umeclidinium/ vilanterol 62.5/25 mcg and tiotropium 18 mcg in chronic obstructive pulmonary disease: Results of a 24-week, randomized, controlled trial

M. Reza Maleki-Yazdi [a,*], Thomas Kaelin [b], Nathalie Richard [c], Michael Zvarich [c], Alison Church [c]

ZEP117115

- a **24-week**, Phase III, multicenter, randomized, blinded, doubledummy, parallel-group study
- **UMEC/VI** 62.5/25 mcg versus **TIO**, 18 mcg
- The primary endpoint: **trough FEV1** at Day 169

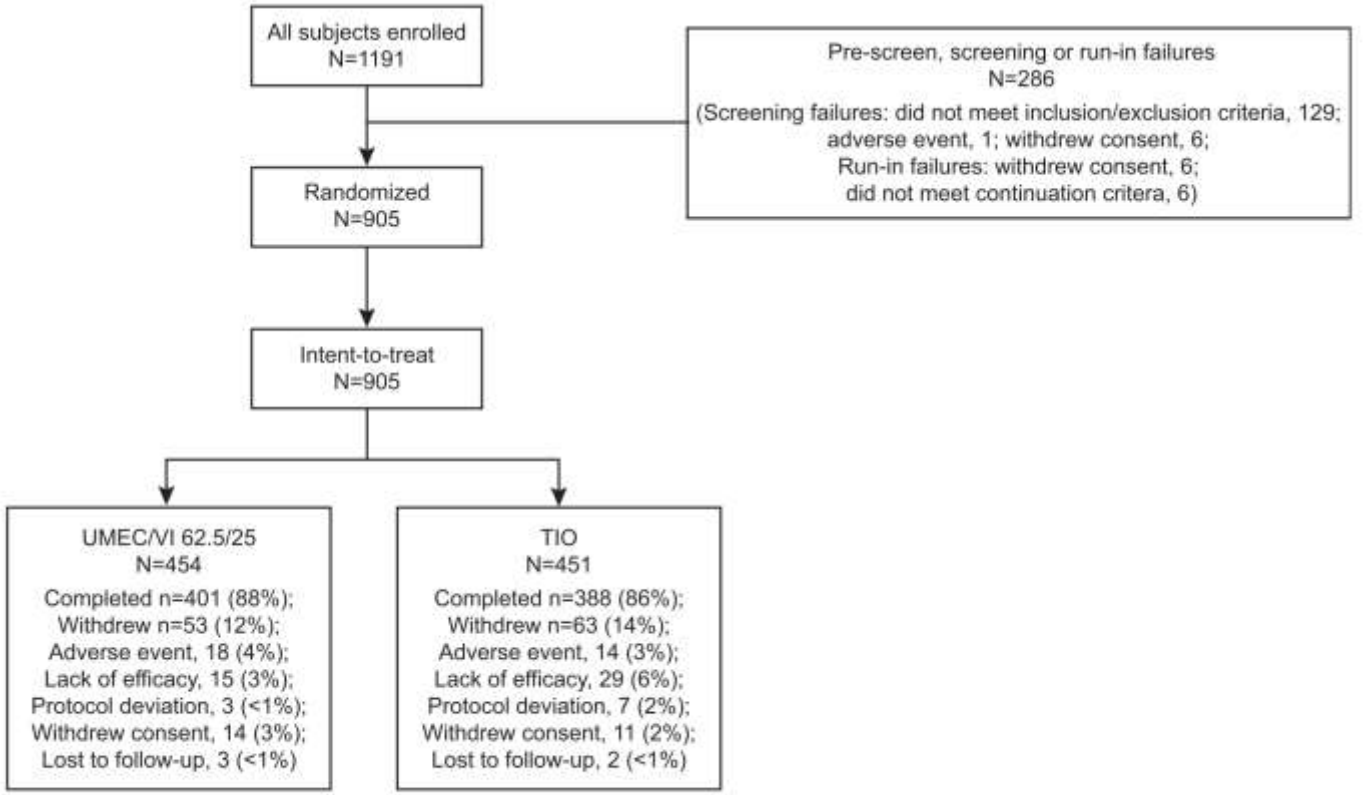


Figure 1 Patient flow. TIO, tiotropium bromide; UMEC, umeclidinium bromide; VI, vilanterol.

Maleki-Yazdi MR et al. Respir Med 2014;108:1752-60 [PMID 25458157]

ZEP117115

Table 1 Patient demographics and characteristics (ITT population).

	UMEC/VI 62.5/25 (N = 454)	TIO (N = 451)
Age (Years), mean (SD)	61.9 (8.41)	62.7 (8.50)
Sex, *n* (%)		
Male	310 (68)	303 (67)
Current smoker at screening,[a] *n* (%)	270 (59)	243 (54)
Smoking pack-years, mean (SD)	44.1 (24.44)	44.4 (25.03)
ICS use (pre-treatment), *n* (%)	247 (54)	237 (53)
Post-salbutamol percent predicted FEV_1, mean (SD)	46.2 (13.02)	46.5 (12.76)
Post-salbutamol FEV_1, L, mean, (SD)	1.41 (0.4854)	1.41 (0.5036)
Albuterol/salbutamol use (mean puffs/day), mean, (SD)	3.3 (3.37)	3.2 (3.16)
Post-salbutamol FEV_1/FVC, mean (SD)	47.82 (10.78)	47.40 (10.92)
GOLD stage, *n* (%)		
II	185 (41)	190 (42)
III	207 (46)	206 (46)
IV	62 (14)	55 (12)
Reversibility to salbutamol, L, mean, (SD)	0.15 (0.150)	0.15 (0.155)
Reversible to salbutamol,[b] *n* (%)	124 (27)	142 (31)
Reversibility to salbutamol and ipratropium, L, mean, (SD)	N = 452 0.25 (0.199)	N = 449 0.25 (0.203)
Reversible to salbutamol and ipratropium,[c] *n* (%)	244 (54)	239 (53)

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, global initiative for chronic lung disease; ICS, inhaled corticosteroids; ITT, intent-to-treat; SD, standard deviation; TIO, tiotropium bromide; UMEC, umeclidinium bromide; VI, vilanterol.

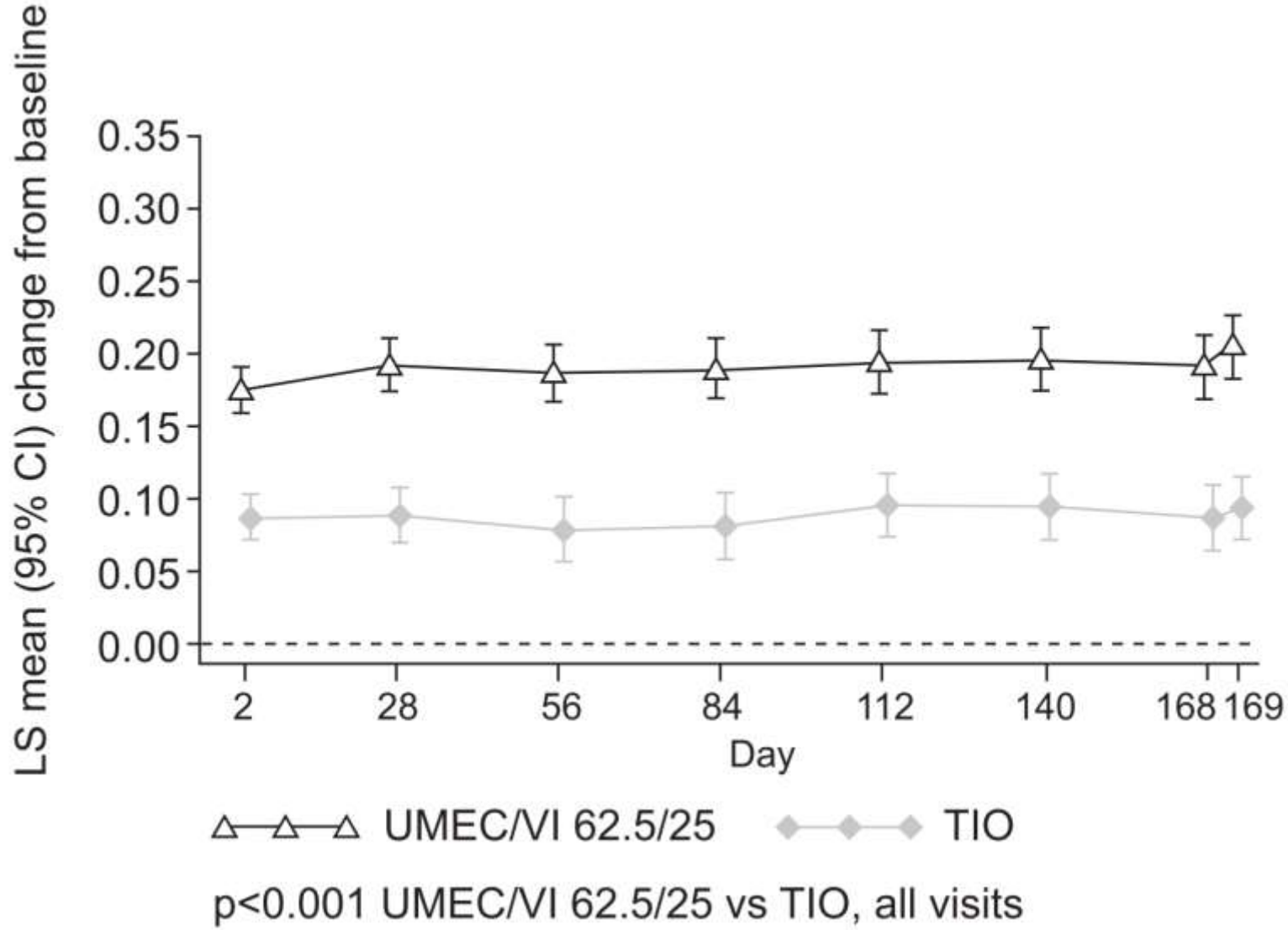
[a] Patients were classed as current smokers if they had smoked within 6 months of the screening visit.

[b] Patients are reversible to salbutamol if they have an increase in FEV_1 of ≥12% and ≥200 mL following administration of salbutamol.

[c] Patients are reversible to salbutamol and ipratropium if they have an increase in FEV1 of ≥12% and ≥200 mL following administration of both salbutamol and ipratropium.

Maleki-Yazdi MR et al. Respir Med 2014;108:1752-60 [PMID 25458157]

LAMA/LABA (UMEC/VIL) vs. LAMA (TIO)
– ZEP117115 (Trough FEV1) –



Maleki-Yazdi MR et al. Respir Med 2014;108:1752-60 [PMID 25458157]

Efficacy of umeclidinium/vilanterol versus umeclidinium and salmete monotherapies in sympto with COPD not receiving i corticosteroids: the EMAX

François Maltais[1*], Leif Bjermer[2], Edward M. Kerwin[3], Paul W.
Isabelle H. Boucot[4], David A. Lipson[7,8], Chris Compton[4], Mitr

- 2431 patients randomised (Analysed ITT population, n=2425)
- Aged 40+ years
- CAT ≥10
- Post-bronchodilator FEV1 **30–80%**
- **≤1 moderate exacerbation** in past year
- **Not receiving ICS, LAMA/LABA**

EMAX

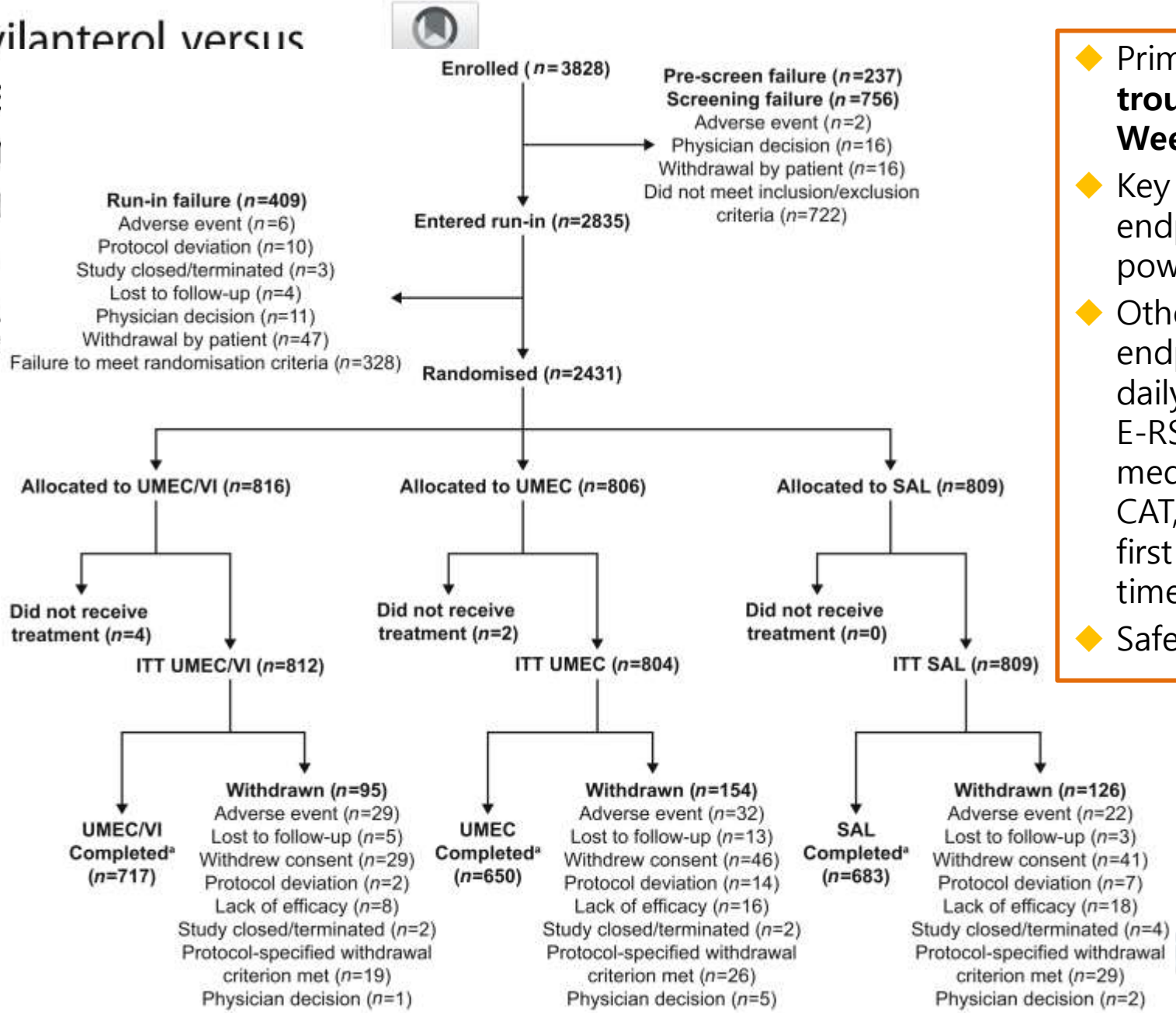


Fig. 1 Patient disposition. [a]Patients were considered to have completed the study if they received study treatment at Week 24 and completed the follow-up contact at Week 25 (±3 days). *ITT*, intent-to-treat; *UMEC*, umeclidinium; *VI*, vilanterol

- Primary endpoint: **trough FEV1 at Week 24**
- Key secondary endpoint: **TDI** (trial powered for TDI)
- Other secondary endpoints: daily symptoms E-RS, rescue medication use, CAT, SGRQ, time to first exacerbation, time to first CID
- Safety

Maltais F et al. Respir Res 2019;20:238 [PMID 31666084]

EMAX

Table 1 Patient demographics and baseline characteristics

Characteristic	UMEC/VI (*N* = 812)	UMEC (*N* = 804)	SAL (*N* = 809)	Total (*N* = 2425)
Age, years, mean (SD)	64.6 (8.4)	64.9 (8.5)	64.4 (8.5)	64.6 (8.5)
Female, n (%)	319 (39)	327 (41)	342 (42)	988 (41)
Race, n (%)				
White	767 (94)	764 (95)	766 (95)	2297 (95)
Black/African American	24 (3)	23 (3)	25 (3)	72 (3)
American Indian/Alaska Native	13 (2)	12 (1)	12 (1)	37 (2)
Asian	5 (< 1)	1 (< 1)	1 (< 1)	7 (< 1)
Multiple[a]	3 (1)	4 (< 1)	5 (< 1)	12 (< 1)
Current smoker at screening, n (%)	394 (49)	396 (49)	413 (51)	1203 (50)
Smoking pack-years, mean (SD)	49.4 (27.7)	47.6 (25.9)	48.1 (25.8)	48.4 (26.5)
Use of LABD during run-in, n (%)[b]	531 (65)	521 (65)	524 (65)	1576 (65)
LAMA	399 (49)	392 (49)	403 (50)	1194 (49)
LABA	130 (16)	142 (18)	132 (16)	404 (17)
No maintenance medication during run-in, n (%)	250 (31)	250 (31)	249 (31)	749 (31)
Moderate COPD exacerbation history in prior year[c], n (%)	123 (15)	124 (15)	146 (18)	393 (16)

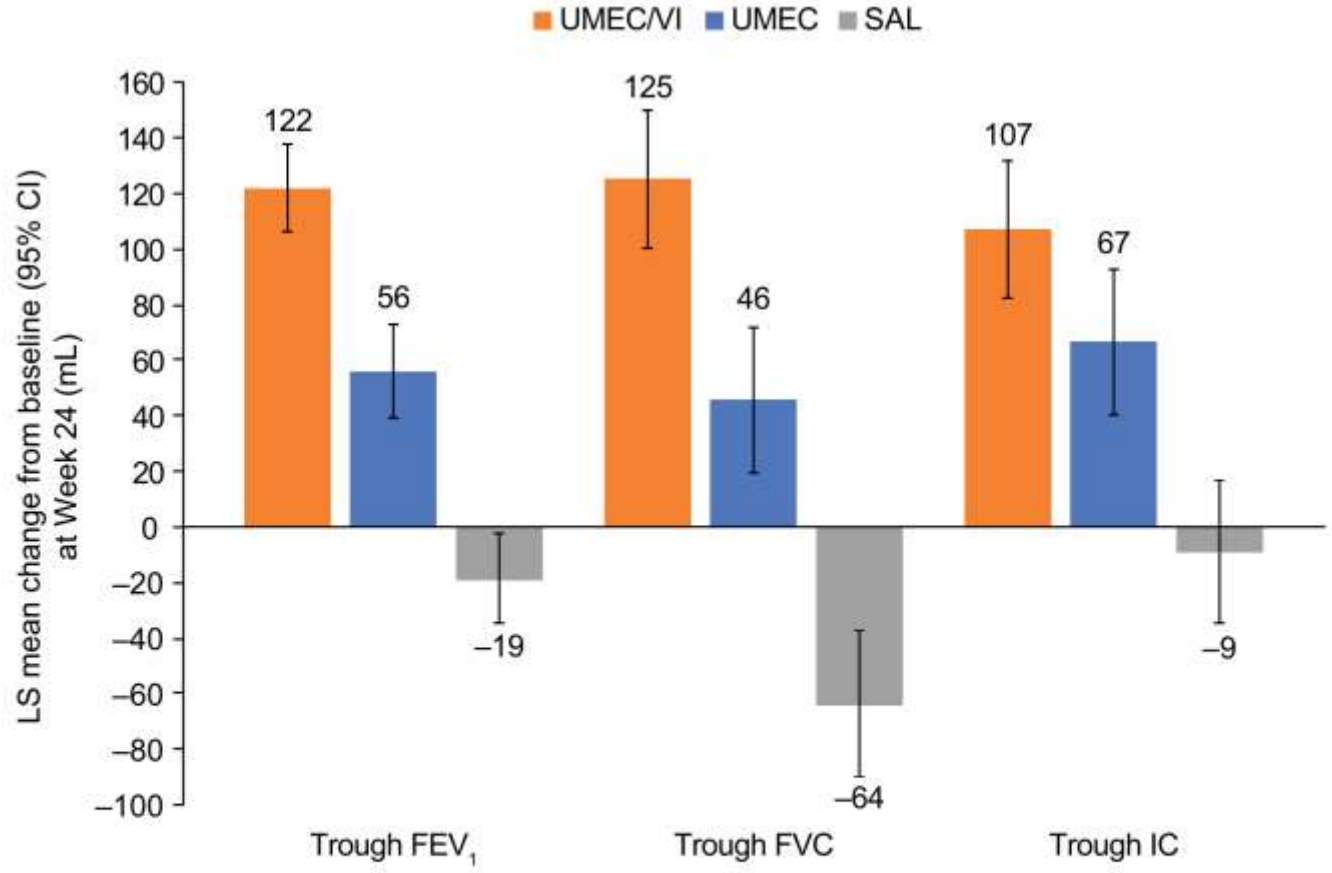
Maltais F et al. Respir Res 2019;20:238 [PMID 31666084]

Moderate COPD exacerbation history in prior year[c], n (%)	123 (15)	124 (15)	146 (18)	393 (16)
Duration of COPD, years, mean (SD)	8.8 (6.9)	7.8 (6.0)	8.3 (6.7)	8.3 (6.6)
Post-salbutamol FEV_1, mL, mean (SD)	1577 (506)	1609 (503)	1600 (523)	1595 (511)
Post-salbutamol % predicted FEV_1, mean (SD)	54.9 (12.8)	55.9 (12.6)	55.6 (12.8)	55.4 (12.7)
Post-salbutamol FEV_1/FVC, mean (SD)	0.51 (0.10)	0.52 (0.10)	0.52 (0.10)	0.52 (0.10)
% reversibility to salbutamol, mean (SD)	10.4 (12.8)	10.2 (13.3)	10.7 (13.3)	10.5 (13.1)
GOLD spirometric grade[d], n (%)				
2	518 (64)	529 (66)	522 (65)	1569 (65)
3	294 (36)	271 (34)	286 (35)	851 (35)
Baseline FEV_1, mL, mean (SD)	1474 (513)	1503 (505)	1495 (533)	1491 (517)
BDI score, mean (SD)	7.0 (1.8)	7.0 (1.9)	7.1 (1.8)	7.01 (1.9)
Baseline E-RS total score	10.7 (5.6)	10.7 (5.8)	10.4 (5.7)	10.6 (5.7)
Baseline SGRQ score, mean (SD)	44.5 (16.1)	45.0 (16.1)	44.6 (16.3)	44.7 (16.2)
Baseline CAT score, mean (SD)	19.1 (5.9)	19.3 (6.2)	19.3 (6.3)	19.2 (6.1)
Baseline rescue salbutamol, puffs/day, mean (SD)	2.2 (2.6)	2.1 (2.3)	2.2 (2.5)	2.2 (2.5)
Any cardiac comorbidities[e], n (%)	111 (14)	136 (17)	117 (14)	364 (15)
Any vascular comorbidities[f], n (%)	444 (55)	434 (54)	448 (55)	1326 (55)

EMAX

Maltais F et al. Respir Res 2019;20:238 [PMID 31666084]

LAMA/LABA (UMEC/VIL) vs. LAMA (UMEC) vs. LABA (VIL)
– EMAX (Trough FEV1, FVC, IC) –



	Difference (95% CI)		
UMEC/VI vs UMEC	66 mL (43, 89), $p < 0.001$	79 mL (42, 116), $p < 0.001$	41 mL (4, 77), $p = 0.028$
UMEC/VI vs SAL	141 mL (118, 164), $p < 0.001$	189 mL (152, 225), $p < 0.001$	116 mL (80, 152), $p < 0.001$

Maltais F et al. Respir Res 2019;20:238 [PMID 31666084]

Symptom

Effect of QVA149 on lung volumes and exercise tolerance in COPD patients: The BRIGHT study

Kai-Michael Beeh [a,*], Stephanie Korn [b], Jutta Beier [a], Dalal Jadayel [c], Michelle Henley [c], Peter D'Andrea [d], Donald Banerji [d]

- Patients with moderate-to-severe COPD were randomized to **QVA149 110/50** mg, **placebo** or **tiotropium** 18 mg once daily in a blinded, 3-period crossover study for 3 weeks.
- The primary endpoint was **exercise endurance time** at **Day 21** for QVA149 versus placebo.

BRIGHT

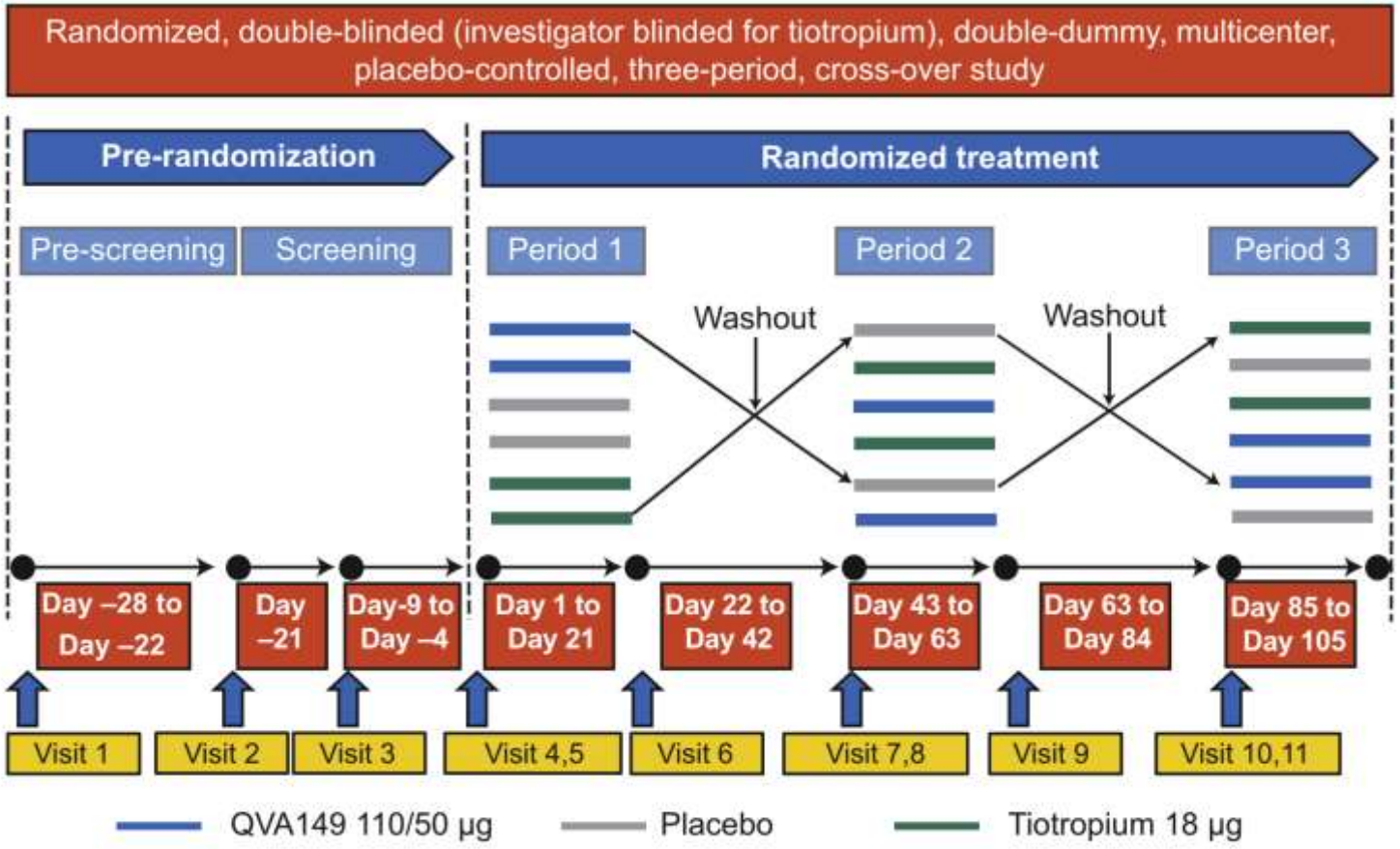


Figure 1 BRIGHT study design.

Beeh KM et al. Respir Med 2014;108:584-92. [PMID: 24534204]

LABA/LAMA (Ind/Gly) vs. Placebo vs. Tiotropium – BRIGHT (Exercise endurance time) –

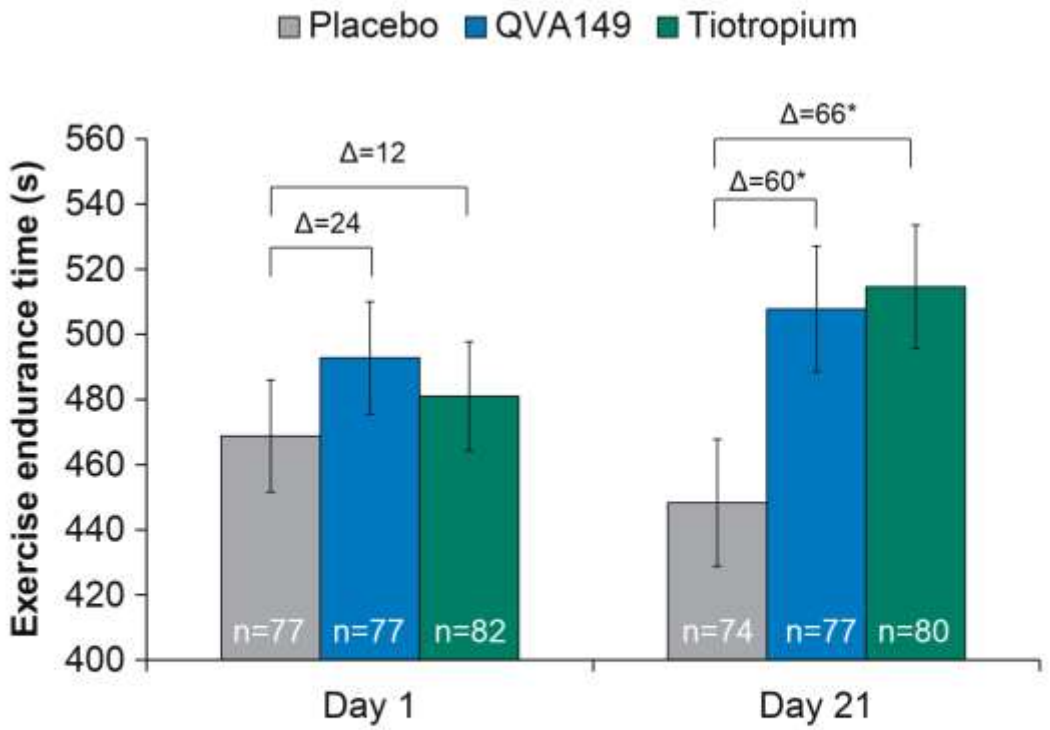
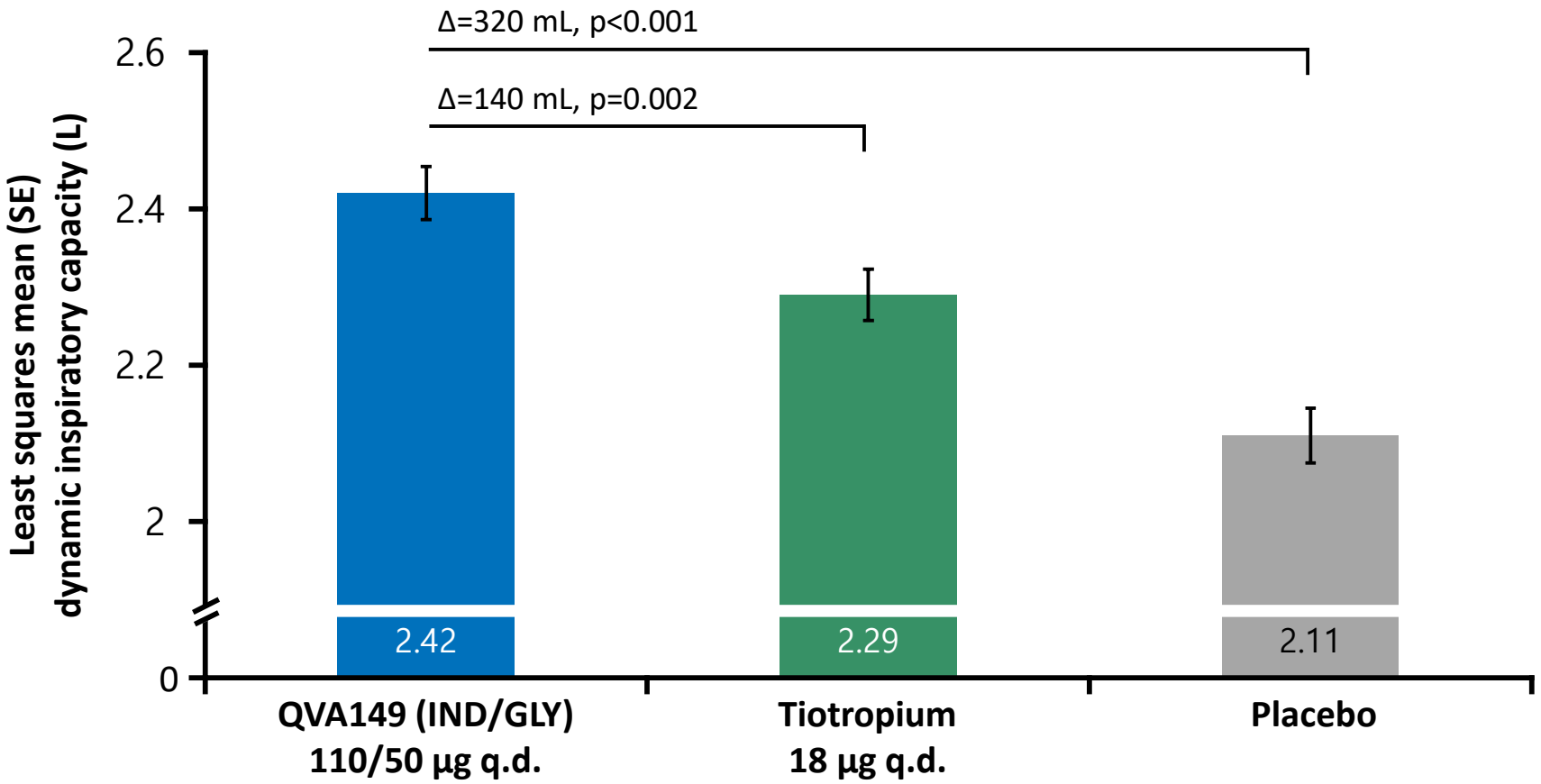


Figure 3 Exercise endurance time (seconds) at Day 1 and Day 21 (Full analysis set).
Data are least squares mean ± standard error; *$p < 0.01$.

- once-daily QVA149 significantly improved exercise endurance time compared with placebo

Beeh KM et al. Respir Med 2014;108:584-92. [PMID: 24534204]

IND/GLY improved dynamic inspiratory capacity at Day 21 vs tiotropium and placebo



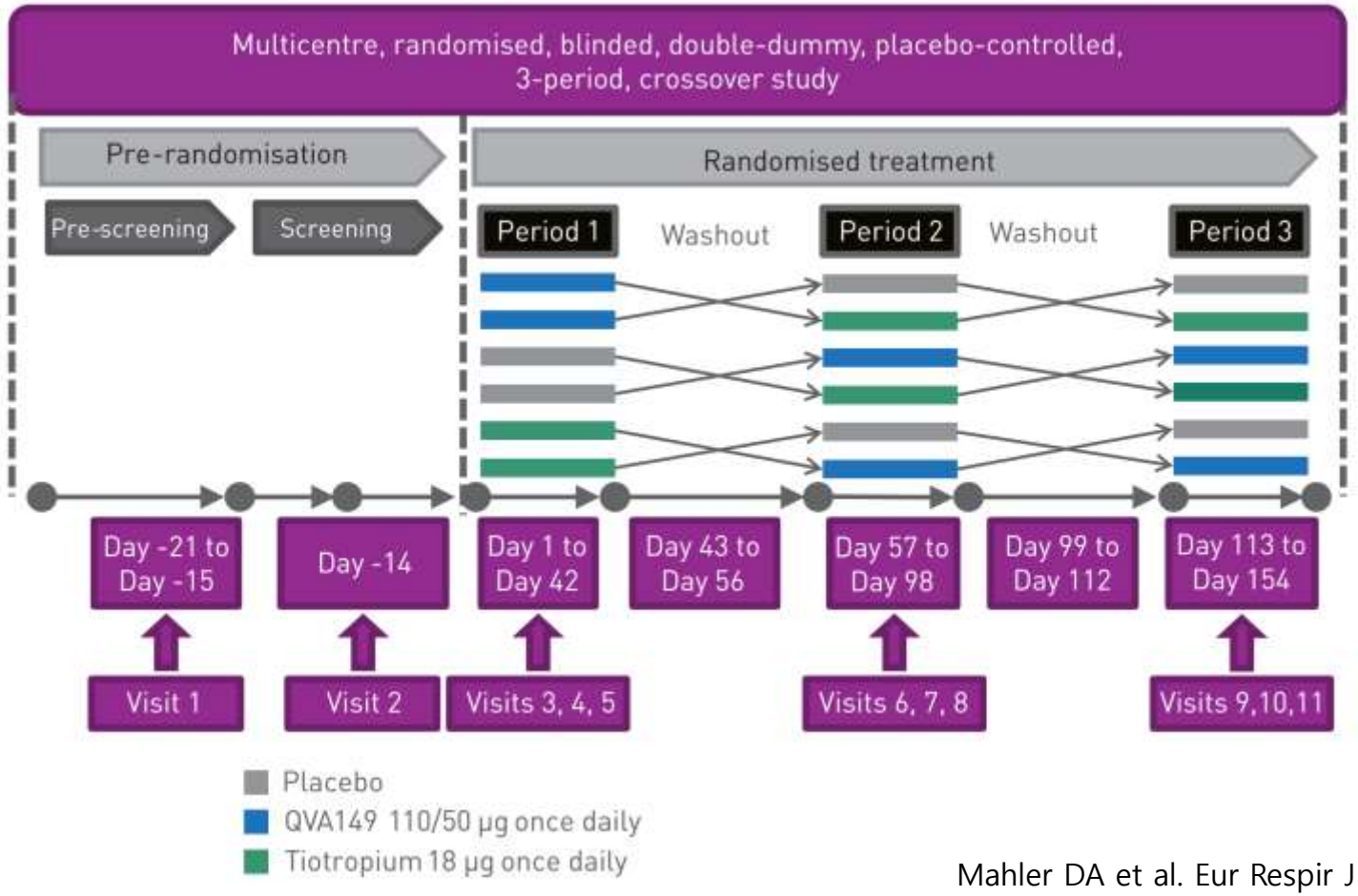
Beeh KM et al. Respir Med 2014;108:584-92. [PMID: 24534204]

Dual bronchodilation with QVA149 reduces patient-reported dyspnoea in COPD: the BLAZE study

Donald A. Mahler[1], Marc Decramer[2], Anthony D'Urzo[3], Heinrich Worth[4], Tracy White[5], Vijay K.T. Alagappan[5], Hungta Chen[5], Nicola Gallagher[6], Károly Kulich[7] and Donald Banerji[5]

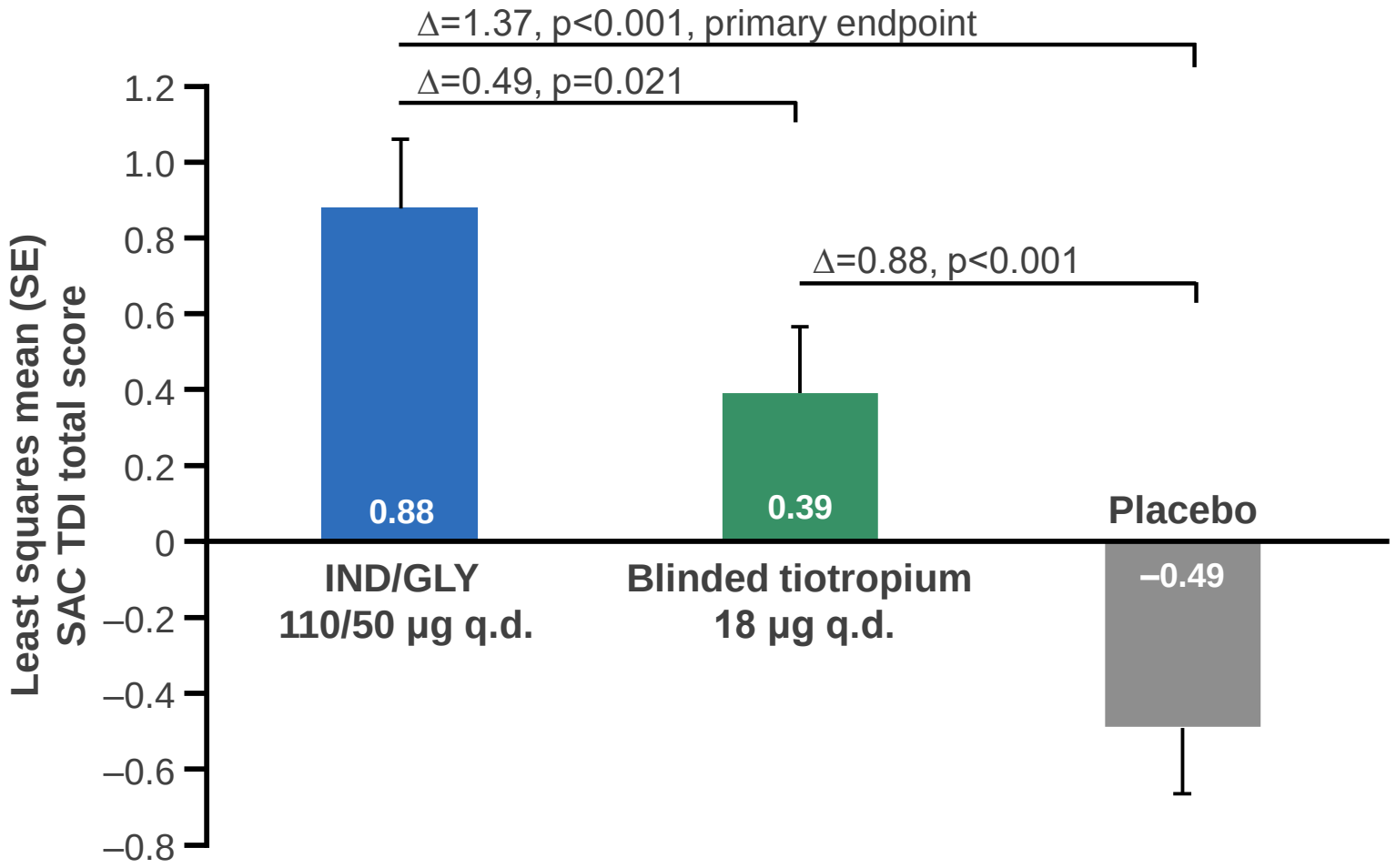
- **247** patients were randomized to once-daily QVA149 110/50 mg, placebo or tiotropium 18 mg.
- Superiority of **QVA149** versus **placebo** (primary objective) and tiotropium (secondary objective) was assessed for improvement in **dyspnoea** via the self-administered computerised (**SAC**) version of the Baseline and Transition **Dyspnoea Index** after 6 weeks.

BLAZE



Mahler DA et al. Eur Respir J 2014;43:1599-609. [PMID: 24176997]

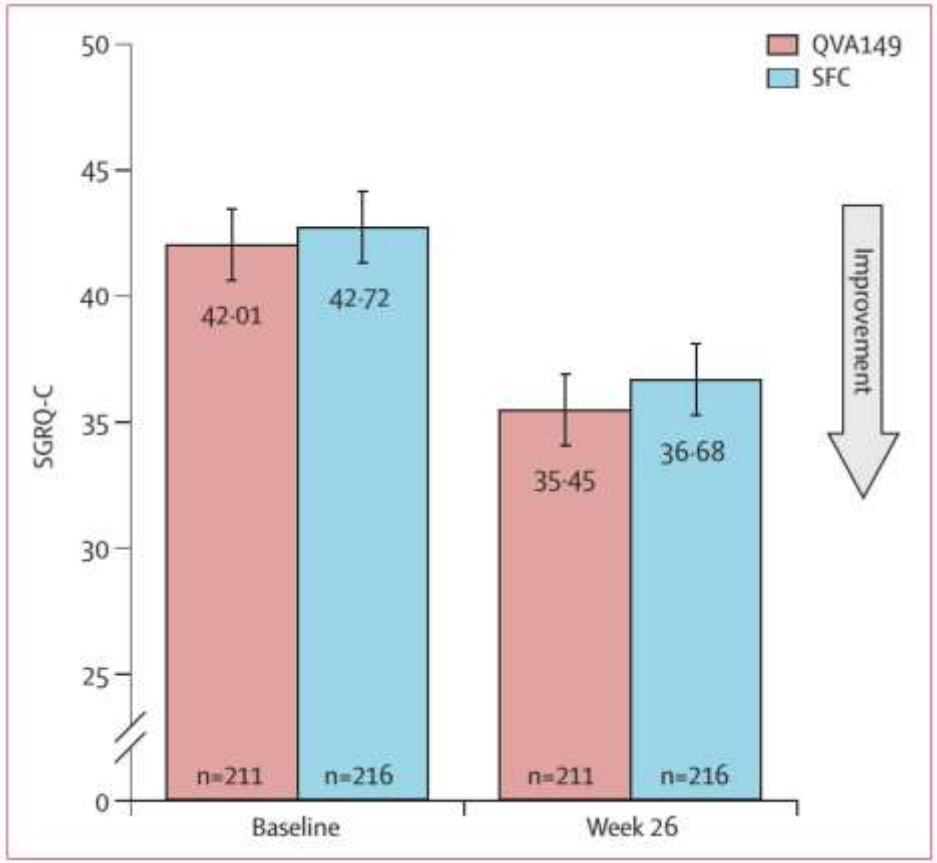
IND/GLY significantly improved SAC TDI total score vs tiotropium and placebo after 6 weeks



Mahler DA et al. Eur Respir J 2014;43:1599-609. [PMID: 24176997]

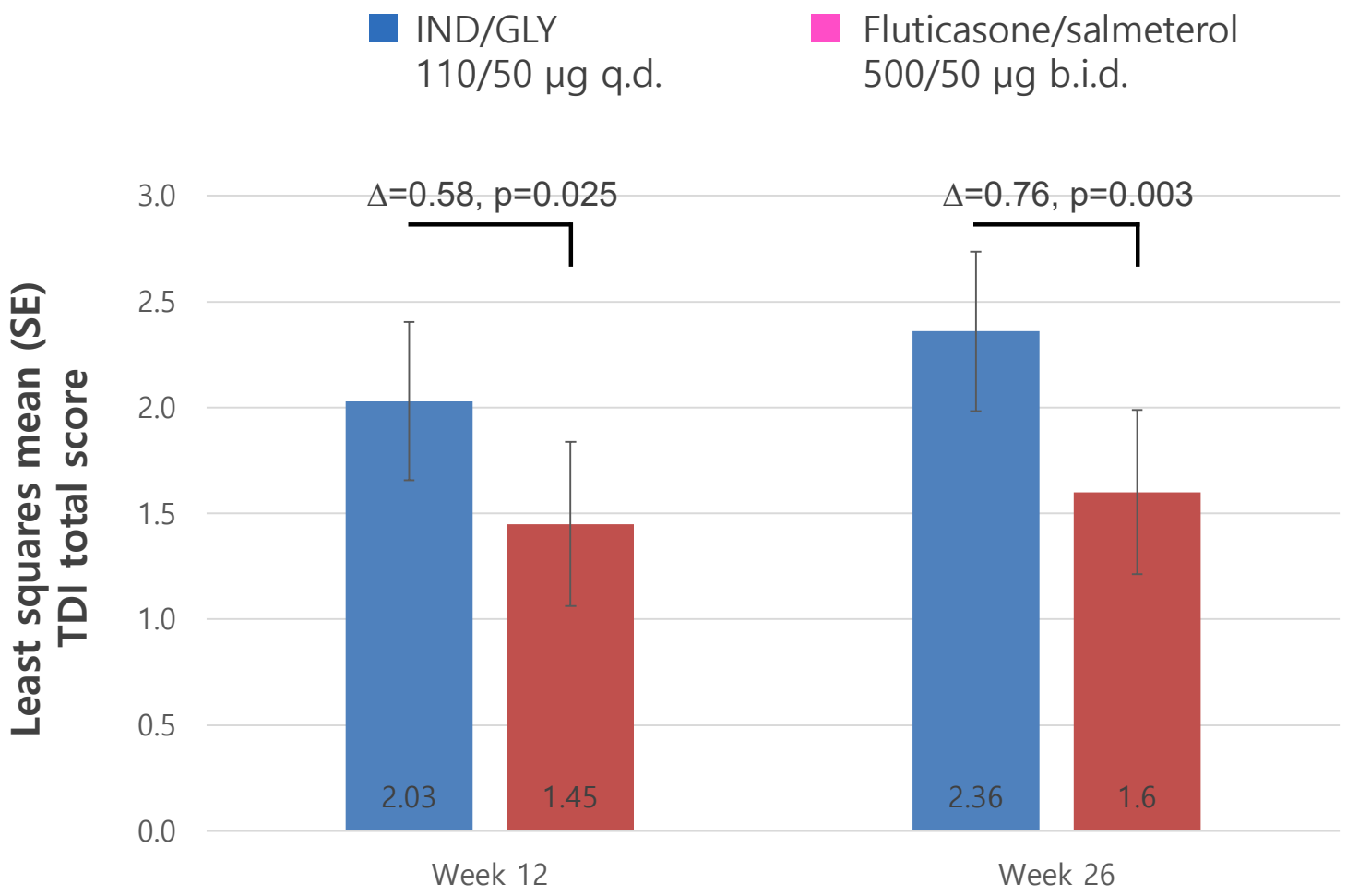
LABA/LAMA (Ind/Gly) vs. ICS/LABA (SFC)
– ILLUMINATE (QOL, SGRQ-C) –

- patients with moderate-to-severe COPD (**without AE** in the year)
- The primary endpoint was to demonstrate the superiority of **IND/GLY** compared with SFC for postBD **FEV1 AUC_{0-12h}** after 26 weeks of treatment.



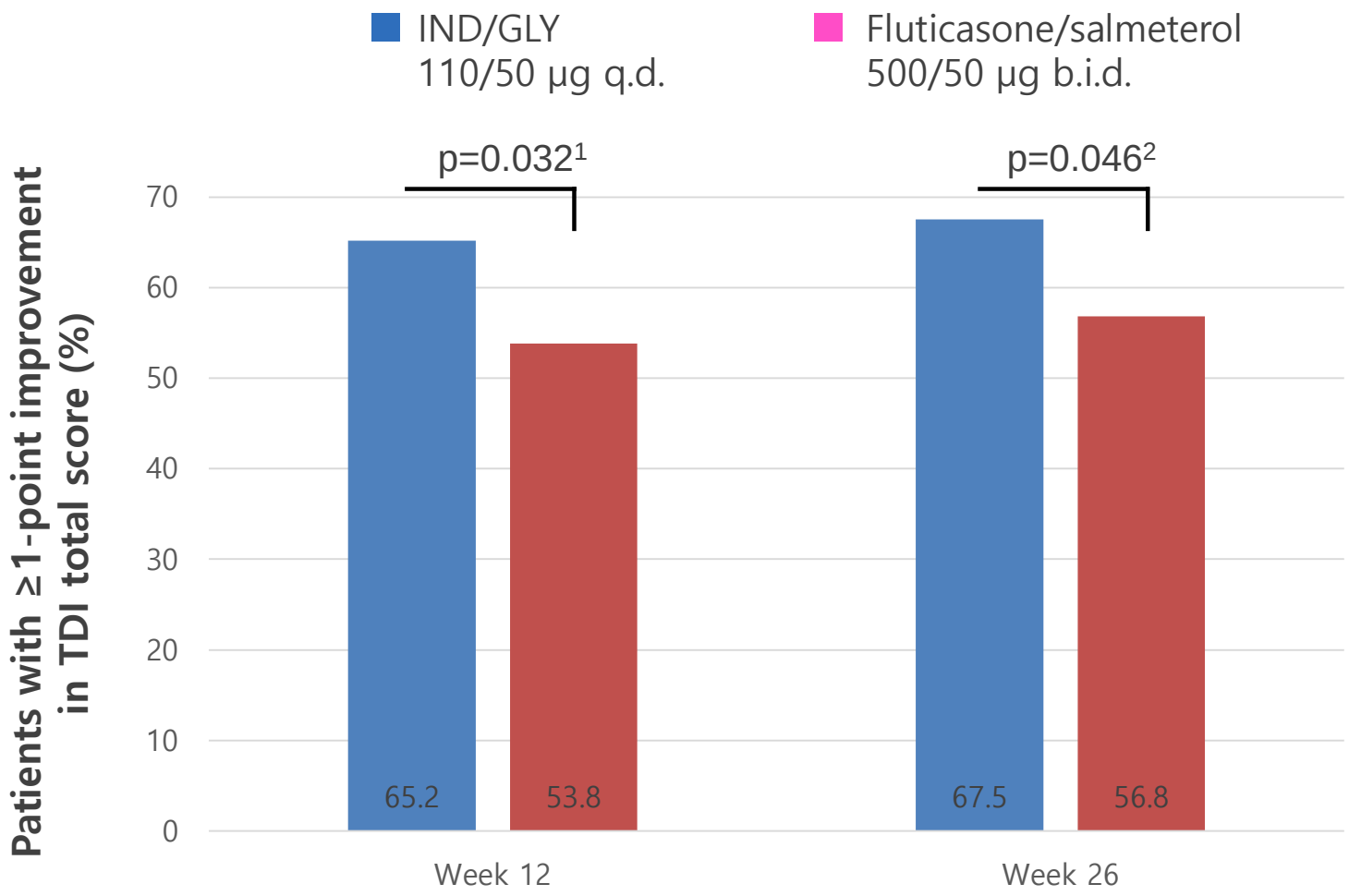
Vogelmeier CF et al. Lancet Respir Med 2013;1:51-60. [PMID: 24321804]

IND/GLY significantly improved TDI total score vs ICS/LABA



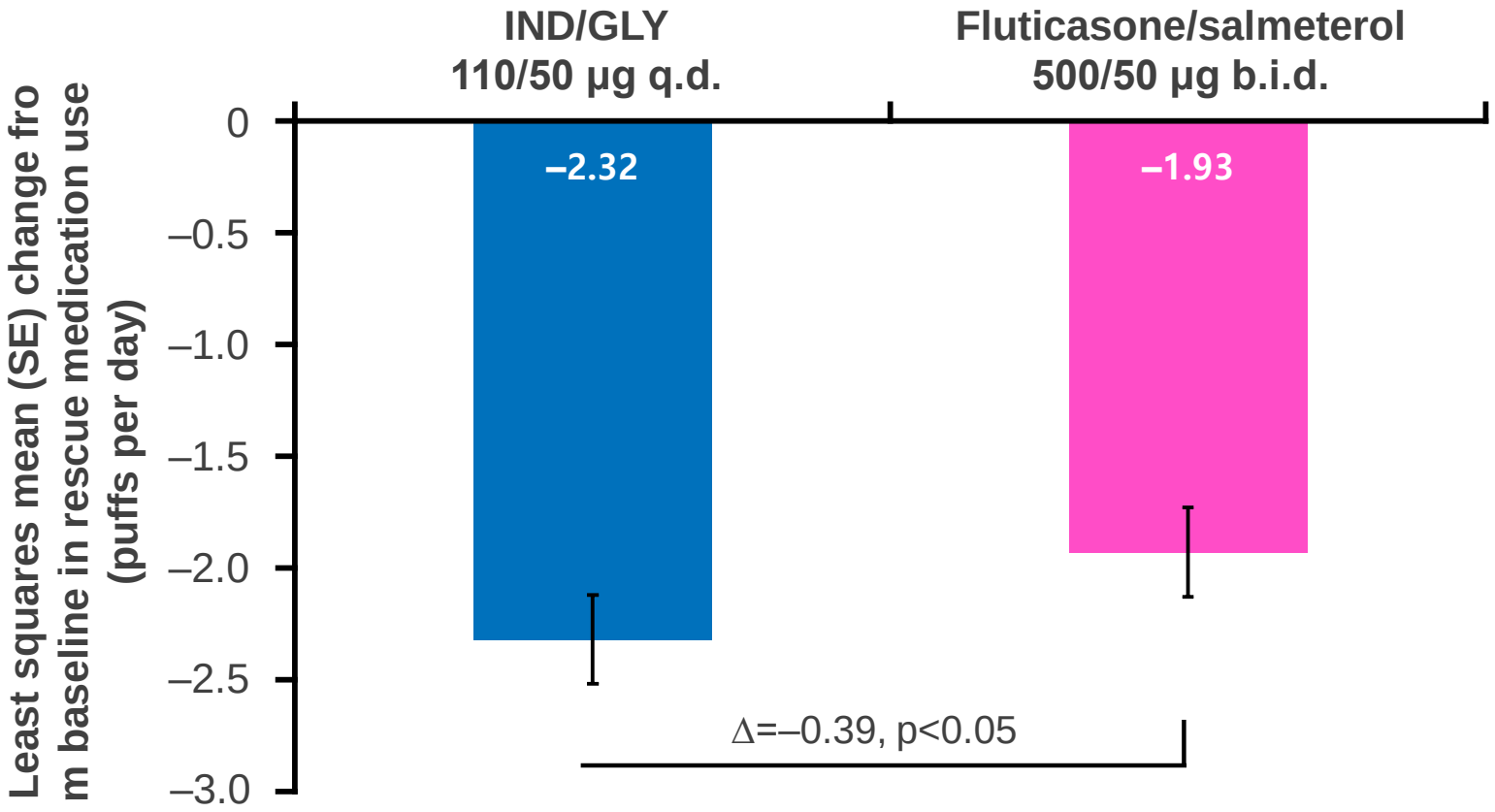
Vogelmeier CF et al. Lancet Respir Med 2013;1:51-60. [PMID: 24321804]

More patients on IND/GLY achieved TDI total score improvement ≥1 vs ICS/LABA



Vogelmeier CF et al. Lancet Respir Med 2013;1:51-60. [PMID: 24321804]

IND/GLY significantly reduced daily use of rescue medication vs LABA/ICS over 26 weeks



Vogelmeier CF et al. Lancet Respir Med 2013;1:51-60. [PMID: 24321804]

LABA/LAMA (TIO/OLO) vs. LAMA (TIO) vs LABA (OLO) – TONADO (SGRQ) –

TABLE 4 St George's Respiratory Questionnaire (SGRQ) score at 24 weeks (full analysis set)

	SGRQ total score[#]	SGRQ responders[¶]
Studies 1237.5+1237.6 common study baseline	43.512±0.259	
Olodaterol 5 µg	38.366±0.396	427/954 (44.8)
Tiotropium 2.5 µg	37.792±0.390	476/960 (49.6)
Tiotropium 5 µg	37.907±0.393	465/955 (48.7)
Tiotropium+olodaterol 2.5/5 µg	37.335±0.385	527/990 (53.2)
Tiotropium+olodaterol 5/5 µg	36.674±0.386	563/979 (57.5)

Data are presented as adjusted mean±SE or n/N (%). Data were obtained from fitting a mixed model for repeated measurements including fixed effects of treatment, planned test day, treatment-by-test-day interaction, baseline and baseline-by-test-day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom. [#]:number of patients contributing to the mixed model for repeated measurements for adjusted mean SGRQ across both studies: tiotropium+olodaterol 5/5 µg n=979; tiotropium+olodaterol 2.5/5 µg n=990; tiotropium 5 µg n=954; tiotropium 2.5 µg n=960; olodaterol 5 µg n=954; [¶]: a reduction in SGRQ total score at week 24 of ⩾4.0 units from baseline.

Buhl R et al. Eur Respir J 2015;45:969-79. [PMID: 25573406]

LABA/LAMA (TIO/OLO) vs. LAMA (TIO) vs LABA (OLO) – TONADO (SGRQ) –

TABLE 5 St George's Respiratory Questionnaire (SGRQ) score at 24 weeks (full analysis set): treatment comparisons

Treatment comparison	SGRQ total score[#]	p-value	Responder analysis[¶] odds ratio[§,f]	p-value
Tiotropium+olodaterol 5/5 µg				
versus olodaterol 5 µg	−1.693±0.553 (−2.778–−0.608)	0.0022	1.670±0.153 (1.395–1.999)	<0.0001
versus tiotropium 5 µg	−1.233±0.551 (−2.313–−0.153)	0.0252	1.426±0.131 (1.192–1.706)	0.0001
Tiotropium+olodaterol 2.5/5 µg				
versus olodaterol 5 µg	−1.031±0.552 (−2.113–0.052)	0.0620	1.405±0.128 (1.175–1.679)	0.0002
versus tiotropium 2.5 µg	−0.456±0.548 (−1.531–0.618)	0.4051	1.157±0.105 (0.969–1.383)	0.1071
versus tiotropium 5 µg	−0.571±0.550 (−1.649–0.507)	0.2988	1.199±0.109 (1.004–1.433)	0.0453
Tiotropium+olodaterol 5/5 µg				
versus tiotropium+olodaterol 2.5/5 µg	−0.662±0.545 (−1.731–0.407)	0.2249	1.189±0.108 (0.995–1.421)	0.0565

Data are presented as adjusted mean±se, unless otherwise stated. Data were obtained from fitting a mixed model for repeated measurements including fixed effects of treatment, planned test day, treatment-by-test-day interaction, baseline and baseline-by-test-day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom. [#]:number of patients contributing to the mixed model for repeated measurements for adjusted mean SGRQ across both studies: tiotropium+olodaterol 5/5 µg n=979; tiotropium+olodaterol 2.5/5 µg n=990; tiotropium 5 µg n=954; tiotropium 2.5 µg n=960; olodaterol 5 µg n=954; [¶]: a reduction in SGRQ total score at week 24 of ⩾4.0 units from baseline. [§]: responder analysis results are from fitting a logistic-regression model with treatment as covariate and a logit link function; [f]: number of patients contributing to SGRQ responder analysis across both studies: tiotropium+olodaterol 5/5 µg n=979; tiotropium+olodaterol 2.5/5 µg n=990; tiotropium 5 µg n=955; tiotropium 2.5 µg n=960; olodaterol 5 µg n=954.

Buhl R et al. Eur Respir J 2015;45:969-79. [PMID: 25573406]

LABA/LAMA (TIO/OLO) vs. LAMA (TIO) vs. Placebo – OTEMPTO (SGRQ) –

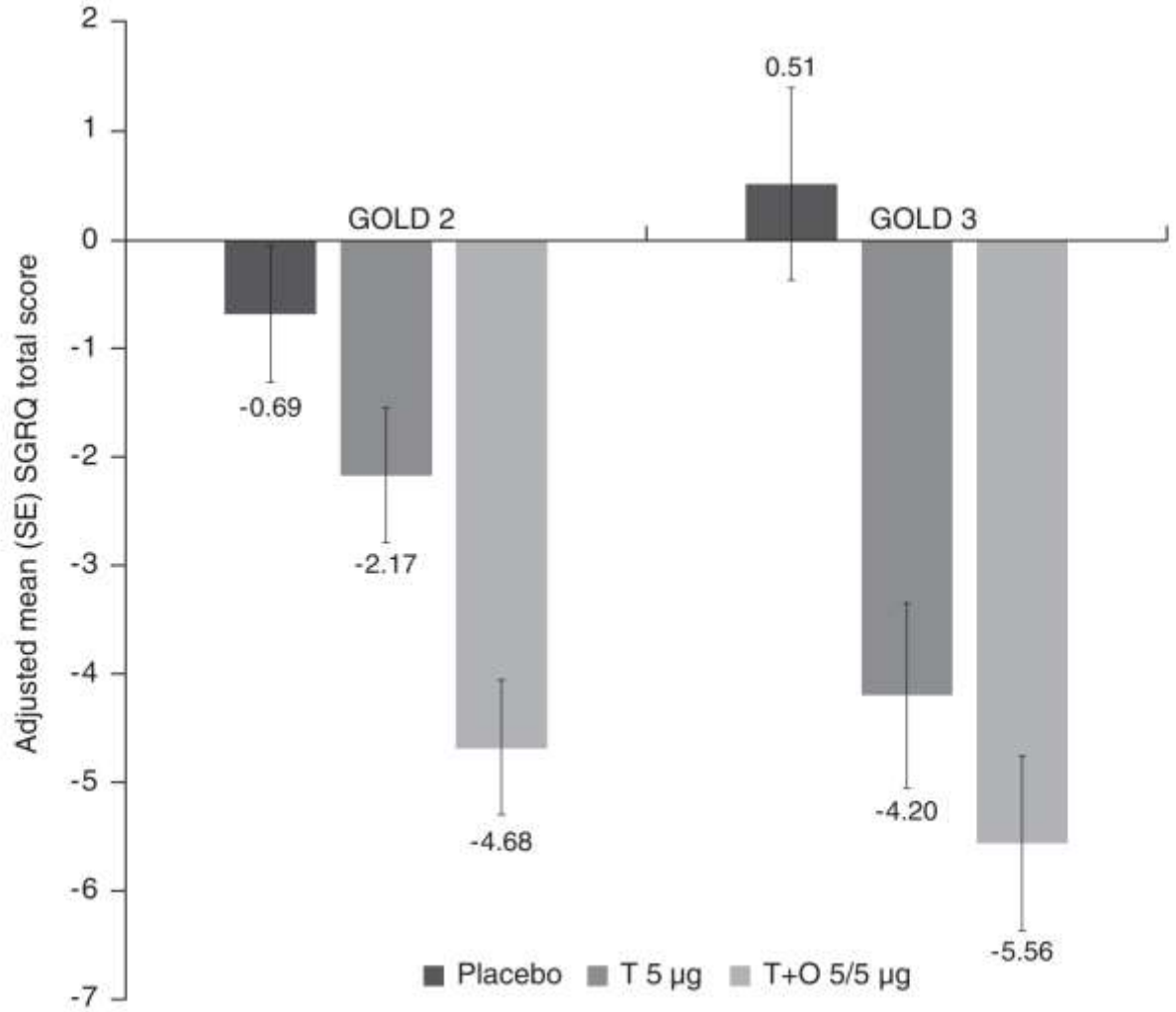
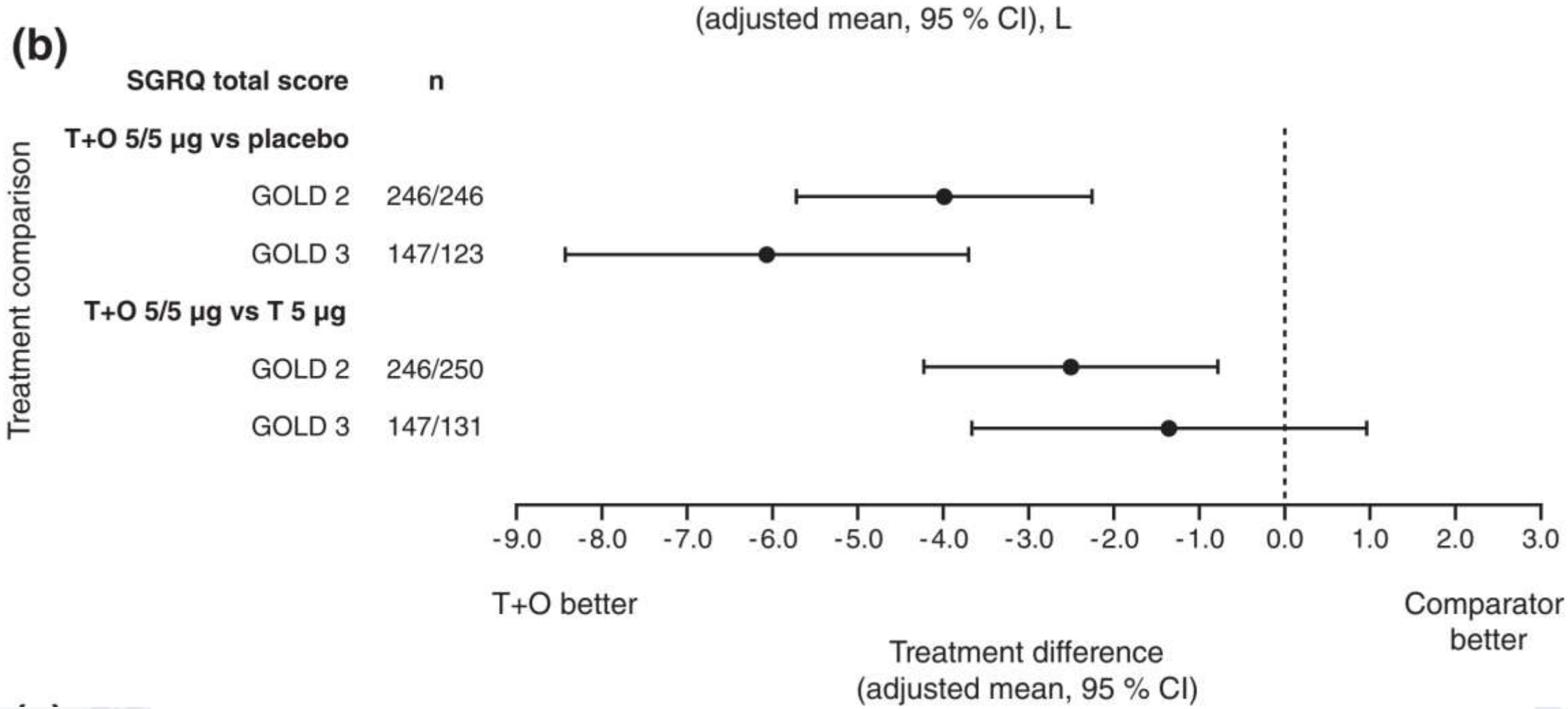


Fig. 3 Adjusted mean SGRQ total score at 12 weeks in patients with GOLD 2 and 3 disease. SGRQ: St George's Respiratory Questionnaire; GOLD: Global initiative for chronic Obstructive Lung Disease; SE: standard error; T: tiotropium; O: olodaterol

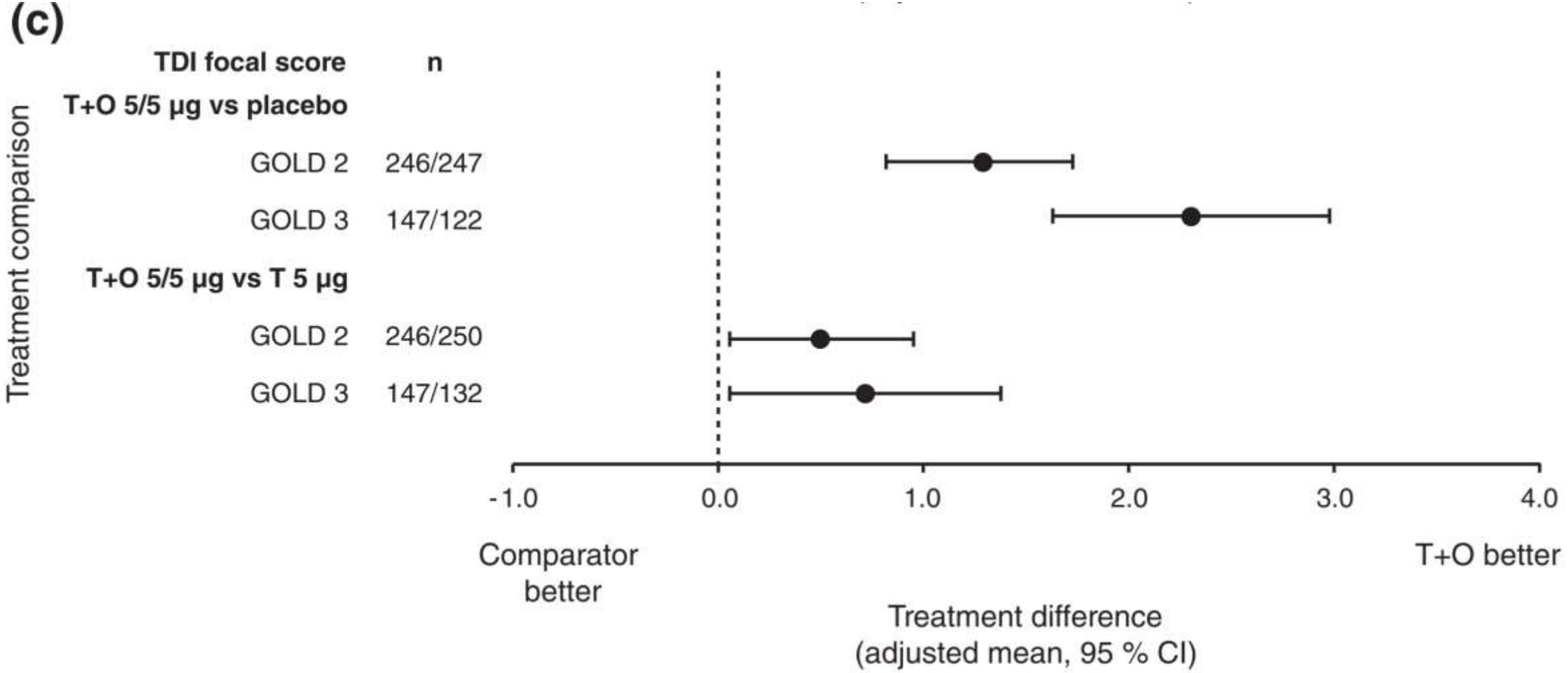
Singh D et al. Respir Res 2016;17:73. [PMID: 27316465]

LAMA/LABA (TIO/OLO) vs. LAMA (TIO) vs. Placebo – OTEMPTO (SGRQ, subgroup: GOLD 2 & 3) –



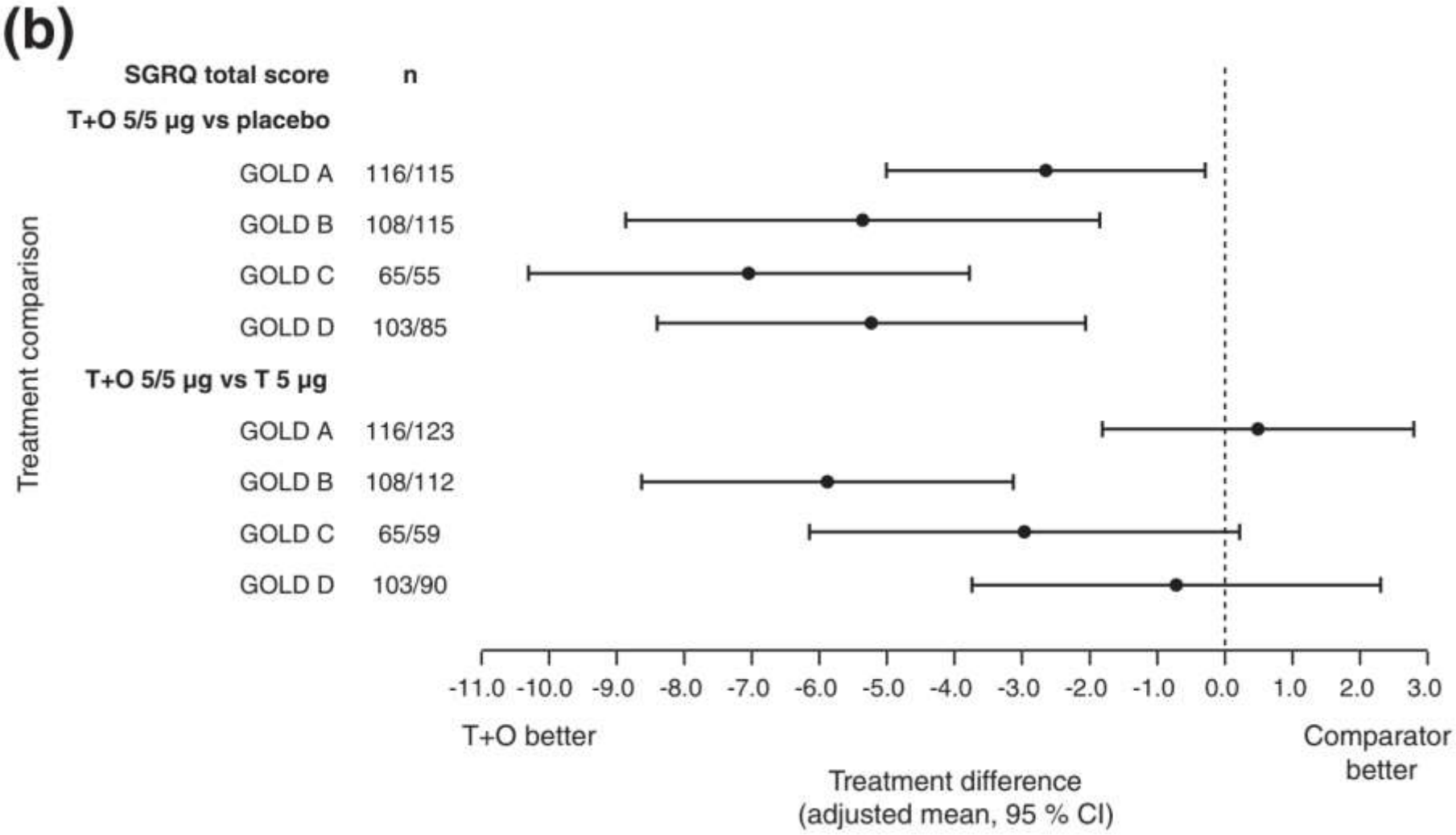
Singh D et al. Respir Res 2016;17:73. [PMID: 27316465]

LAMA/LABA (TIO/OLO) vs. LAMA (TIO) vs. Placebo – OTEMPTO (TDI, subgroup: GOLD 2 & 3) –



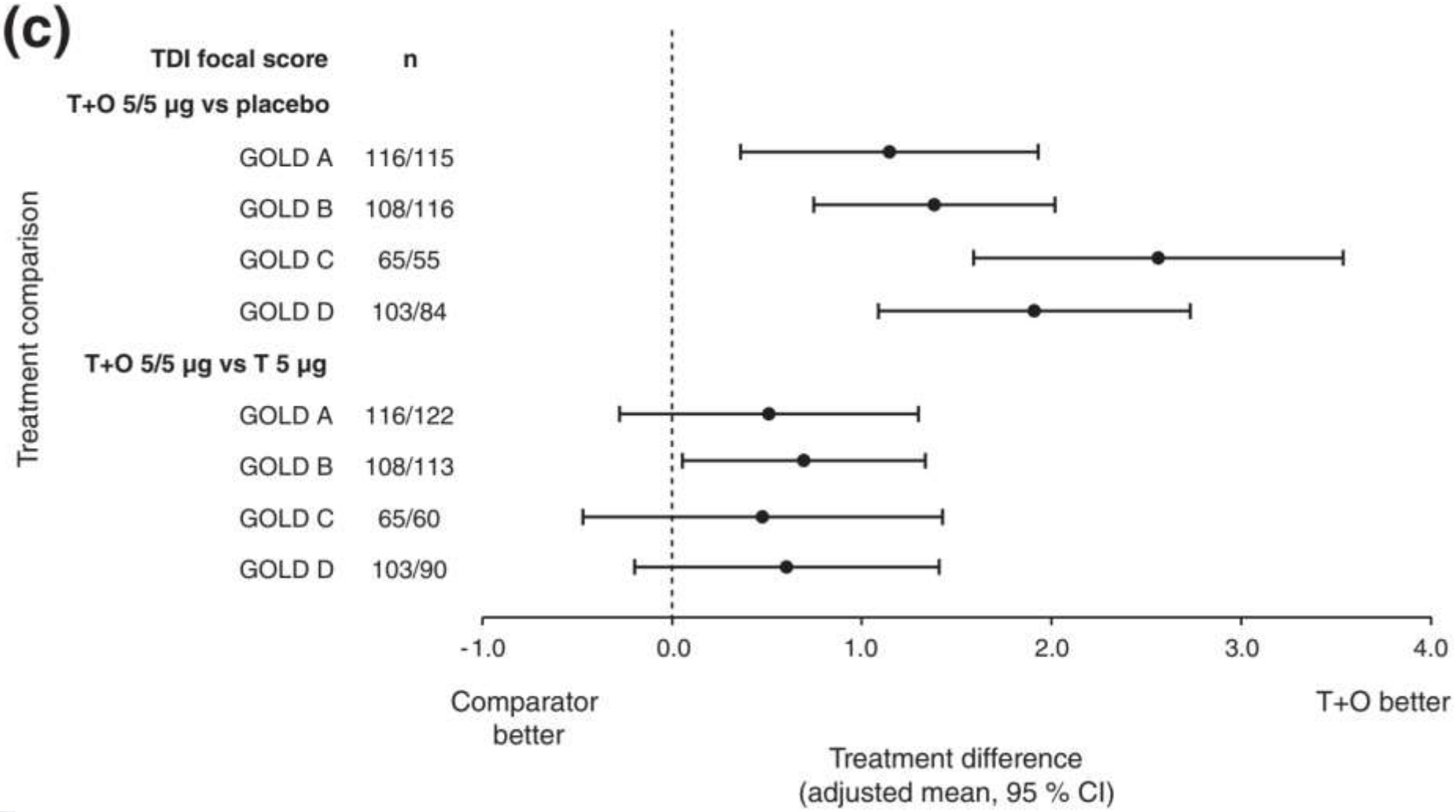
Singh D et al. Respir Res 2016;17:73. [PMID: 27316465]

LAMA/LABA (TIO/OLO) vs. LAMA (TIO) vs. Placebo – OTEMPTO (SGRQ, subgroup: GOLD ABCD) –



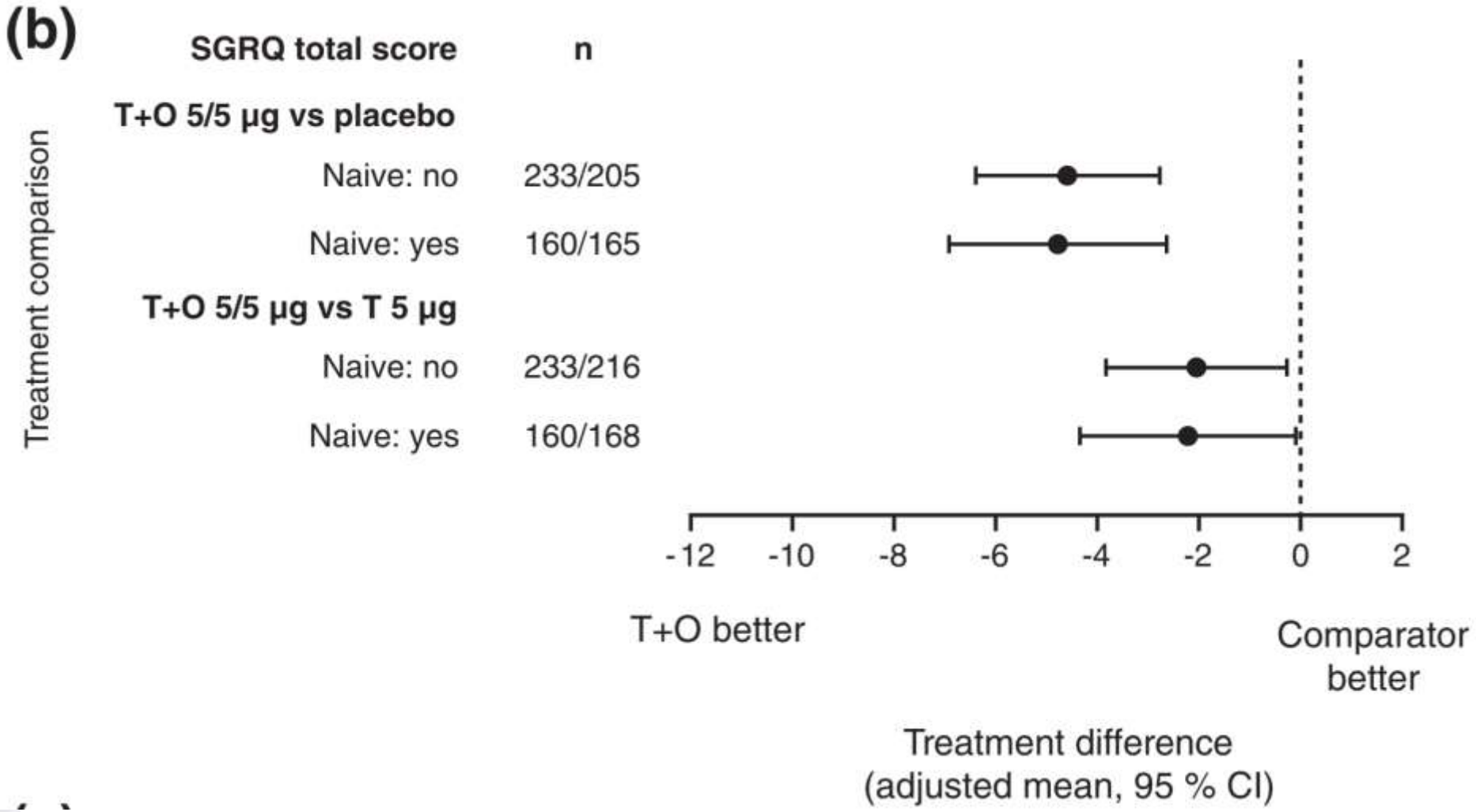
Singh D et al. Respir Res 2016;17:73. [PMID: 27316465]

LAMA/LABA (TIO/OLO) vs. LAMA (TIO) vs. Placebo – OTEMPTO (TDI, subgroup: GOLD ABCD) –



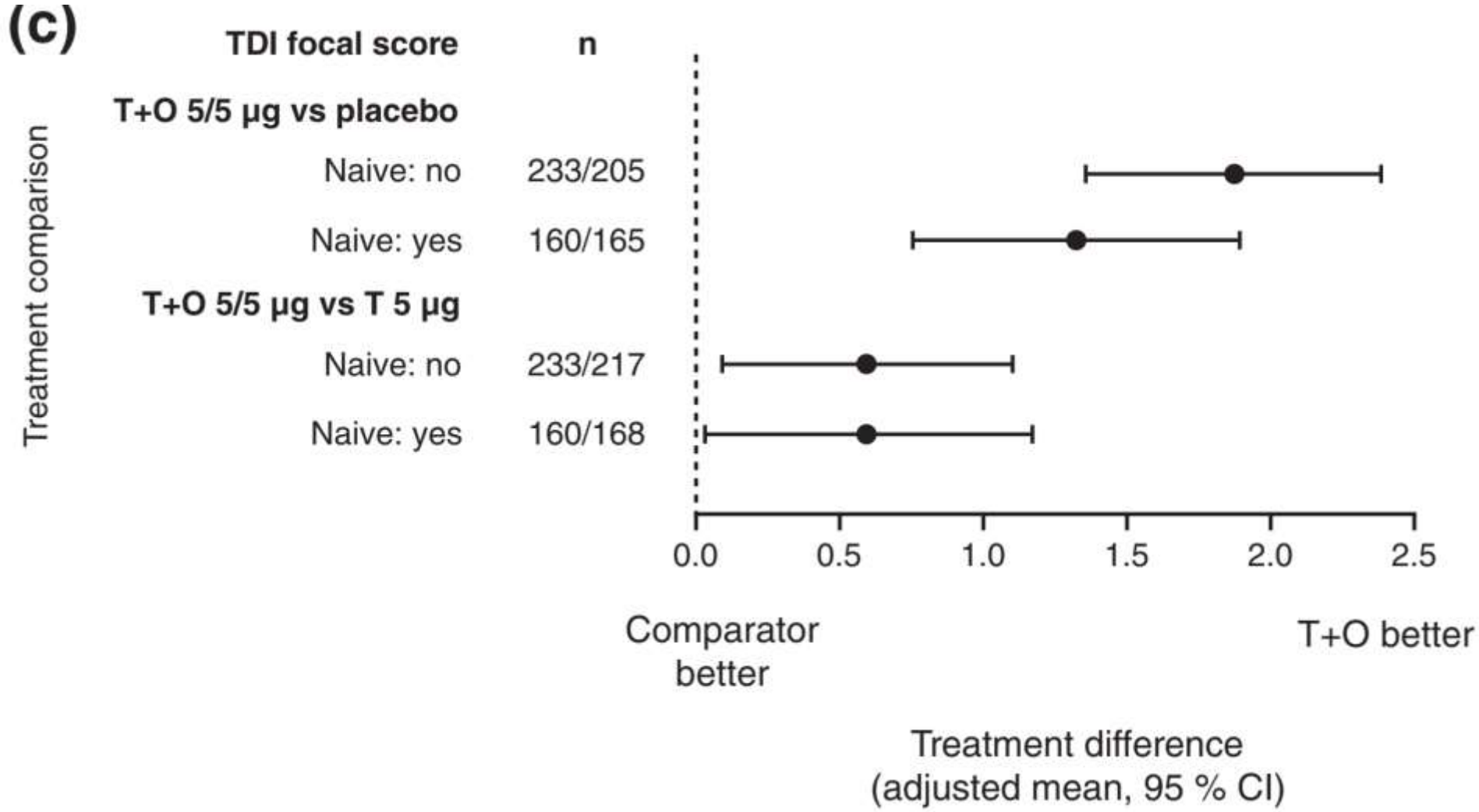
Singh D et al. Respir Res 2016;17:73. [PMID: 27316465]

LAMA/LABA (TIO/OLO) vs. LAMA (TIO) vs. Placebo – OTEMPTO (SGRQ, subgroup: Tx-naive) –



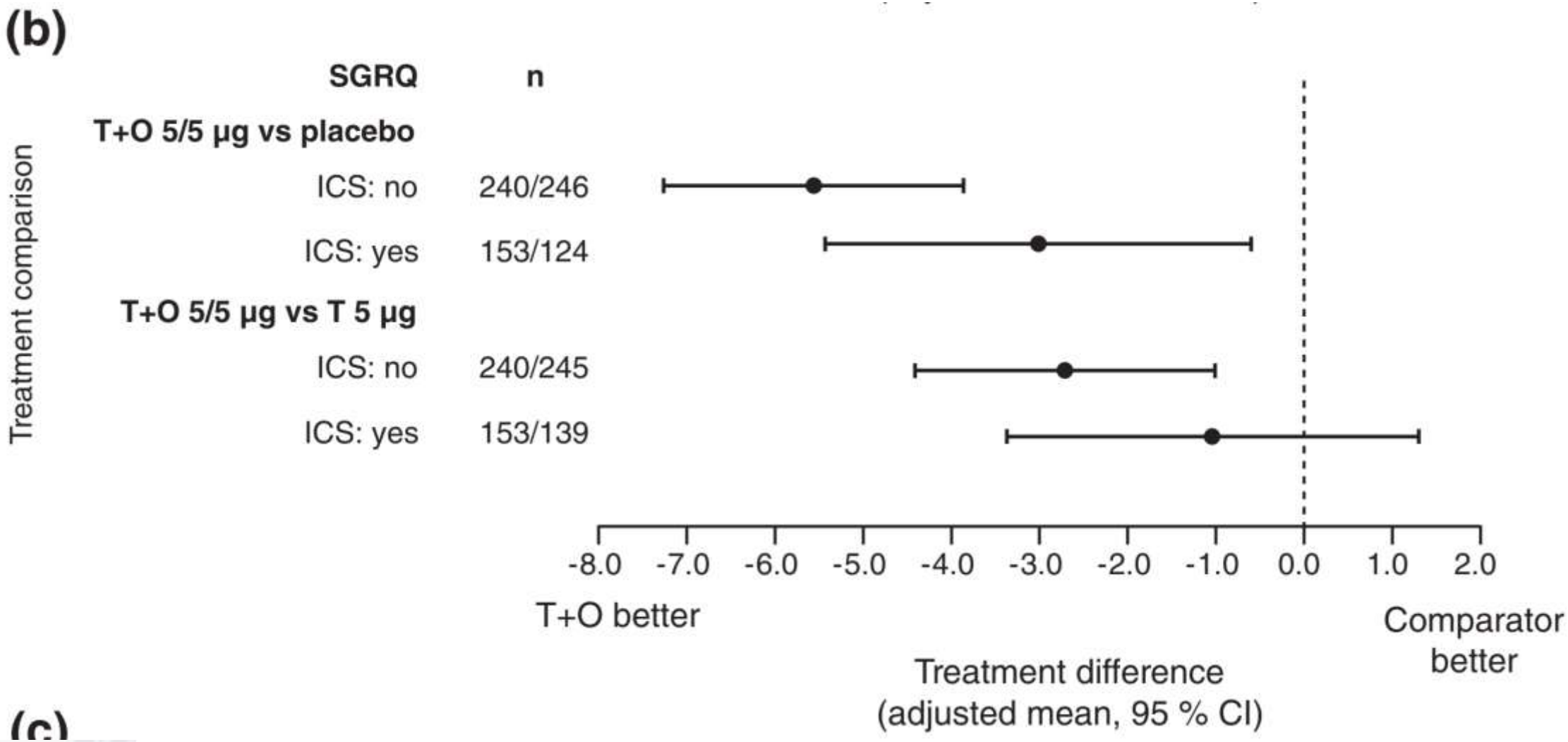
Singh D et al. Respir Res 2016;17:73. [PMID: 27316465]

LAMA/LABA (TIO/OLO) vs. LAMA (TIO) vs. Placebo – OTEMPTO (TDI, subgroup: Tx-naive) –



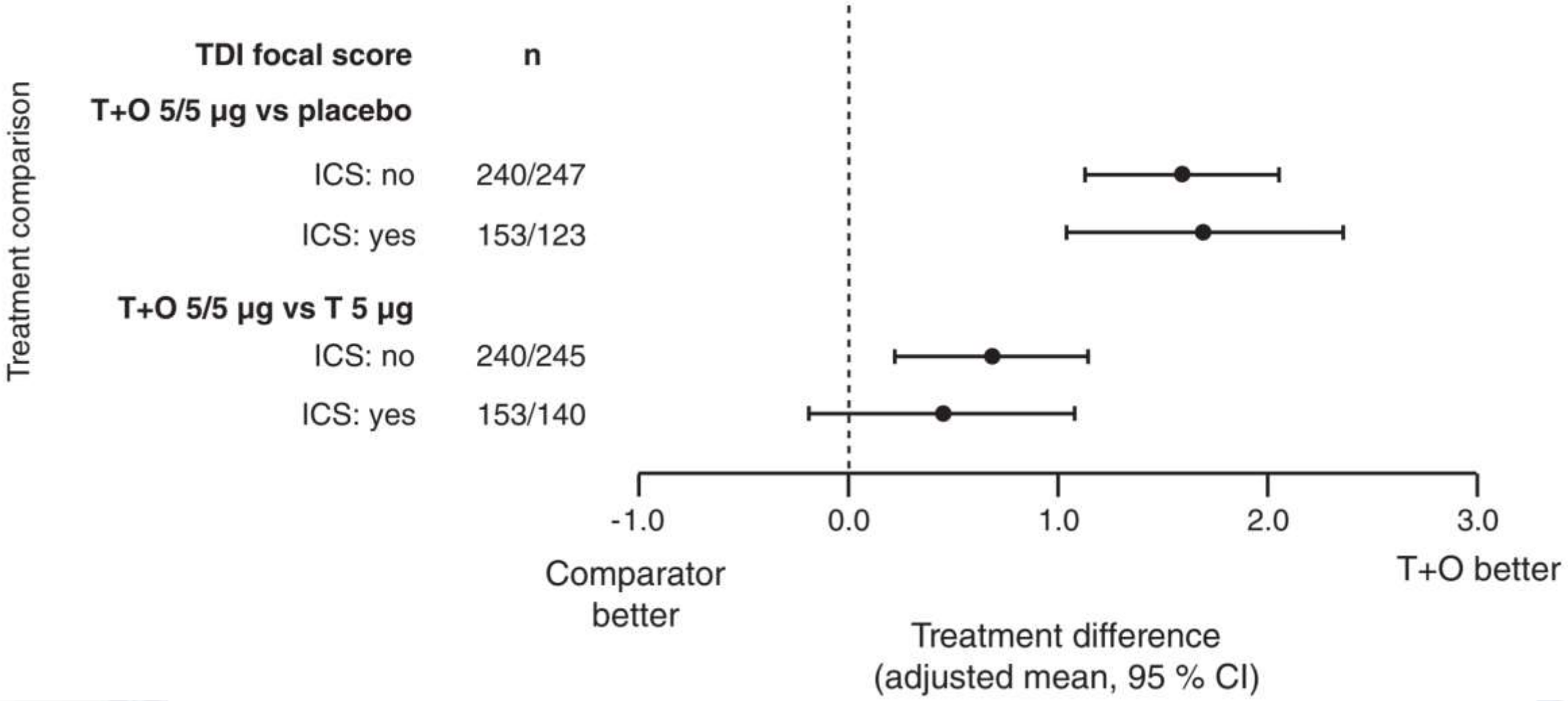
Singh D et al. Respir Res 2016;17:73. [PMID: 27316465]

LAMA/LABA (TIO/OLO) vs. LAMA (TIO) vs. Placebo – OTEMPTO (SGRQ, subgroup: ICS) –



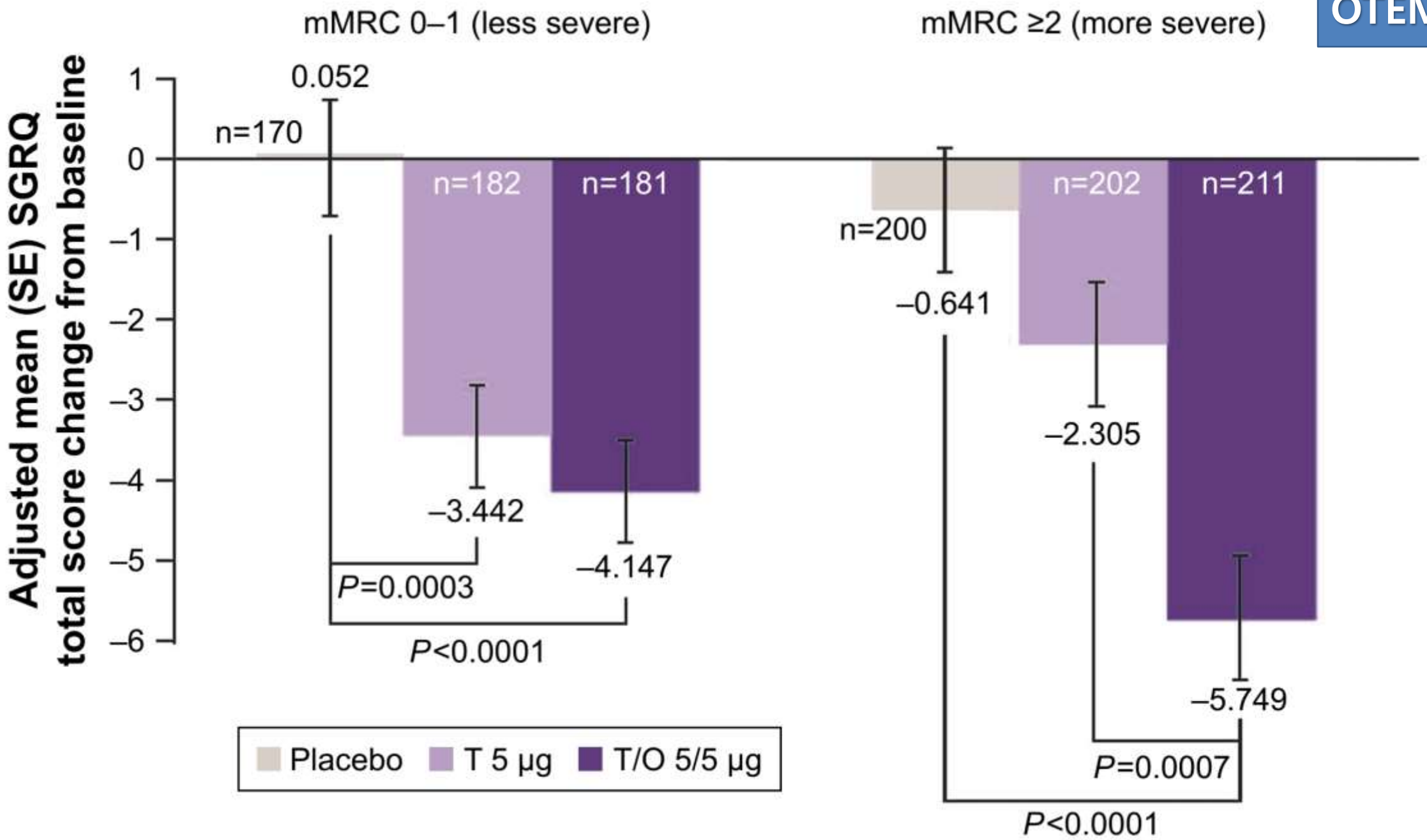
Singh D et al. Respir Res 2016;17:73. [PMID: 27316465]

LAMA/LABA (TIO/OLO) vs. LAMA (TIO) vs. Placebo – OTEMPTO (TDI, subgroup: ICS) –



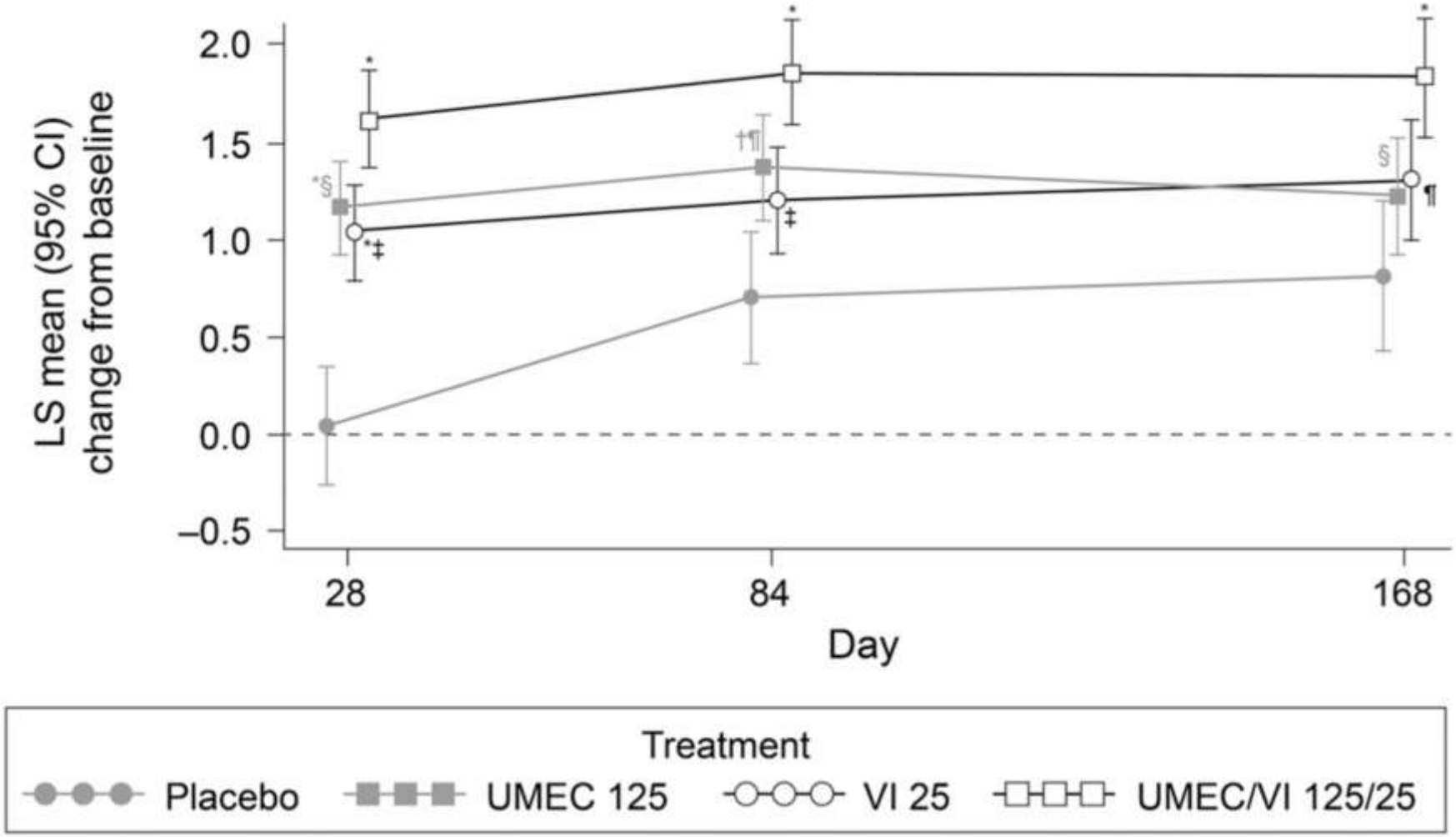
Singh D et al. Respir Res 2016;17:73. [PMID: 27316465]

OTEMTPTO



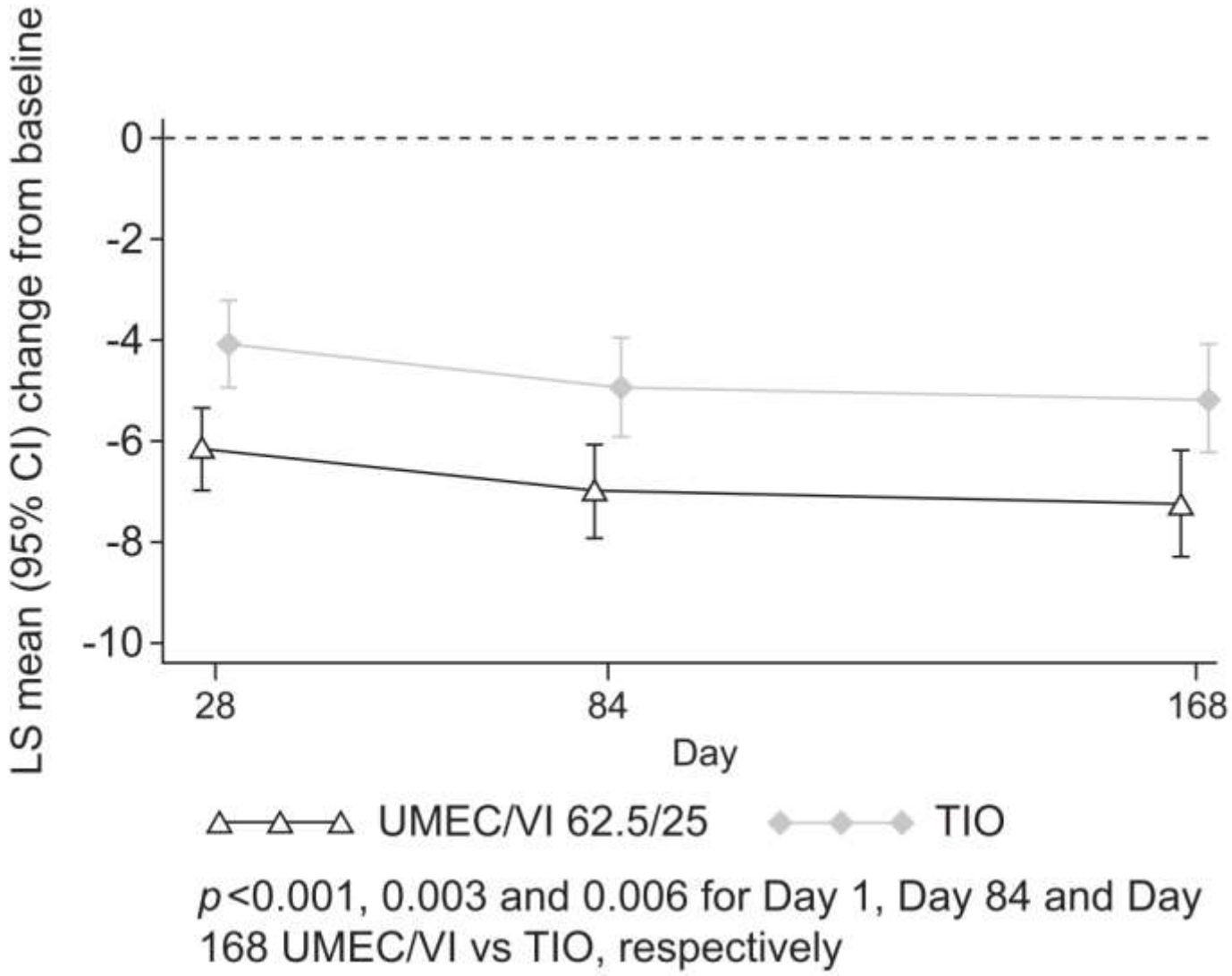
Martinez FJ et al. Int J Chron Obstruct Pulmon Dis 2019;14:181-94. [PMID: 30655665]

LAMA/LABA (UMEC/VIL) vs. LAMA (UMEC) vs. LABA (VIL) – DB2113361 (TDI) –



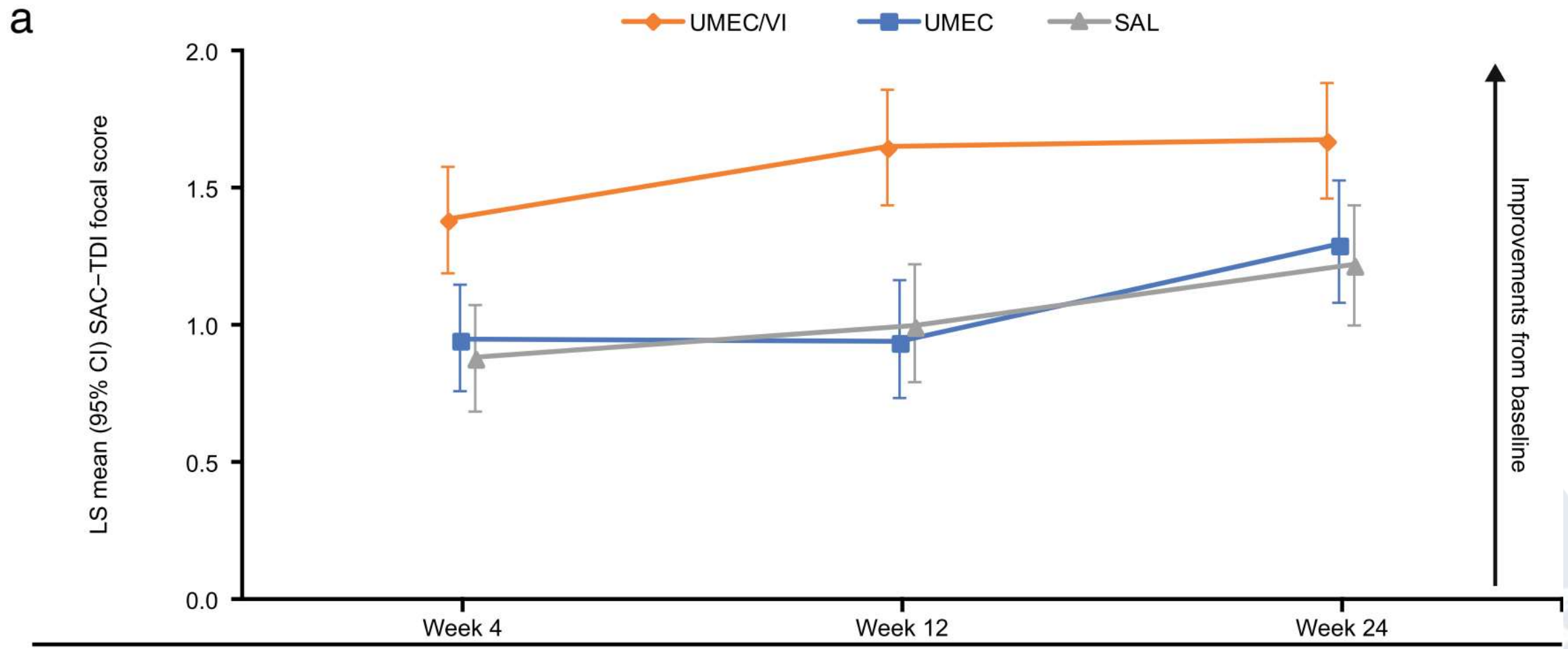
Celli B et al. Chest 2014;145:981-91 [PMID 24385182]

LAMA/LABA (UMEC/VIL) vs. LAMA (TIO)
– ZEP117115 (SGRQ) –



Maleki-Yazdi MR et al. Respir Med 2014;108:1752-60 [PMID 25458157]

LAMA/LABA (UMEC/VIL) vs. LAMA (UMEC) vs. LABA (VIL)
– EMAX (SAC-TDI) –

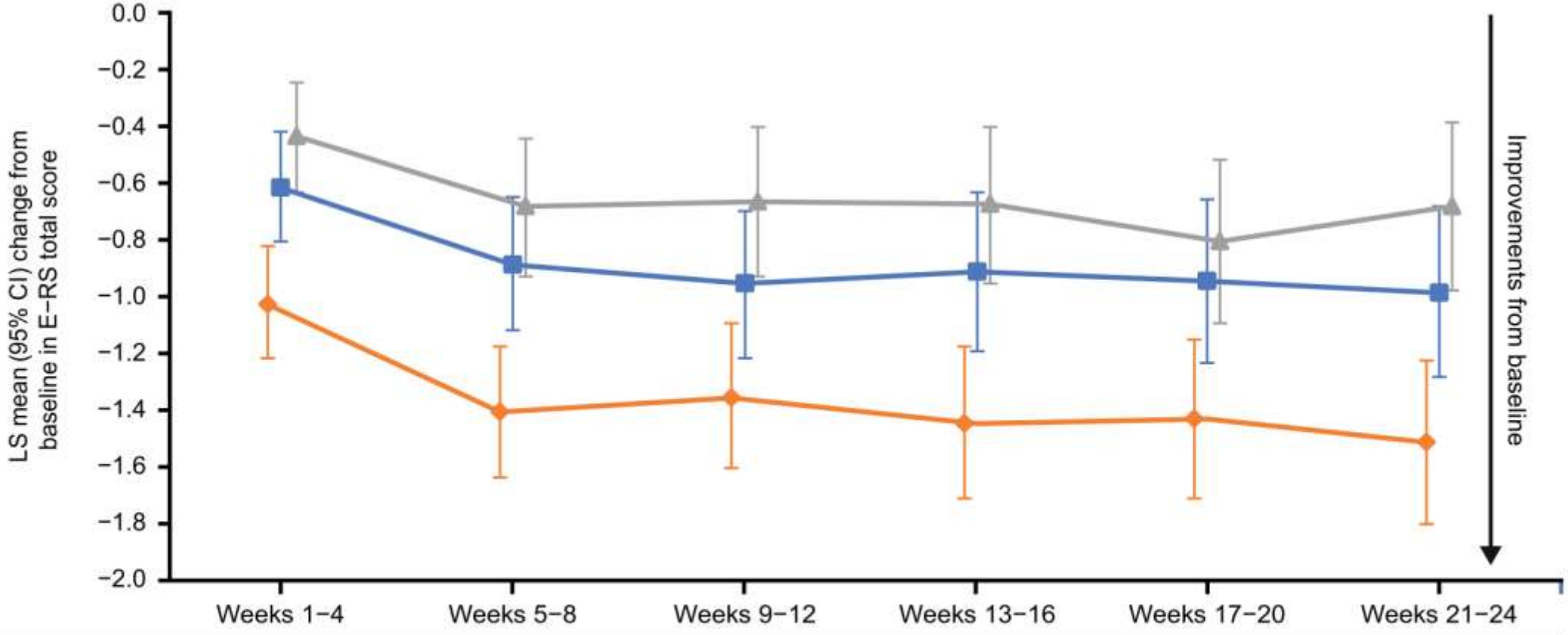


	Difference (95% CI)		
UMEC/VI vs UMEC	0.44 (0.16, 0.71), $p = 0.002$	0.70 (0.40, 1.00), $p < 0.001$	0.37 (0.06, 0.68), $p = 0.018$
UMEC/VI vs SAL	0.51 (0.24, 0.78), $p < 0.001$	0.64 (0.34, 0.94), $p < 0.001$	0.45 (0.15, 0.76), $p = 0.004$

Maltais F et al. Respir Res 2019;20:238 [PMID 31666084]

LAMA/LABA (UMEC/VIL) vs. LAMA (UMEC) vs. LABA (VIL)
– EMAX (E-RS) –

b

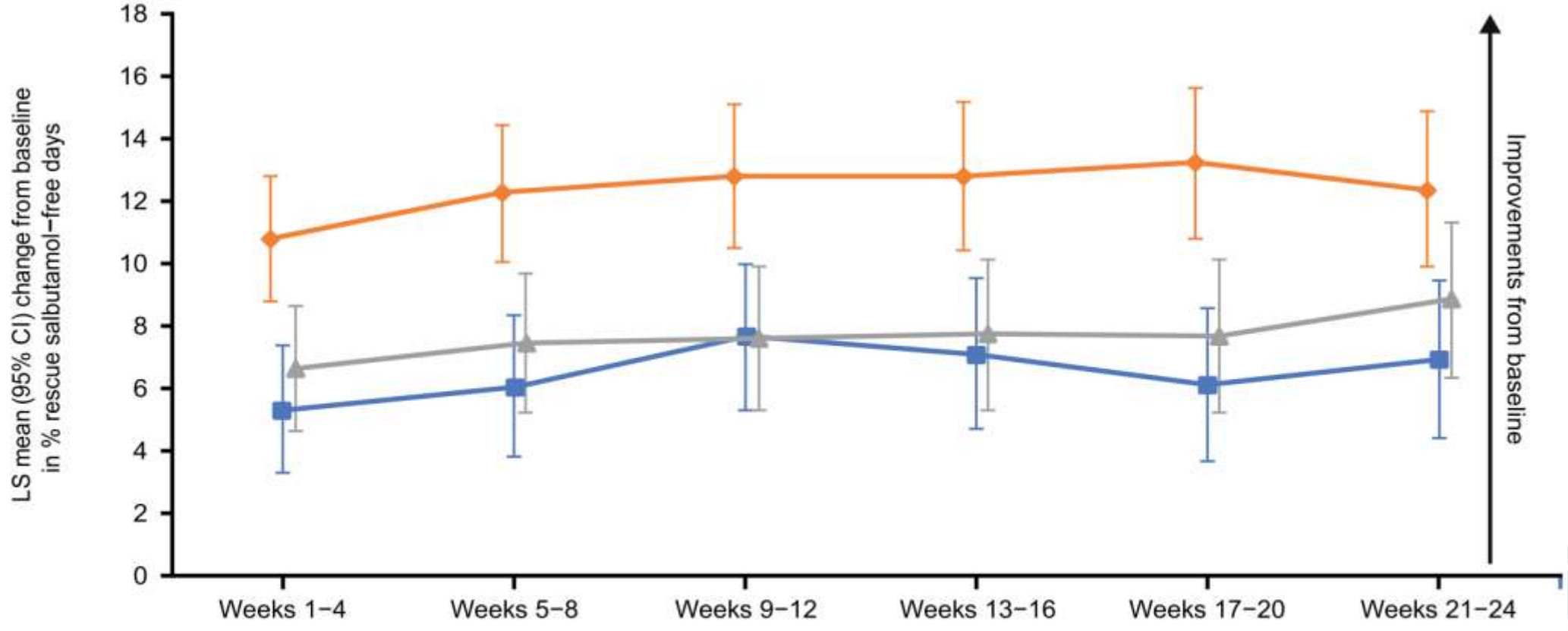


	Difference (95% CI)					
UMEC/VI vs UMEC	−0.41 (−0.69, −0.13), $p = 0.004$	−0.52 (−0.86, −0.19), $p = 0.002$	−0.40 (−0.76, −0.04), $p = 0.031$	−0.53 (−0.92, −0.14), $p = 0.007$	−0.49 (−0.90, −0.09), $p = 0.018$	−0.53 (−0.95, −0.11), $p = 0.013$
UMEC/VI vs SAL	−0.58 (−0.86, −0.31), $p < 0.001$	−0.72 (−1.05, −0.39), $p < 0.001$	−0.69 (−1.05, −0.32), $p < 0.001$	−0.77 (−1.15, −0.38), $p < 0.001$	−0.63 (−1.04, −0.23), $p = 0.002$	−0.83 (−1.25, −0.42), $p < 0.001$

Maltais F et al. Respir Res 2019;20:238 [PMID 31666084]

LAMA/LABA (UMEC/VIL) vs. LAMA (UMEC) vs. LABA (VIL)
– EMAX (Rescue Salbutamol-free Day) –

C



	Difference (95% CI)					
UMEC/VI vs UMEC	5.48 (2.62, 8.33), $p < 0.001$	6.18 (3.03, 9.33), $p < 0.001$	5.16 (1.88, 8.44), $p = 0.002$	5.67 (2.28, 9.06), $p = 0.001$	7.11 (3.68, 10.55), $p < 0.001$	5.44 (1.91, 8.97), $p = 0.003$
UMEC/VI vs SAL	4.17 (1.32, 7.02), $p = 0.004$	4.80 (1.66, 7.94), $p = 0.003$	5.20 (1.93, 8.47), $p = 0.002$	5.05 (1.66, 8.43), $p = 0.003$	5.53 (2.11, 8.95), $p = 0.002$	3.53 (0.01, 7.04), $p = 0.049$

Maltais F et al. Respir Res 2019;20:238 [PMID 31666084]

RWE of LABA/LAMA:
Lung Function & QOL

Real World Data of LABA/LAMA Fixed Combination

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Vahelva Respimat

(Olodaterol/Tiotropium)

Anoro Ellipta

(Vilanterol/Umeclidinium)

Xoterna Breezhaler

(Indacaterol/Glycopyrronium)

Pulmonary Function & QoL: Indacaterol/Glycopyrronium

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RESEARCH Open Access

CrossMark

Efficacy and safety of direct switch to indacaterol/glycopyrronium in patients with moderate COPD: the CRYSTAL open-label randomised trial

Claus F. Vogelmeier[1*], Mina Gaga[2], Maryam Aalamian-Mattheis[3], Timm Greulich[1], Jose M. Marin[4,5], Walter Castellani[6], Vincent Ninane[7], Stephen Lane[8], Xavier Nunez[9], Francesco Patalano[3], Andreas Clemens[3†], Konstantinos Kostikas[3†] and on behalf of the CRYSTAL study investigators

- **Prospective, multi-center, 12-week, randomized, open-label, pragmatic study, June 2014~April 2016**
- **IND/GLY vs. ICS/LABA or LABA or LAMA**
- **Study Population**
  - Symptomatic patients with moderate COPD who directly switch from their current COPD therapy regimen to either GLY or IND/GLY
  - Men and women aged ≥40 years with a clinical diagnosis of moderate COPD (GOLD 2013), and current or ex-smokers who have a smoking history of at least 10 pack-years

- **Outcomes**

- Primary

: To demonstrate at Week 12

– Superiority of GLY versus SABA and/or SAMA as monotherapy or in free or FDC on trough FEV_1

– Non-inferiority of GLY versus LABA or LAMA monotherapy on trough FEV_1

– Superiority of IND/GLY versus LABA and ICS either in free or in FDC on trough FEV_1

– Superiority of IND/GLY versus LABA or LAMA monotherapy on trough FEV_1

- Co-Primary

: To demonstrate at Week 12

– Superiority of GLY versus SABA and/or SAMA as monotherapy or in free or FDC on transition dyspnea index (TDI)

– Non-inferiority of GLY versus LABA or LAMA monotherapy on TDI

– Superiority of IND/GLY versus LABA and ICS in free or FDC on TDI

– Superiority of IND/GLY versus LABA or LAMA monotherapy on TDI

Vogelmeier CF et al. Respiratory Research 2017;18:140

Pulmonary Function & QoL: Indacaterol/Glycopyrronium

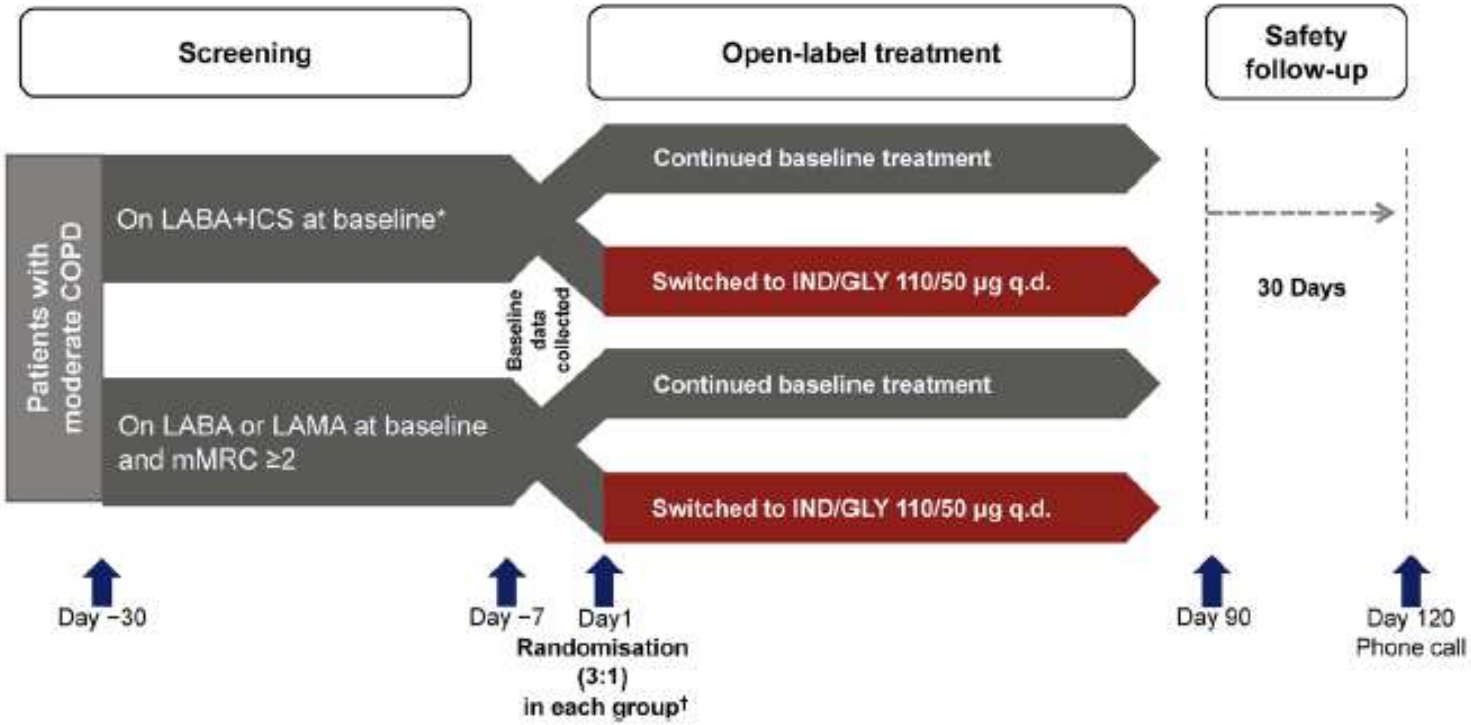

Fig. 1 CRYSTAL study design (groups switched to IND/GLY). *Free or fixed-dose combination. †Randomisation ratio (switched: baseline treatments) = 3:1 by stratifying background medications. All comparisons were for superiority of the switched treatment. COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; IND/GLY, indacaterol/glycopyrronium; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council; q.d., once daily; SABA, short-acting β_2-agonist; SAMA, short-acting muscarinic antagonist

Vogelmeier CF et al. Respiratory Research 2017;18:140

Pulmonary Function: Indacaterol/Glycopyrronium

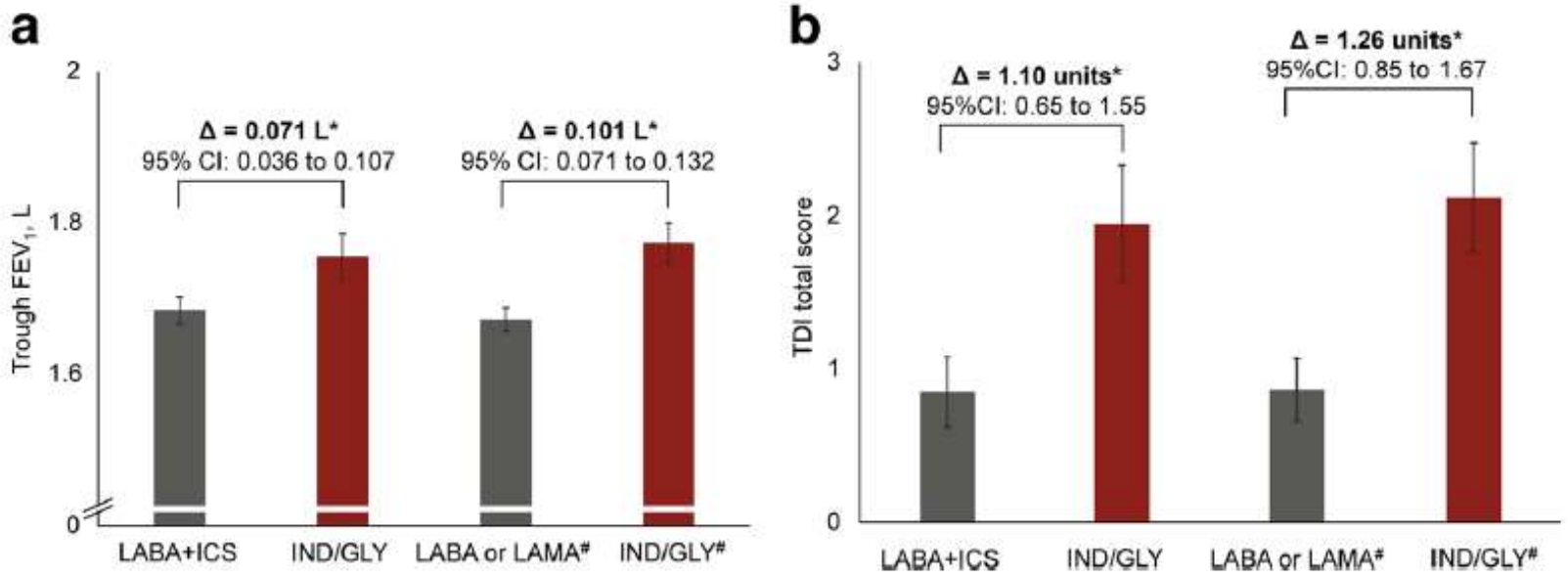

Fig. 2 Change from baseline in (**a**) trough FEV_1 and (**b**) TDI total scores with IND/GLY versus comparators at Week 12 (ITT population). *$P < 0.0001$. #Patients had an mMRC score ≥ 2. Data are least squares means (95% CI). Δ, treatment difference; CI, confidence interval; FEV_1, forced expiratory volume in 1 s; IND/GLY, indacaterol/glycopyrronium; ITT, intention-to-treat; LABA + ICS, long-acting β_2-agonist + inhaled corticosteroid; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council; TDI, transition dyspnoea index

Vogelmeier CF et al. Respiratory Research 2017;18:140

Quality of Life: CCQ

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"Wellness in COPD" tool table/grid

KEY

Very poor | Not good enough, if this criterion is important | Good enough | Recommended | Highly recommended

Tool/ Criteria	Validity/ Reliability	Responsive	Primary Care Population	Practical/ Easy to Administer	Tested in Practice	Other Languages
AQ20	●	☺	☺	●	☺	☹
BPQ-S	●	☺	☺	☺	☹	☹
CARS	☺	☹	☹	☺	☹	☹
CAT	●	☺	●	☺	☺	☺
CCQ	●	●	●	●	●	●
CRQ	●	☺	●	☺	●	☺
MRC-D	☺	☺	●	●	●	☺
RIQ-MON10	☺	☺	☺	☺	☹	☹
SGRQ	●	●	☺	☺	☺	●

Clinical COPD questionnaire

Please circle the number of the response that best describes how you have been feeling during the past week
(Only one response for each question)

On average, during the past week, how often did you feel:	never	hardly ever	a few times	several times	many times	a great many times	almost all the time
1 Short of breath at rest?	0	1	2	3	4	5	6
2 Short of breath doing physical activities?	0	1	2	3	4	5	6
3 Concerned about getting a cold or your breathing getting worse?	0	1	2	3	4	5	6
4 Depressed (down) because of your breathing problems?	0	1	2	3	4	5	6
In general, during the past week, how much of the time:							
5 Did you cough?	0	1	2	3	4	5	6
6 Did you produce phlegm?	0	1	2	3	4	5	6
On average, during the past week, how limited were you in these activities because of your breathing problems:	not limited at all	very slightly limited	slightly limited	moderately limited	very limited	extremely limited	totally limited/or unable to do
7 Strenuous physical activities (such as climbing stairs, hurrying, doing sports)?	0	1	2	3	4	5	6
8 Moderate physical activities (such as walking, housework, carrying things)?	0	1	2	3	4	5	6
9 Daily activities at home (such as dressing, washing yourself)?	0						
10 Social activities (such as talking, being with children, visiting friends/ relatives)?	0						

- Symptoms State
- Mental State
- Functional State

* The CCQ is copyrighted. It may not be altered, sold (paper or electronic), translated or adapted for another medium without the permission of T. van der Molen, Dept of General practice, University Medical Center Groningen, postbus 196, 9700 AD Groningen, The Netherlands.

폐쇄성 만성 호흡기 질환 임상용 질문지

지난 7일 동안 당신이 느낀 바를 가장 잘 나타내 주는 숫자에 **동그라미** 해주십시오.
(한 문항에 **하나의** 응답만 해주십시오)

평균적으로 **지난 7일 동안** 당신은 얼마나 자주 다음과 같은 느낌을 받았습니까?	전혀 그런 적 없었다	거의 그런 적 없었다	가끔 그랬다	여러 번 그랬다	많이 그랬다	대부 많이 그랬다	거의 항상 그랬다
1. **가만히 쉴 때도** 숨이 찼다.	0	1	2	3	4	5	6
2. **신체적 활동을 할 때** 숨이 찼다.	0	1	2	3	4	5	6
3. 감기에 걸리거나 숨쉬기가 더 나빠질까봐 **신경이 쓰였다.**	0	1	2	3	4	5	6
4. 호흡 문제로 인해 **우울(낙담)했다.**	0	1	2	3	4	5	6
일반적으로 **지난 7일 동안,** 당신은 다음과 같은 문제를 얼마나 자주 경험 하셨습니까?							
5. **기침**을 했다.	0	1	2	3	4	5	6
6. **가래**가 끓었다.	0	1	2	3	4	5	6
평균적으로 **지난 7일 동안** 당신은 **호흡 문제로 인해** 다음과 같은 활동에 얼마나 많은 지장을 받았습니까?	전혀 지장 받지 않았다	아주 약간 지장 받았다	약간 지장 받았다	어느 정도 지장 받았다	심하게 지장 받았다	대부 심하게 지장 받았다	완전히 지장 받았다 / 또는 전혀 활동할 수 없었다
7. **격한 신체적 활동** (예를 들면 계단 오르기, 급히 서두르기, 운동 하기)	0	1	2	3	4	5	6
8. **보통의 신체적 활동** (예를 들면 걷기, 집안 일, 물건 옮기기)	0	1	2	3	4	5	6
9. **집에서 하는 일상적 활동** (예를 들면 옷 입기, 씻기)	0	1	2	3	4	5	6
10. **대인관계 활동** (예를 들면 대화하기, 아이들과 함께 하기, 친구나 친척 방문하기)	0	1	2	3	4	5	6

Quality of Life: Indacaterol/Glycopyrronium

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Table 3 Effects of a direct switch to IND/GLY from baseline treatments on CAT, CCQ and rescue medication use (ITT population)

	LABA + ICS *n* = 269	IND/GLY *n* = 811	LABA or LAMA[a] *n* = 268	IND/GLY[a] *n* = 811
Total CAT score, change from baseline at Week 12	−0.4 (4.8)	−1.4 (5.4)	−0.9 (5.0)	−1.9 (5.3)
Patients who achieved MCID in total CAT score (≥2 units difference from baseline), *n* (%)	89 (33.1%)	311 (38.4%)	112 (41.8%)	351 (43.3%)
CAT responders (decrease ≥2 units; OR [95% CI])	1.44 (1.06 to 1.95)		1.12 (0.83 to 1.50)	
Total CCQ score, change from baseline at Week 12	−0.1 (0.7)	−0.2 (0.8)*	−0.1 (0.8)	−0.3 (0.8)***
Patients who achieved MCID in the total CCQ score (≥0.4 units difference from baseline), *n* (%)	64 (23.8%)	243 (30.0%)	74 (27.6%)	293 (36.1%)
CCQ responders (decrease ≥0.4 units; OR [95% CI])	1.53 (1.10 to 2.12)		1.58 (1.16 to 2.17)	
Number of puffs of rescue medication over 12 weeks	1.6 (1.7)	1.1 (1.4)****	1.4 (1.4)	1.1 (1.3)***
Percentage of days without rescue medication use over 12 weeks	41.7 (42.9)	49.9 (43.4)**	38.8 (42.6)	46.7 (42.6)**

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$
[a]Patients had an mMRC score ≥ 2

Vogelmeier CF et al. Respiratory Research 2017;18:140

Pulmonary Function & QoL: Indacaterol/Glycopyrronium

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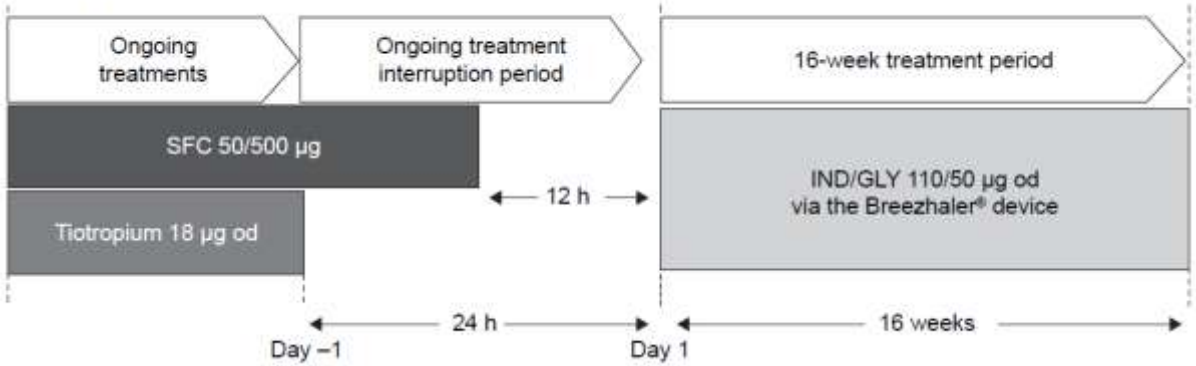
ORIGINAL RESEARCH

Real-life effectiveness of indacaterol–glycopyrronium after switching from tiotropium or salmeterol/fluticasone therapy in patients with symptomatic COPD: the POWER study

- **Real-life, multicenter, post-approval, prospective, 16-week interventional, open-label, single-arm study**
- **Moderate-to-severe COPD, who remained symptomatic on Tio or SFC**

- **End Points**
  - Primary
    - Absolute change from baseline in pre-dose trough FEV1 after 16 weeks of treatment
  - Secondary
    - Change in pre-dose trough FEV1 between baseline and 4 weeks of treatment,
    - Change in the CAT score after 4 and 16 weeks of treatment
    - Change from baseline in dyspnea index (transition dyspnea index [TDI]) at Weeks 4 and 16
    - Safety was assessed by monitoring adverse events (AEs) and serious AEs (SAEs)

Study design



Kaplan A, et al. Int J Chron Obstruct Pulmon Dis 2019;14:249-260.

Pulmonary Function: Indacaterol/Glycopyrronium

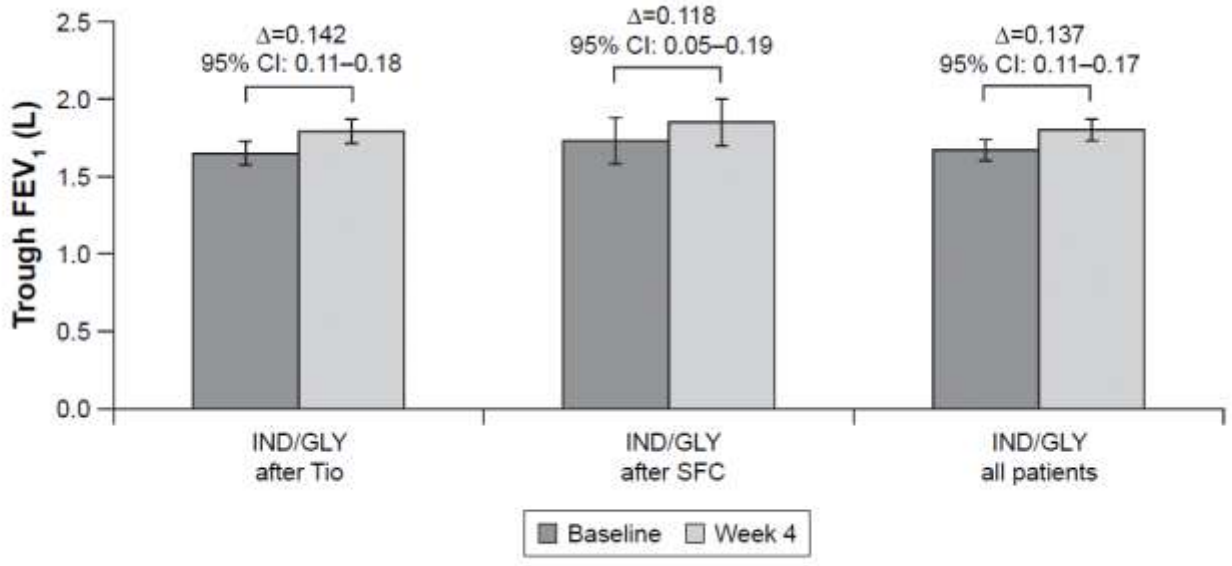


Figure 4 Change from baseline in trough FEV_1 at Week 4 (ITT population).

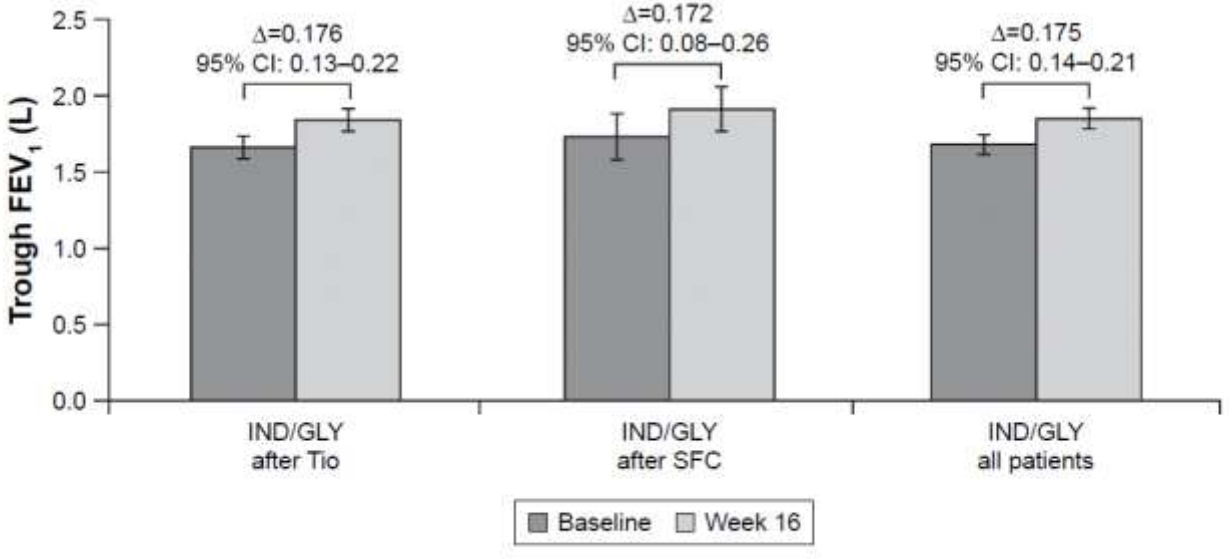


Figure 3 Change from baseline in trough FEV_1 at Week 16 (ITT population).

Kaplan A, et al. Int J Chron Obstruct Pulmon Dis 2019;14:249-260.

Dyspnea and QoL: Indacaterol/Glycopyrronium

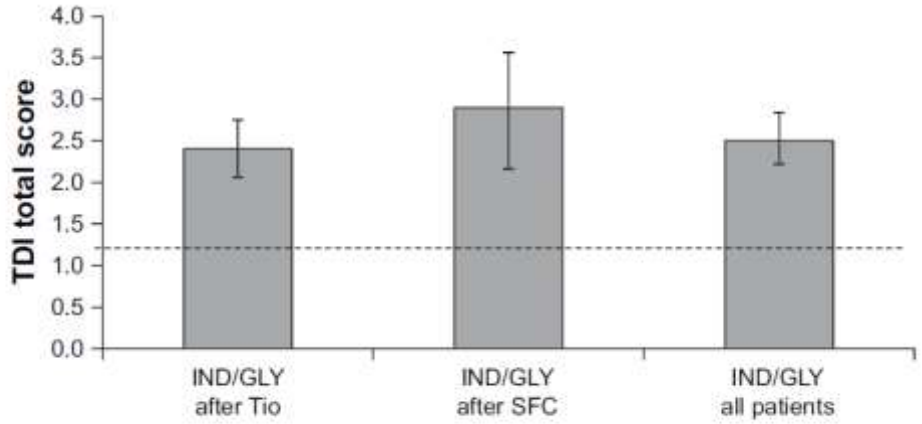


Figure 5 Change from baseline in TDI score at Week 16 (ITT population).

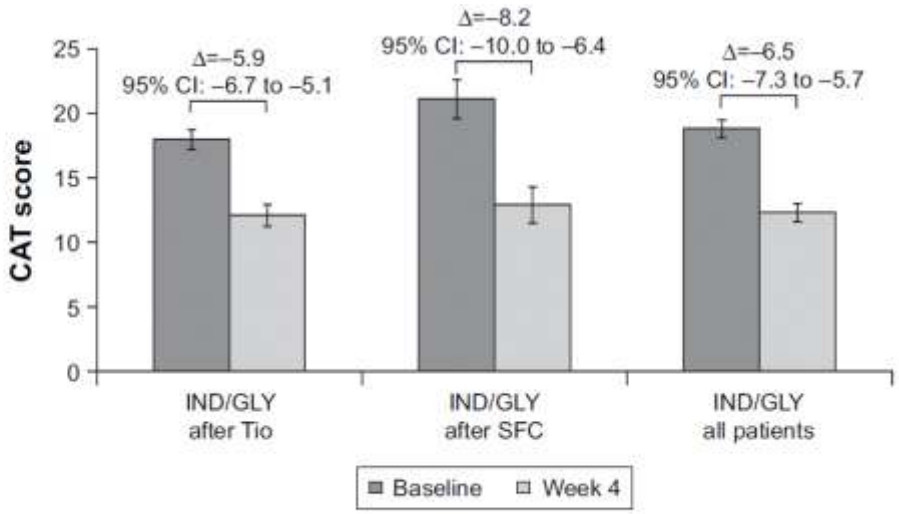


Figure 6 Change from baseline in CAT score at Week 16 (ITT population).

Kaplan A, et al. Int J Chron Obstruct Pulmon Dis 2019;14:249-260.

Quality of Life: Tiotropium/Olodaterol

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- **Open-label non-interventional study, Mar 2017 ~ Nov 2018.**
- **Tio/Olo under real-world conditions for ~6 weeks**
- **Outcome**
  - **Primary**
    - Proportion of patients achieving a decrease of ⩾0.4 points in Clinical COPD Questionnaire (CCQ) score.
  - **Secondary**
    1) Changes in total CCQ score and CCQ-4 score from V1 to V2
    2) Patients' general condition at V1 and V2
    3) patient satisfaction and willingness to continue treatment with Tio/Olo at V2

- **Inclusion**
  1) written informed consent prior to participation
  2) aged ⩾40 years
  3) diagnosed with COPD and having an indication for treatment with a combination of two long-acting bronchodilators (LAMA/LABA) according to approved SmPC and GOLD strategy report 2017 (GOLD COPD groups B–D)
  4) treatment with Tio/Olo according to SmPC at the discretion of the physician

- **Exclusion**
  1) contraindications according to the Tio/Olo SmPC
  2) already on a LAMA/LABA combination (free or fixed dose) in the 6 weeks prior to study entry
  3) continuing LABA/inhaled corticosteroid (ICS) treatment in parallel with Tio/Olo (to avoid double-dosing of LABA)
  4) pregnant or lactating
  5) current participation in any clinical trial or any other non-interventional study of a drug or device.

Gillissen A, et al. ERJ Open Res 2021;7:00004-2021.

Quality of Life: Tiotropium/Olodaterol

- **Germany, 114 sites**
- **Patient screened: N=1,351 / Full analysis set: N=1,140**

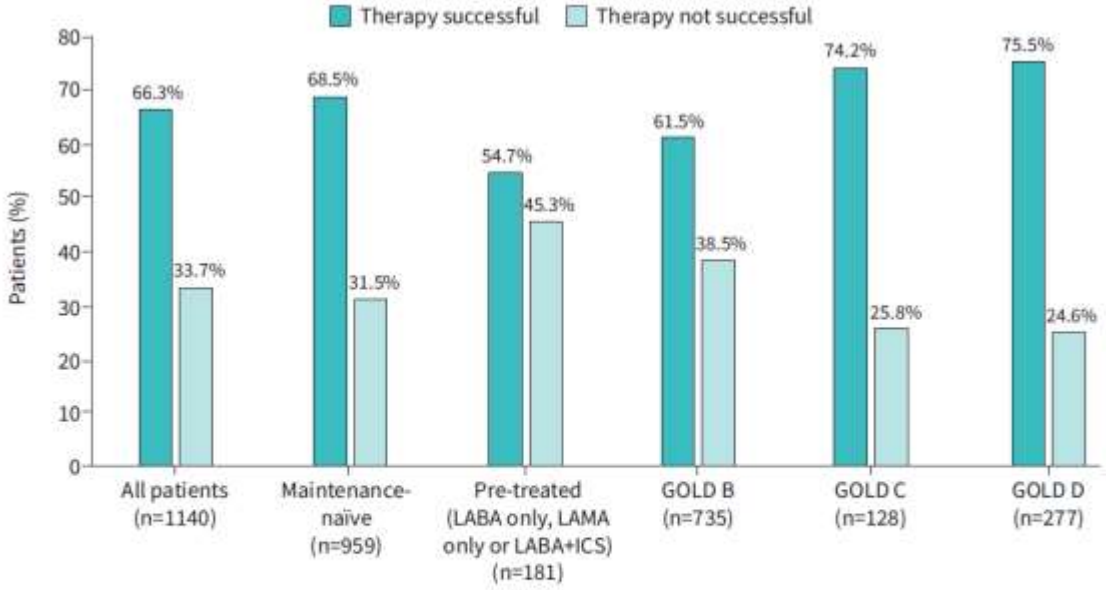


FIGURE 2 Proportion of patients achieving therapeutic success at visit 2. Therapeutic success was defined as a 0.4-point decrease in Clinical COPD Questionnaire score between visit 1 and visit 2. LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroid; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

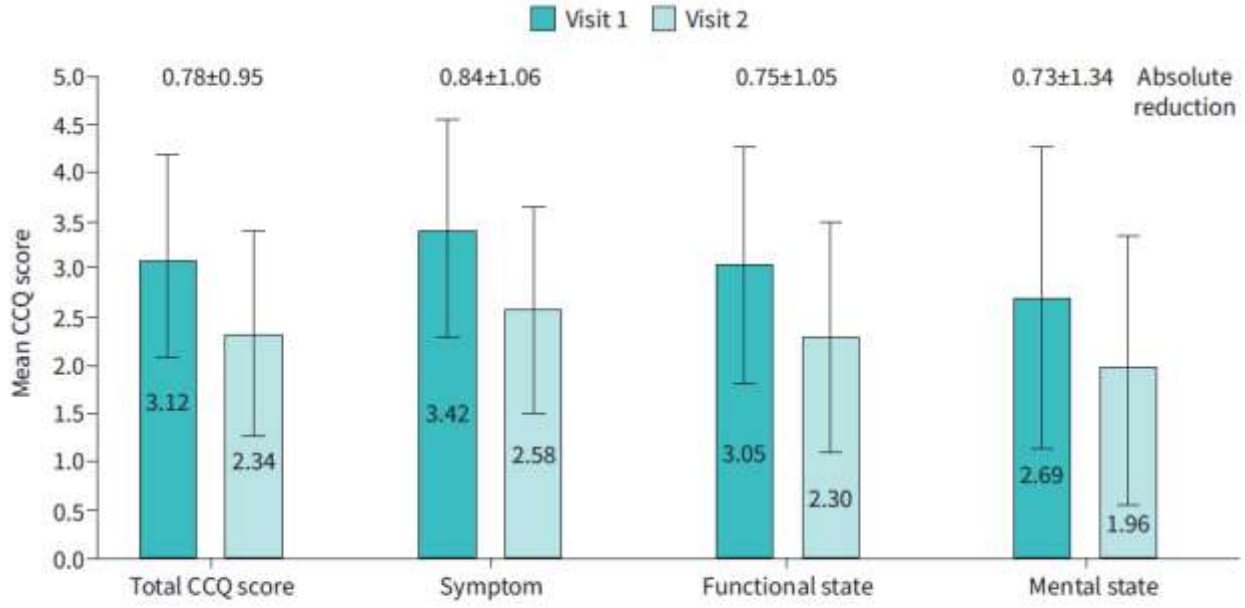


FIGURE 3 Absolute change in Clinical COPD Questionnaire (CCQ) score from visit 1 to visit 2. Data are presented as mean±SD.

Gillissen A, et al. ERJ Open Res 2021;7:00004-2021.

Quality of Life: Tiotropium/Olodaterol

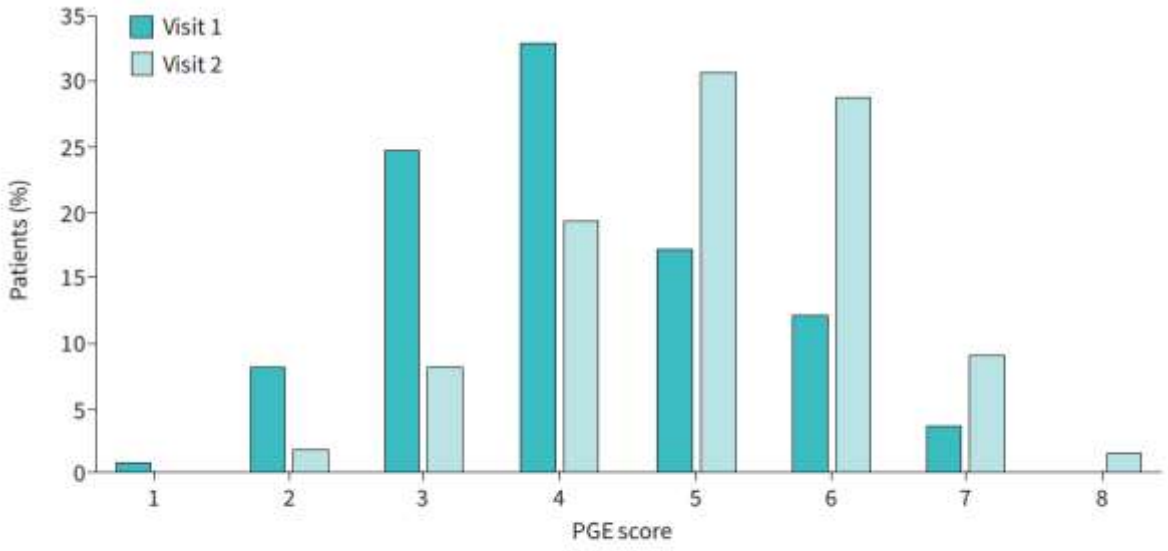


FIGURE 4 Patients' general condition (Physician's Global Evaluation (PGE) score) at visits 1 and 2. PGE score 1–2=poor, 3–4=satisfactory, 5–6=good, 7–8=excellent.

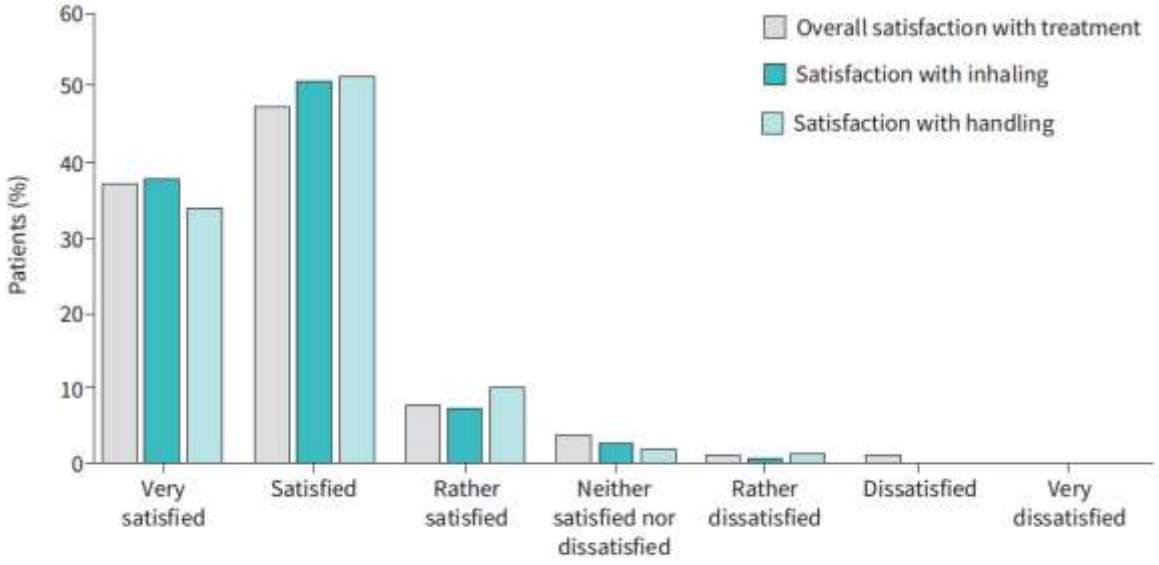


FIGURE 5 Patient satisfaction with tiotropium/olodaterol treatment overall, and in terms of inhaling from, and handling of the device at visit 2. Visit 2 was ~6 weeks after visit 1 (baseline).

Gillissen A, et al. ERJ Open Res 2021;7:00004-2021.

Acute Exacerbation of COPD

LABA/LAMA (Ind/Gly) vs. LABA (Ind) vs. LAMA (Gly) vs. LAMA (Tio)
– SHINE (AE) –

- 2144 patients with moderate-to-severe COPD (GOLD II or III) and no AE in 1 year (74.6%)
- Ind/Gly (110/50) : Ind (150) : Gly (50) : Tio (18, open label) : placebo = 2:2:2:2:1
- The primary end-point: **trough FEV1 at week 26**

	Placebo	QVA149 110/50 µg	Indacaterol 150 µg	Glycopyrronium 50 µg	Tiotropium 18 µg
Subjects n	232	474	476	473	480
Patients with any adverse event	134 (57.8)	261 (55.1)	291 (61.1)	290 (61.3)	275 (57.3)
COPD	91 (39.2)	137 (28.9)	153 (32.1)	150 (31.7)	138 (28.8)
Nasopharyngitis	23 (9.9)	31 (6.5)	35 (7.4)	46 (9.7)	40 (8.3)
Cough	8 (3.4)	26 (5.5)	38 (8.0)	18 (3.8)	21 (4.4)
Upper respiratory tract infection	13 (5.6)	20 (4.2)	32 (6.7)	20 (4.2)	24 (5.0)
Oropharyngeal pain	7 (3.0)	17 (3.6)	7 (1.5)	10 (2.1)	10 (2.1)
Viral upper respiratory tract infection	7 (3.0)	15 (3.2)	11 (2.3)	13 (2.7)	12 (2.5)
Bacterial upper respiratory tract infection	13 (5.6)	10 (2.1)	13 (2.7)	15 (3.2)	22 (4.6)
Lower respiratory tract infection	5 (2.2)	9 (1.9)	15 (3.2)	7 (1.5)	12 (2.5)
Back pain	5 (2.2)	8 (1.7)	11 (2.3)	17 (3.6)	8 (1.7)
Serious adverse events	13 (5.6)	22 (4.6)	26 (5.5)	29 (6.1)	19 (4.0)
Adjudicated CCV events					
Atrial fibrillation/flutter, new onset	0	2 (0.4)	3 (0.6)	2 (0.4)	1 (0.2)
Serious CCV events	1 (0.4)	0	6 (1.3)	7 (1.5)	4 (0.8)
MACE	0	0	2 (0.4)	3 (0.6)	3 (0.6)
Nonfatal myocardial infarction	0	0	0	1 (0.2)	0
Nonfatal stroke	0	0	1 (0.2)	0	2 (0.4)
Heart failure requiring hospitalisation	0	0	1 (0.2)	1 (0.2)	0
Coronary revascularisation[#]	0	0	0	1 (0.2)	2 (0.4)
Non-MACE	1 (0.4)	0	4 (0.8)	6 (1.3)	3 (0.6)
Deaths[*]	0	1 (0.2)	2 (0.4)	1 (0.2)	3 (0.6)
Discontinuations					
Due to an adverse event	10 (4.3)	6 (1.3)	24 (5.0)	14 (3.0)	10 (2.1)
Due to a SAE	3 (1.3)	3 (0.6)	11 (2.3)	6 (1.3)	5 (1.0)

- COPD exacerbation; **39.2%** in the **placebo** group and **28.9%**, 32.1%, 31.7% and **28.8%** in the **IND/GLY**, indacaterol, glycopyrronium and **tiotropium** groups, respectively

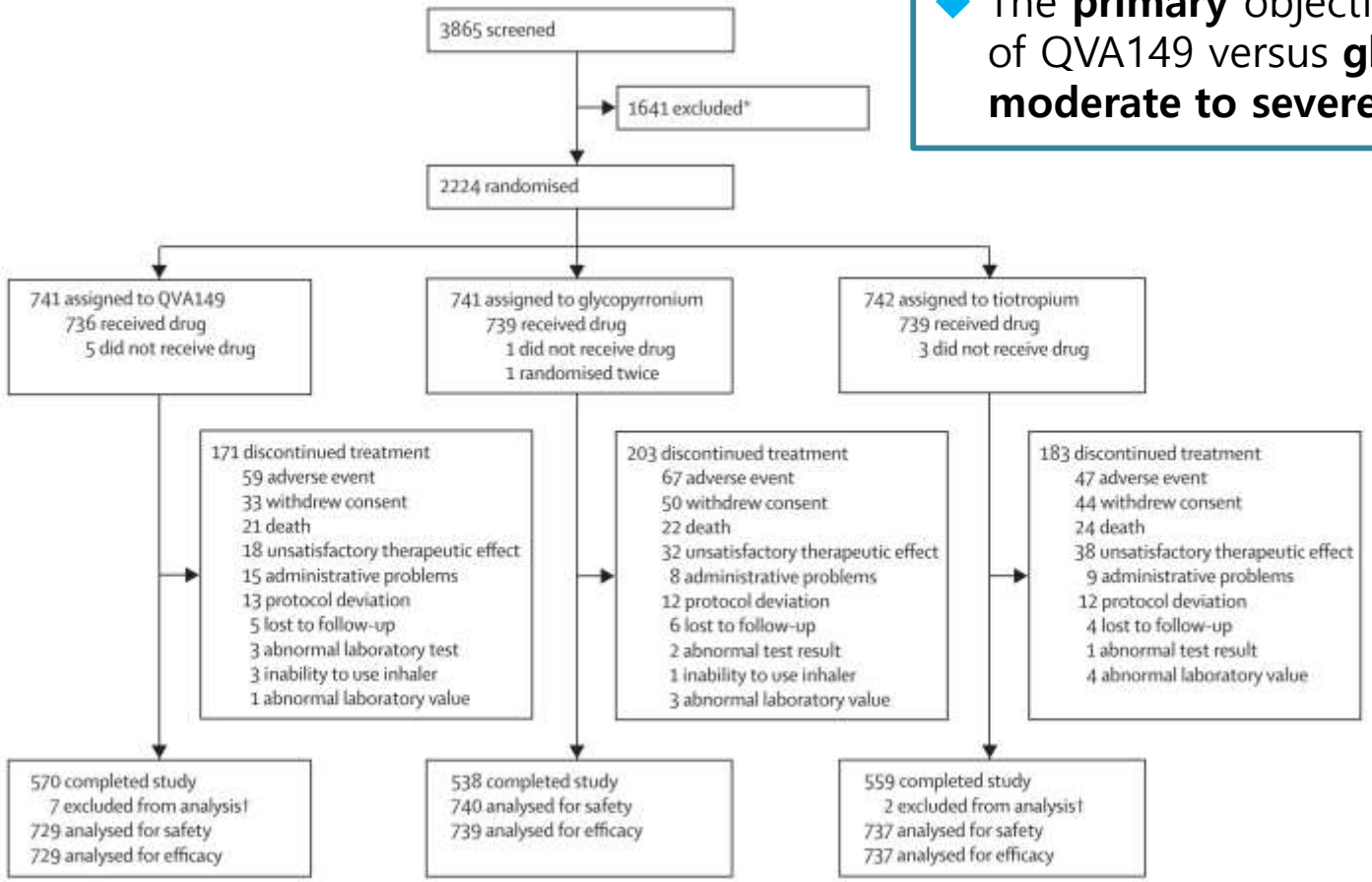
Bateman ED et al. Eur Respir J 2013;42:1484-94. [PMID: 23722616]

Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study

Jadwiga A Wedzicha, Marc Decramer, Joachim H Ficker, Dennis E Niewoehner, Thomas Sandström, Angel Fowler Taylor, Peter D'Andrea, Christie Arrasate, Hungta Chen, Donald Banerji

SPARK

- 2224 patients
  - aged ≥40 years
  - GOLD stages III–IV
  - **one or more moderate AE** in the past year
- Tx
  - **QVA149**, **glycopyrronium** 50 µg, or **tiotropium** 18 µg for 64 weeks
- The **primary** objective was to show **superiority** of QVA149 versus **glycopyrronium** for rate of **moderate to severe** COPD **exacerbations**



Wedzicha JA et al. Lancet Respir Med 2013;1:199-209. [PMID: 24429126]

Baseline Characteristics
– SPARK –

A2304 SPARK

	QVA149 (n=729)	Glycopyrronium (n=740)	Tiotropium (n=737)
Age (years)	63·1 (8·1)	63·1 (8·0)	63·6 (7·8)
Men	556 (76%)	542 (73%)	553 (75%)
Race			
White	594 (81%)	605 (82%)	613 (83%)
Asian	89 (12%)	92 (12%)	79 (11%)
Black	4 (1%)	5 (1%)	7 (1%)
Other	42 (6%)	38 (5%)	38 (5%)
Severity of airflow limitation			
Severe*	578 (79%)	584 (79%)	581 (79%)
Very severe	150 (21%)	155 (21%)	156 (21%)
Duration of COPD (years)	7·2 (5·8)	7·1 (5·3)	7·2 (5·5)
Number of COPD exacerbations in previous year			
0	8 (1%)	13 (2%)	11 (1%)
1	557 (76%)	572 (77%)	552 (75%)
≥2	164 (22%)	155 (21%)	174 (24%)
Inhaled corticosteroid use at baseline	546 (75%)	557 (75%)	559 (76%)

Wedzicha JA et al. Lancet Respir Med 2013;1:199-209. [PMID: 24429126]

LABA/LAMA (Ind/Gly) vs. LAMA (Gly, Tio) – SPARK (AE)–

A2304 SPARK

- 2,224 patients with 1 AE in the previous 1 year & postBD FEV1 < 50 % ; 64 weeks
- Primary end point: superiority of **IND/GLY vs. glycopyrronium** for rate of **moderate to severe** COPD exacerbations

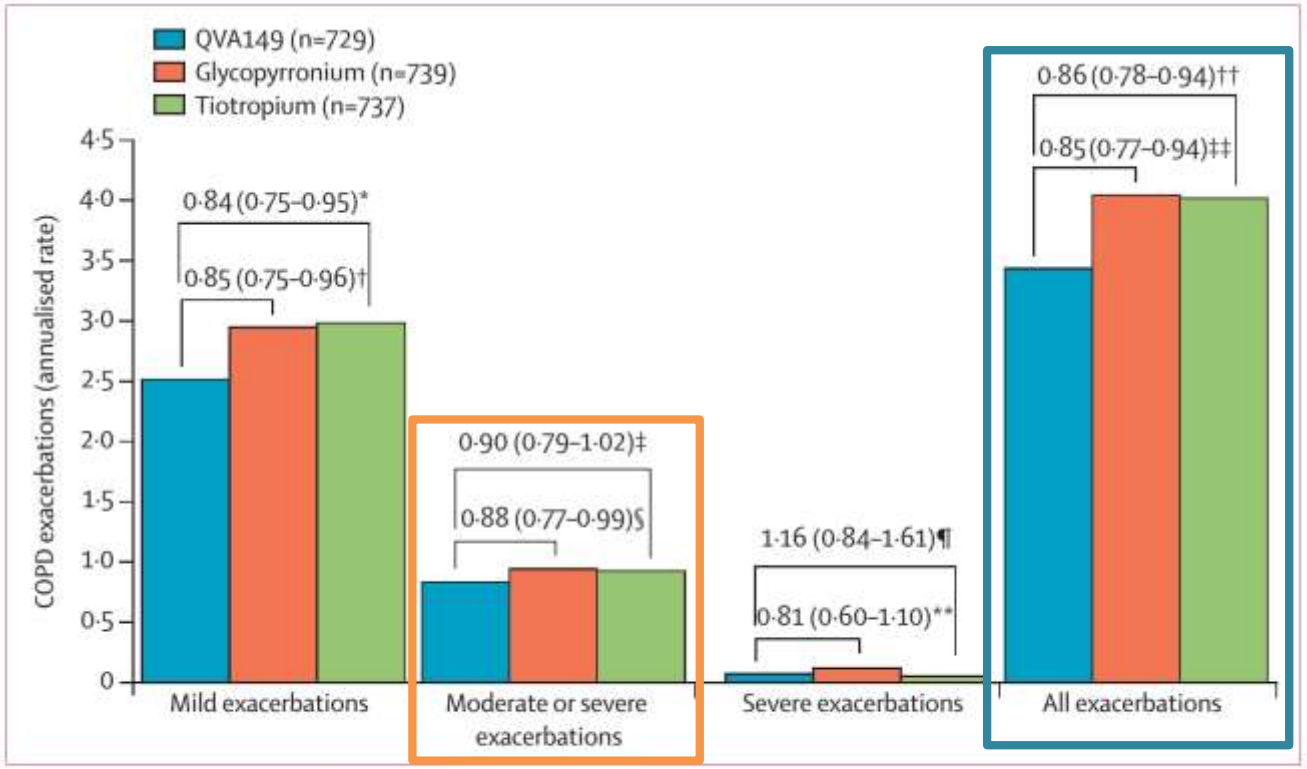


Figure 2: **Annualised rate of COPD exacerbations, by treatment group**
Values are rate reduction (95% CI; p value). *p=0·0052. †p=0·0072. ‡p=0·096. §p=0·038. ¶p=0·36. **p=0·18. ††p=0·0017. ‡‡p=0·0012.

Wedzicha JA, et al. The Lancet Respiratory Medicine 2013;1:199-209.

LABA/LAMA (Ind/Gly) vs. LAMA (Gly, Tio) – SPARK (AE) –

A2304 SPARK

- 2,224 patients with 1 AE in the previous 1 year & postBD FEV1 < 50 % ; 64 weeks
- Primary end point: superiority of IND/GLY vs. glycopyrronium for rate of moderate to severe COPD exacerbations

Section 12. Analysis of moderate to severe COPD exacerbations by ICS use

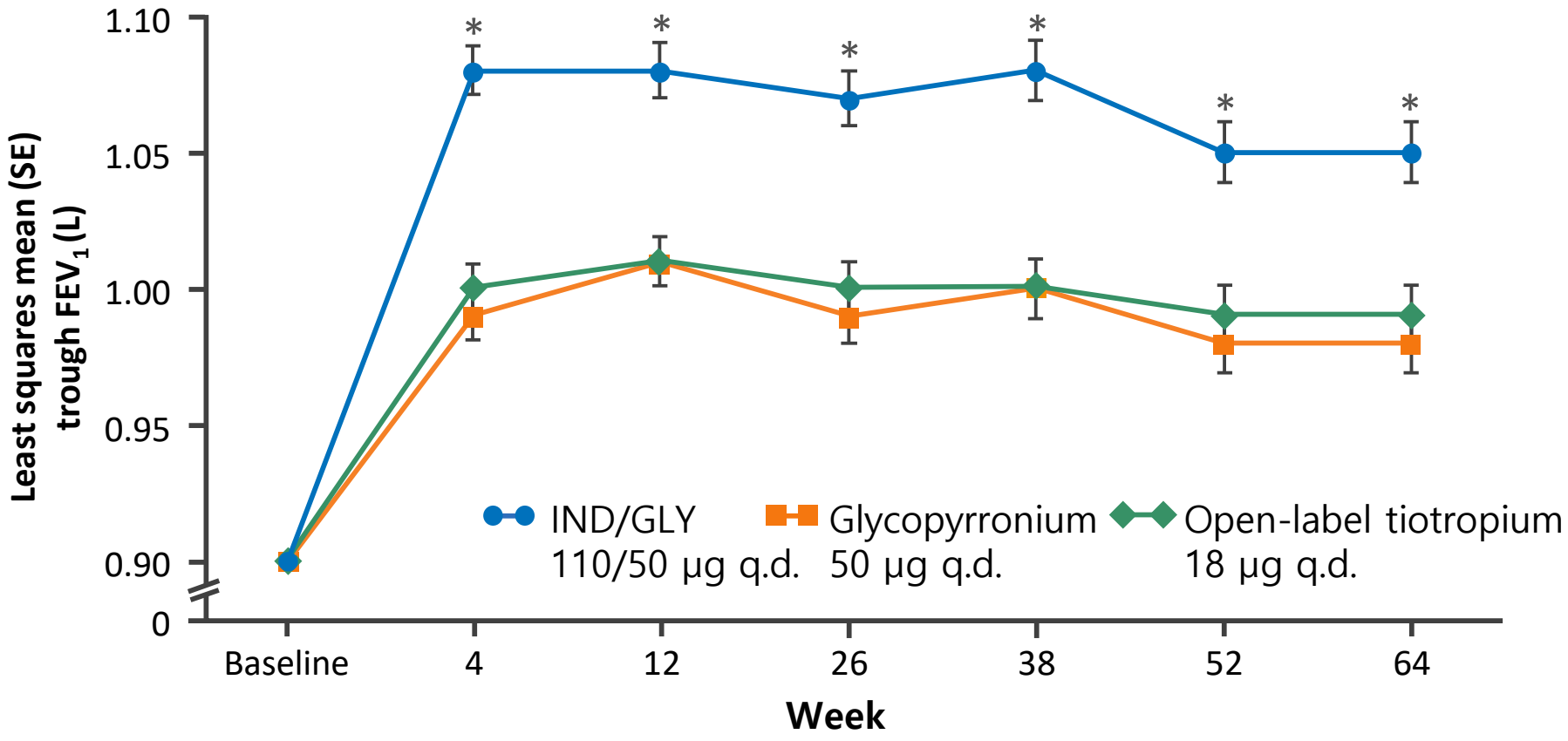
	Treatment	Annualized Rate (95% CI)	Comparison	Rate Ratio 95% CI	p value
No ICS use	QVA149 (n=183)	0.77 (0.63, 0.95)	QVA149 vs glycopyrronium	1.04 (0·78, 1.38)	0·81
			QVA149 vs tiotropium	0·99 (0·75, 1.30)	0·93
	Glycopyrronium (n=183)	0.75 (0.60, 0.93)	Glycopyrronium vs tiotropium	0·95 (0·72, 1·27)	0·74
	Tiotropium (n=178)	0.78 (0.64, 0.96)			
ICS use	QVA149 (n=546)	0·96 (0·86, 1.08)	QVA149 vs glycopyrronium	0·84 (0·73, 0·97)	0·015
			QVA149 vs tiotropium	0·88 (0·76, 1·01)	0·067
	Glycopyrronium (n=556)	1.14 (1.03, 1.28)	Glycopyrronium vs tiotropium	1·04 (0·91, 1·20)	0·55
	Tiotropium (n=559)	1.10 (0·98, 1·23)			

Wedzicha JA, et al. The Lancet Respiratory Medicine 2013;1:199-209.

LABA/LAMA (Ind/Gly) vs. LAMA (Gly, Tio) – SPARK (FEV_1) –

A2304 SPARK

- 2,224 patients with **1 AE in the previous 1 year** & postBD FEV1 < 50 % ; 64 weeks
- Primary end point: superiority of IND/GLY vs. glycopyrronium for rate of moderate to severe COPD exacerbations



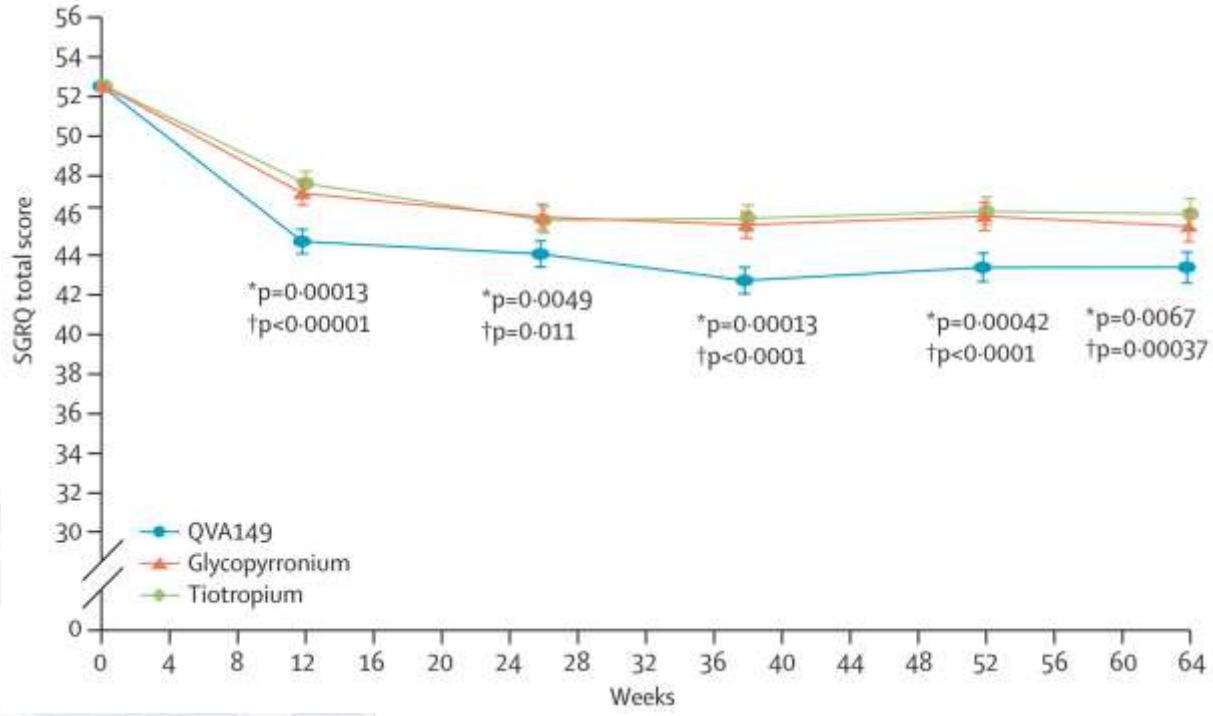
- *At all time points, p<0.001 vs glycopyrronium and open-label tiotropium

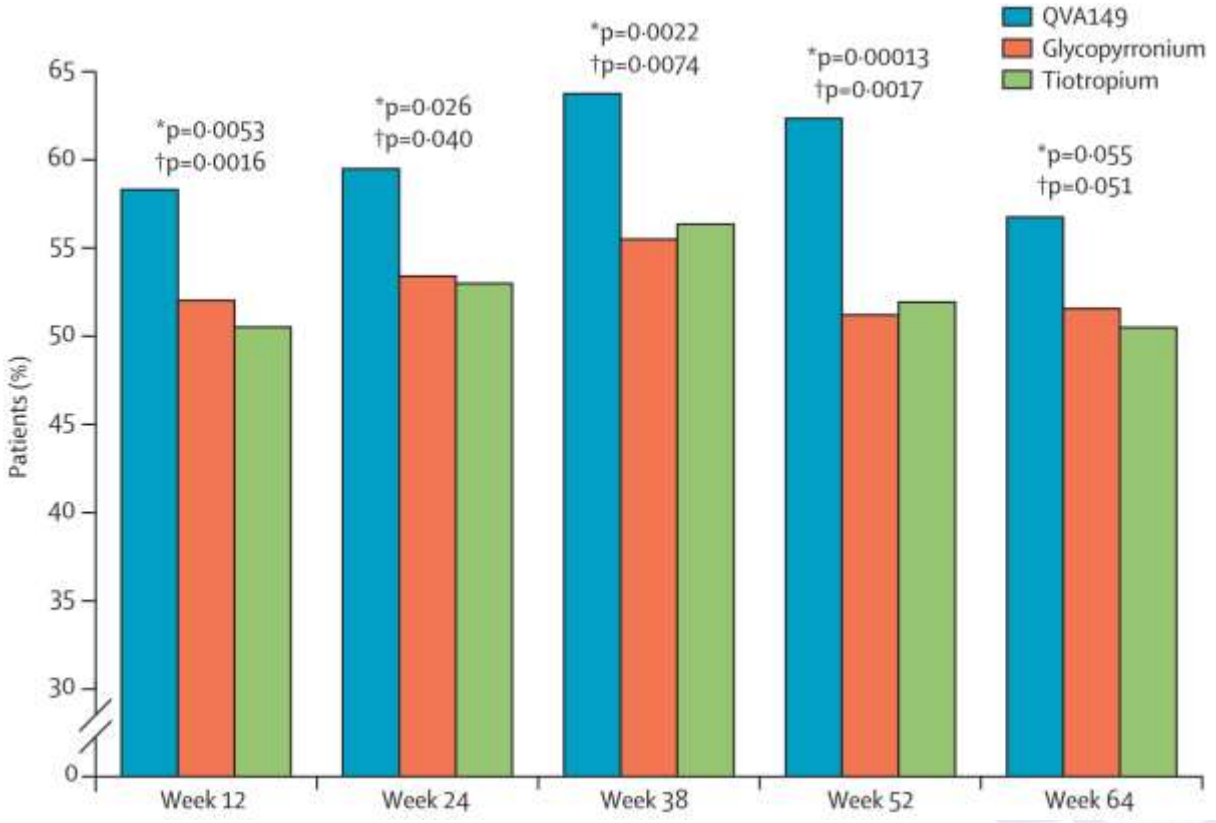
Wedzicha JA et al. Lancet Respir Med 2013;1:199-209. [PMID: 24429126]

LABA/LAMA (Ind/Gly) vs. LAMA (Gly, Tio)
– SPARK (QOL, SGRQ) –

A2304 SPARK

- 2,224 patients with **1 AE in the previous 1 year** & postBD FEV1 < 50 % ; 64 weeks
- Primary end point: superiority of IND/GLY vs. glycopyrronium for rate of moderate to severe COPD exacerbations



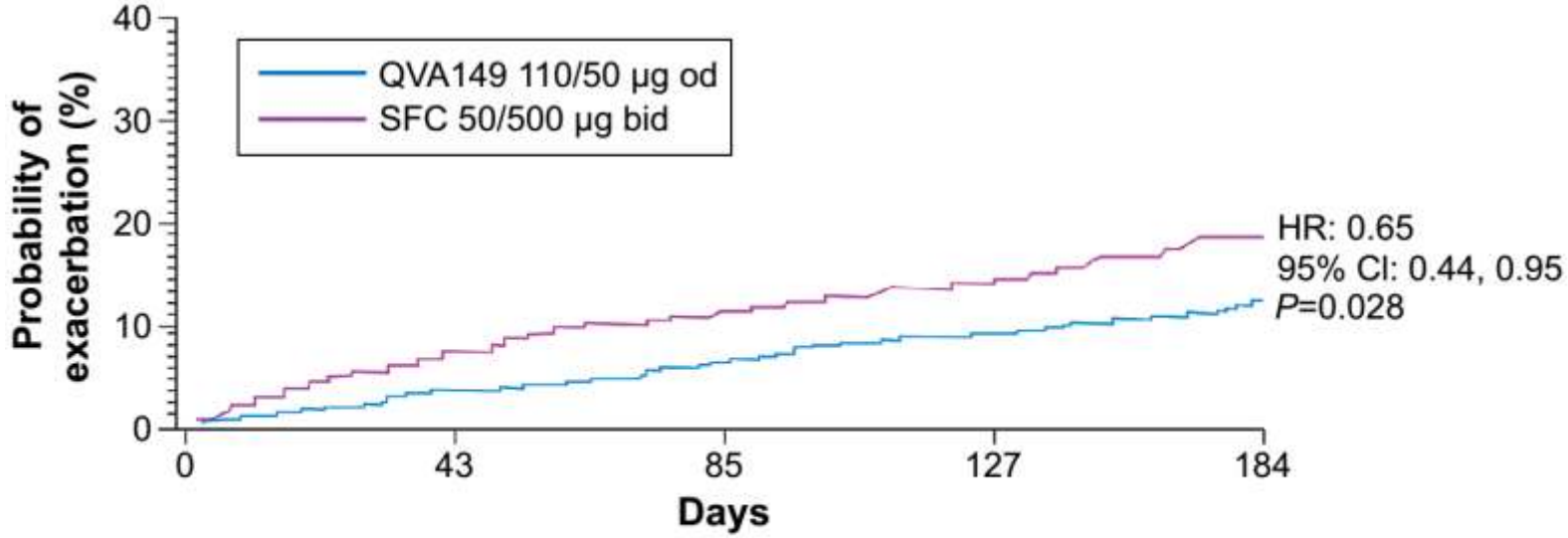


Wedzicha JA et al. Lancet Respir Med 2013;1:199-209. [PMID: 24429126]

LABA/LAMA (Ind/Gly) vs. ICS/LABA (SFC) – LANTERN –

- 676 moderate-to-severe COPD patients with **a history of AE ≤ 1** in the previous year
- Primary end point: non-inferiority for trough **FEV1** at week 26

Kaplan–Meier plots of the time to first moderate or severe COPD exacerbation over 26 weeks of treatment

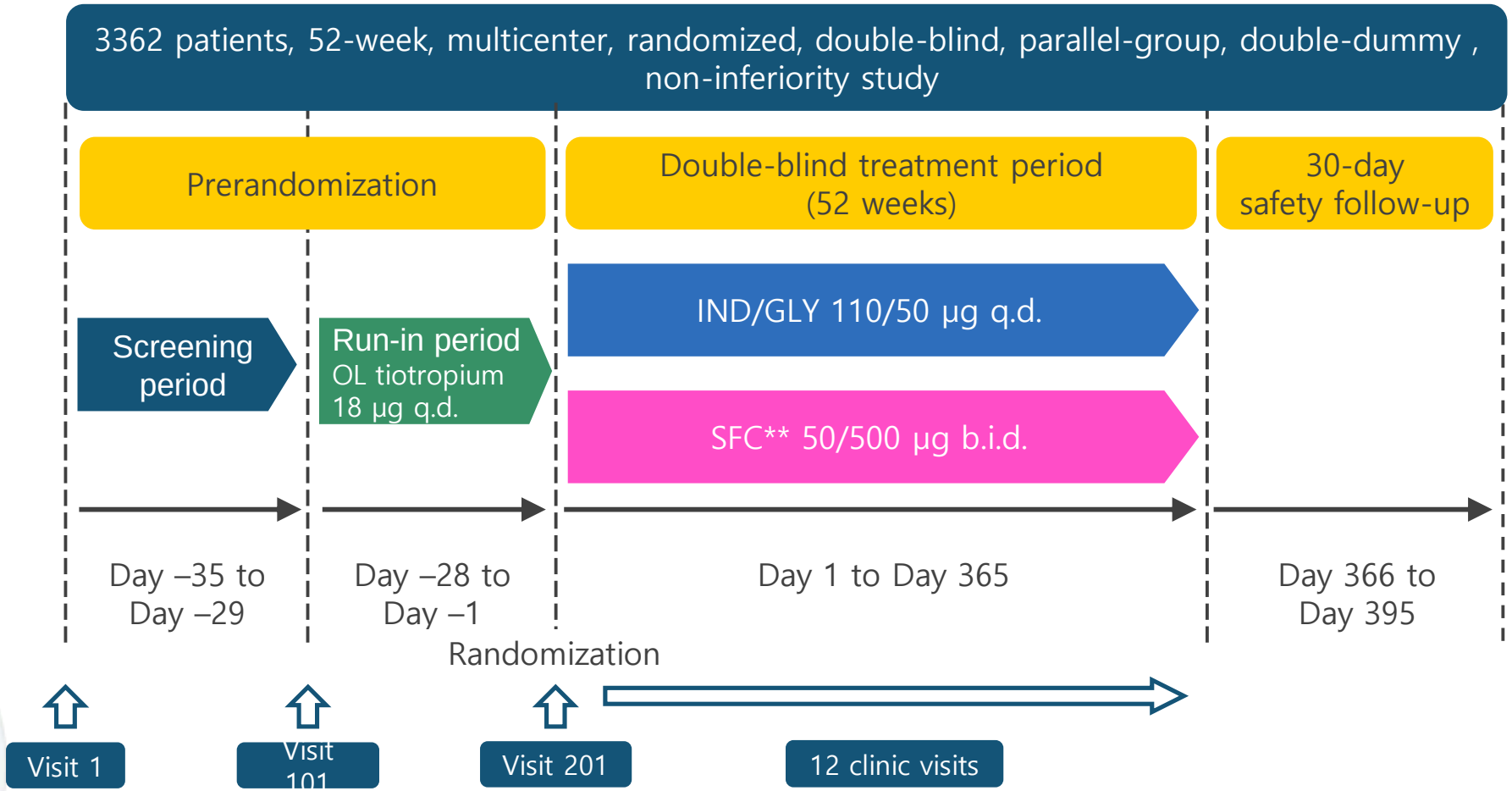


Patients with exacerbation (%)				
QVA149: 0 (0.0%)	12 (3.3%)	20 (5.5%)	31 (8.6%)	43 (12.1%)
SFC: 0 (0.0%)	24 (6.6%)	38 (10.5%)	48 (13.4%)	67 (18.9%)

Zhong N, et al. Int J Chron Obstruct Pulmon Dis 2015;10:1015-26.

LABA/LAMA (Ind/Gly) vs. ICS/LABA (SFC)
– FLAME (Design) –

- **mMRC ≥ 2; FEV1 ≥ 25 and < 60 %; AE ≥1 in the previous year**
- The primary outcome **was the annual rate of all COPD exacerbations**.



Wedzicha JA et al. N Engl J Med 2016;374:2222-34. [PMID: 27181606]

Inclusion / Exclusion criteria
– FLAME –

INCLUSION

Patients eligible for inclusion in the study were required to fulfill all of the following criteria:

1. Written informed consent was obtained before any assessment was performed.
2. Male or female adults aged ≥40 years.
3. Patients with stable chronic obstructive pulmonary disease (COPD) according to the Global Initiative for chronic Obstructive Lung Disease (GOLD) 2011 strategy.
4. Current or ex-smokers with a smoking history of at least 10 pack-years (defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years).
5. Patients with a post-bronchodilator forced expiratory volume in 1 second (FEV_1) ≥25 and <60% of the predicted normal value, and post-bronchodilator FEV_1/forced expiratory volume (FVC) <0.70 at the start of the run-in epoch (Visit 101, Day –28; **Fig. S1**). Post- refers to 1 hour after sequential inhalation of 84 µg (or equivalent dose) of ipratropium bromide and 400 µg of salbutamol.
6. A documented history of at least 1 COPD exacerbation in the previous 12 months for which treatment with systemic corticosteroids and/or antibiotics was administered.
7. Patients taking stable COPD medication (long-acting bronchodilators and/or inhaled corticosteroids, for example), for at least 60 days prior to Visit 1 (screening).
8. Patients with a modified Medical Research Council (mMRC) grade of at least 2 (on a scale of 0–4, with higher scores indicating more severe dyspnea; a minimum clinically important difference has not been determined[1]) at the start of the run-in epoch (Visit 101, Day –28).

EXCLUSION

Patients fulfilling any of the following criteria were not eligible for inclusion in the study. No additional exclusions were applied by the investigator, in order to ensure that the study population was representative of all eligible patients.

1. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human Chorionic Gonadotropin laboratory test.
2. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they were using effective methods of contraception during dosing of study treatment. Women were considered post-menopausal and not of child-bearing potential if they had had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or had had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman had been confirmed by follow-up hormone level assessment was she considered not of child-bearing potential.
3. Patients with Type I or uncontrolled Type II diabetes.
4. Patients with a history of long QT syndrome or whose QTc measured at the start of the run-in epoch (Visit 101; Fridericia method) was prolonged (>450 ms for males and females) and confirmed by a central assessor. These patients were not re-screened.
5. Patients who had a clinically significant electrocardiogram abnormality at the start of the run-in period (Visit 101) or double-blind treatment epoch (Visit 201). These patients were not re-screened.
6. Patients who had a clinically significant laboratory abnormality at the start of the run-in period (Visit 101).

Wedzicha JA et al. N Engl J Med 2016;374:2222-34. [PMID: 27181606]

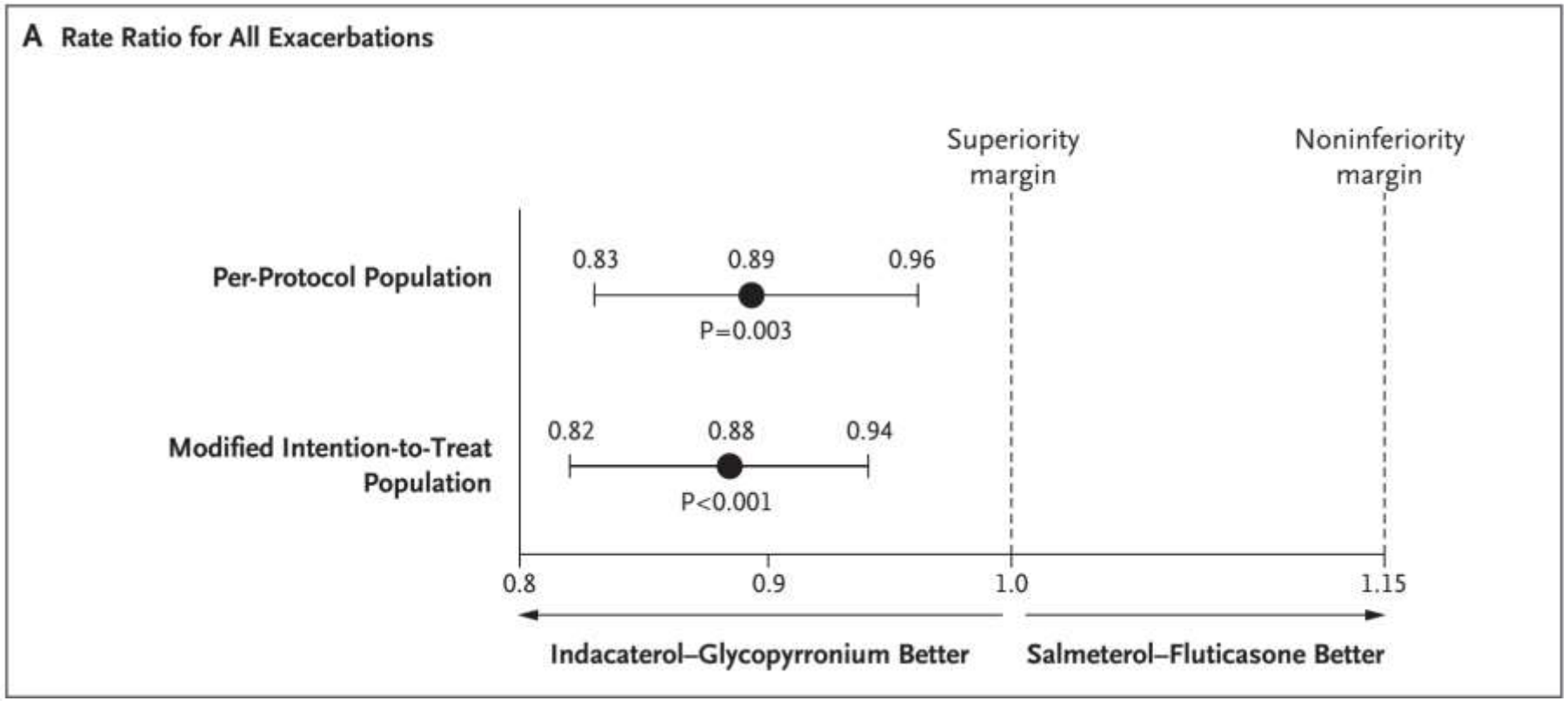
Inclusion / Exclusion criteria (2)
– FLAME –

7. Patients who had clinically significant renal, cardiovascular (such as but not limited to unstable ischemic heart disease, New York Heart Association Class III/IV left ventricular failure, myocardial infarction), arrhythmia (see below for patients with atrial fibrillation), neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological abnormalities which could interfere with the assessment of the efficacy and safety of the study treatment.
8. Patients with paroxysmal (e.g. intermittent) atrial fibrillation were excluded. Patients with persistent atrial fibrillation as defined by continuous atrial fibrillation for at least 6 months and controlled with a rate control strategy (i.e. selective beta blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) for at least 6 months could have been considered for inclusion. In such patients, atrial fibrillation had to be present at the start of the run-in period and treatment epoch (Visit 101 and Visit 102) with a resting ventricular rate <100/min. At Visit 101, the atrial fibrillation was confirmed by central reading.
9. Patients contraindicated for treatment with, or having a history of reactions/ hypersensitivity to, any of the following inhaled drugs, drugs of a similar class or any component thereof:
    - anticholinergic agents
    - long-acting β_2-agonist (LABA) and short-acting β_2-agonist (SABA)
    - sympathomimetic amines
    - lactose or any of the other excipients of trial medication
10. Patients with a history of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there was evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin.
11. Patients with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia or bladder-neck obstruction or moderate-to-severe renal impairment or urinary retention. Benign prostatic hyperplasia patients who were stable on treatment could have been considered.
12. Patients who had not achieved an acceptable spirometry result at the start of the run-in period (Visit 101) in accordance with American Thoracic Society/European Respiratory Society criteria for acceptability (one retest could be performed for patients who did not meet the acceptability criteria).
13. Patients who had a COPD exacerbation that resulted in treatment with antibiotics and/or systemic corticosteroids and/or hospitalization in the 6 weeks prior to Visit 1.
14. Patients who developed a COPD exacerbation of any severity (mild/moderate/severe) between screening (Visit 1) and treatment epoch (Visit 201) were not eligible but were permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation.
15. Patients who had a respiratory tract infection within 4 weeks prior to screening (Visit 1).
16. Patients who developed a respiratory tract infection between screening and prior to treatment were not eligible, but were permitted to be re-screened 4 weeks after the resolution of the respiratory tract infection.
17. Patients requiring long-term oxygen therapy prescribed for >12 hours per day.
18. Patients with any history of asthma.
19. Patients with an onset of respiratory symptoms, including a COPD diagnosis prior to age 40 years.
20. Patients with a blood eosinophil count >600/mm^3 at the start of the run-in period (Visit 101).
21. Patients with allergic rhinitis who used an H_1-antagonist or intra-nasal corticosteroids intermittently (treatment with a stable dose or regimen was permitted).
22. Patients with concomitant pulmonary disease (e.g. lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension).
23. Patients with clinically significant bronchiectasis.
24. Patients with a diagnosis of α-1 anti-trypsin deficiency.
25. Patients with active pulmonary tuberculosis, unless confirmed by imaging to be no longer active.
26. Patients with pulmonary lobectomy or lung volume reduction surgery or lung transplantation.
27. Patients participating in or planning to participate in the active phase of a supervised pulmonary rehabilitation program during the study (maintenance program was permitted).
28. Patients receiving any of the prohibited medications.
29. Patients receiving any COPD-related medications in the classes specified in **Table S1** had to undergo the required washout period prior to the start of the run-in period (Visit 101) and follow the adjustment to treatment program.
30. Patients receiving selective serotonin reuptake inhibitors, intra-nasal corticosteroids, H_1-antagonists, or inactivated influenza, pneumococcal or any other inactivated vaccine, were excluded unless the medication had been stable for the specified period and the stated conditions had been met.
31. Use of other investigational drugs/devices (approved or unapproved) at the time of enrollment, or within 30 days or 5 half-lives of the screening visit (Visit 1), whichever was longer.
32. Patients unable to use an electronic patient diary and Exacerbations of Chronic Obstructive Pulmonary Disease Tool: patient-reported outcome (EXACT PRO) diary.
33. Patients unable to use a dry powder inhaler device, Metered Dose Inhaler (MDI) or a pressurized MDI (rescue medication), or unable to comply with the study regimen.

Wedzicha JA et al. N Engl J Med 2016;374:2222-34. [PMID: 27181606]

LABA/LAMA (Ind/Gly) vs. ICS/LABA (SFC) – FLAME (AE) –

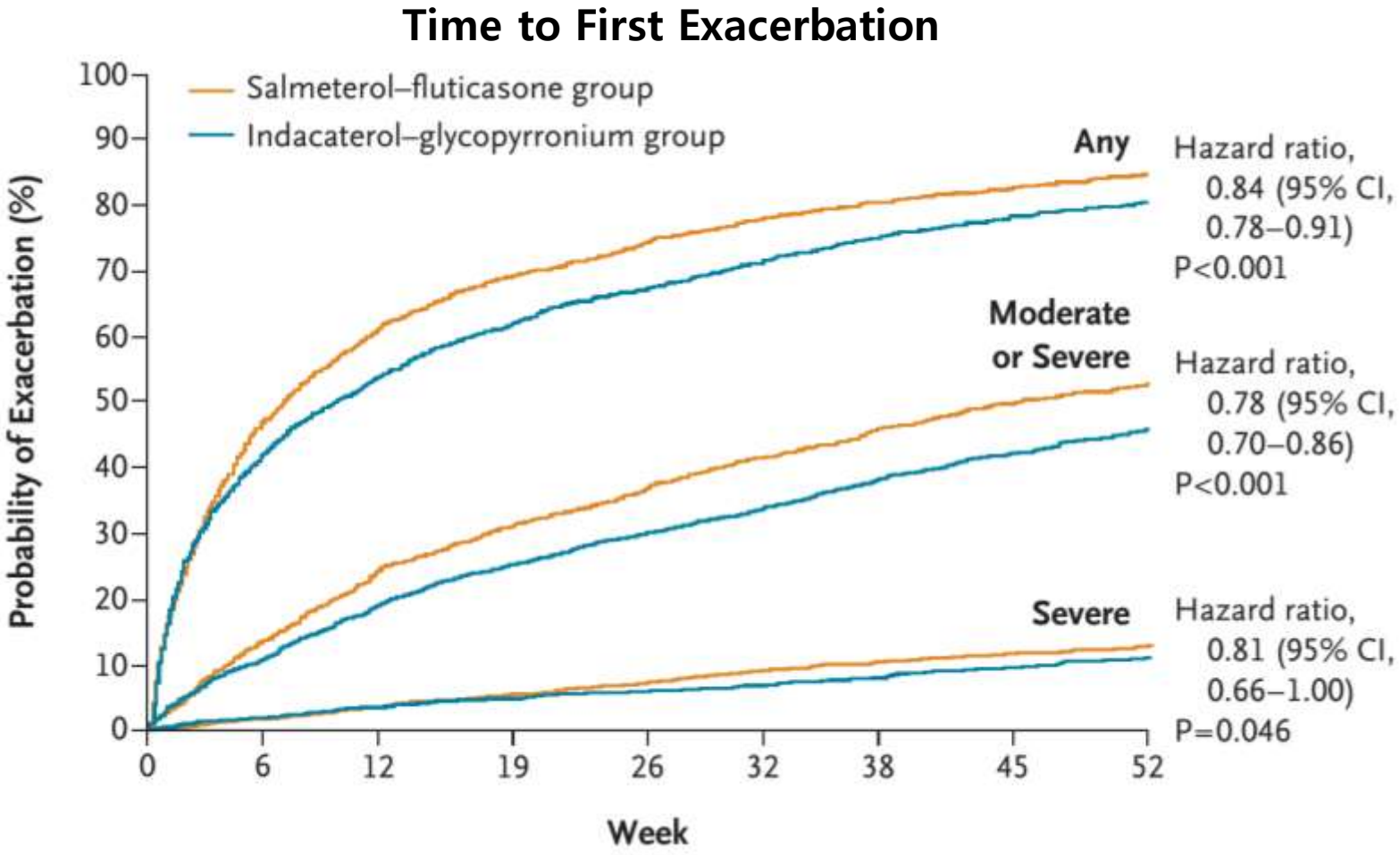
- mMRC ≥ 2; FEV1 ≥ 25 and < 60 %; AE ≥1 in the previous year
- The primary outcome was the annual rate of all COPD exacerbations



Wedzicha JA, *et al. New England Journal of Medicine 2016;374:2222-34.*

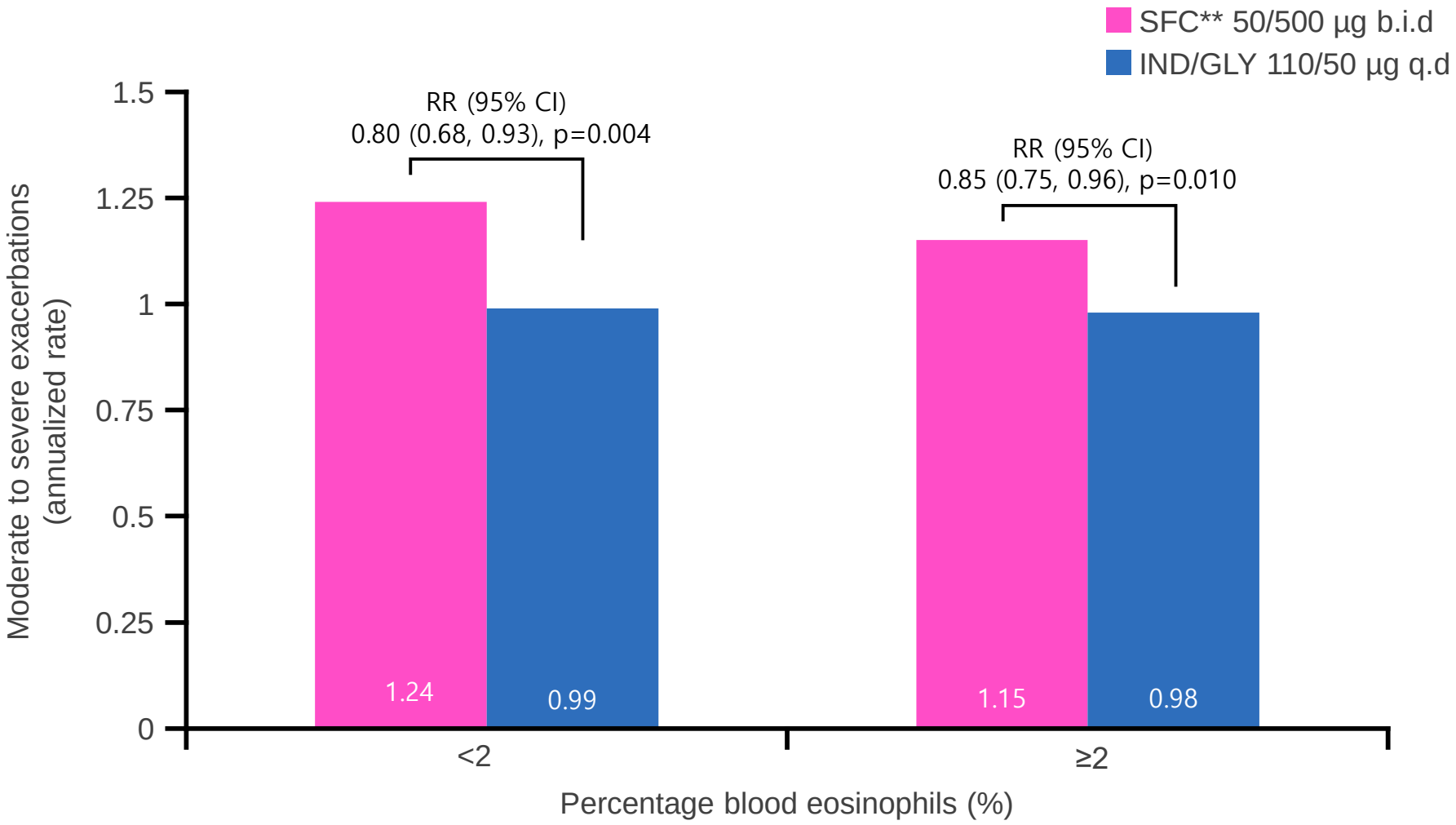
LABA/LAMA (Ind/Gly) vs. ICS/LABA (SFC) – FLAME (AE) –

- mMRC ≥ 2; FEV1 ≥ 25 and < 60 %; AE ≥1 in the previous year
- The primary outcome was the annual rate of all COPD exacerbations.



Wedzicha JA, *et al. New England Journal of Medicine 2016;374:2222-34.*

LABA/LAMA (Ind/Gly) vs. ICS/LABA (SFC) – FLAME (Annual Mod to Severe AE) –



Wedzicha JA, *et al. New England Journal of Medicine 2016;374:2222-34.*

Clinically Important Deterioration (CID) in the FLAME Study

- **CID** was defined as **≥100 mL** decrease in forced expiratory volume in 1 s (**FEV1**) or **≥ 4-unit** increase in St. George's Respiratory Questionnaire (**SGRQ**) total score or a moderate-to-severe COPD **exacerbation**

Table 1 Baseline demographics and clinical characteristics (randomized set)

Characteristics	Indacaterol/glycopyrronium 110/50 μg o.d. (*n* = 1680)	Salmeterol/fluticasone 50/500 μg b.i.d. (*n* = 1682)
Age, years	64.6 ± 7.89	64.5 ± 7.70
Men, *n* (%)	1299 (77.3)	1258 (74.8)
COPD severity[a], *n* (%)		
Moderate, GOLD 2	560 (33.3)	563 (33.5)
Severe, GOLD 3	973 (57.9)	981 (58.3)
Very severe, GOLD 4	133 (7.9)	124 (7.4)
High risk and more symptoms (Group D)	1265 (75.3)	1249 (74.3)
Current smokers, *n* (%)	664 (39.5)	669 (39.8)
Number of COPD exacerbations in the previous year, *n* (%)		
1	1355 (80.7)	1355 (80.6)
≥ 2	324 (19.3)	325 (19.3)
SGRQ-C total score[b]	47.3 (15.8)	47.2 (15.9)
Post-bronchodilator FEV_1, L	1.2 ± 0.34	1.2 ± 0.35
Post-bronchodilator FEV_1, % predicted	44.0 ± 9.48	44.1 ± 9.43
Post-bronchodilator FEV_1/FVC, %	41.7 ± 9.82	41.5 ± 9.89

Anzueto AR, Respir Res 2018;19:121 [PMID 29925383]

Clinically Important Deterioration (CID) in the FLAME Study

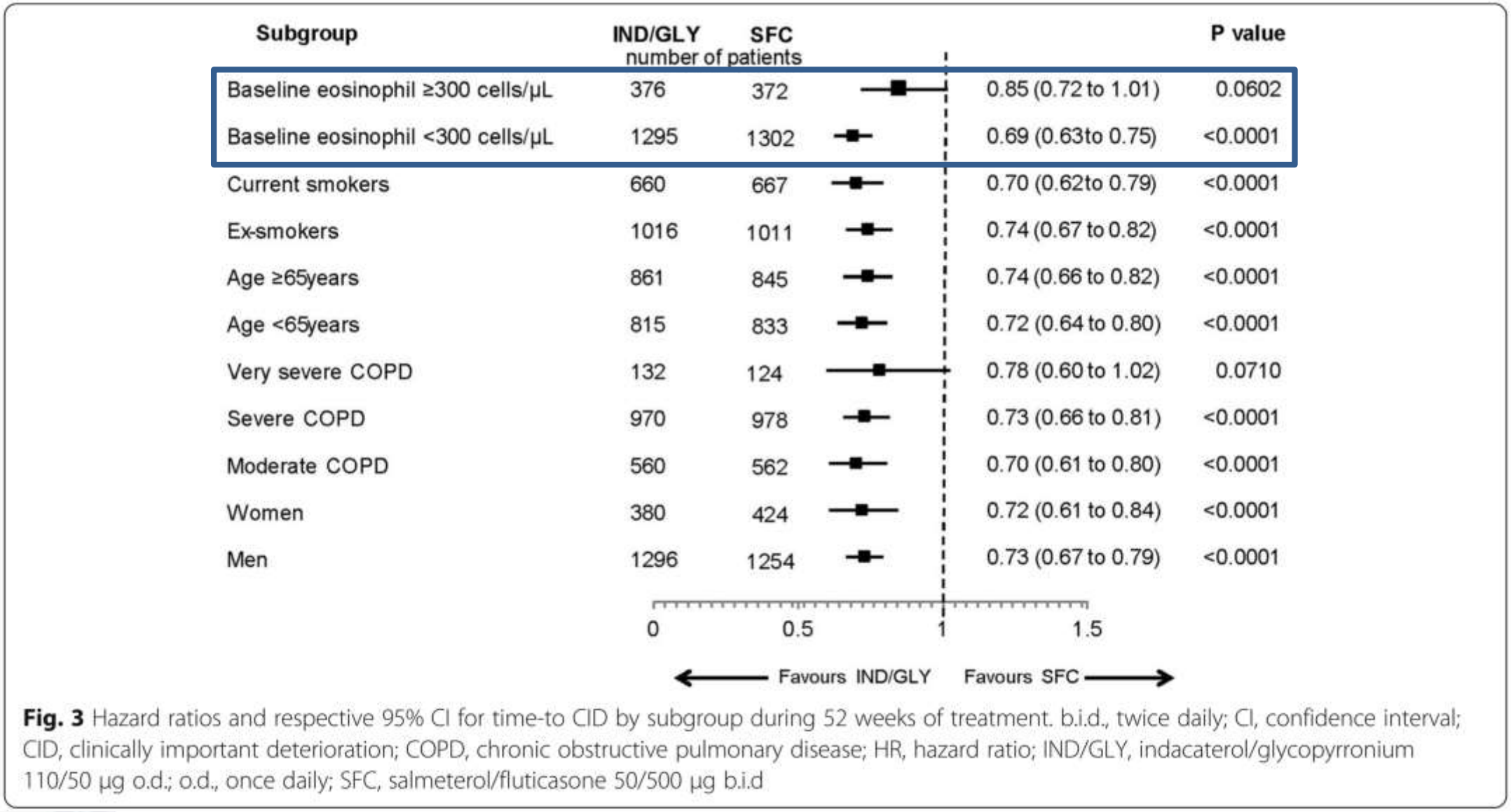


Fig. 3 Hazard ratios and respective 95% CI for time-to CID by subgroup during 52 weeks of treatment. b.i.d., twice daily; CI, confidence interval; CID, clinically important deterioration; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; IND/GLY, indacaterol/glycopyrronium 110/50 µg o.d.; o.d., once daily; SFC, salmeterol/fluticasone 50/500 µg b.i.d

Anzueto AR, Respir Res 2018;19:121 [PMID 29925383]

Subgroup Analyses from the FLAME study

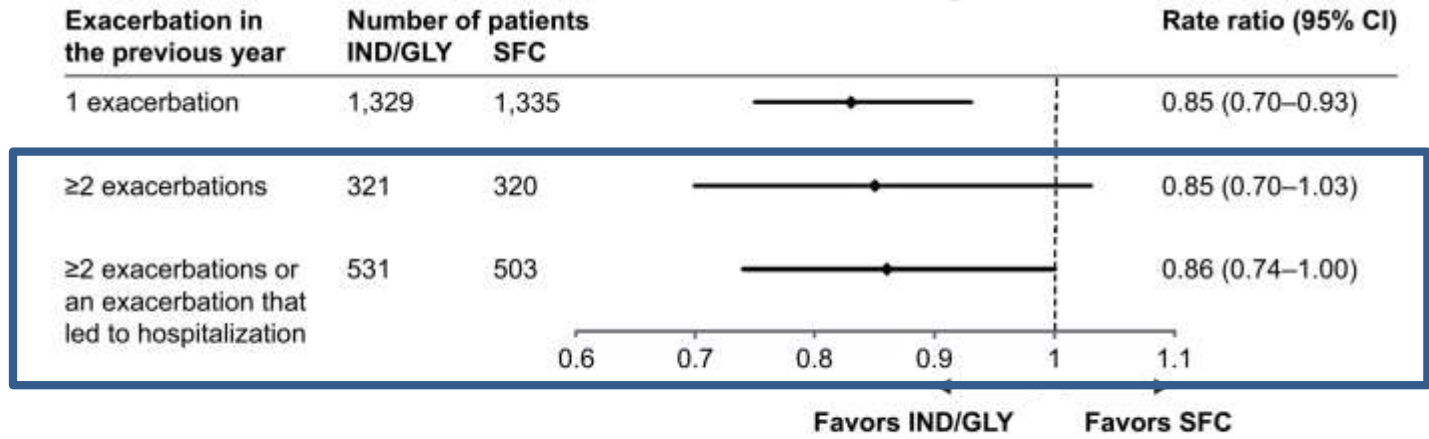


Figure 1 Annualized rate of moderate or severe COPD exacerbations in different subgroups of patients based on prior exacerbations (full analysis set).
Abbreviations: IND/GLY, indacaterol/glycopyrronium; SFC, salmeterol/fluticasone.

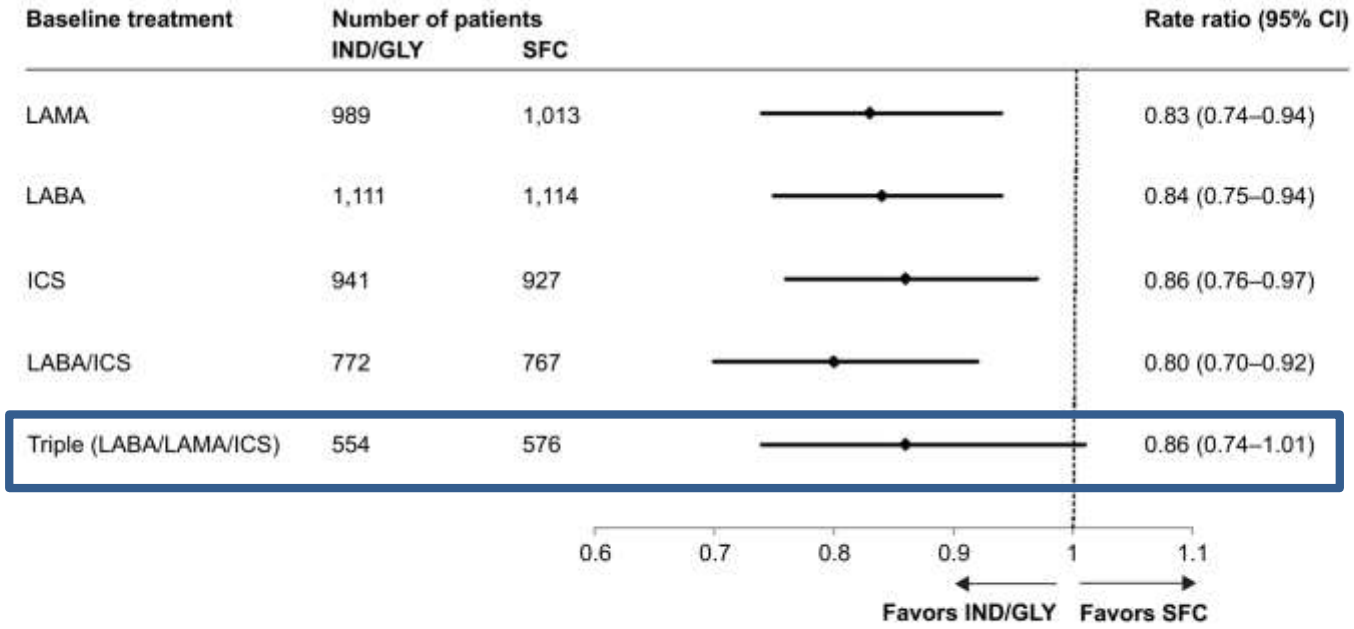


Figure 3 Annualized rate of moderate or severe COPD exacerbations based on previous treatment (full analysis set).
Abbreviations: ICS, inhaled corticosteroid; IND/GLY, indacaterol/glycopyrronium; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; SFC, salmeterol/fluticasone.

Vogelmeier CF, Int J Chron Obstruct Pulmon Dis 2018;13:1125-34 [PMID 29692607]

Subgroup Analyses from the FLAME study

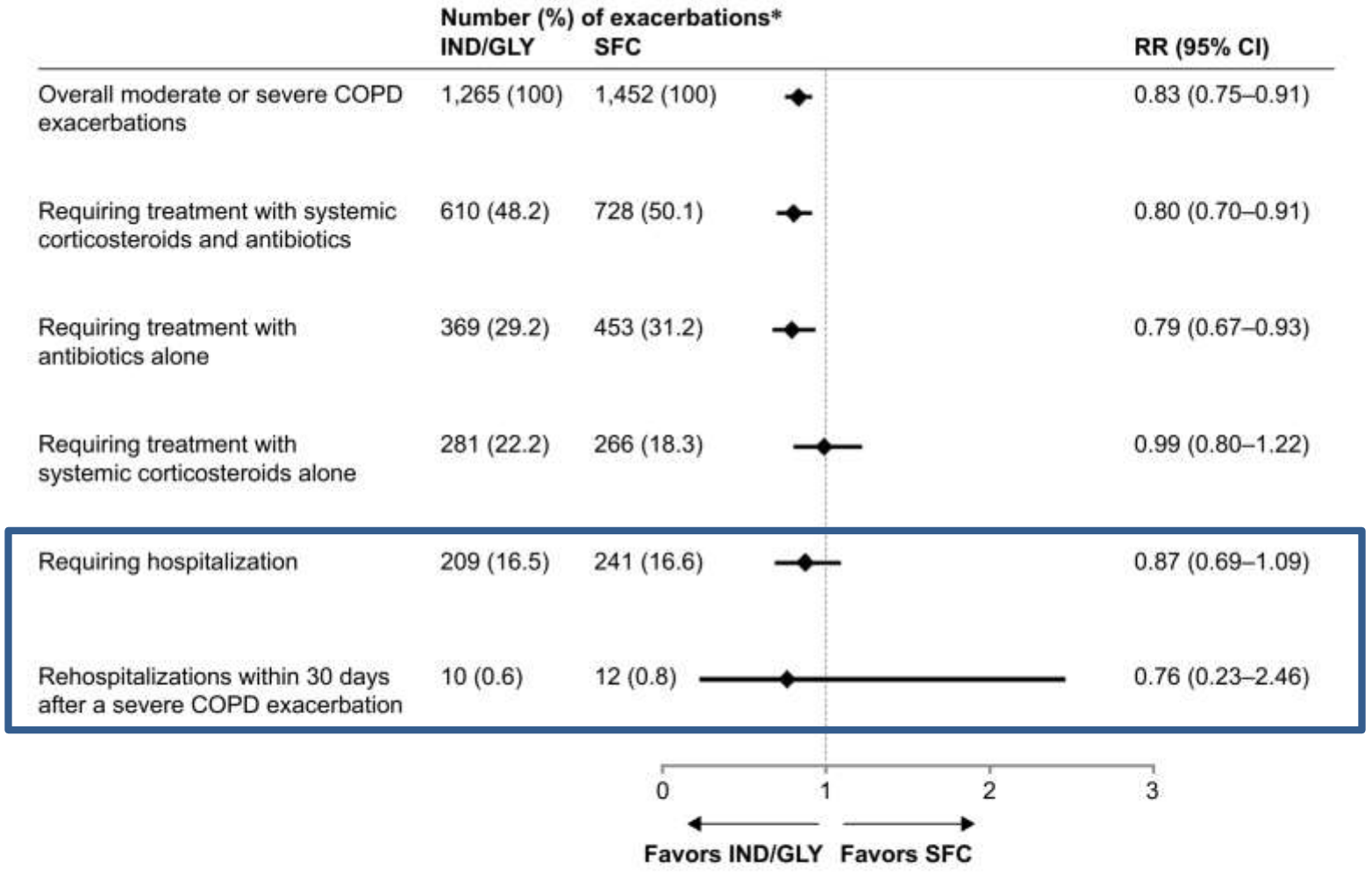
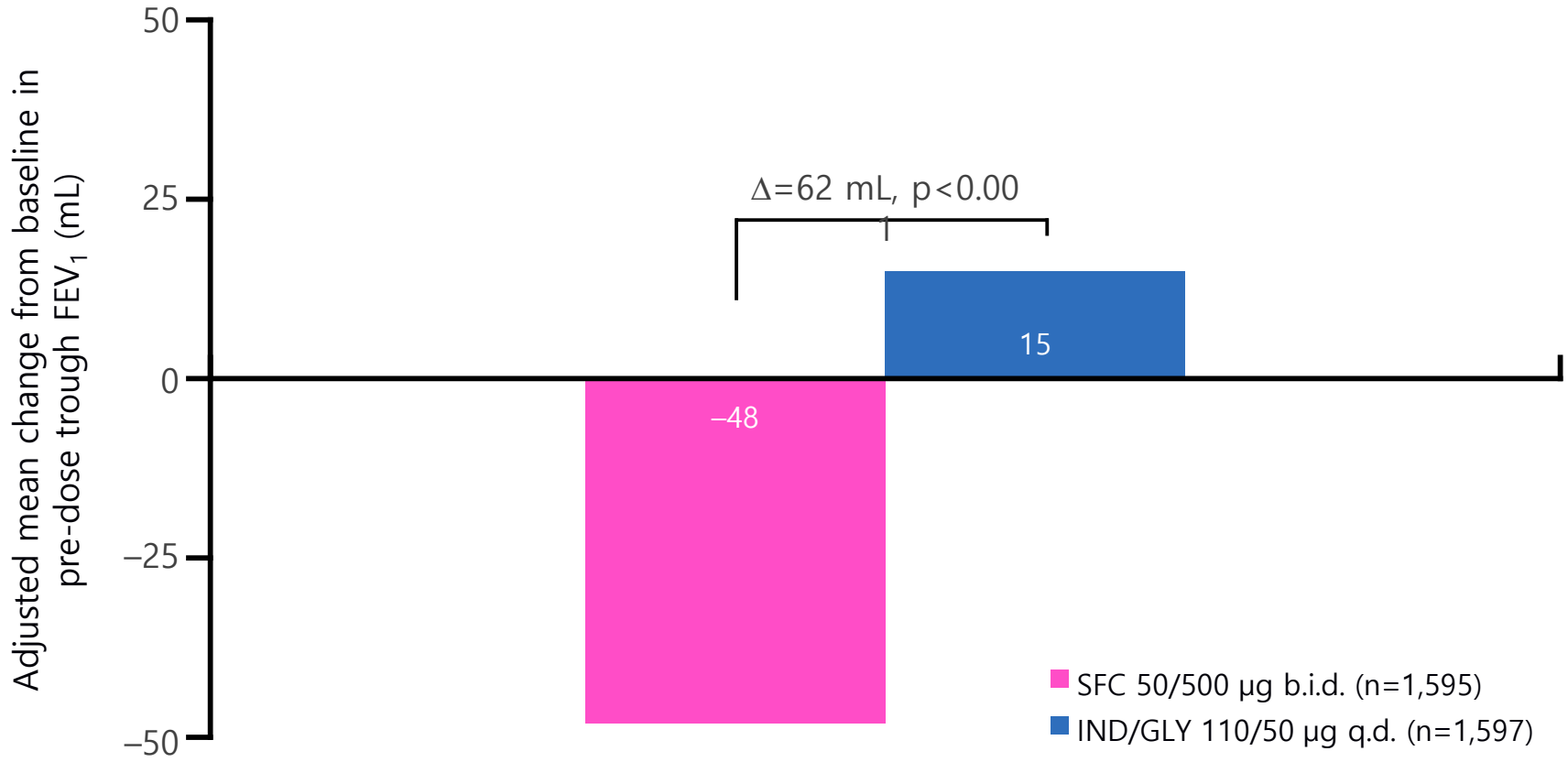


Figure 4 Number and RR of moderate or severe COPD exacerbations according to HCRU with IND/GLY versus SFC during the treatment period.
Notes: *If an exacerbation satisfies multiple criteria (eg, required treatment with a medication and later required hospitalization), then the event is counted in each category (row) satisfied. Thus, the percentages do not add up to 100%.
Abbreviations: HCRU, health care resource utilization; IND/GLY, indacaterol/glycopyrronium; RR, rate ratio; SFC, salmeterol/fluticasone.

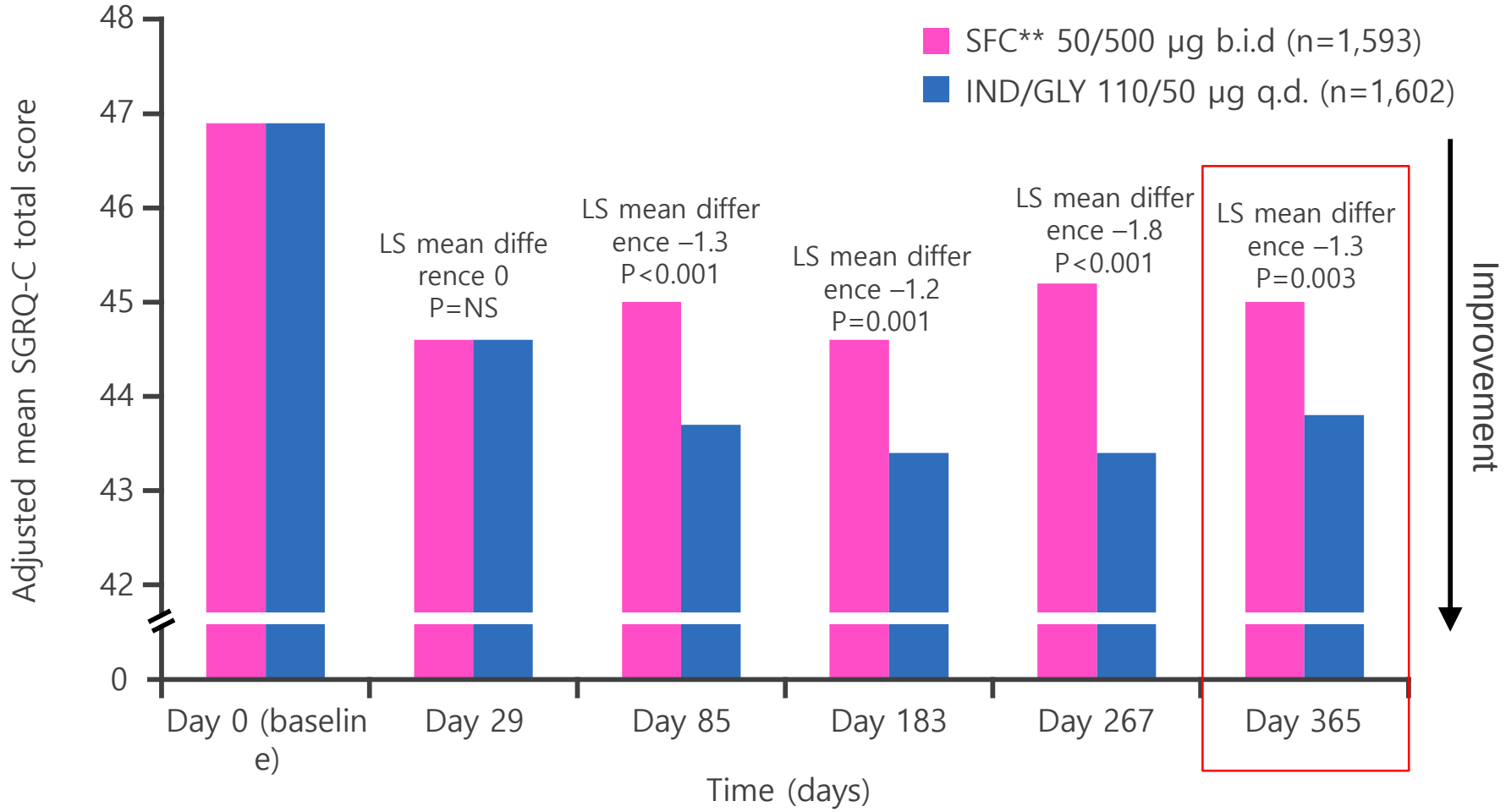
Vogelmeier CF, Int J Chron Obstruct Pulmon Dis 2018;13:1125-34 [PMID 29692607]

LABA/LAMA (Ind/Gly) vs. ICS/LABA (SFC) – FLAME (FEV_1) –



Wedzicha JA, *et al. New England Journal of Medicine 2016;374:2222-34.*

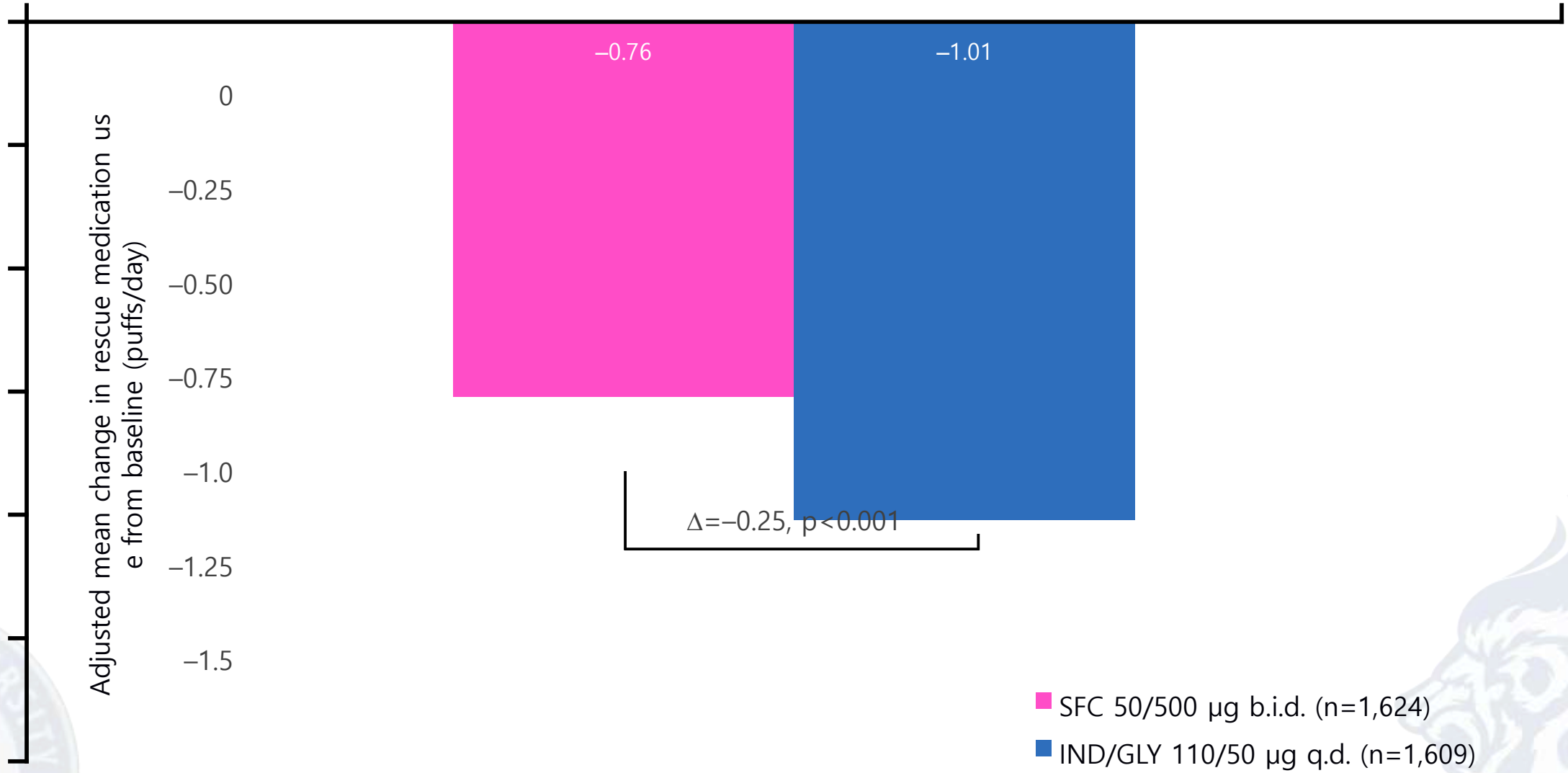
LABA/LAMA (Ind/Gly) vs. ICS/LABA (SFC) – FLAME (QOL) –



- SGRQ-C responder rates: IND/GLY 49.2%; SFC 43.7% (OR 1.30; p<0.001)

Wedzicha JA, *et al. New England Journal of Medicine 2016;374:2222-34.*

LABA/LAMA (Ind/Gly) vs. ICS/LABA (SFC)
– FLAME (Rescue Medication Use) –



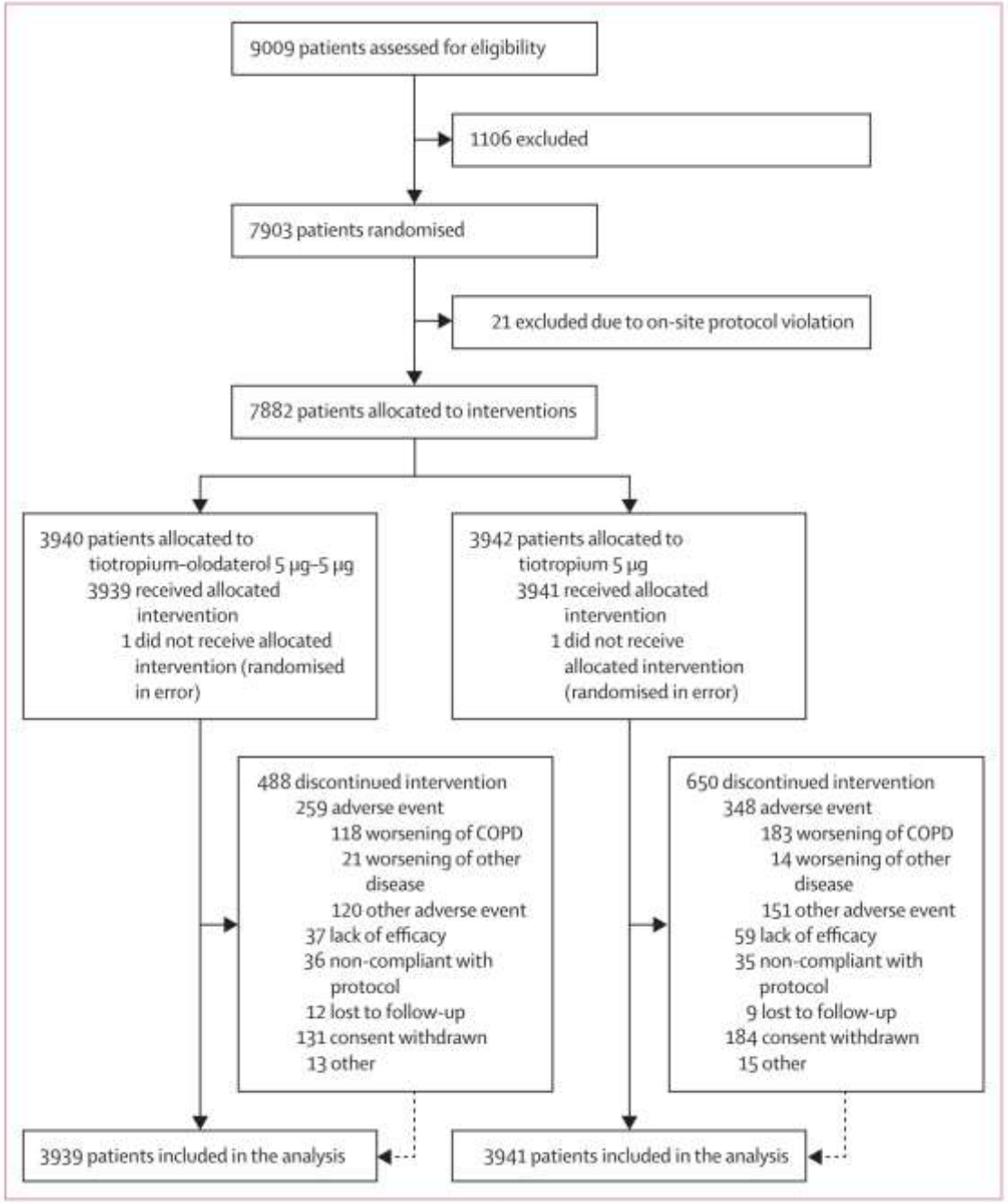
Wedzicha JA, *et al. New England Journal of Medicine 2016;374:2222-34.*

Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO): a double-blind, randomised, parallel-group, active-controlled trial

Peter M A Calverley, Antonio R Anzueto, Kerstine Carter, Lars Grönke, Christoph Hallmann, Christine Jenkins, Jadwiga Wedzicha, Klaus F Rabe

- A **52-week**, double-blind, randomised, parallel-group, active-controlled trial
- The primary endpoint was the **rate of moderate and severe COPD exacerbations** from the first dose of medication until 1 day after last drug administration
- Patients using **inhaled corticosteroids continued** this therapy
- 7880 patients were recruited

DYNAGYTO



Calverley PMA et al. Lancet Respir Med 2018;6:337-44. [PMID: 29605624]

DYNAGYTO

Study endpoints

Primary endpoint#
Annualised rate of moderate-to-severe COPD exacerbations

Key secondary endpoint#
Time to first moderate-to-severe COPD exacerbation

Other secondary endpoints+

- Annualised rate of exacerbations leading to hospitalisation
- Time to first COPD exacerbation leading to hospitalisation
- Time to all-cause mortality

Calverley PMA et al. Lancet Respir Med 2018;6:337-44. [PMID: 29605624]

DYNAGYTO

Inclusion / Exclusion criteria

Key inclusion criteria

≥40 years of age

Diagnosis of COPD

Post-bronchodilator FEV_1/FVC <70%

Post-bronchodilator FEV_1 <60% of predicted normal

Documented history of ≥1 moderate-to-severe exacerbation in the previous 12 months required treatment with systemic corticosteroids and/or antibiotics and/or related hospitalisation

Current or ex-smokers with a smoking history of >10-pack years

Key exclusion criteria

Significant disease other than COPD

Current documented diagnosis of asthma

Life-threatening cardiac arrhythmia

Patients with severe emphysema requiring endobronchial interventions within 6 months prior to screening

Diagnosis of thyrotoxicosis

History of cystic fibrosis

Known active tuberculosis

Calverley PMA et al. Lancet Respir Med 2018;6:337-44. [PMID: 29605624]

DYNAGYTO

	Tiotropium–olodaterol group (n=3939)	Tiotropium group (n=3941)
Sex		
Male	2785 (71%)	2841 (72%)
Female	1154 (29%)	1100 (28%)
Race		
American Indian–Alaska Native	77 (2%)	64 (2%)
Asian	557 (14%)	607 (15%)
Black–African American	58 (2%)	52 (1%)
Native Hawaiian–Pacific Islander	3 (<1%)	5 (<1%)
White	3134 (80%)	3113 (79%)
Multiple	22 (1%)	20 (1%)
Missing*	88 (2%)	80 (2%)
Age (years)	66·5 (8·4)	66·3 (8·5)
Smoking status		
Current smoker	1434 (36%)	1478 (38%)
Ex-smoker	2505 (64%)	2462 (62%)
Never smoked†	0	1 (<1%)
Smoking history (pack-years)	44·8 (24·4)	44·7 (25·2)
SGRQ (total score)	48·1 (17·7)	47·4 (17·7)
Post-bronchodilator FEV_1‡		
Mean (L)	1·177 (0·385)	1·197 (0·377)
% predicted	44·6 (37·5)	44·5 (11·5)

	Tiotropium–olodaterol group (n=3939)	Tiotropium group (n=3941)
GOLD class (2017)		
A	260 (7%)	308 (8%)
B	1922 (49%)	1895 (48%)
C	176 (4%)	176 (4%)
D	1569 (40%)	1547 (39%)
Missing	12 (<1%)	15 (<1%)
Patients with ≥2 exacerbations, or ≥1 severe exacerbations in the previous year	1754 (45%)	1733 (44%)
Respiratory medication		
LABA only	122 (3%)	135 (3%)
LAMA only	365 (9%)	350 (9%)
ICS only	107 (3%)	93 (2%)
LABA–ICS	1031 (26%)	1005 (26%)
LAMA–ICS	78 (2%)	88 (2%)
LAMA–LABA	461 (12%)	478 (12%)
LAMA–LABA–ICS	1555 (39%)	1577 (40%)
Neither	220 (6%)	215 (5%)

Calverley PMA, Lancet Respir Med 2018;6:337-44 [PMID 29605624]

LAMA/LABA (TIO/OLO) vs. LAMA (OLO) – DYNAGITO (Mod to Severe AE) –

	Adjusted rate of events per patient-year (95% CI)		Rate ratio	95% CI	p value
	Tiotropium–olodaterol group	Tiotropium group			
Primary endpoint					
Moderate and severe exacerbations	0·90 (0·84–0·96)*	0·97 (0·90–1·03)*	0·93	0·85–1·02* (0·87–1·00)†	0·0498
Other prespecified endpoints					
Moderate and severe exacerbations					
Treated with antibiotics only	0·27 (0·25-0·29)	0·25 (0·23–0·27)	1·07	0·96–1·20	0·21
Treated with corticosteroids only	0·14 (0·12–0·15)	0·17 (0·15–0·19)	0·80	0·68–0·94	0·0068
Treated with antibiotics and corticosteroids in combination	0·48 (0·45–0·52)	0·53 (0·50–0·57)	0·91	0·83–1·00	0·045
Severe exacerbations	0·24 (0·22–0·27)	0·27 (0·25–0·30)	0·89	0·78–1·02	0·090
Exacerbations leading to hospitalisation	0·18 (0·16–0·20)	0·20 (0·18–0·22)	0·89	0·76–1·03	0·13

*99% CI, prespecified level of significance. †95% CI.

Table 2: **Annualised rate of exacerbations**

Calverley PMA, Lancet Respir Med 2018;6:337-44 [PMID 29605624]

Annualized rate of moderate or severe exacerbations analyzed using multiple covariates models similar to those used in previous COPD trials

Covariates Model	Rate ratio (Tio vs Tio/olo)	95% CI	*p*-value	Dispersion parameter
SPARK/FLAME -like	0.89	(0.84, 0.96)	0.0010	0·7419
HERMES -like	0.91	(0.85, 0.98)	0.0080	0·8499
TRINITY/TRILOGY-like	0.89	(0.84, 0.96)	0.0011	0·7809

SPARK/FLAME-like: Treatment, baseline smoking status, ICS use at screening, severity of airflow limitation and region as fixed effects with baseline total symptom score (scale 0−18, higher=worse) and 1−year exacerbation history as covariates.

HERMES-like: Treatment, sex, smoking status, country and baseline LABA use fixed effects and age and baseline post−bronchodilator percent predicted FEV_1 as covariates.

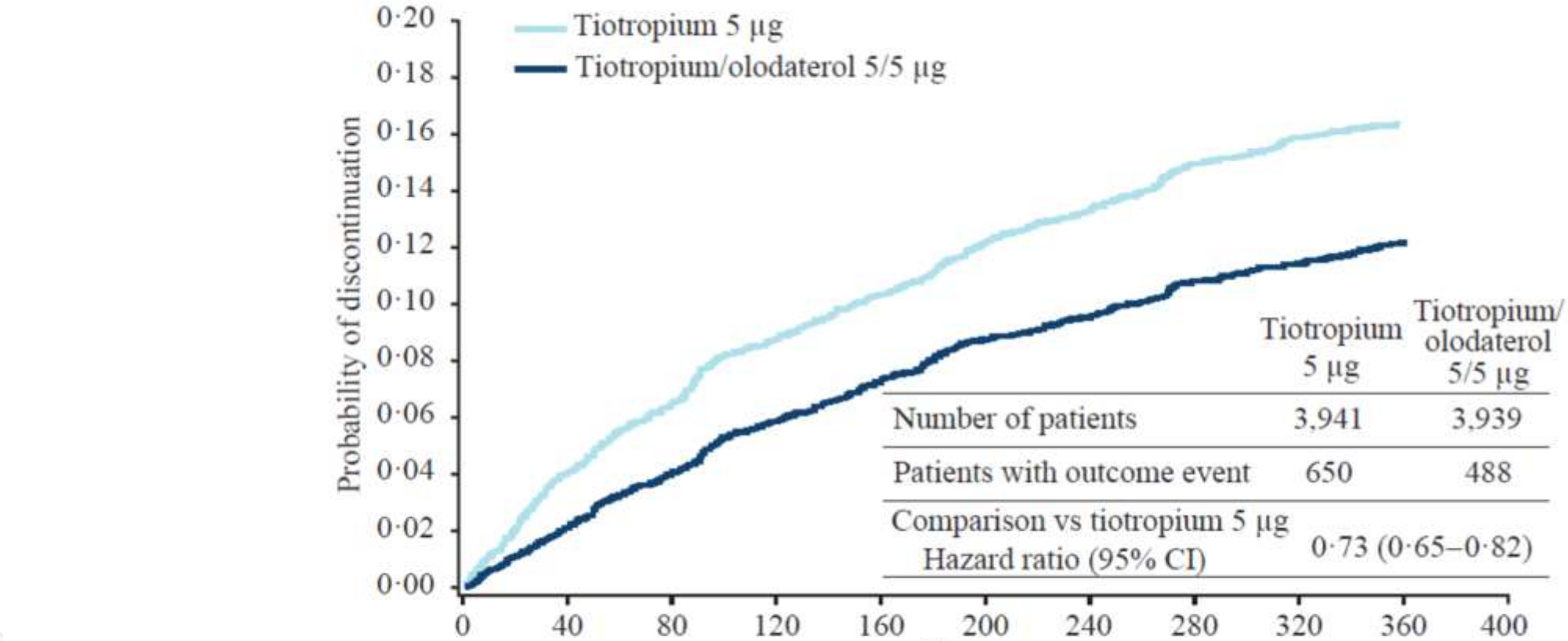
TRINITY/TRILOGY-like: Treatment, country, severity of airflow limitation and smoking status as fixed effects and 1-year history of exacerbations as a covariate.

- Results after this **adjustment** showed treatment differences between tiotropium and tiotropium/olodaterol for all three different models with rate ratios between 0.89 and 0.91 (95% CI between 0.84 and 0.98), **nominal p-values <0.01**, and reduced dispersion parameters

Calverley PMA, Lancet Respir Med 2018;6:337-44 [PMID 29605624]

Patients Who Discontinued Early in the DYNAGYTO Study

Supplementary Figure 1. Time to treatment discontinuation.



CI, confidence interval.

Calverley PMA, Lancet Respir Med 2018;6:337-44 [PMID 29605624]

Patients Who Discontinued Early in the DYNAGYTO Study

Supplementary Table 4. Differences in baseline characteristics in patients who discontinued early and those who completed the trial.

Characteristic	Discontinued early (N=1,138)	Completed as planned (N=6,742)	Total (N=7,880)
Concomitant therapy at baseline – n (%)			
LABA only	32 (2·8)	225 (3·3)	257 (3·3)
LAMA only	65 (5·7)	650 (9·6)	715 (9·1)
ICS only	33 (2·9)	167 (2·5)	200 (2·5)
LABA/ICS	210 (18·5)	1,826 (27·1)	2,036 (25·8)
LAMA/ICS	17 (1·5)	149 (2·2)	166 (2·1)
LAMA/LABA	147 (12·9)	792 (11·7)	939 (11·9)
LAMA/LABA/ICS	578 (50·8)	2,554 (37·9)	3,132 (39·7)
None	56 (4·9)	379 (5·6)	435 (5·5)
Exacerbation history in previous year – n (%)			
1 moderate exacerbation	541 (47·5)	3,850 (57·1)	4,391 (55·7)
≥2 moderate or ≥1 severe exacerbation	597 (52·5)	2,890 (42·9)	3,487 (44·3)
FEV_1 percent predicted - mean (SD)	41·1 (12·6)	45·1 (29·4)	44·5 (27·7)
GOLD Stage – n (%)			
2	305 (26·8)	2,479 (36·8)	2,784 (35·3)
3	591 (51·9)	3,448 (51·1)	4,039 (51·3)
4	235 (20·7)	757 (11·2)	992 (12·6)

Calverley PMA, Lancet Respir Med 2018;6:337-44 [PMID 29605624]

Patients Who Discontinued Early in the DYNAGYTO Study

Supplementary Table 5. Variables identified as predictive of discontinuation using a stepwise regression.

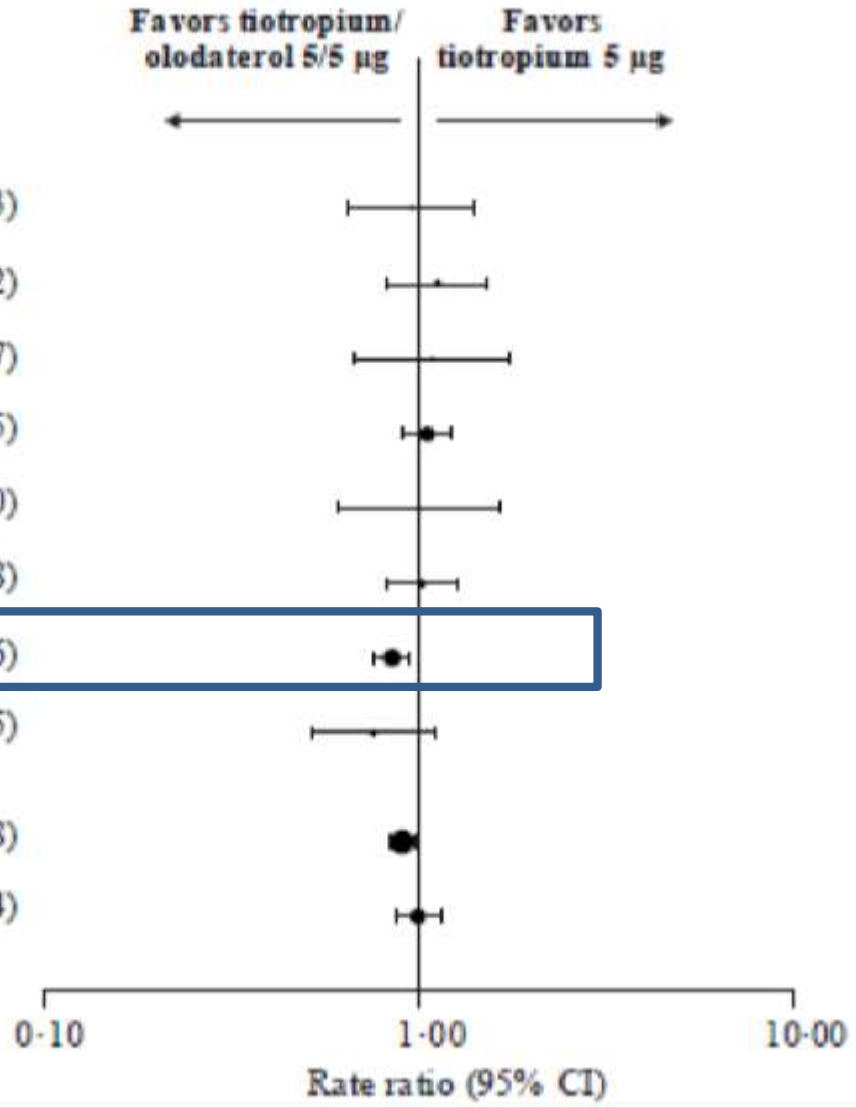
Variable	Chi square
Region	<0·0001
Screening post-bronchodilator FEV_1 % predicted	<0·0001
Age	<0·0001
Baseline CAT score	<0·0001
Number of exacerbations leading to hospitalization in the year prior to randomization	0·0003
Sex	0·0078
Number of exacerbations treated with steroids and antibiotics in the year prior to randomization	0·0148
Inhaled corticosteroid use at baseline[a]	0·0339

[a]Any inhaled corticosteroid use at baseline (yes/no).
CAT, COPD Assessment Test; FEV_1, forced expiratory volume in 1 second.

Calverley PMA, Lancet Respir Med 2018;6:337-44 [PMID 29605624]

Annualized rate of moderate or severe exacerbations by baseline therapy

Concomitant therapy at baseline	N	Adjusted incidence rate Tio 5 µg	T/O 5/5 µg	Rate ratio (95% CI)
LABA only	257	0·73	0·70	0·959 (0·646–1·423)
LAMA only	715	0·62	0·70	1·123 (0·823–1·532)
ICS only	200	0·84	0·91	1·091 (0·674–1·767)
LABA/ICS	2,036	0·74	0·78	1·053 (0·913–1·215)
LAMA/ICS	166	1·01	1·01	1·007 (0·611–1·660)
LAMA/LABA	939	0·87	0·89	1·020 (0·827–1·258)
LAMA/LABA/ICS	3,132	1·31	1·11	0·847 (0·766–0·936)
Neither LAMA, LABA, nor ICS	435	0·62	0·47	0·757 (0·523–1·095)
Any ICS	5,534	1·07	0·97	0·911 (0·841–0·988)
No ICS	2,346	0·74	0·73	0·995 (0·859–1·154)



Calverley PMA, Lancet Respir Med 2018;6:337-44 [PMID 29605624]

DB2113373

Risk of a first exacerbation with UMEC/VI in low-risk patients

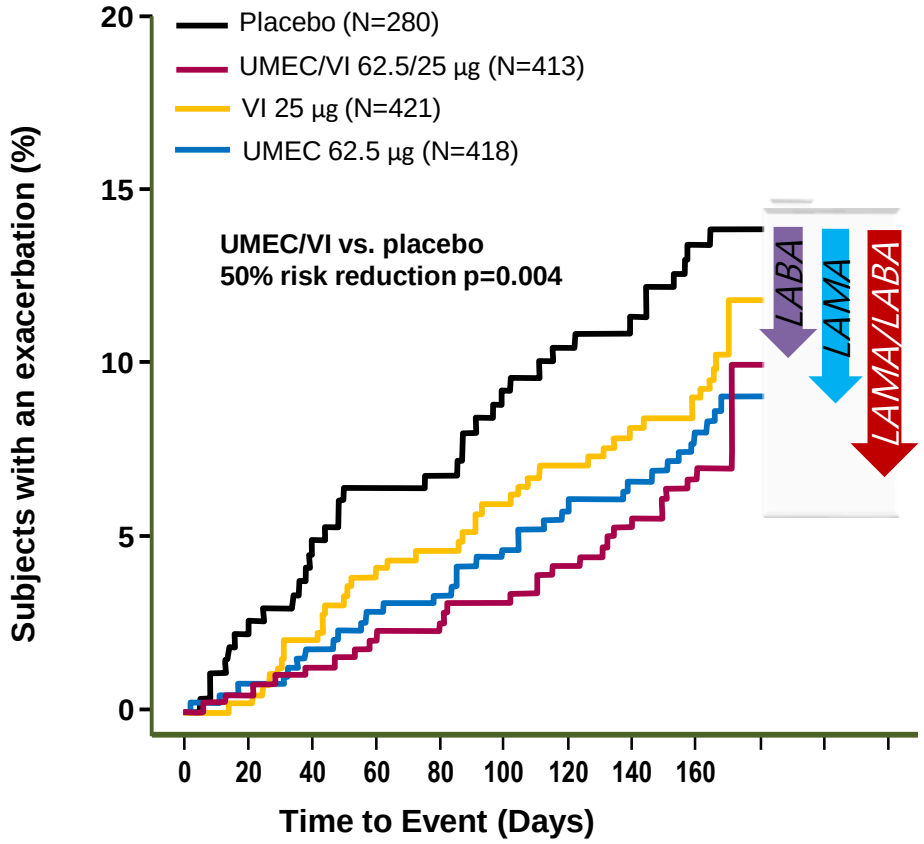


Table 2 Summary of additional efficacy measures.

	Placebo (N = 280)	UMEC 62.5 (N = 418)	VI 25 (N = 421)	UMEC/VI 62.5/25 (N = 413)
Time to first COPD exacerbation				
HR vs placebo (95% CI)	—	0.6‡ (0.4, 1.0)	0.7 (0.4, 1.1)	0.5† (0.3, 0.8)

Donohue JF et al. Respir Med 2013;107:1538-46 [PMID 23830094]

LAMA/LABA (UMEC/VIL 125/25) vs. LAMA (UMEC 125) vs. LABA (VIL)

– DB2113361 (AE) –

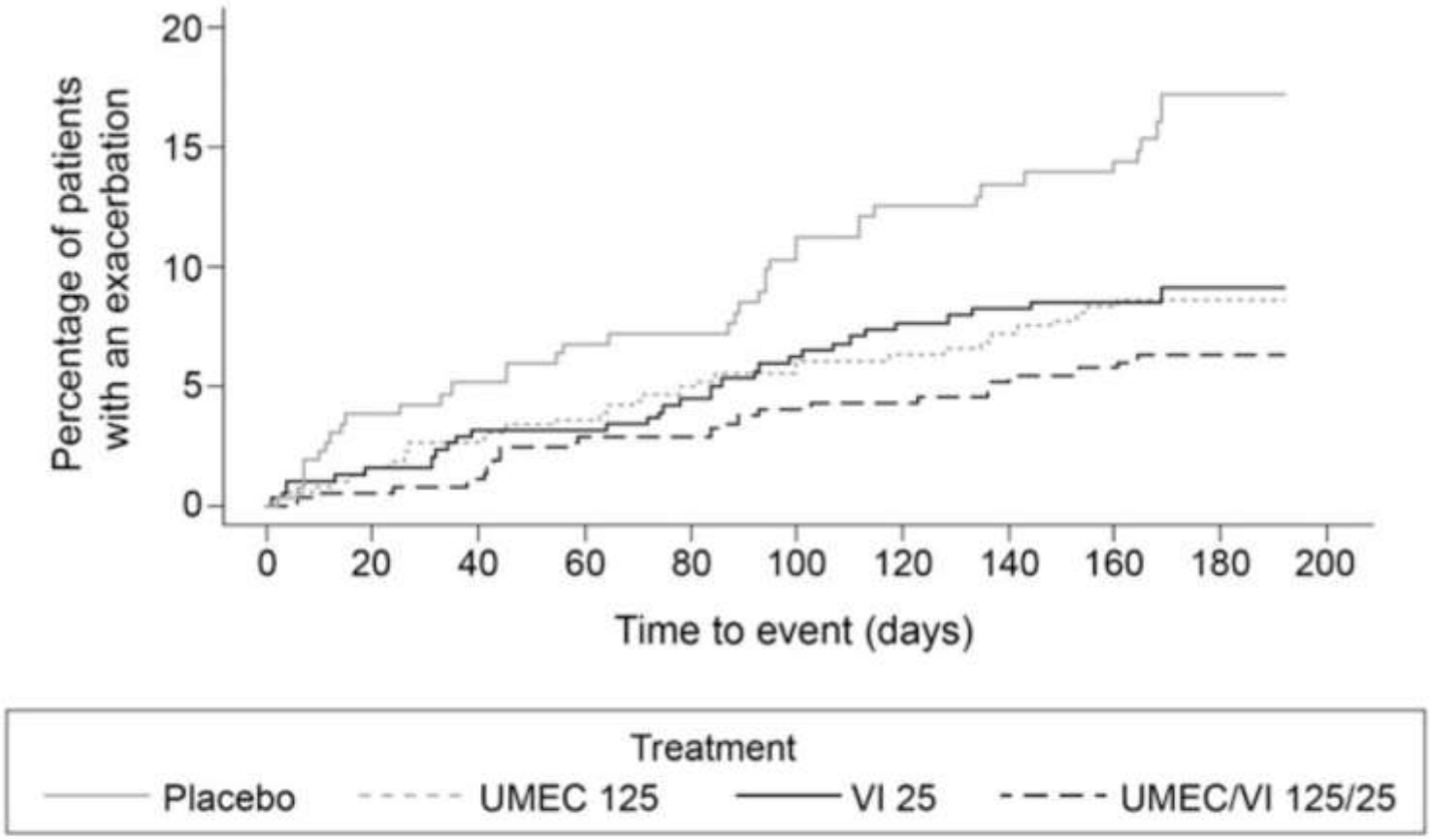


FIGURE 5. Kaplan-Meier plot of time-to-first COPD exacerbation (intent-to-treat population). See Figure 1 legend for expansion of abbreviations.

Celli B et al. Chest 2014;145:981-91 [PMID 24385182]

LAMA/LABA (UMEC/VIL) vs. LAMA (TIO) – ZEP117115 (Time to First AE) –

SUPPLEMENTARY FILE 11. TIME TO FIRST EXACERBATION

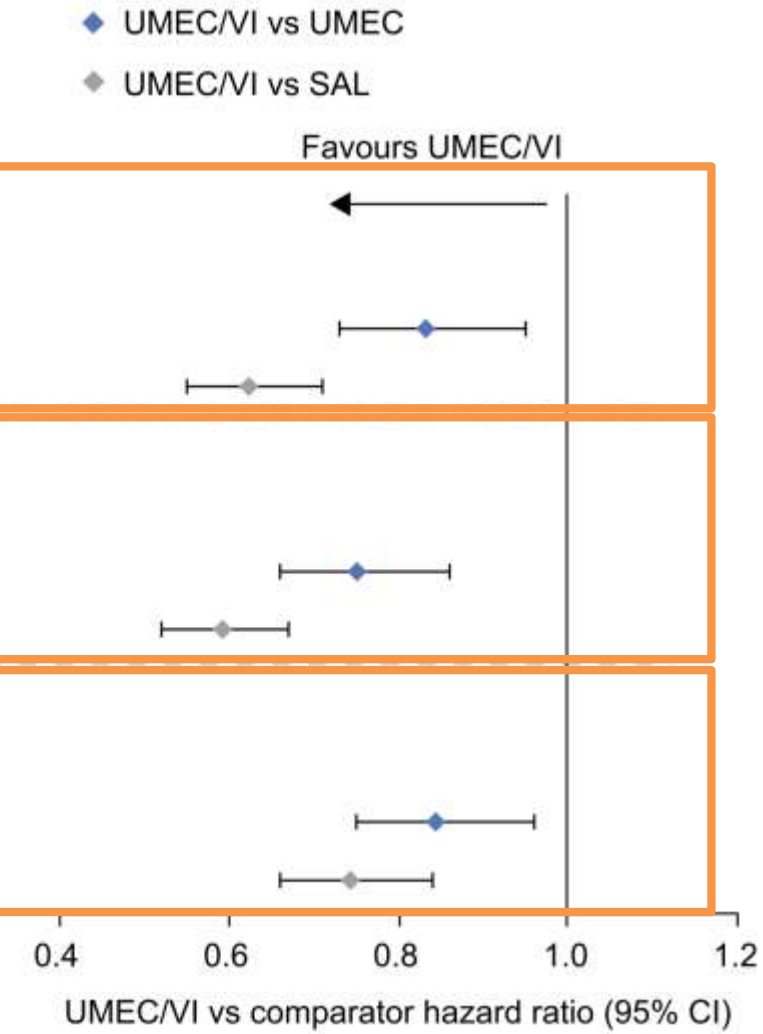
	UMEC/VI 62.5/25 mcg N=454	TIO 18 mcg N=451
Subjects with on-treatment exacerbation, n (%)	16 (4)	29 (6)
of these, subjects receiving ICS, n (%)	12 (75)	20 (69)
Time to first on-treatment COPD exacerbation, days		0.5 (0.3, 1.0)
HR (95% CI)		0.044
UMEC/VI 62.5/25 versus TIO		
p-value		

CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; ICS, inhaled corticosteroid; TIO, tiotropium; UMEC, umeclidinium bromide; VI, vilanterol.

Maleki-Yazdi MR et al. Respir Med 2014;108:1752-60 [PMID 25458157]

LAMA/LABA (UMEC/VIL) vs. LAMA (UMEC) vs. LABA (VIL)
– EMAX (Risk of a First CID up to Day 168) –

Treatment	Incidence of CID n/N[a] (%)	% Probability of event (95% CI)	UMEC/VI vs comparator HR (95% CI)	P-value
Composite CID definitions				
A) Exacerbation[b], FEV_1, SGRQ				
UMEC/VI	430/780 (55)	52.8 (49.3, 56.5)	–	–
UMEC	439/741 (59)	60.2 (56.5, 63.9)	0.83 (0.73, 0.95)	0.006
SAL	545/758 (72)	69.5 (66.1, 72.8)	0.62 (0.55, 0.71)	< 0.001
B) Exacerbation[b], FEV_1, CAT				
UMEC/VI	402/781 (51)	49.3 (45.8, 53.0)	–	–
UMEC	449/743 (60)	60.4 (56.7, 64.1)	0.75 (0.66, 0.86)	< 0.001
SAL	530/758 (70)	67.1 (63.7, 70.5)	0.59 (0.52, 0.67)	< 0.001
C) Exacerbation[b], CAT, SGRQ, TDI[c]				
UMEC/VI	500/791 (63)	61.3 (57.8, 64.8)	–	–
UMEC	524/761 (69)	69.8 (66.3, 73.2)	0.84 (0.75, 0.96)	0.007
SAL	578/775 (75)	73.4 (70.1, 76.5)	0.74 (0.66, 0.84)	< 0.001



Maltais F et al. Respir Res 2019;20:238 [PMID 31666084]

Symptoms and Exacerbations: Tiotropium/Olodaterol

고려대학교 KOREA UNIVERSITY

RESEARCH Open Access

Real-world effectiveness of early intervention with fixed-dose tiotropium/olodaterol vs tiotropium in Japanese patients with COPD: a high-dimensional propensity score–matched cohort analysis

Shigeo Muro[1*], Masaru Suzuki[2], Shuhei Nakamura[3], Jocelyn Ruoyi Wang[4], Elizabeth M. Garry[4], Wataru Sakamoto[3] and Sabrina de Souza[5]

- **Japanese hospital-based database (Medical Data Vision Co.,Ltd., Tokyo), April 2015~March 2019 [Extended March 2020]**
- **Retrospective, new-user, active-comparator cohort study using high-dimensional propensity sores (hdPS).**
- **Tio/Olo vs. Tio**
- **Outcome**
  - **Primary**
    - Time-to-escalation to triple therapy
  - **Secondary**
    - Time-to-first moderate or severe exacerbation
    - Time-to-all-cause inpatient mortality, MACE, use home oxygen therapy

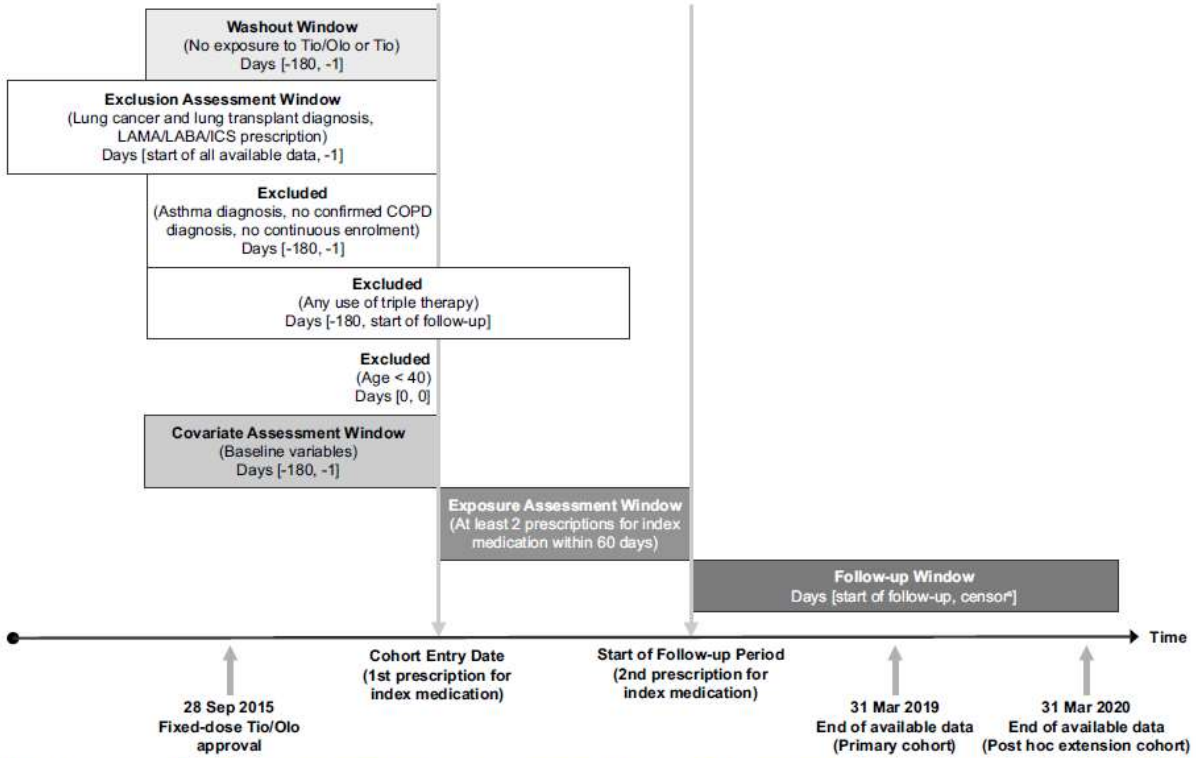


Fig. 1 Study design. *The follow-up ends at the earliest occurrence of the outcome, or at inpatient death, disenrollment, a maximum of 360 days, or the end of the study period. *COPD* chronic obstructive pulmonary disorder, *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *Tio* tiotropium, *Tio/Olo* tiotropium/olodaterol

Muro S, et al. Respir Res 2021;22:180.

Symptoms and Exacerbations: Tiotropium/Olodaterol

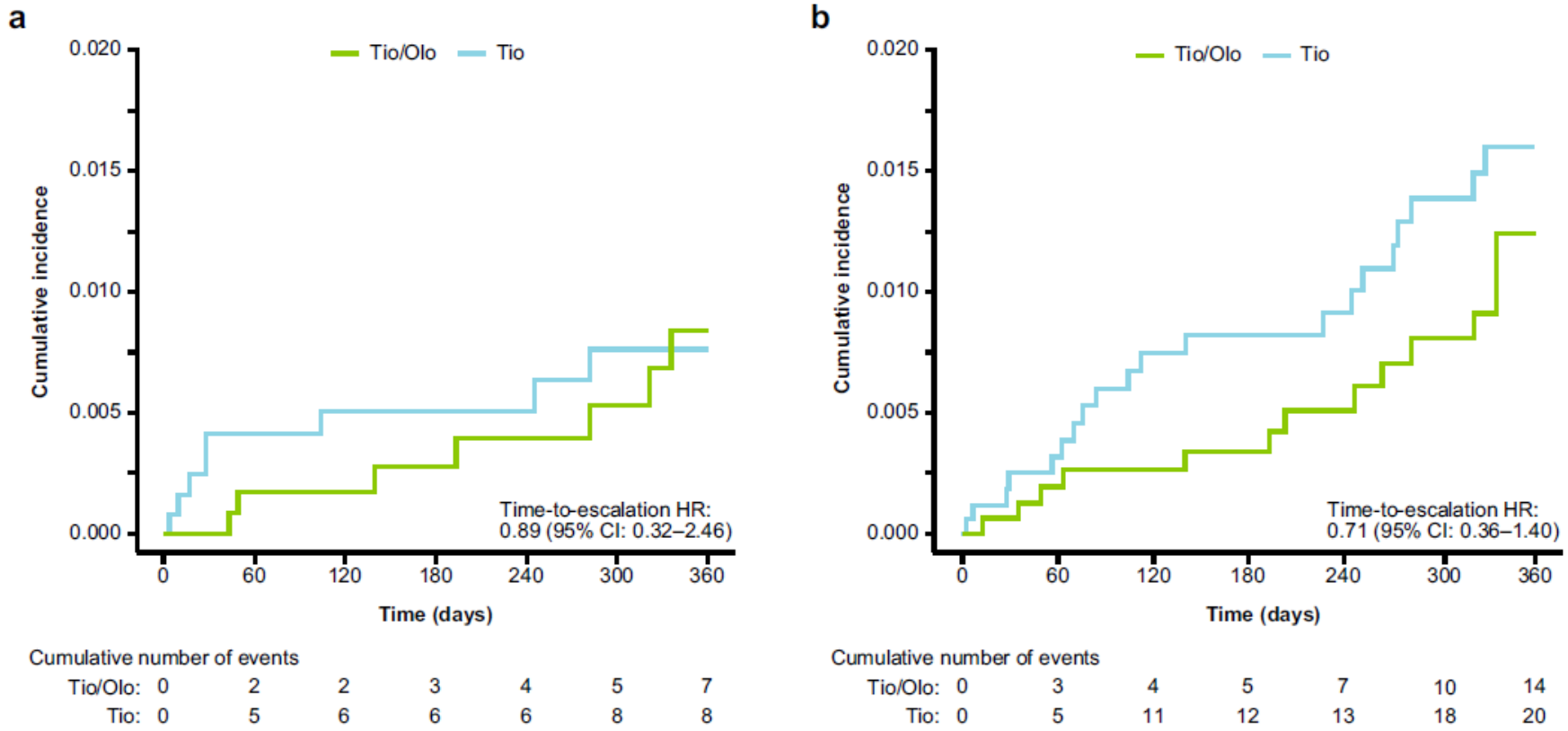


Fig. 3 Kaplan–Meier curves of escalation to triple therapy (fixed-dose or concurrent LAMA/LABA/ICS) for the hdPS-matched cohort. Data are shown for the prespecified study period (1 April 2015 to 31 March 2019) (**a**) and the post hoc extension period (1 April 2015 to 31 March 2020) (**b**). *CI* confidence interval, *hdPS* high-dimensional propensity score, *HR* hazard ratio, *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *Tio* tiotropium, *Tio/Olo* tiotropium/olodaterol

Muro S, et al. Respir Res 2021;22:180.

Symptoms and Exacerbations: Tiotropium/Olodaterol

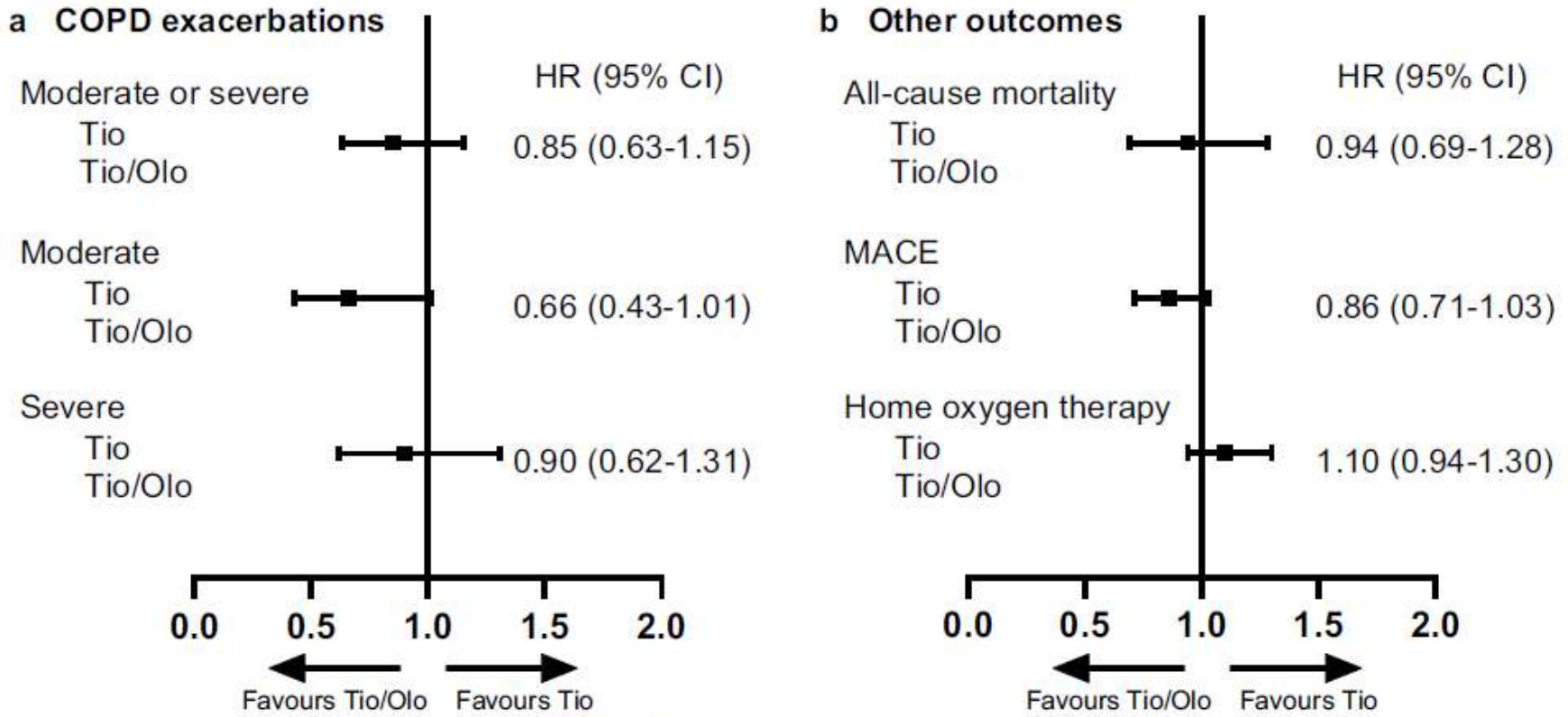


Fig. 4 Risk of a first COPD exacerbation (**a**) and other secondary outcomes (**b**). Data are shown for the hdPS-matched cohort (primary analysis) during the prespecified study period (1 April 2015 to 31 March 2019). Risk was assessed on the time-to-event outcome. *CI* confidence interval, *COPD* chronic obstructive pulmonary disorder, *hdPS* high-dimensional propensity score, *HR* hazard ratio, *MACE* major adverse cardiovascular event, *Tio* tiotropium, *Tio/Olo* tiotropium/olodaterol

Muro S, et al. Respir Res 2021;22:180.

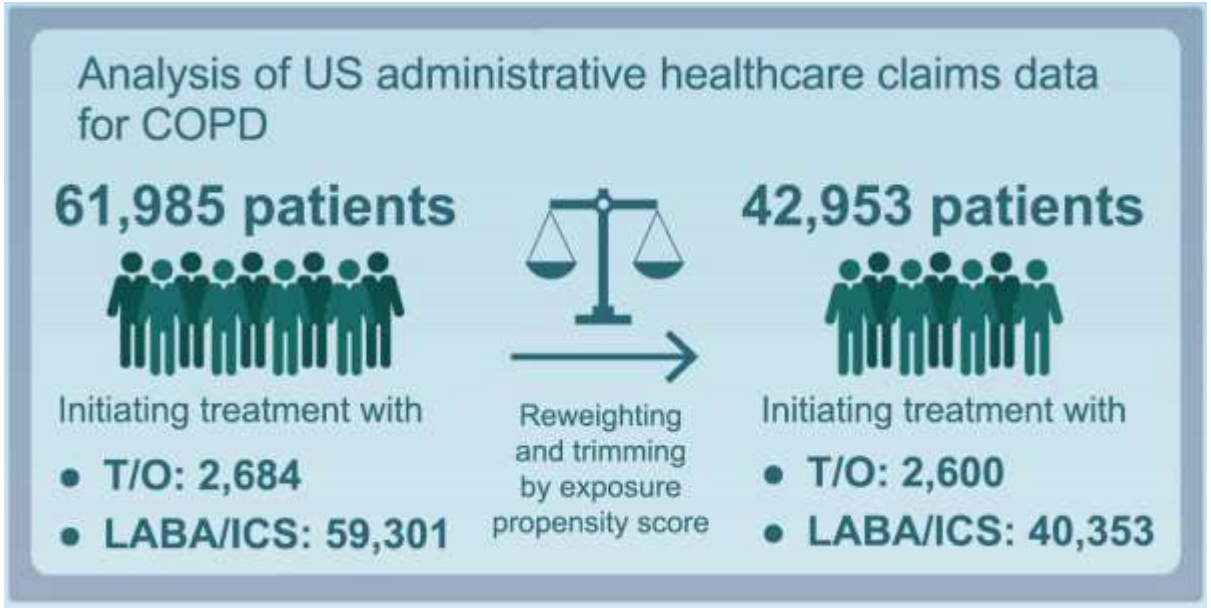
Symptoms and Exacerbations: Tiotropium/Olodaterol

ORIGINAL RESEARCH

Effectiveness and Safety of COPD Maintenance Therapy with Tiotropium/Olodaterol versus LABA/ICS in a US Claims Database

Jennifer K. Quint · Jukka Montonen · Daina B. Esposito · Xintong He · Leslie Koerner · Laura Wallace · Alberto de la Hoz · Marc Miravitlles

- **Non-interventional database study**
- **US administrative healthcare claim date (US HealthCore Integrated Research Database^{SM}), January 2013~March 2019**
- **Tio/Olo vs. ICS/LABA**
- **Outcome**
  - **Primary**
    - Risk of first COPD exacerbation
  - **Secondary**
    - Risk of hospitalization for CAP
    - Risk of escalation to triple therapy
    - Combined risk of any one of the above



Quint JK, et al. Adv Ther 2021;38:2249-2270.

Symptoms and Exacerbations: Tiotropium/Olodaterol

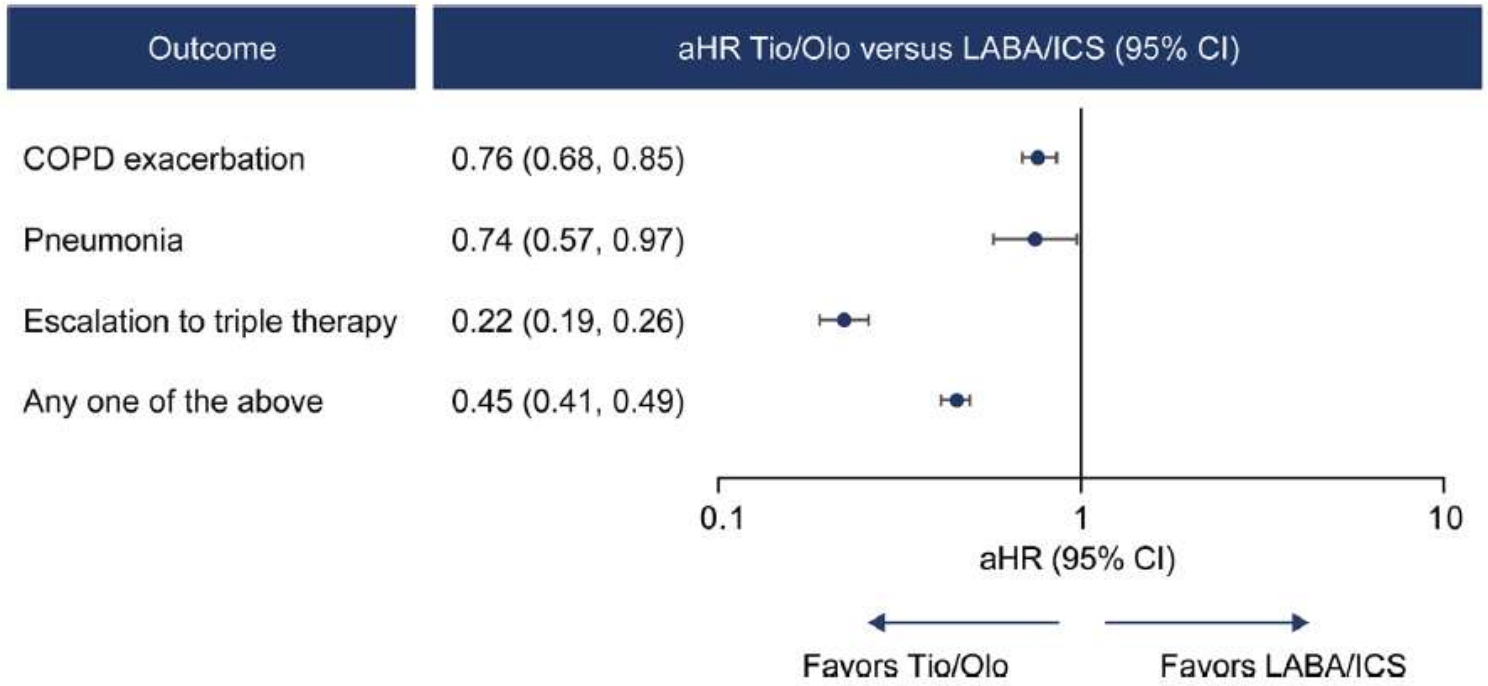


Fig. 2 Risk of exacerbation, pneumonia, escalation to triple therapy, or a combination of these events (exacerbation, or pneumonia, or escalation to triple therapy) in patients receiving tiotropium/olodaterol versus LABA/ICS. Hazard ratios were derived using Cox proportional hazard models. The Cox proportional hazard model was further adjusted for patient characteristics found to be imbalanced after application of the propensity score, where imbalance was defined as standardized differences greater than 10%. aHR adjusted hazard ratio, CI confidence interval, COPD chronic obstructive pulmonary disease, ICS inhaled corticosteroids, LABA long-acting β_2-agonist, Olo olodaterol, Tio tiotropium

Quint JK, et al. Adv Ther 2021;38:2249-2270.

Symptoms and Exacerbations: Tiotropium/Olodaterol

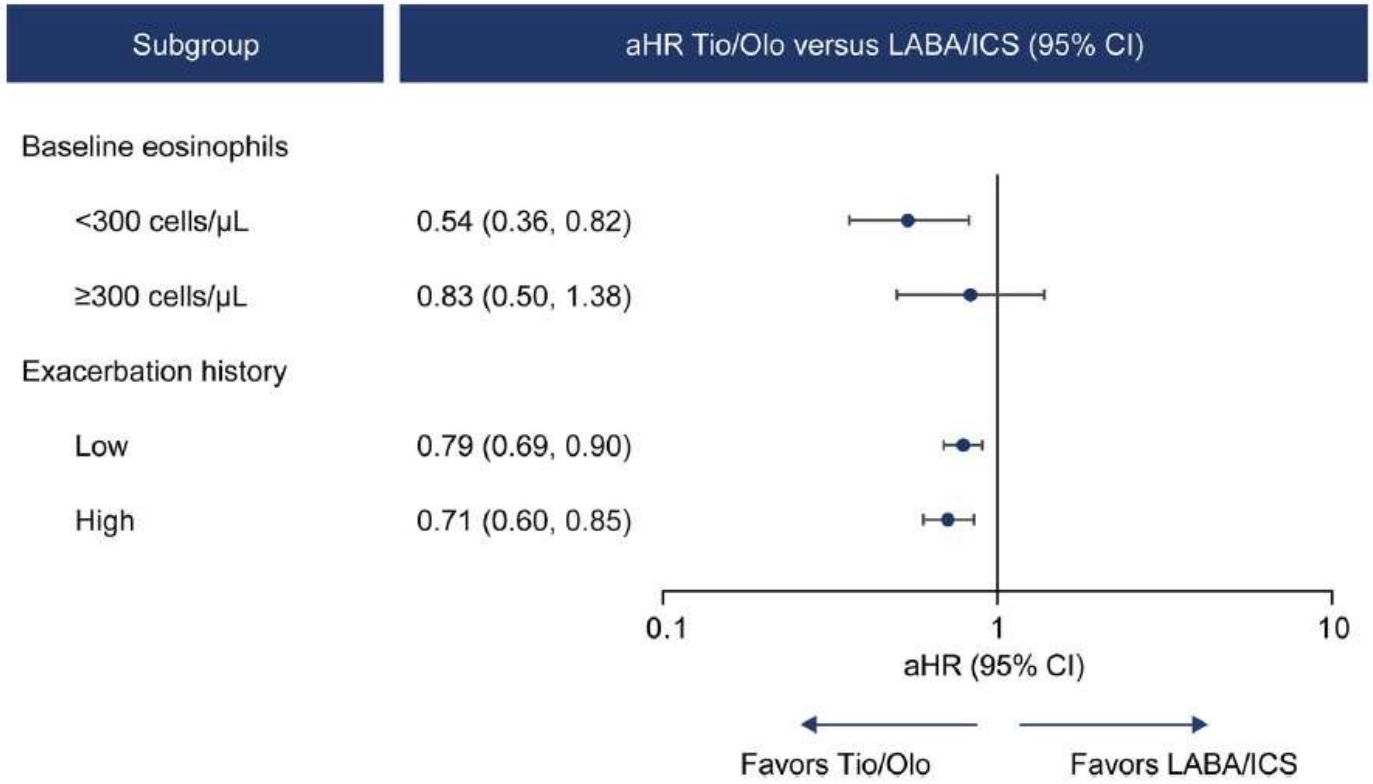


Fig. 3 Subgroup analyses for the risk of exacerbations in patients receiving tiotropium/olodaterol versus LABA/ICS. Hazard ratios were derived using Cox proportional hazard models. The Cox proportional hazard model was further adjusted for patient characteristics found to be imbalanced after application of the propensity score, where imbalance was defined as standardized differences greater than 10%. aHR adjusted hazard ratio, CI confidence interval, ICS inhaled corticosteroids, LABA long-acting β_2-agonist, Olo olodaterol, Tio tiotropium

Quint JK, et al. Adv Ther 2021;38:2249-2270.

Exacerbation and Medical Cost : Umeclidinium/Vilanterol

고려대학교 KOREA UNIVERSITY

Open Access Full Text Article ORIGINAL RESEARCH

Umeclidinium/Vilanterol Compared with Fluticasone Propionate/Salmeterol, Budesonide/Formoterol, and Tiotropium as Initial Maintenance Therapy in Patients with COPD Who Have High Costs and Comorbidities

- **Retrospective, matched cohort study using propensity score matching**
- **Optum's de-identified Clinformatics Data Mart database, January 2013~December 2019**
- **UMEC/VI vs. FP/SAL, B/F, TIO**
- **Eligibility Criteria**
  1) age ≥40 years at index
  2) ≥1 pre-index COPD diagnosis, no pre-index asthma diagnosis
  3) 2 months of continuous insurance coverage pre-index
  4) high pre-index costs (≥80th percentile of IMT population) and comorbidities (Quan- Charlson comorbidity index ≥3).

- **Outcome**
  - **Primary**
    - On-treatment COPD-related medical costs (per patient per year)
  - **Secondary**
    - Time-to-first and rates per 100 person-days of moderate, severe, and overall COPD related exacerbation during on-treatment period.

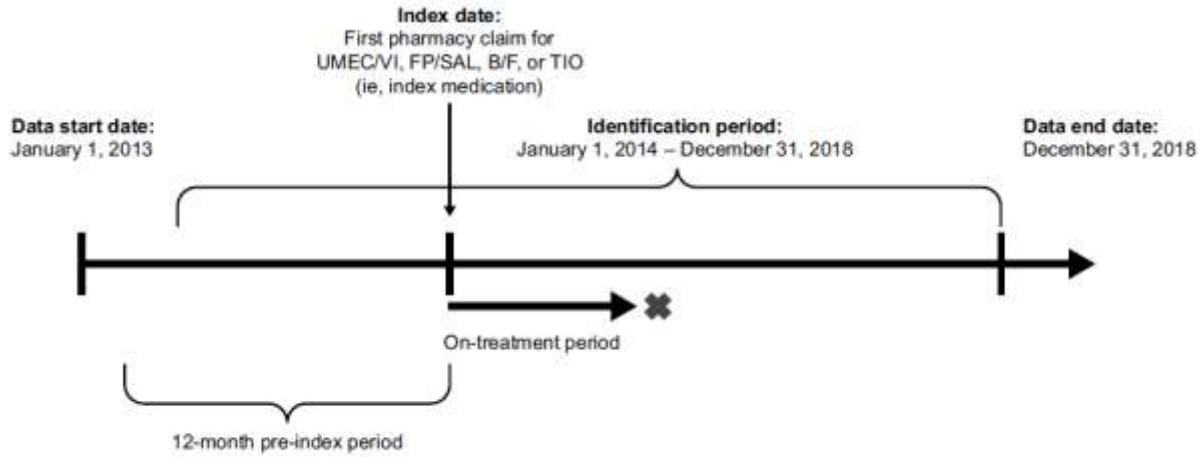


Figure 1 Study design.
Abbreviations: B/F, budesonide/formoterol; FP/SAL, fluticasone propionate/salmeterol; TIO, tiotropium; UMEC/VI, umeclidinium/vilanterol.

Kalhan R, et al. Int J Chron Obstruct Pulmon Dis 2021;16:1149-1161.

Exacerbation and Medical Cost : Umeclidinium/Vilanterol

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Table 2 On-Treatment Medical Costs PPPY for UMEC/VI versus FP/SAL, B/F, and TIO Matched Cohorts

	Medical Costs, $[b] PPPY, Mean (SD)		Cost Difference (95% CI)	*P*-value
	UMEC/VI (N=1194)	**FP/SAL (N=1194)**	–	–
Total COPD-related[a] medical costs	28,823 (65,220)	35,411 (92,590)	−6587 (−13,661, −21)	0.048
Hospitalizations	14,961 (47,032)	18,793 (54,422)	−3832 (−8183, 613)	0.072
ER visits	3719 (30,675)	6580 (62,666)	−2862 (−6775, 387)	0.100
Outpatient visits	9360 (28,210)	9254 (35,078)	106 (−3181, 2759)	0.942
Other visits	784 (2849)	784 (2916)	0 (−342, 314)	0.998
Total all-cause medical costs	79,603 (127 705)	94,312 (166 284)	−14,709 (−29,239, 724)	0.060
	UMEC/VI (N=1441)	**B/F (N=1441)**	–	–
Total COPD-related[a] medical costs	30,104 (66,821)	34,737 (80,979)	−4633 (−11,354, 1554)	0.156
Hospitalizations	15,745 (47,196)	18,631 (55,724)	−2887 (−7361, 1685)	0.188
ER visits	3466 (28,689)	4077 (29,383)	−610 (−2106, 1130)	0.401
Outpatient visits	10,141 (31,466)	10,242 (38,813)	−102 (−4191, 3122)	0.906
Other visits	752 (2769)	1787 (28,994)	−1035 (−3148, 167)	0.216
Total all-cause medical costs	87,463 (144 600)	102 158 (186 293)	−14,695 (34,688, 3098)	0.128
	UMEC/VI (N=1277)	**TIO (N=1277)**	–	–
Total COPD-related[a] medical costs	30,022 (66,372)	35,581 (73,944)	−5559 (−11,541, 670)	0.080
Hospitalizations	15,750 (48,130)	20,890 (59,541)	−5140 (−9838, 35)	0.052
ER visits	3619 (29,892)	4411 (17,246)	−793 (−2314, 857)	0.301
Outpatient visits	9866 (28,961)	9598 (33,649)	268 (−2351, 2663)	0.878
Other visits	787 (2879)	681 (3043)	106 (−201, 407)	0.481
All-cause total	85,819 (138,079)	91,161 (156,275)	−5342 (−20,926, 8996)	0.501

Notes: [a]COPD-related costs were defined as claims with a primary or secondary diagnosis of COPD. [b]Medical costs are inflated to US dollars 2019 using the US Medical Care consumer price index from the Bureau of Labor Statistics from the US Department of Labor.

Abbreviations: B/F, budesonide/formoterol; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ER, emergency room; FP/SAL, fluticasone propionate/salmeterol; PPPY, per patient per year; SD, standard deviation; TIO, tiotropium; UMEC/VI, umeclidinium/vilanterol.

Kalhan R, et al. Int J Chron Obstruct Pulmon Dis 2021;16:1149-1161.

Exacerbation and Medical Cost : Umeclidinium/Vilanterol

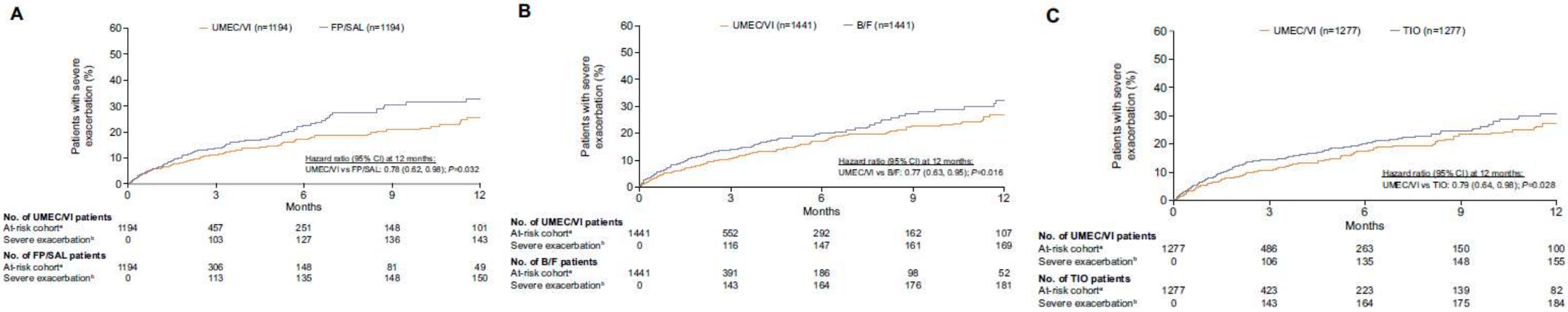

Figure 3 Kaplan–Meier curves for time-to-first severe exacerbation during the on-treatment period for (A) UMEC/VI versus FP/SAL, (B) UMEC/VI versus B/F, and (C) UMEC/VI versus TIO matched cohorts. [a]Number of patients still observed at the specific point in time. [b]Severe COPD-related exacerbation defined as an inpatient hospitalization with a diagnosis code for COPD in the primary position.

Abbreviations: B/F, budesonide/formoterol; CI, confidence interval; FP/SAL, fluticasone propionate/salmeterol; TIO, tiotropium; UMEC/VI, umeclidinium/vilanterol.

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Table 3 Rate of on-Treatment COPD-Related Severe Exacerbations for UMEC/VI versus FP/SAL, B/F, and TIO and Matched Cohorts

	Number of Events		Rate (per 100 Person Days)		Rate Ratio (95% CI)	*P*-value
	UMEC/VI (N=1194)	**FP/SAL (N=1194)**	**UMEC/VI (N=1194)**	**FP/SAL (N=1194)**	–	–
On-treatment period, mean (SD)	144.9 (185.3)	107.5 (153.0)	–	–	–	–
Total person-days	173,045	128,367	–	–	–	–
Severe exacerbations	170	172	0.10	0.13	0.73 (0.59, 0.91)	0.008
	UMEC/VI (N=1441)	**B/F (N=1441)**	**UMEC/VI (N=1441)**	**B/F (N=1441)**	–	–
On-treatment period, mean (SD)	139.5 (176.9)	102.5 (139.9)	–	–	–	–
Total person-days	201,019	147,676	–	–	–	–
Severe exacerbations	203	203	0.10	0.14	0.73 (0.59, 0.93)	0.012
	UMEC/VI (N=1277)	**TIO (N=1277)**	**UMEC/VI (N=1277)**	**TIO (N=1277)**	–	–
On-treatment period, mean (SD)	143.2 (183.3)	130.3 (167.5)	–	–	–	–
Total person-days	182,822	166,413	–	–	–	–
Severe exacerbations	186	205	0.10	0.12	0.83 (0.68, 1.04)	0.080

Abbreviations: B/F, budesonide/formoterol; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FP/SAL, fluticasone propionate/salmeterol; TIO, tiotropium; UMEC/VI, umeclidinium/vilanterol.

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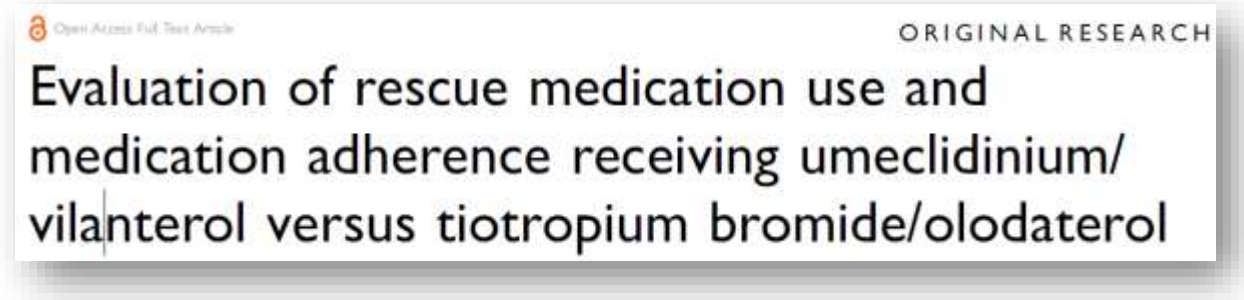
Rescue Med. Use : Umeclidinium/Vilanterol



- **Outcome**
  - **Primary**
    - Rescue medication use
  - **Secondary**
    - Medication adherence

- **Retrospective observational study**
- **Optum's de-identified Clinformatics Data Mart dat**
- **June 2015~November 2016**
- **UMEC/VI vs. Tio/Olo**

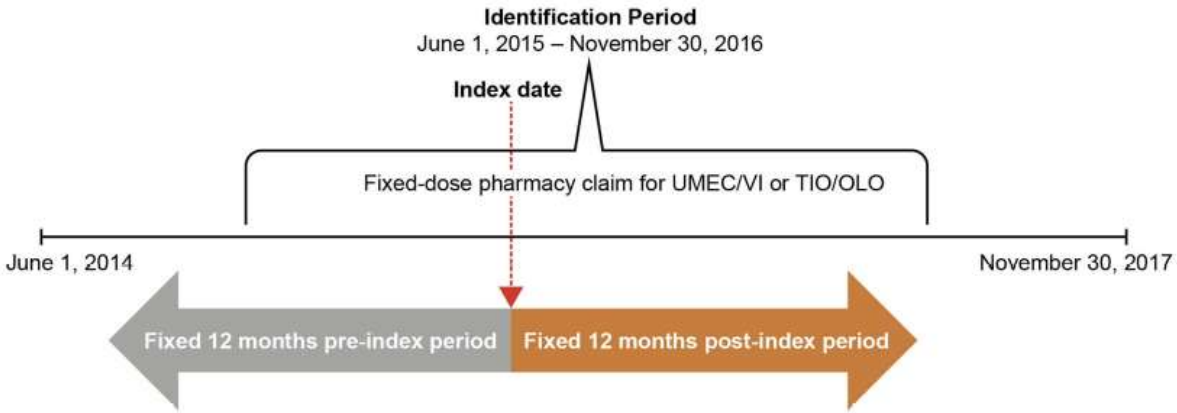


Figure 1 Study design.

Moretz, et al. Int J Chron Obstruct Pulmon Dis 2019;14:2047-2060.

Rescue Med. Use : Umeclidinium/Vilanterol

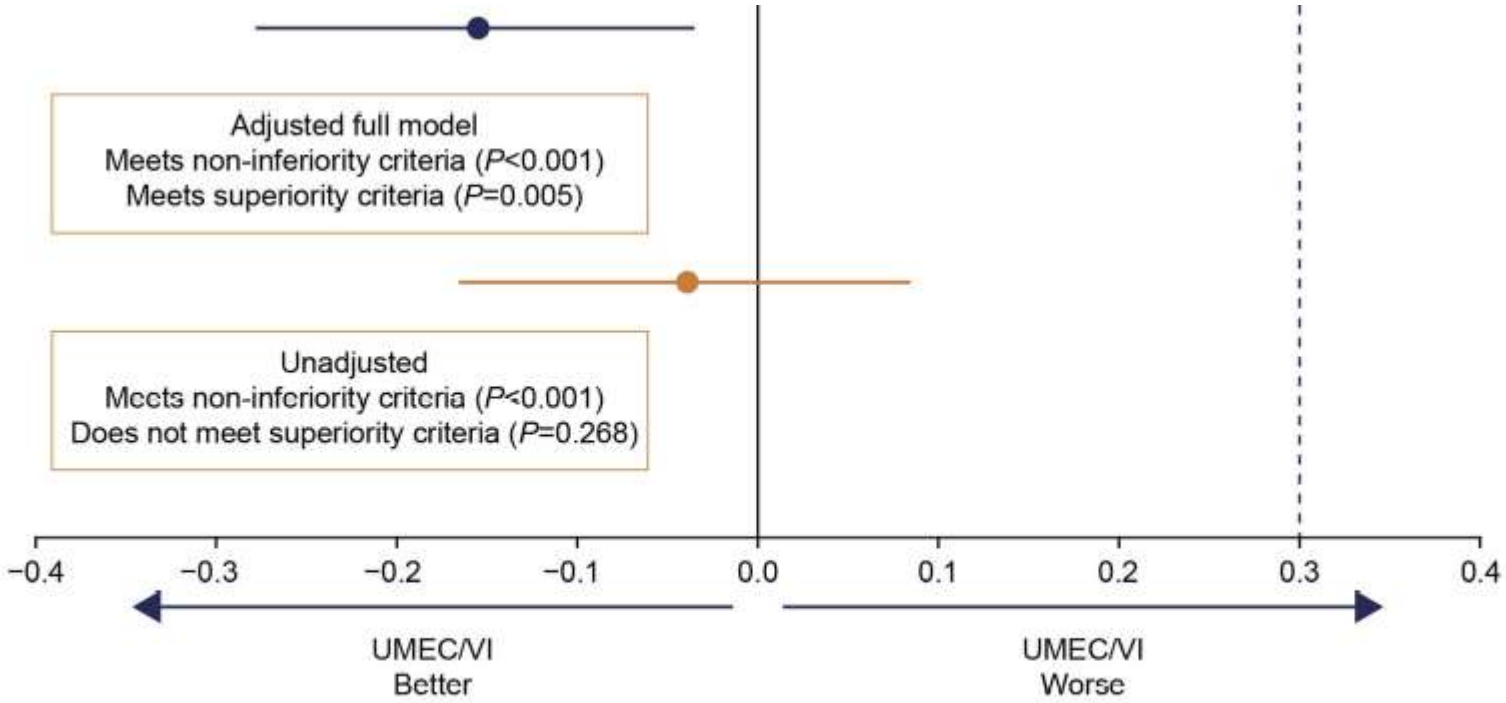


Figure 3 ITT analysis of difference in rescue medication use between the UMEC/VI and TIO/OLO cohorts. Covariates included in the adjusted model are shown in Table S2.

Moretz, et al. Int J Chron Obstruct Pulmon Dis 2019;14:2047-2060.

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