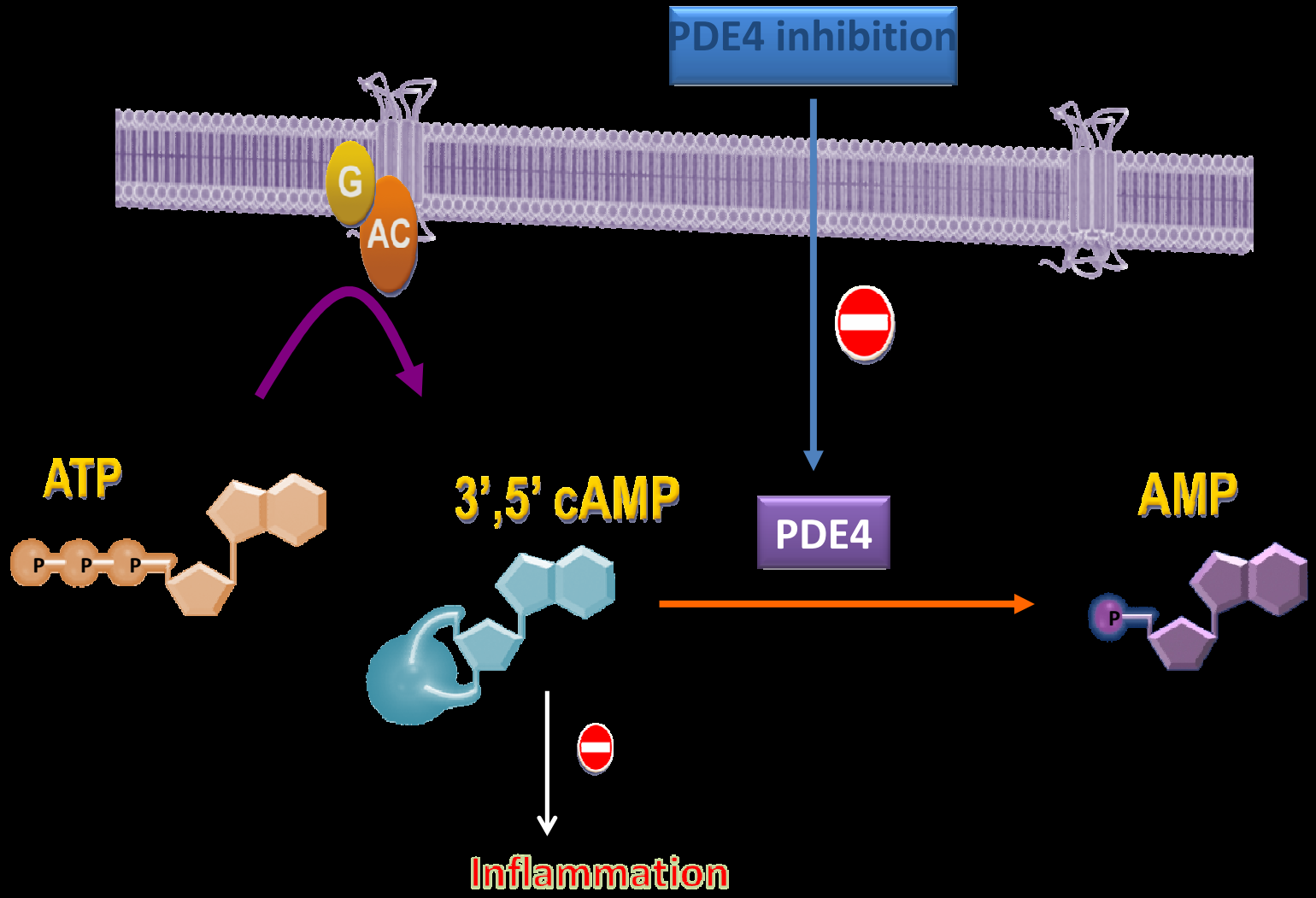
Roflumilast: Οι κλινικές μελέτες

Επαμεινώνδας Ν. Κοσμάς

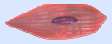
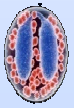
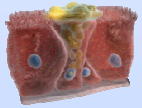
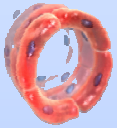
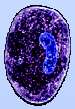
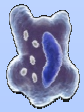
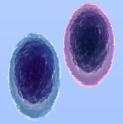
Δ/ντής Πνευμονολογικού Τμήματος Νοσοκομείου Metropolitan

PDE4 PLAYS AN IMPORTANT ROLE IN INFLAMMATION



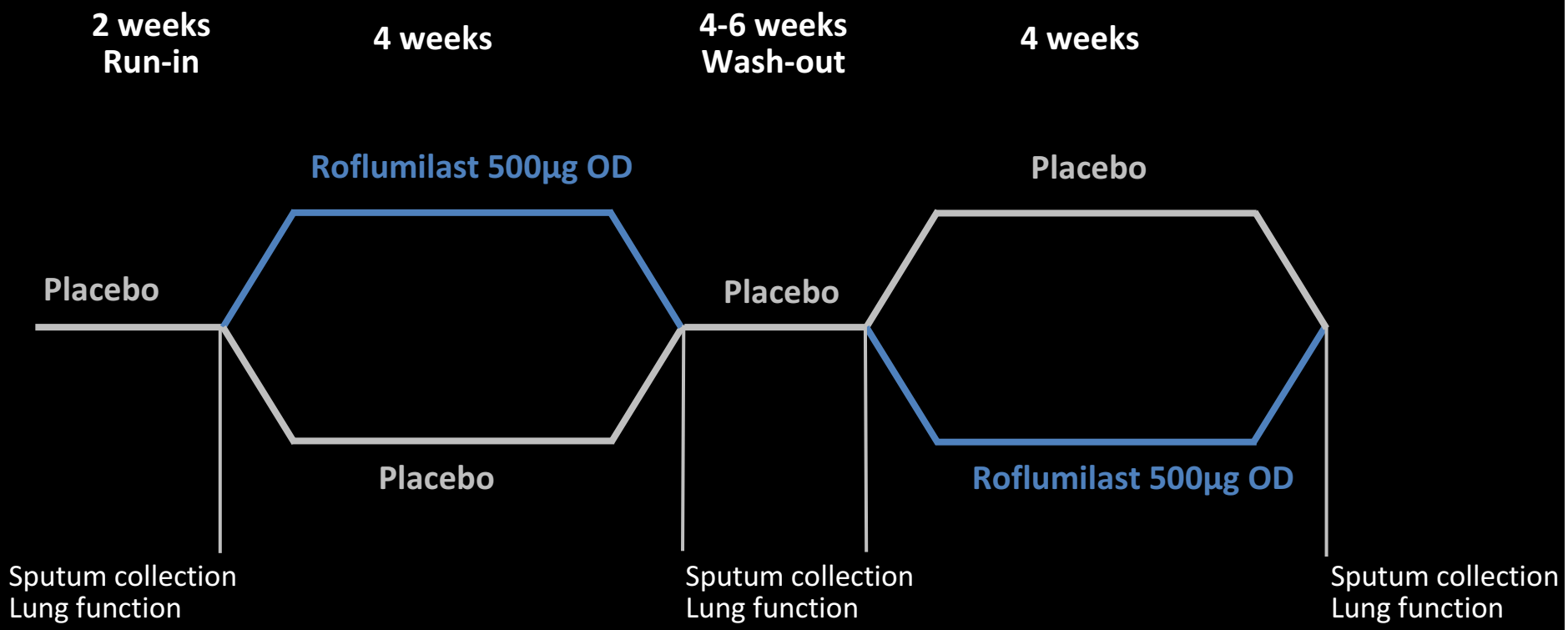
Adapted from Rabe KF. *Expert Rev Resp Med* 2010;4: 543–555.

THE PDE4 ENZYME IS EXPRESSED IN KEY INFLAMMATORY CELLS INVOLVED IN COPD

Leukocyte	PDE isoform	Structural Cells	PDE isoform
 Mast cells	4, 7	 Airway smooth muscle	1, 2, 3, 4, 5, 7
 Eosinophils	4, 7	 Epithelial cells	1, 2, 3, 4, 5, 7, 8
 Neutrophils	4, 7	 Endothelial cells	2, 3, 4, 5
 Monocytes	1, 3, 4, 7	 Sensory nerve	1, 3, 4
 Macrophages	1, 3, 4, 5, 7	 Cholinergic nerves	1, 3, 4
 T-cells ($CD4^+$ and $CD8^+$)	3, 4, 7		

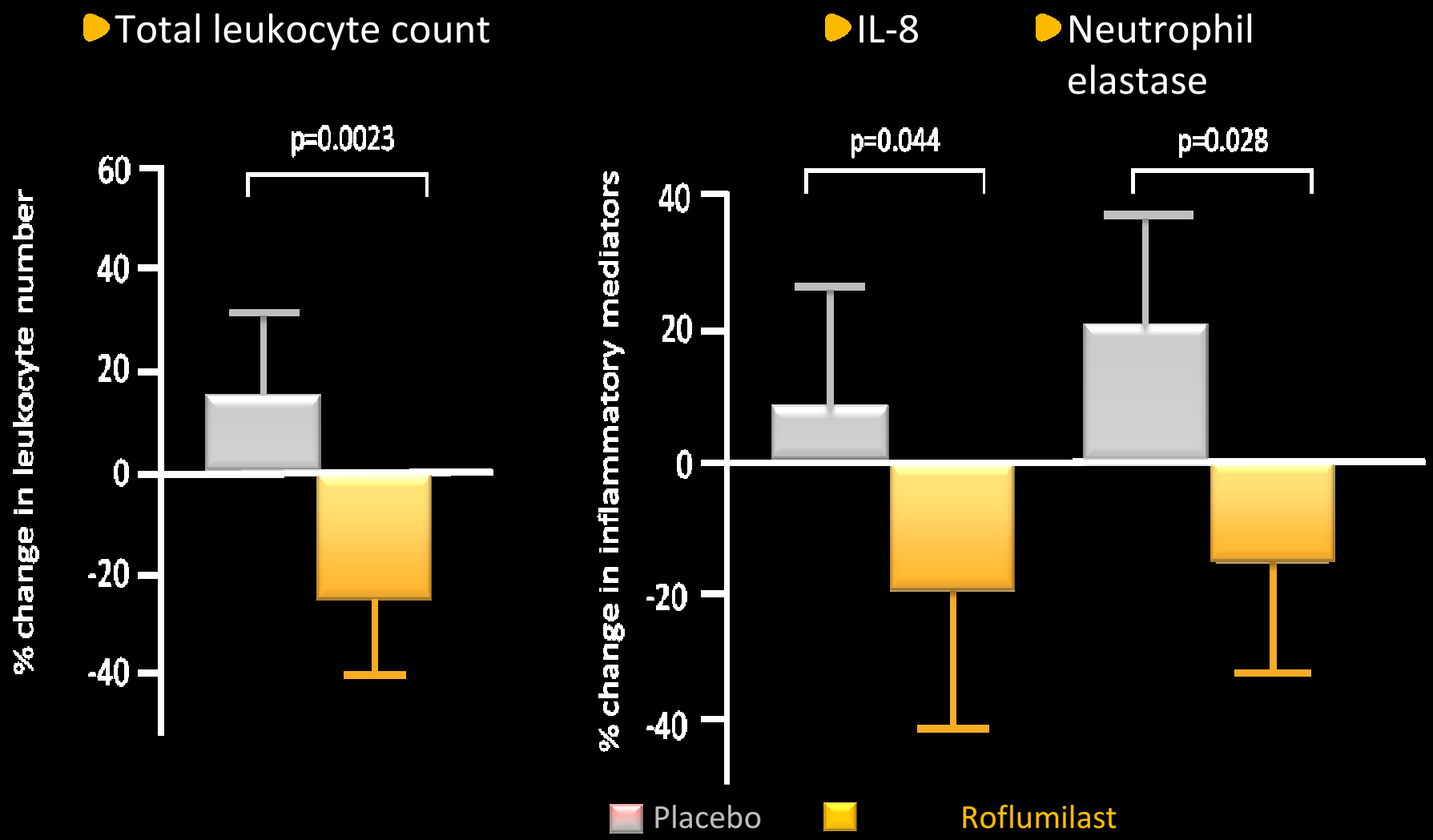
Adapted from: Giembycz MA. *Monaldi Arch Chest Dis* **2002**;57:48-64.

The ANTI-inflammatory Effects of ROFLUMILAST were evaluated in a 4-WEEK CROSSOVER STUDY



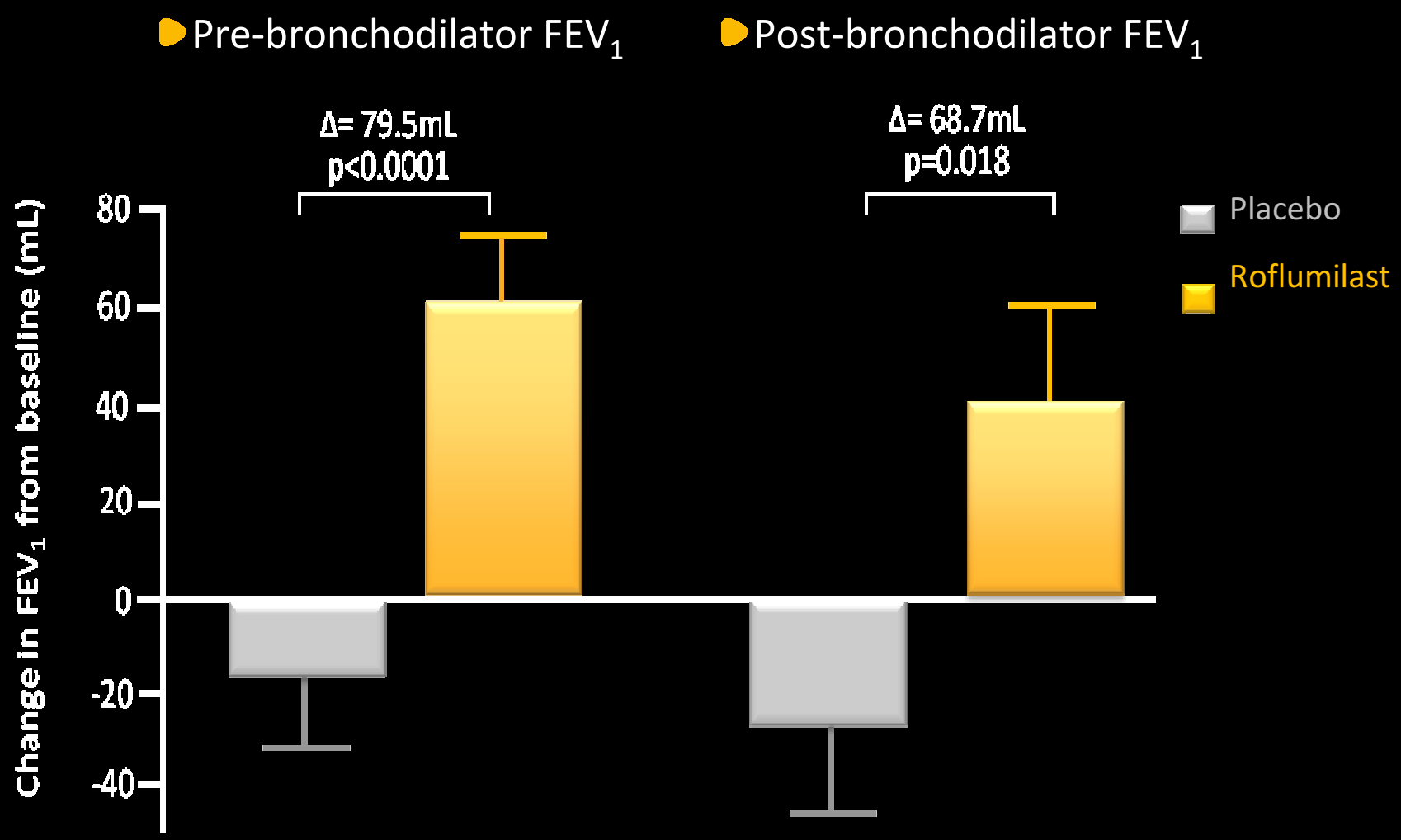
Grootendorst DC, Gauw SA, Verhoosel RM, et al. *Thorax* **2007**;62;1081-1087.

ROFLUMILAST REDUCED LEVELS OF INFLAMMATORY MARKERS IN SPUTUM SAMPLES



Grootendorst DC, Gauw SA, Verhoosel RM, et al. *Thorax* **2007**;62;1081-1087.

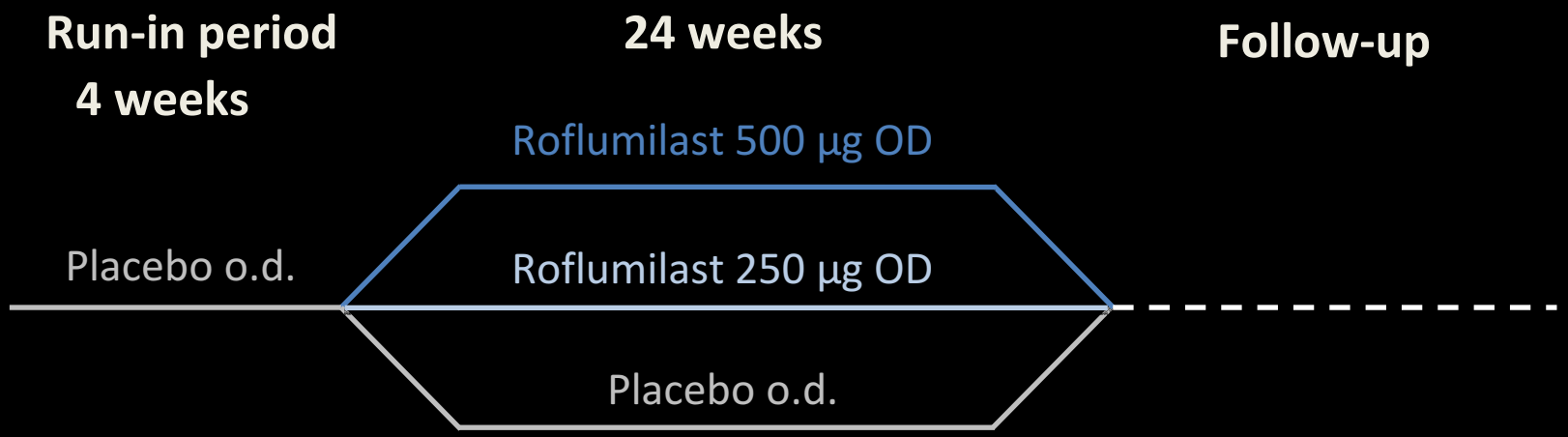
ROFLUMILAST improved PRE- and POST-BRONCHODILATOR FEV_1 levels



Grootendorst DC, Gauw SA, Verhoosel RM, et al. *Thorax* **2007**;62;1081-1087.

RECORD was a 6-MONTH DOSE-RANGING STUDY

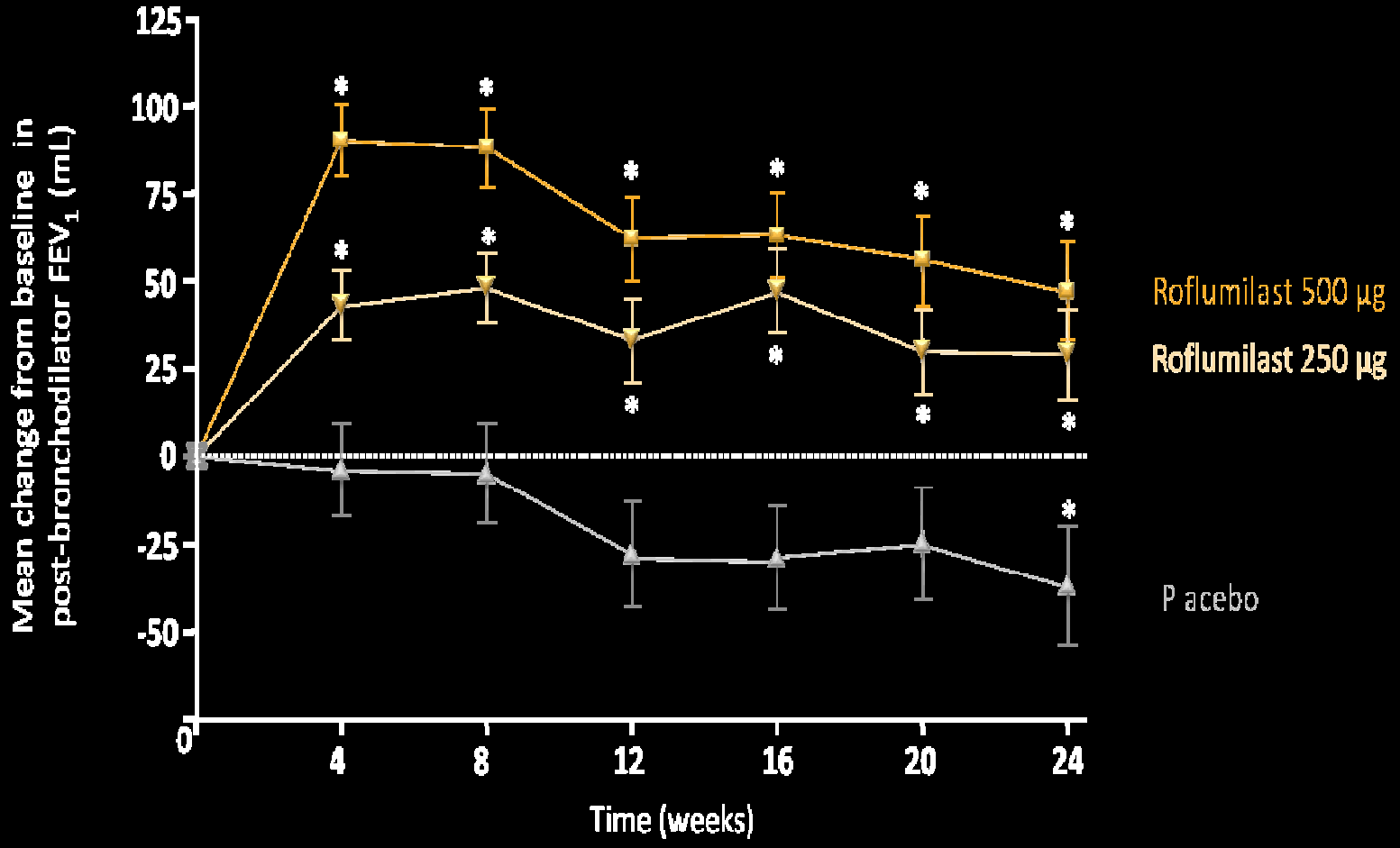
- Phase III, multicentre, double-blind, randomized, placebo-controlled
- 1,411 patients with COPD treated for 24 weeks



Rabe KF, Bateman ED, O'Donnell D, et al. *Lancet.* **2005**;366:563-571.

OD = Once daily

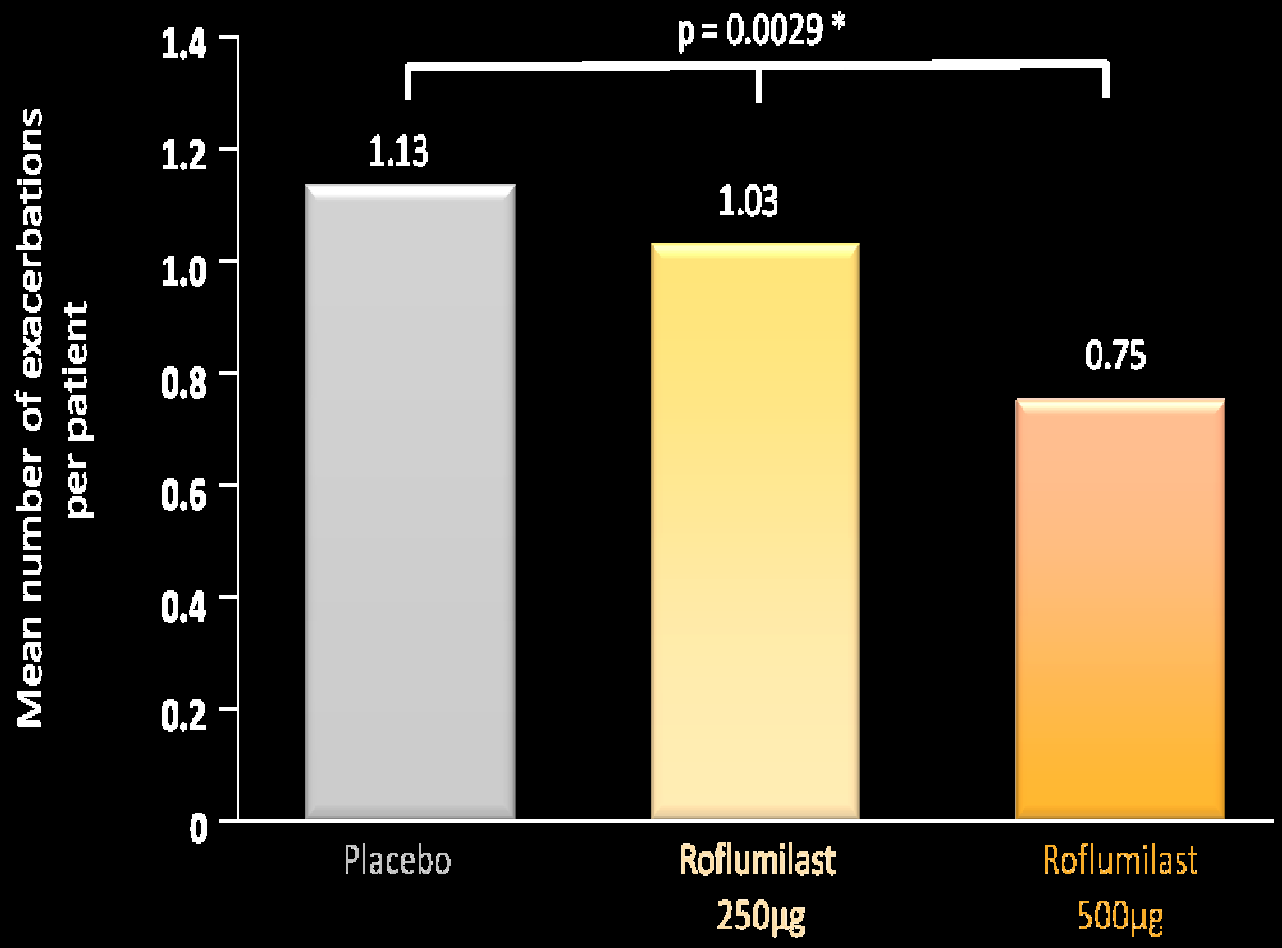
RECORD – Roflumilast improved lung function in patients with moderate to severe COPD



Rabe KF, Bateman ED, O'Donnell D, et al. *Lancet* **2005**;366:563-571.

* p<0.05 vs baseline

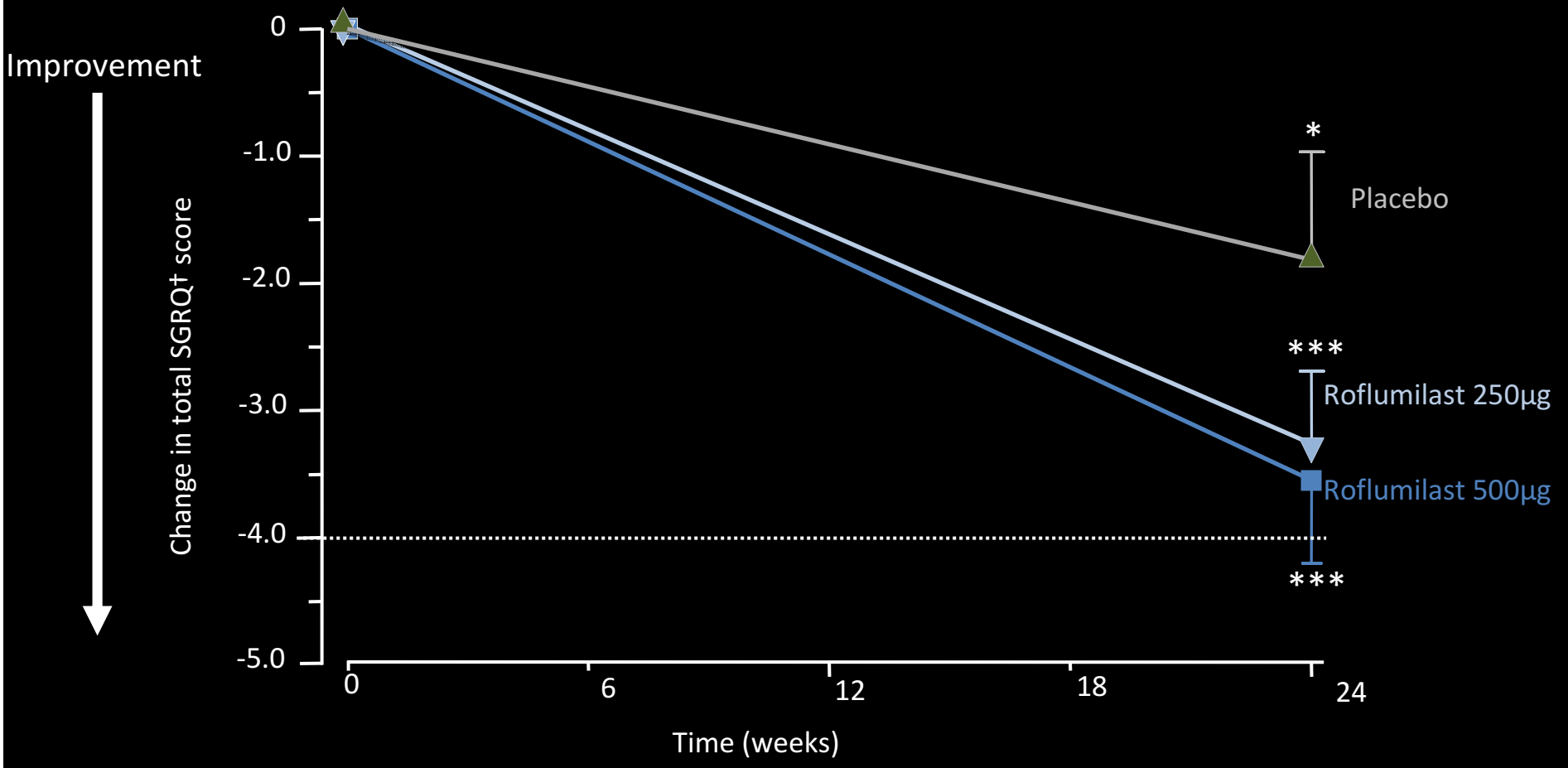
RECORD – ROFLUMILAST REDUCED EXACERBATIONS IN PATIENTS WITH MODERATE TO SEVERE COPD



Rabe KF, Bateman ED, O'Donnell D, et al. *Lancet* **2005**;366:563-571.

* p<0.05

RECORD – roflumilast improved total SGRQ score in COPD patients

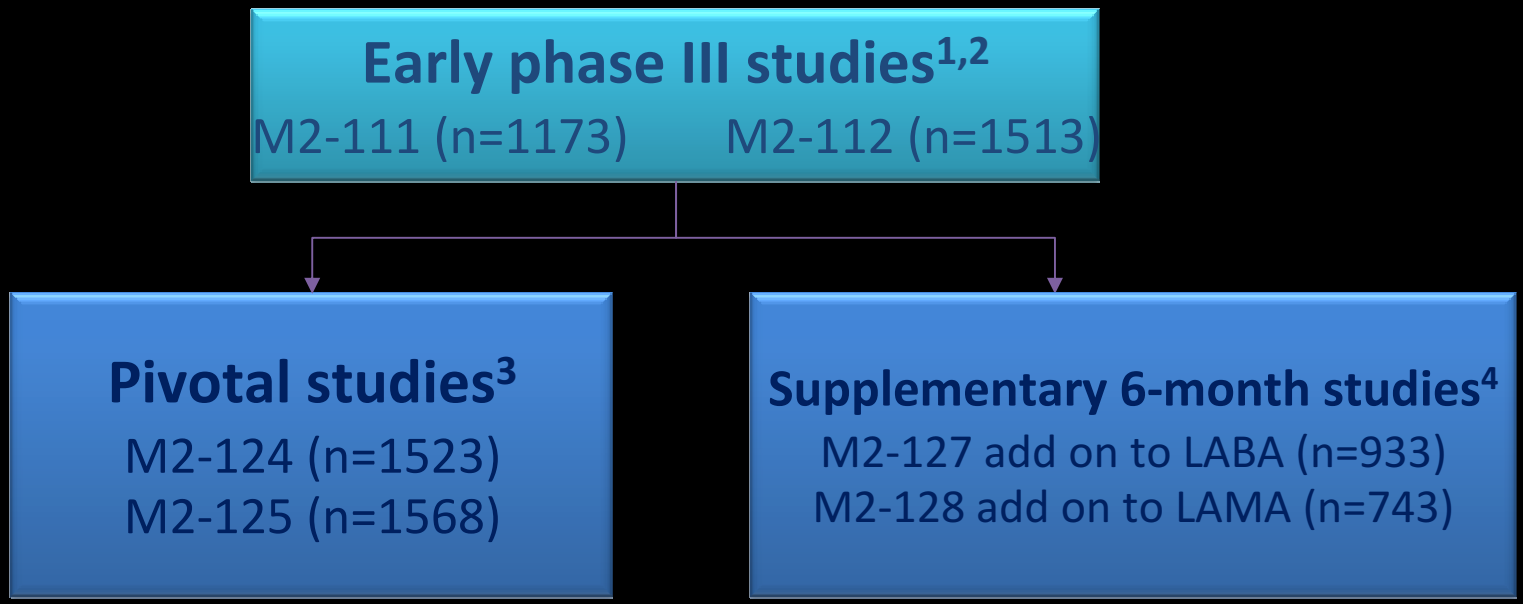


† SGRQ = St George's Respiratory Questionnaire

LS Mean and SEM
* p<0.05, *** p<0.0001 for change versus baseline

Rabe KF, Bateman ED, O'Donnell D, et al. *Lancet* **2005**;366:563-571.

The Roflumilast clinical study programme



1. Calverley PMA, et al. *Am J Respir Crit Care Med* **2007**;176:154-161.
2. Rennard SI, et al. *Respiratory Research* **2011**,12:18.
3. Calverley PMA, et al. *Lancet* **2009**;374:685–694.
4. Fabbri LM, et al. *Lancet* **2009**;374:695-703.

LABA = Long-acting β_2-agonist
LAMA = Long-acting muscarinic antagonist

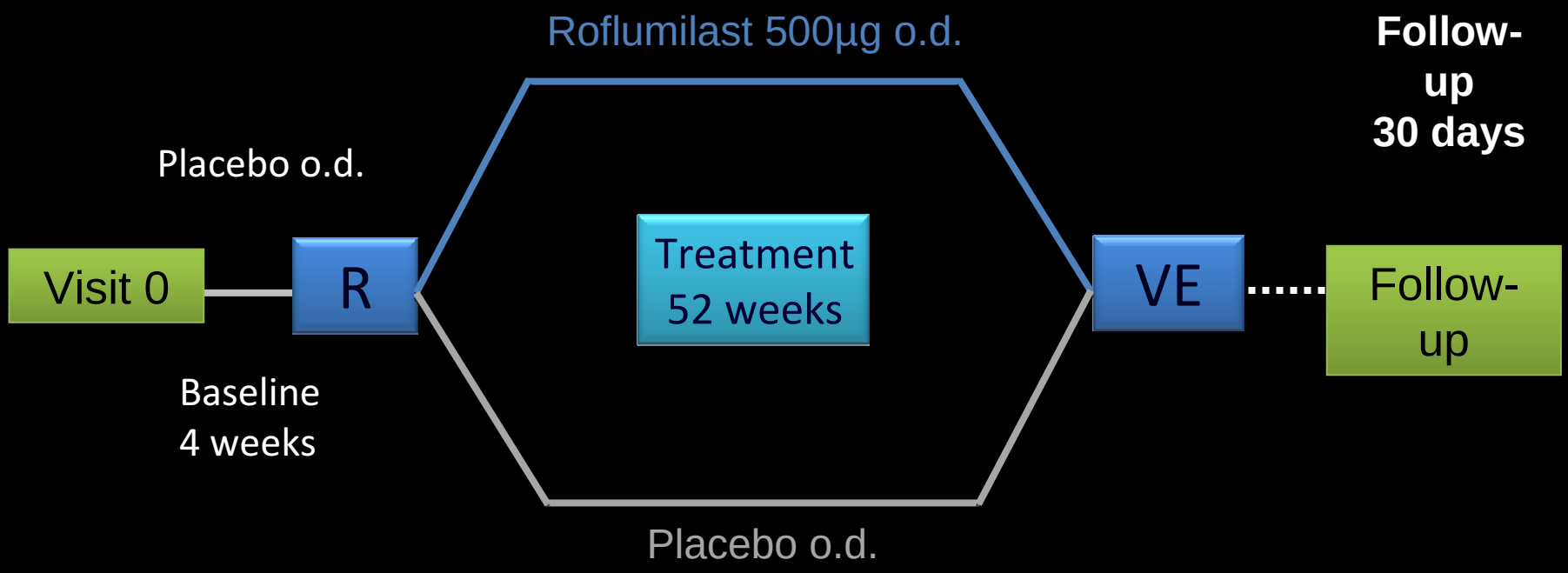
M2-111 & M2-112 Study design and patients

- Two 12-month randomized, double-blind, parallel-group studies
- Following a 4-week, single blind run-in period, patients were randomized to receive roflumilast 500µg or placebo once daily for 52 weeks
- Allowed concomitant medication: ICS and SAMA (if used at stable doses before study entry)
- Key inclusion criteria:
  - Patients ≥ 40 years, current or ex-smoker (≥ 10 pack years)
  - COPD as defined by ATS (M2-111) or GOLD (M2-112)
  - Clinically stable with unchanged COPD treatment within 4 weeks of baseline
  - Post-bronchodilator FEV_1 ≤ 50% predicted; post-bronchodilator FEV_1:FVC ratio ≤ 0.70
  - No history of exacerbations required

ICS = Inhaled corticosteroids
SAMA = Short-acting antimuscarinic antagonists
FEV_1 = Forced expiratory volume in 1 second
FVC = Forced vital capacity

Rennard SI, Calverley PMA, Goehring UM, et al. *Respiratory Research* **2011**; 12: 18.

Design of early phase III studies M2-111 & M2-112



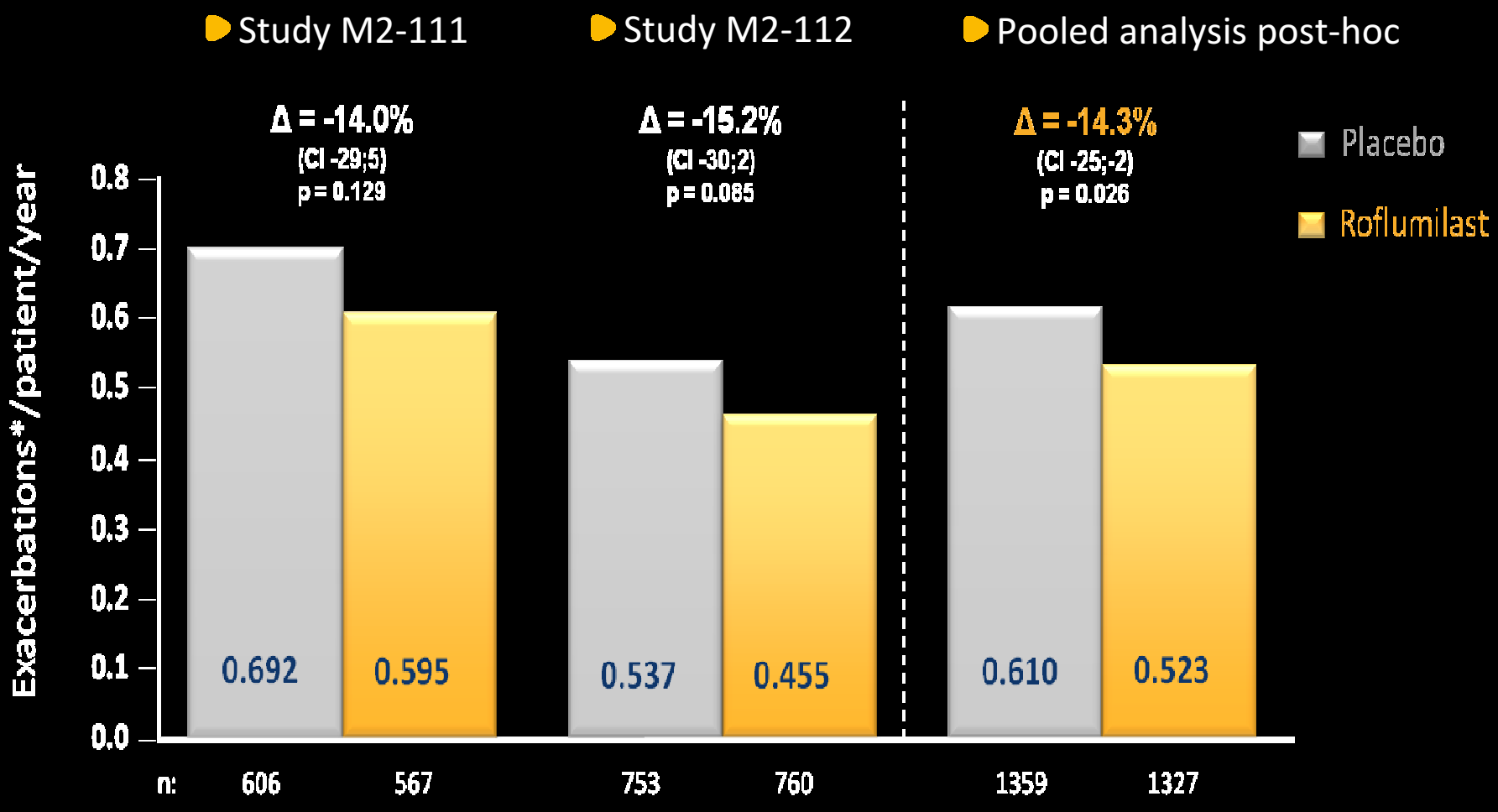
Allowed concomitant medication: ICSs (≤2000µg BDP or equivalent)
Approximately 60% of all patients were on ICS treatment

R = randomization
VE = Visit end
dipropionate
o.d. = once daily

ICS = Inhaled corticosteroids
BDP = Beclomethasone

Calverley PMA, Sanchez-Toril F, McIvor A, et al. *Am J Respir Crit Care Med* **2007**;176:154-161.

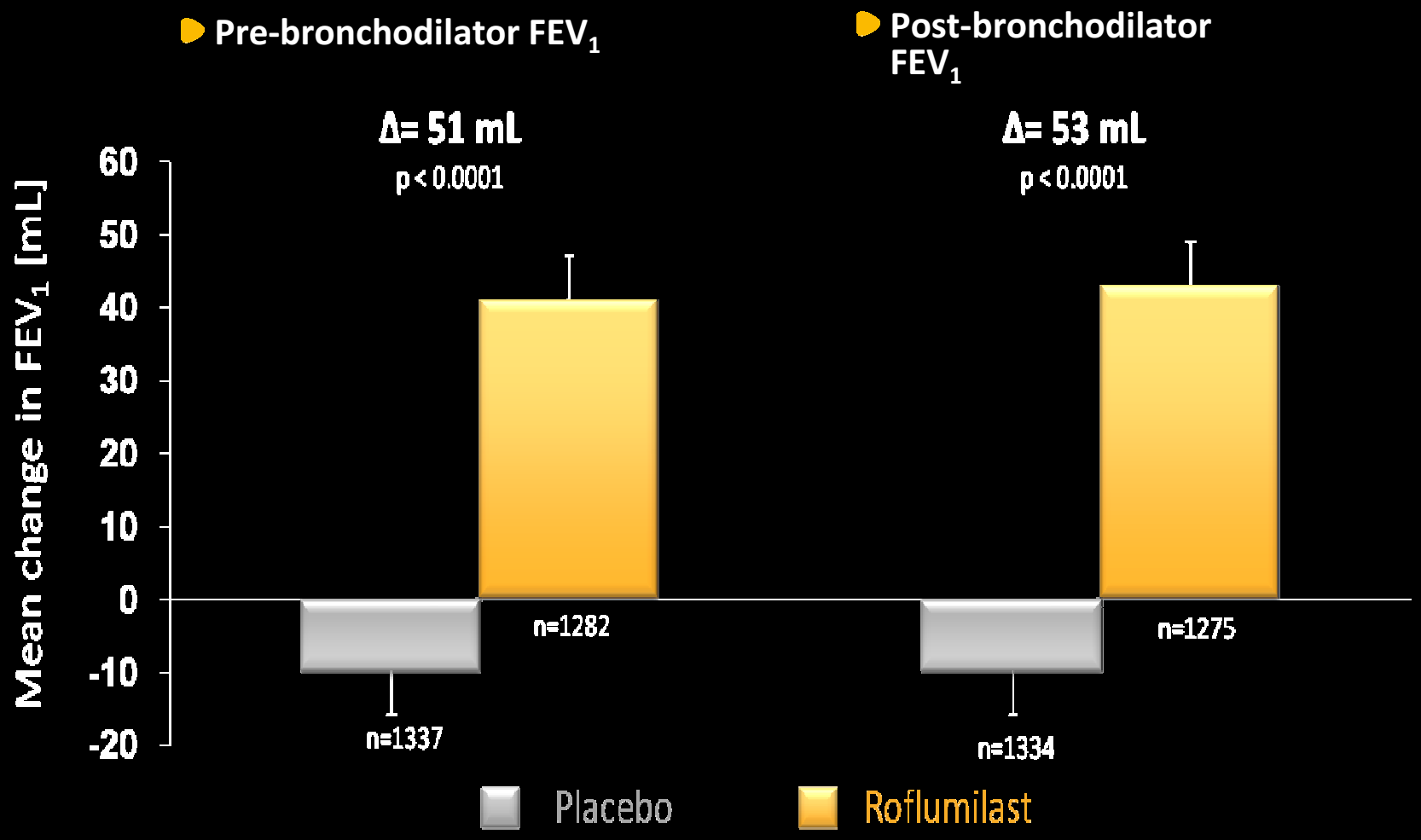
Pooled analysis revealed lower exacerbation rates with roflumilast



Rennard SI, Calverley PMA, Goehring UM, et al. *Respiratory Research* **2011**; 12: 18.

*Moderate or severe exacerbations treated with systemic steroids or leading to hospitalization or death

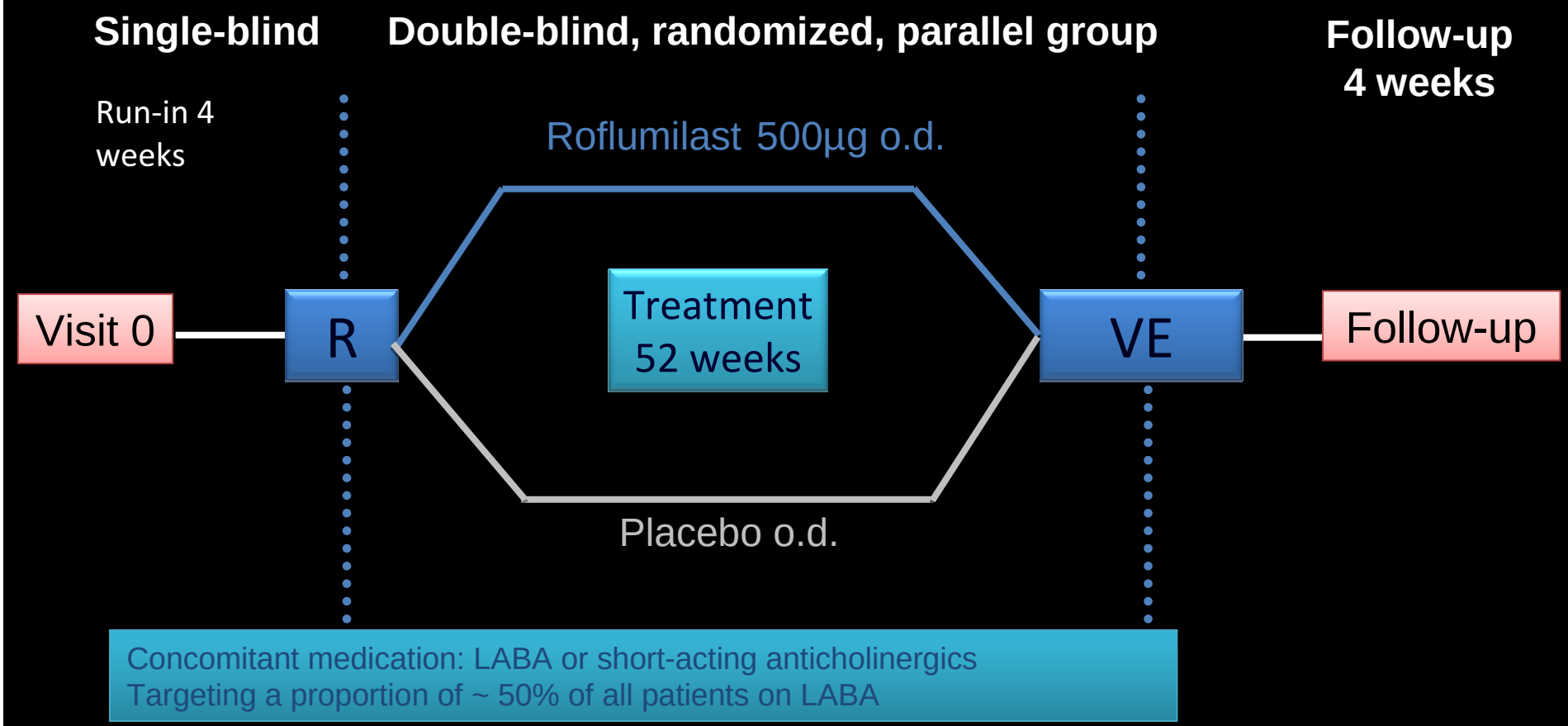
PRE- AND POST-BRONCHODILATOR FEV_1 (M2-111 & M2-112 POOLED DATA)



Rennard SI, Calverley PMA, Goehring UM, et al. *Respiratory Research* **2011**; 12: 18.

FEV_1 = Forced expiratory volume in 1 second

Design of pivotal studies M2-124 & M2-125



R = randomization
VE = Visit end

o.d. = Once daily
LABA = Long-acting β_2-agonist

Calverley PMA, Rabe,KF, Goehring UM et al. *Lancet* **2009**;374:685–694.

12-month pivotal study Population and endpoints

- Two pivotal 12-month studies
- Patients (pooled study population n=3091):
  - COPD associated with chronic bronchitis*
  - History of exacerbations
  - Severe airflow limitation (FEV_1 ≤50% of predicted)
- Treatments:
  - Once-daily roflumilast 500µg or placebo
  - Concomitant use of LABAs or regular short-acting bronchodilators allowed
- Primary endpoints:
  - Pre-bronchodilator FEV_1
  - Exacerbation rate (moderate to severe)

*Chronic productive cough for 3 months in each of the 2 years prior to baseline visit

LABA: Long-acting β_2-agonist FEV_1 = Forced expiratory volume in one second

Calverley PMA, Rabe,KF, Goehring UM et al. *Lancet* **2009**;374:685–694.

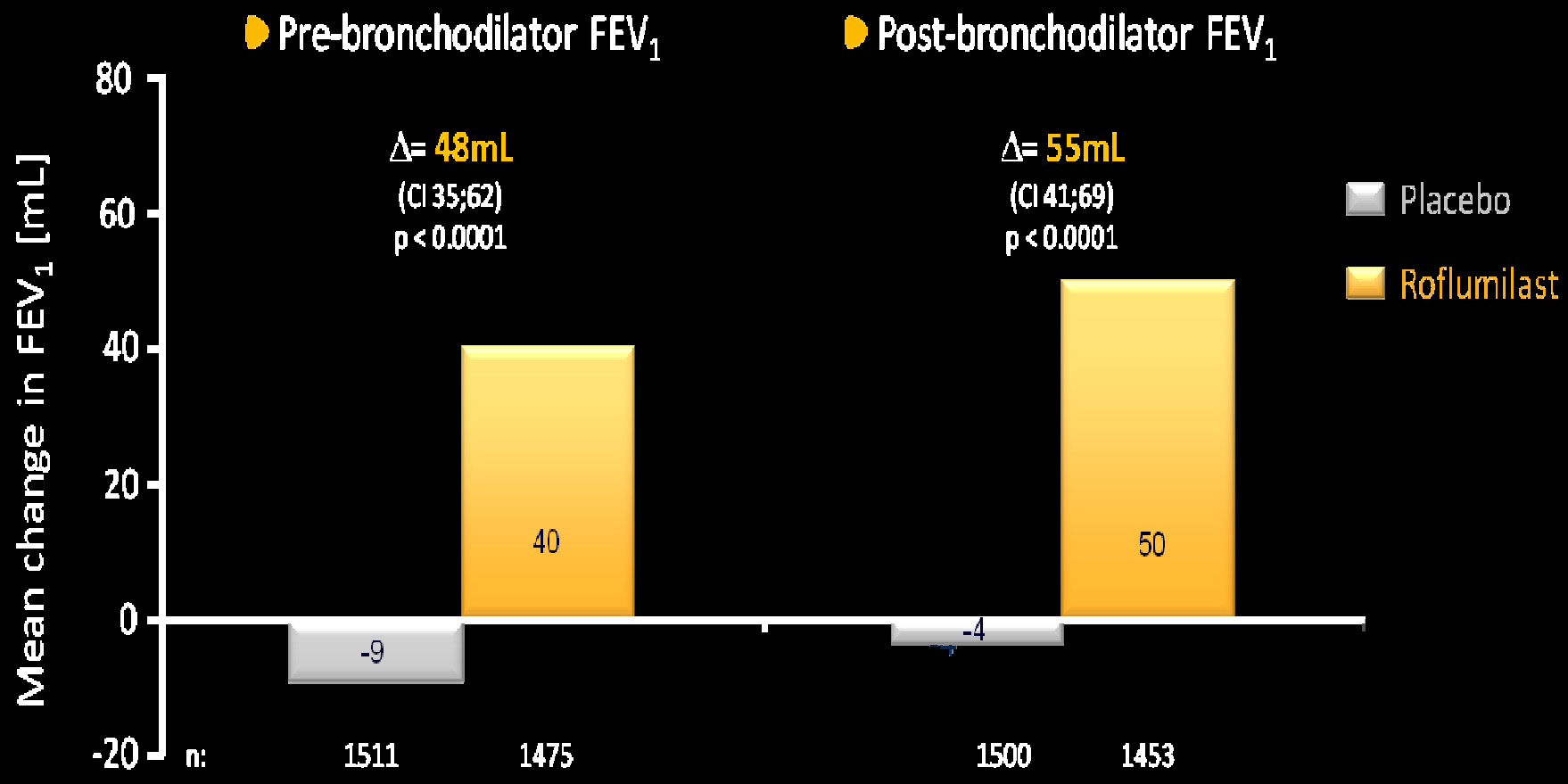
12-month pivotal study Patient Baseline Characteristics

	Roflumilast (n=1537)	Placebo (n=1554)
Median age in years	64 (9)	64 (9)
Men, n (%)	1150 (75)	1186 (76)
Cigarette pack-years	48 (25)	47 (23)
Current smoker, n (%)	635 (41)	643 (41)
Pre-bronchodilator FEV_1, L	1.01	1.02
Post-bronchodilator FEV_1, L	1.10	1.11
Pre-bronchodilator FEV_1, % of predicted	33.0	33.4
Post-bronchodilator FEV_1, % of predicted	36.1	36.4
Post-bronchodilator FEV_1/FVC, %	42.3	42.0
COPD severity – Severe COPD, n (%) – Very severe COPD, n (%)	943 (61) 463 (30)	989 (64) 440 (28)
Body mass index, kg/m^2	25.8	25.7

Data are expressed as mean (SD), unless otherwise stated
FEV_1 = Forced expiratory volume in 1 second
FVC = Forced vital capacity

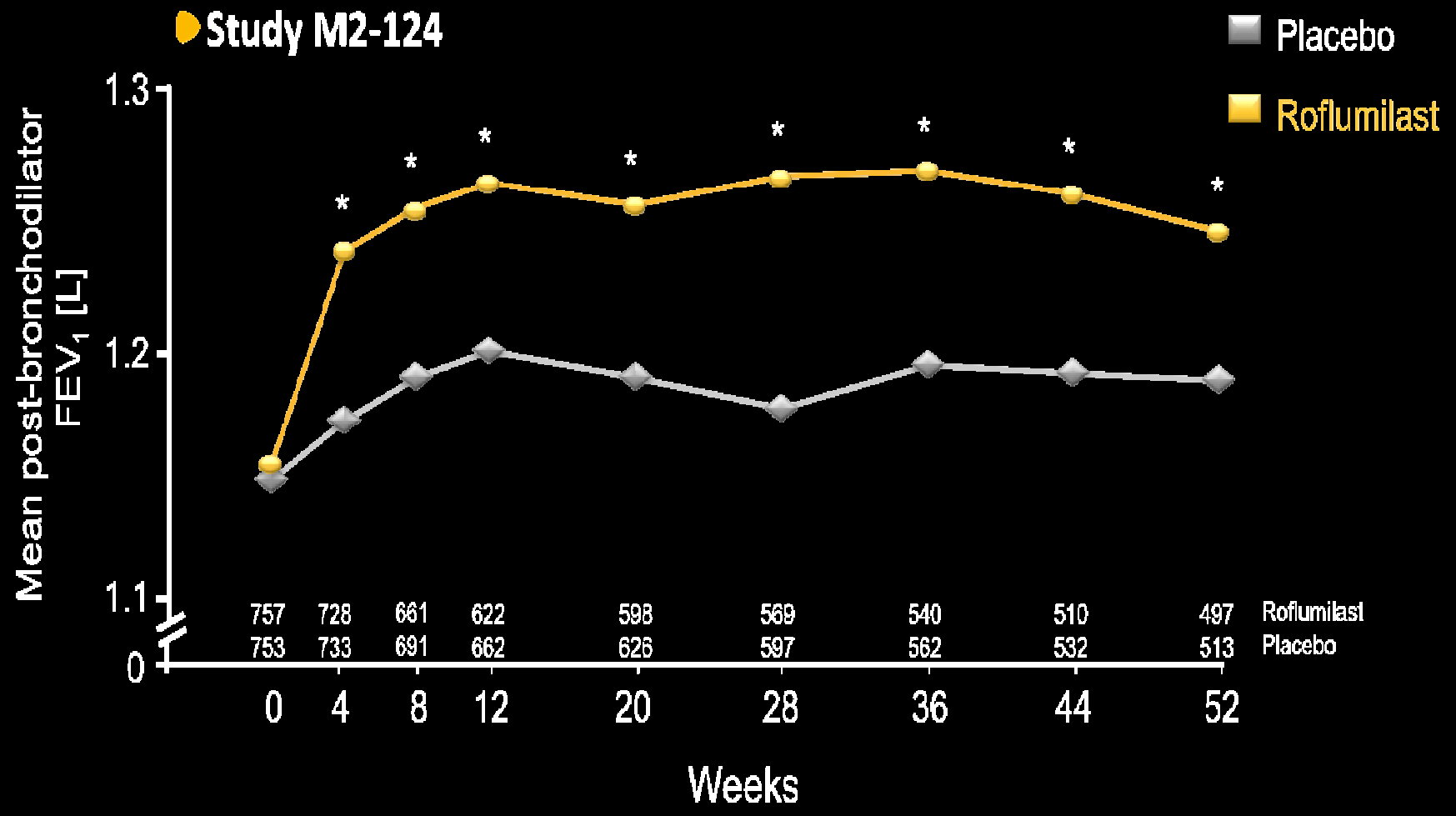
Calverley PMA, Rabe,KF, Goehring UM et al. *Lancet* **2009**;374:685–694.

Roflumilast significantly improved lung function in 12-month clinical studies



Calverley PMA, Rabe,KF, Goehring, UM et al. *Lancet* **2009**;374:685–694.

Lung Function improved in roflumilast-treated patients after 4 weeks of treatment

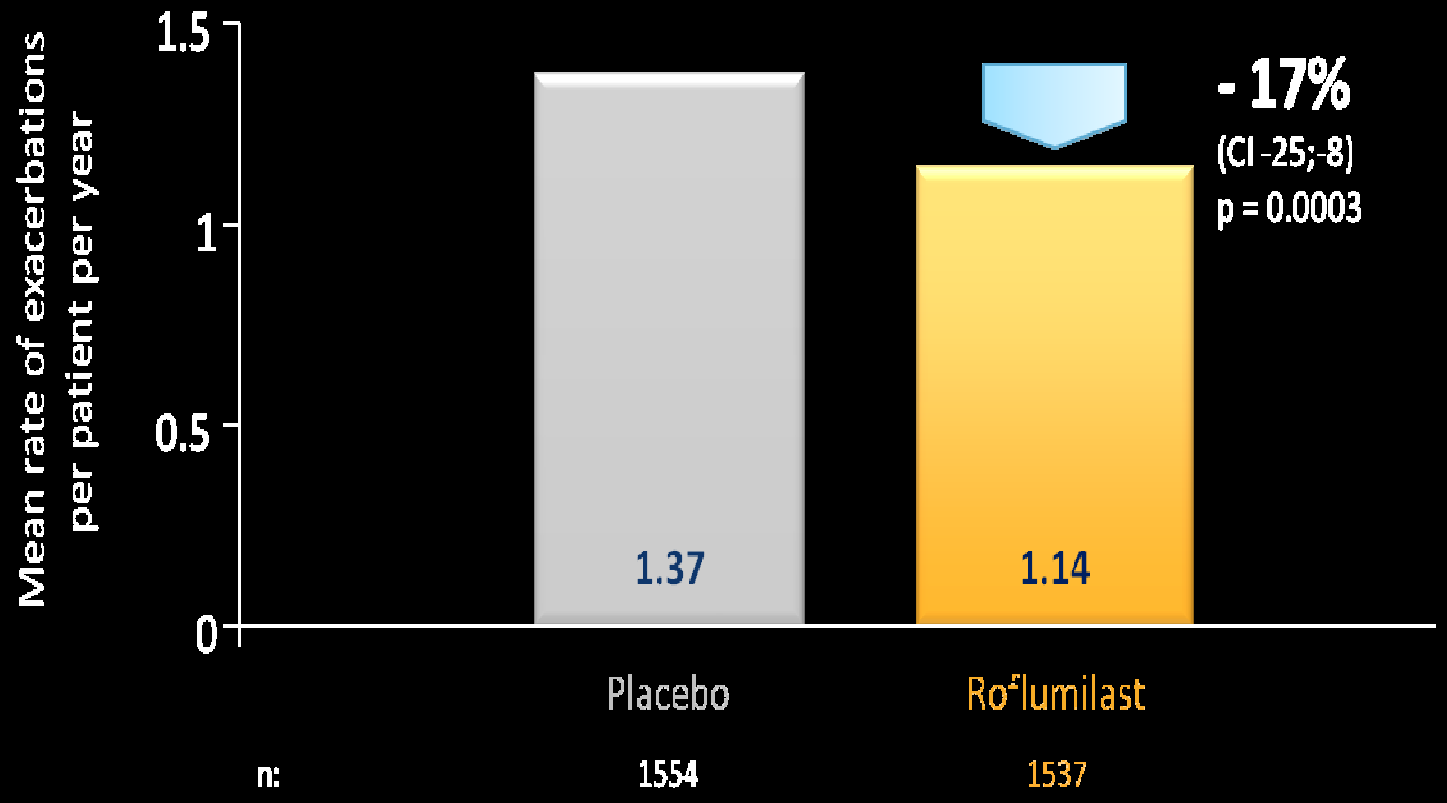


*Statistically significant difference from baseline
FEV_1: Forced expiratory volume in 1 second

Adapted from Calverley PMA, Rabe,KF, Goehring, UM et al. *Lancet* **2009**;374:685–694.

Roflumilast significantly reduced the rate of moderate/severe exacerbations

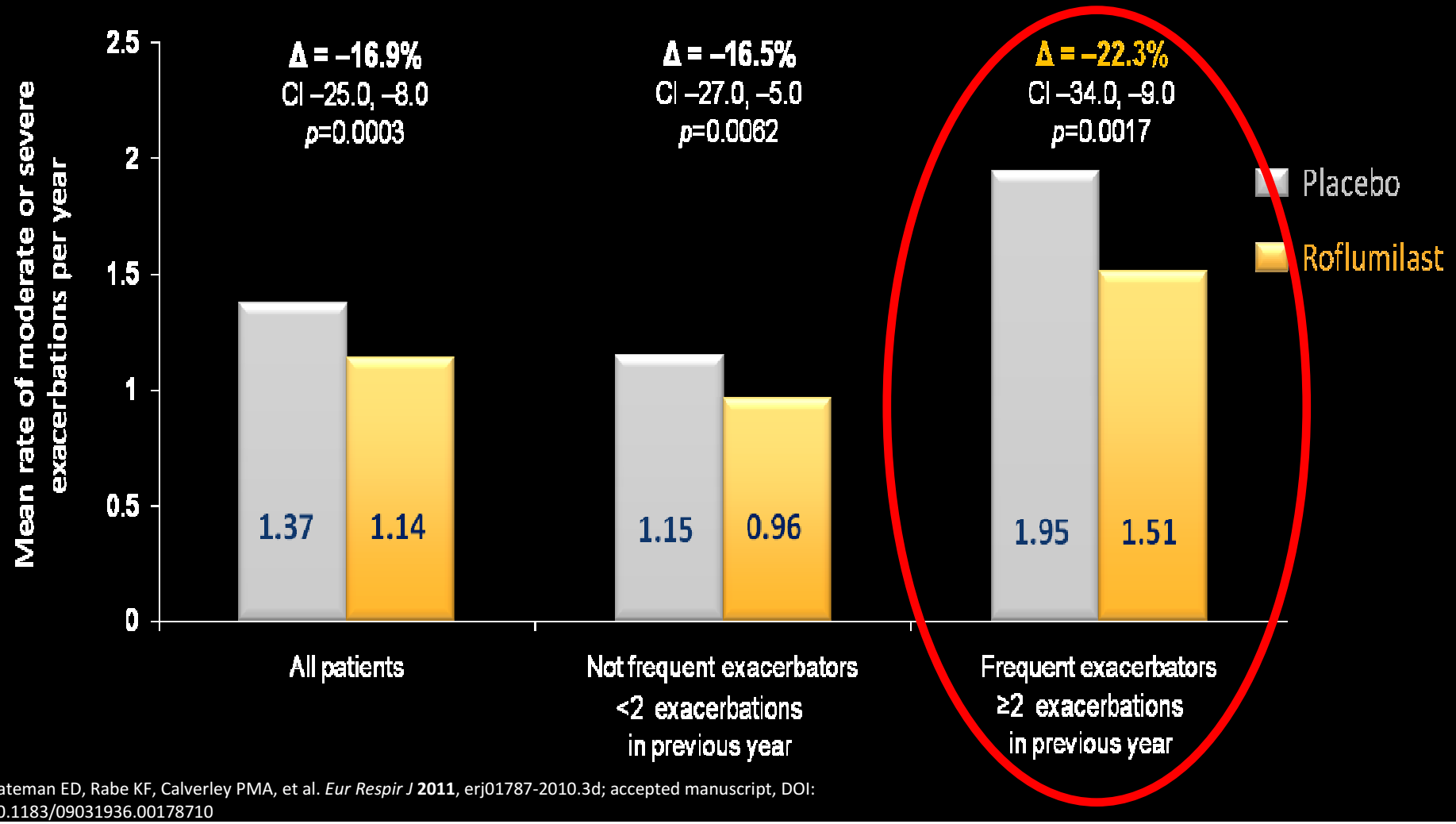
- Co-primary endpoint: Exacerbation rate



Calverley PMA, Rabe,KF, Goehring, UM et al. *Lancet* **2009**;374:685–694.

Greatest benefits of roflumilast were observed in FREQUENT EXACERBATORS

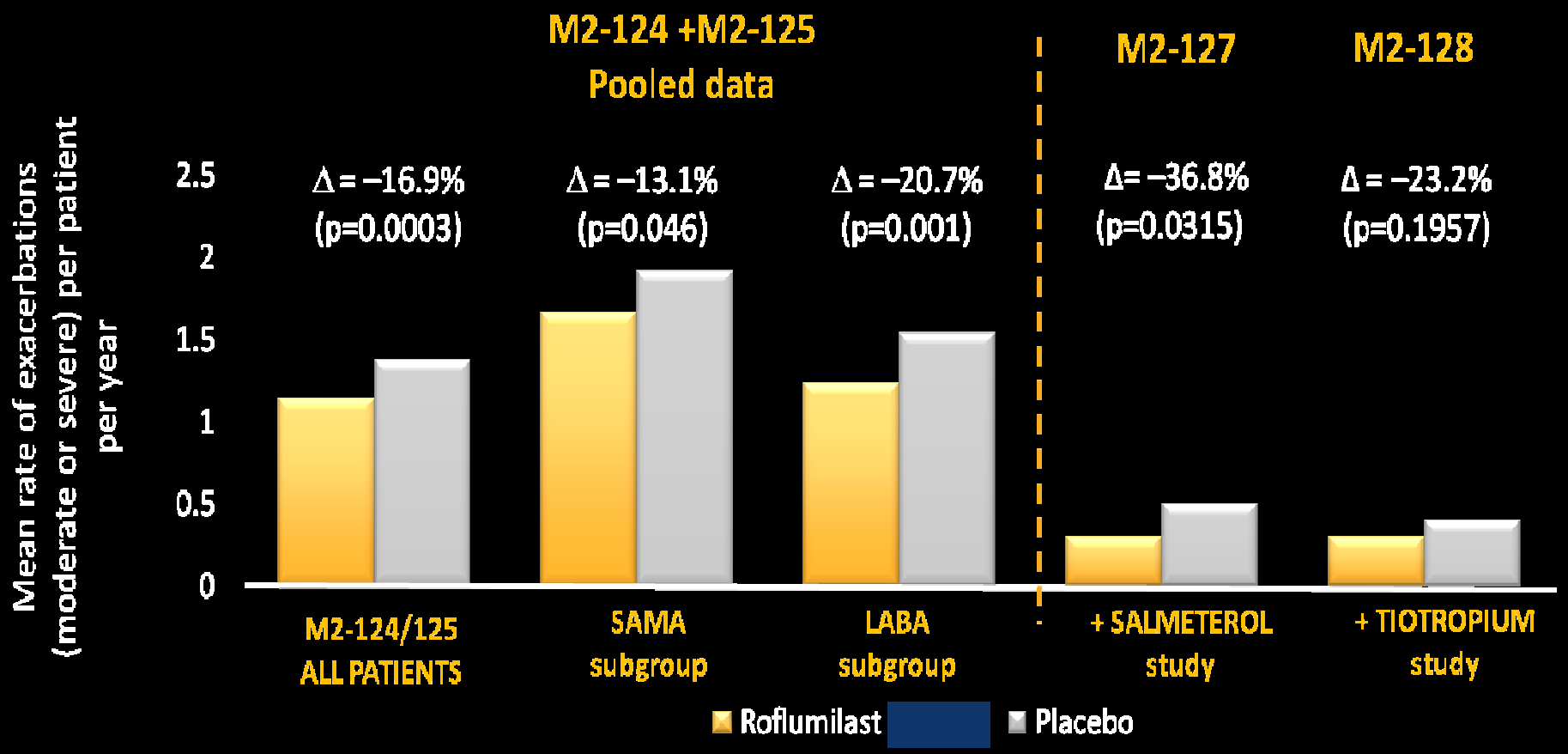
- M2-124 and M2-125 pooled post hoc analysis



Bateman ED, Rabe KF, Calverley PMA, et al. *Eur Respir J* **2011**, erj01787-2010.3d; accepted manuscript, DOI: 10.1183/09031936.00178710

Efficacy of roflumilast when added to long-acting bronchodilators

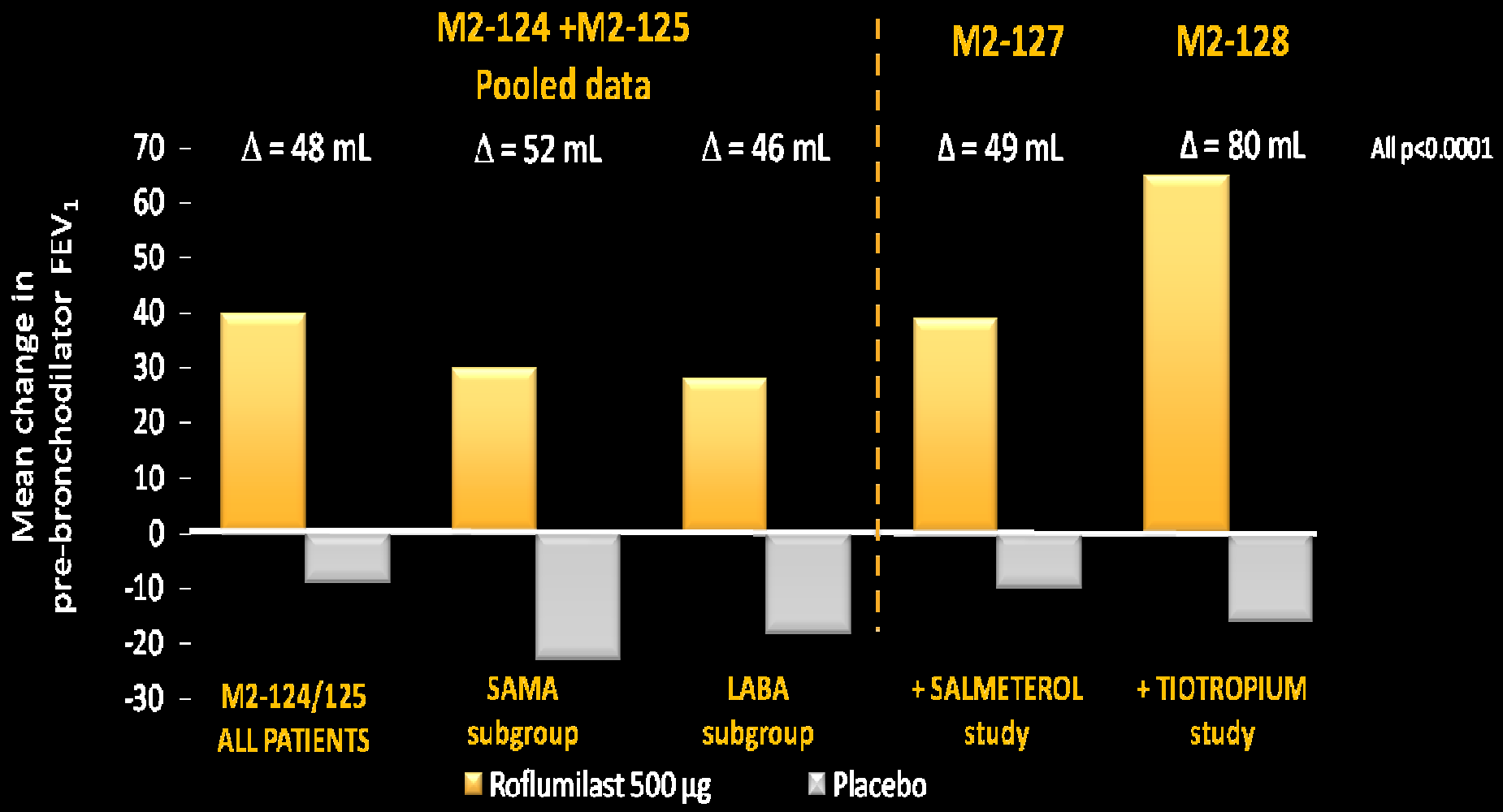
Roflumilast Reduced exacerbations when ADDED to BRONCHODILATORS



LABA = Long-acting β_2-agonist
SAMA = Short-acting muscarinic antagonist

Rabe KF. *Br J Pharm* **2011**;163:53-67.

Roflumilast Improved lung function when ADDED to BRONCHODILATORS



Rabe KF. *Br J Pharm* **2011**;163:53-67.

LABA = Long-acting β_2-agonist
SAMA = Short-acting muscarinic antagonist

Efficacy of roflumilast when added to INHALED CORTICOSTEROIDS

M2-111 & M2-112 Patient baseline characteristics by concomitant ICS

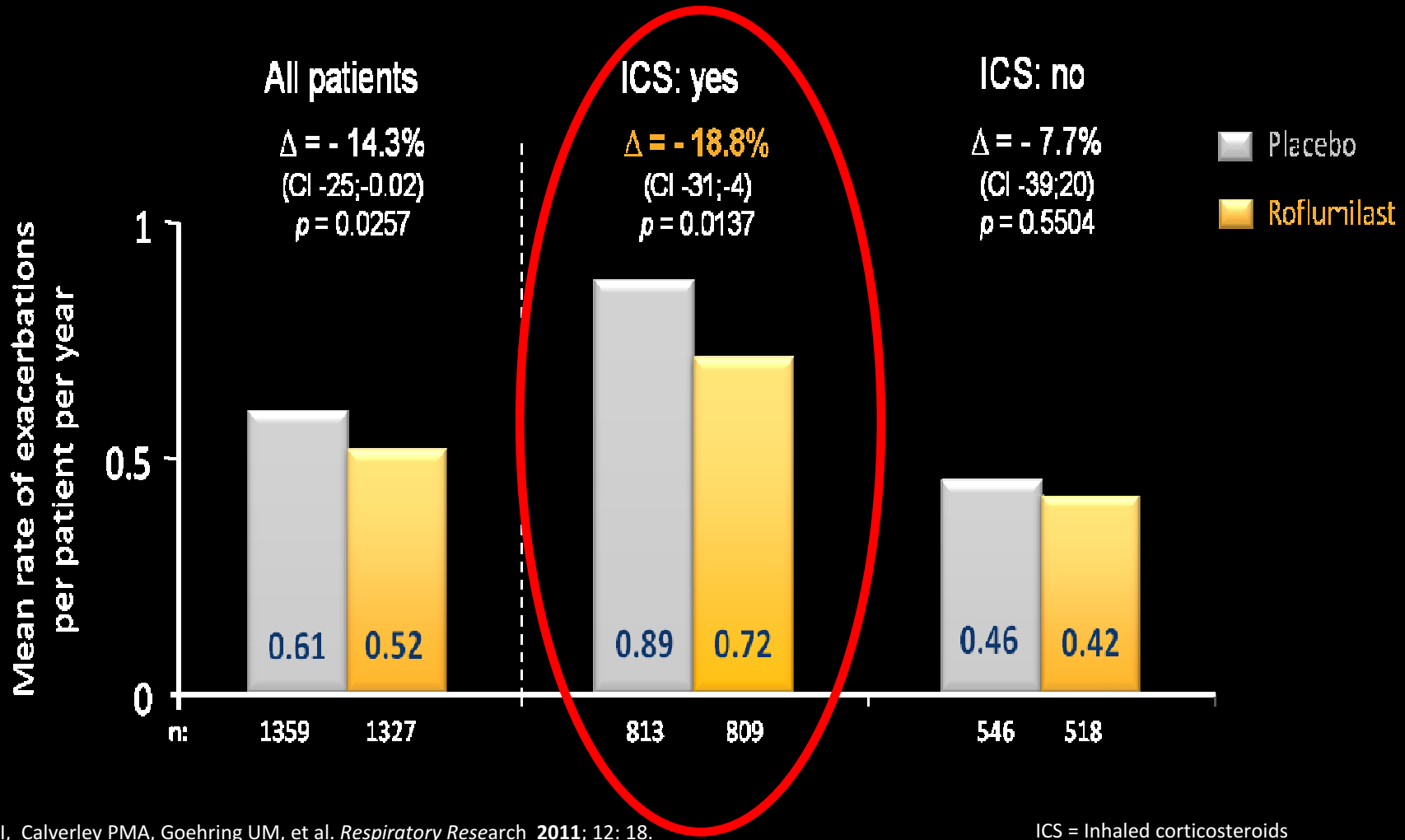
	Concomitant ICS treatment		No ICS treatment	
	Placebo (n=813)	Roflumilast (n=809)	Placebo (n=546)	Roflumilast (n=518)
Age, years (range)	64 (40-89)	65 (40-87)	65 (41-86)	64 (40-88)
Pre-bronchodilator FEV_1, % predicted	32 (±9%)	32 (±10%)	34 (±10%)	34 (±11%)
Post-bronchodilator FEV_1, % predicted	36 (±10%)	36 (±10%)	38 (±10%)	38 (±11%)
Post-bronchodilator FEV_1/FVC, % predicted	41 (±11%)	41 (±11%)	43 (±11%)	43 (±11%)

Data are expressed as mean (SD), unless otherwise stated
FEV_1 = Forced expiratory volume in 1 second
FVC = Forced vital capacity

Rennard SI, Calverley PMA, Goehring UM, et al. *Respiratory Research* **2011**; 12: 18.

Roflumilast reduced exacerbation rate when added to ICS

- M2-111 and M2-112 pooled post hoc analysis

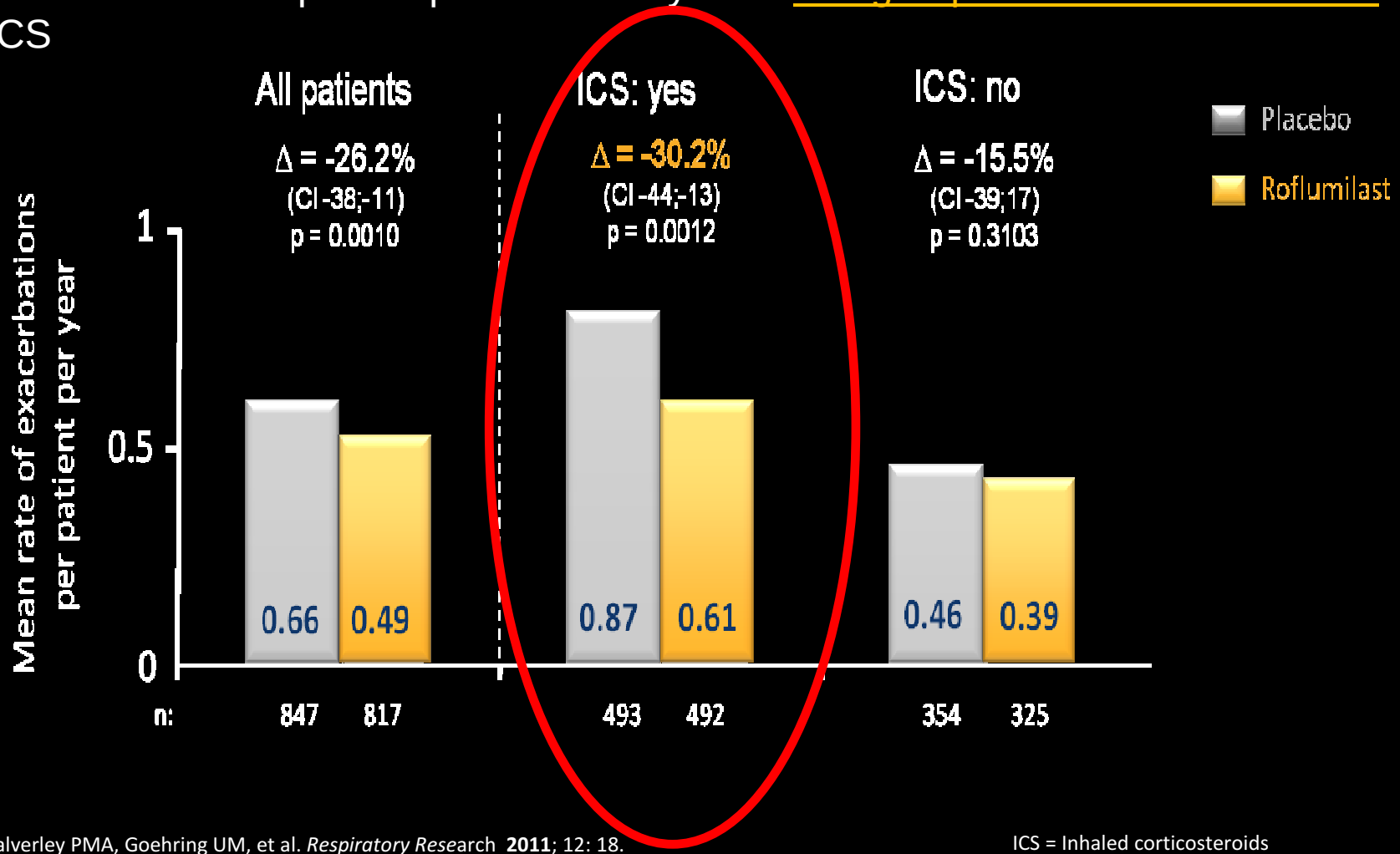


Rennard SI, Calverley PMA, Goehring UM, et al. *Respiratory Research* **2011**; 12: 18.

ICS = Inhaled corticosteroids

Roflumilast reduced exacerbation rate when added to ICS

- M2-111 and M2-112 pooled post hoc analysis of sub-group with chronic bronchitis +/- ICS



Rennard SI, Calverley PMA, Goehring UM, et al. *Respiratory Research* **2011**; 12: 18.

ICS = Inhaled corticosteroids

IDENTIFICATION OF RESPONSIVE patient SUBGROUP

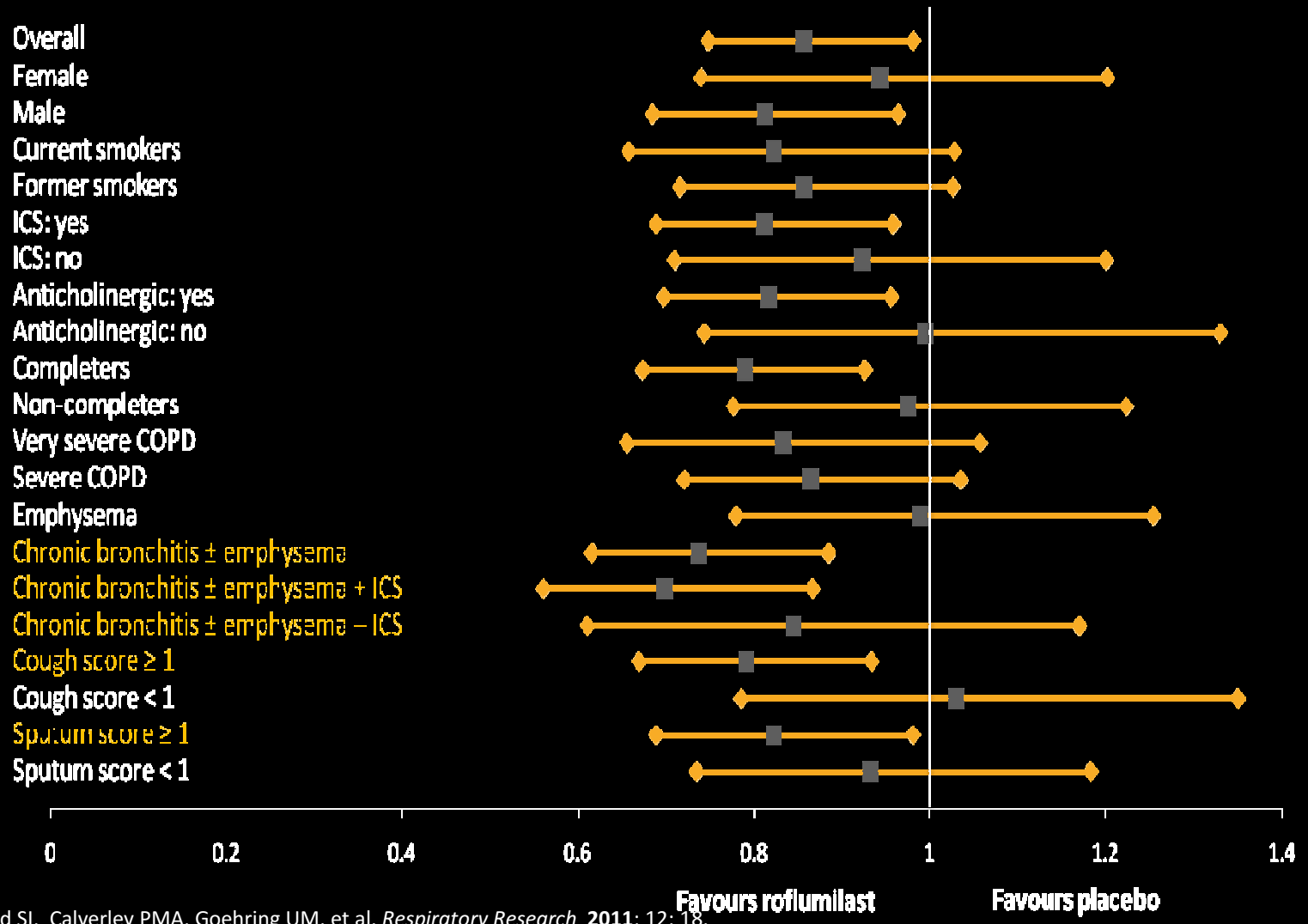
Analyses made to Identify RESPONSIVE sub-GROUPS

- **The co-primary endpoints (pre-bronchodilator FEV_1 and rate of moderate or severe exacerbations per patient per year) were analyzed additionally in subgroups stratified by:**
  - Sex
  - Smoking status
  - Concomitant use of ICS
  - Concomitant use of anticholinergics
  - Study completion status
  - COPD severity (severe, very severe)
  - History of chronic bronchitis or emphysema (investigator diagnosed)
  - Cough/sputum score one week before randomization

Rennard SI, Calverley PMA, Goehring UM, et al. *Respiratory Research* **2011**; 12: 18.

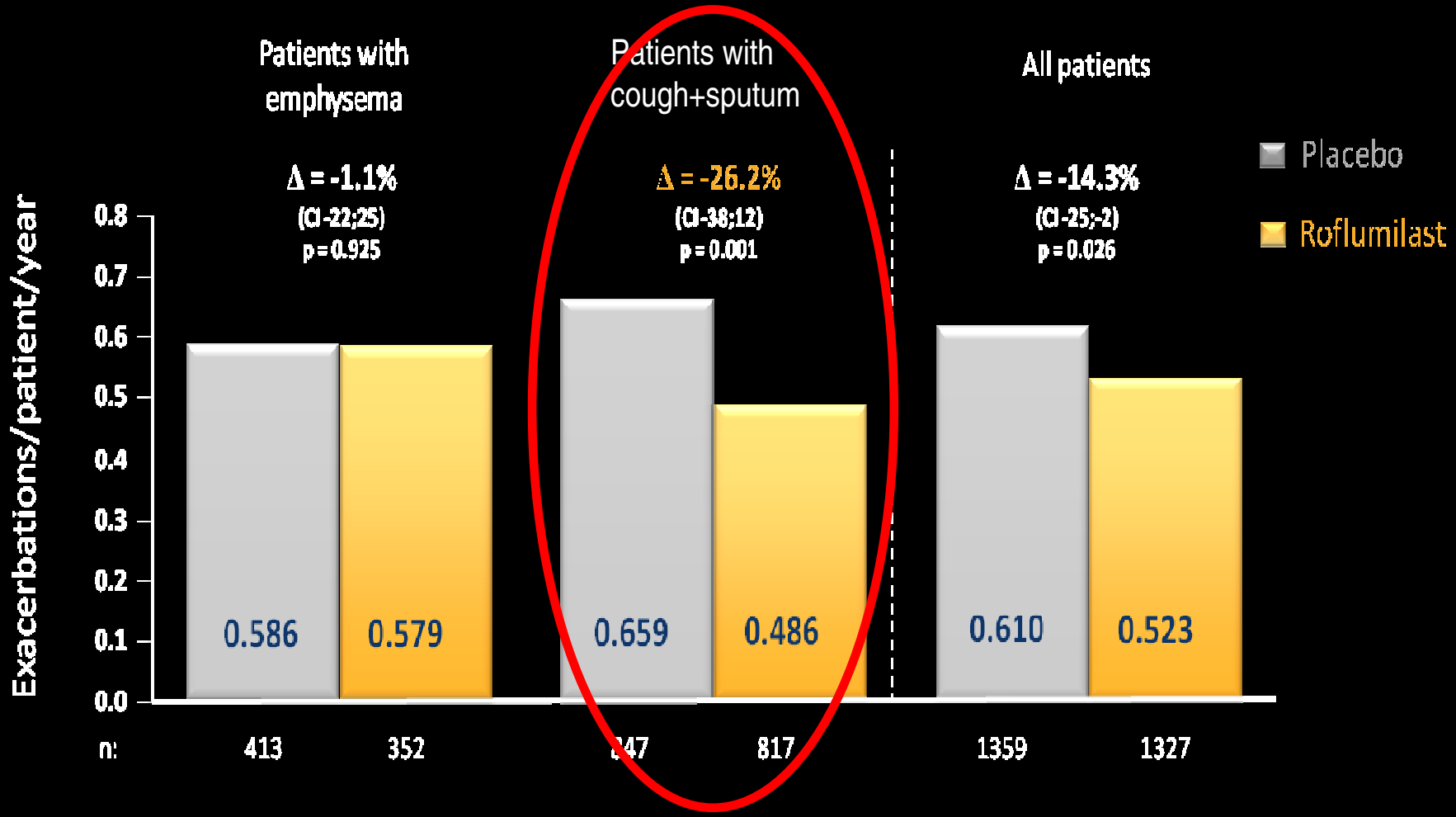
ICS = Inhaled corticosteroids

THE EFFECT OF ROFLUMILAST ON EXACERBATIONS WAS GREATEST IN PATIENTS WITH CHRONIC COUGH AND SPUTUM



Rennard SI, Calverley PMA, Goehring UM, et al. *Respiratory Research* **2011**; 12: 18.

The effect of roflumilast on exacerbations was greatest in patients with chronic cough and sputum

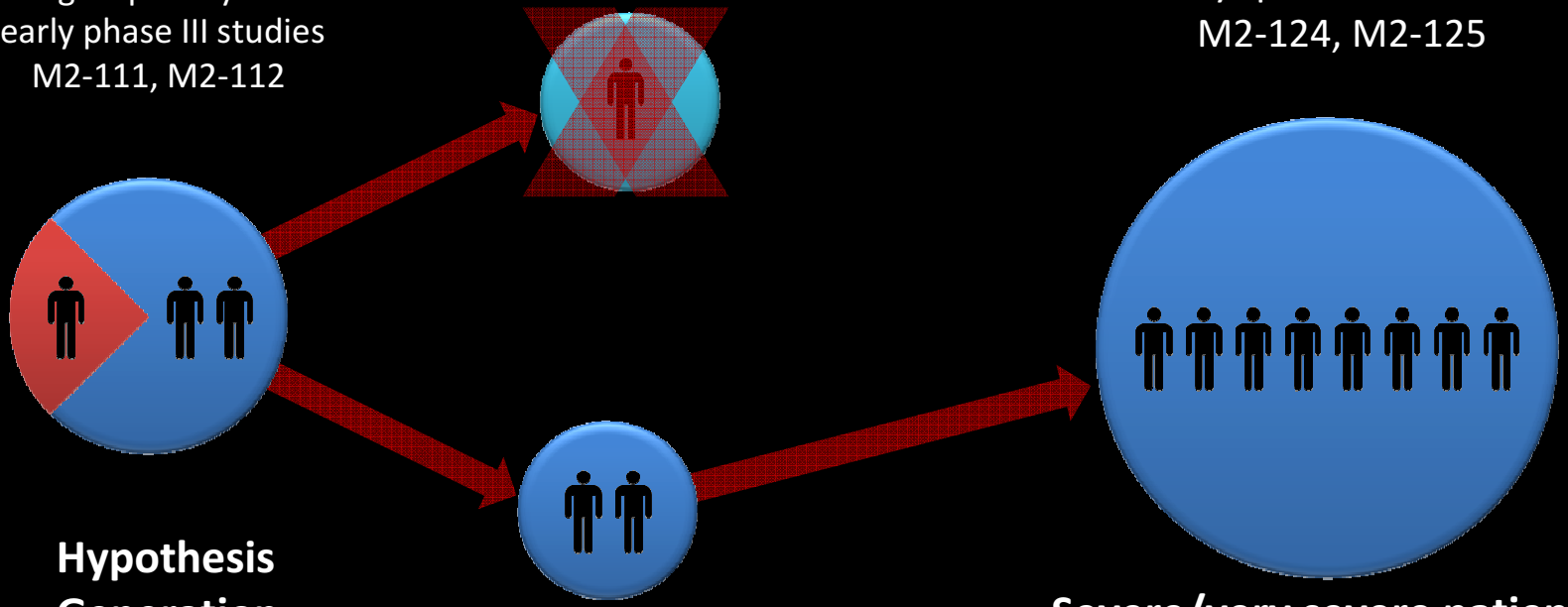


Rennard SI, Calverley PMA, Goehring UM, et al. *Respiratory Research* **2011**; 12: 18.

Evolution of Roflumilast clinical programme

IDENTIFICATION OF TARGET PATIENT POPULATION

Subgroup analyses of early phase III studies M2-111, M2-112



Confirmatory 1-yr pivotal studies M2-124, M2-125

Hypothesis Generation

- **Severe/very severe patients**
- **History of chronic cough and sputum**
- **History of exacerbations**

SAFETY

Roflumilast was GENERALLY well tolerated in clinical studies

- Side effects associated with Roflumilast therapy were **typically mild to moderate**
- They occurred mainly within the **first weeks of therapy** and mostly **resolved on continued treatment**

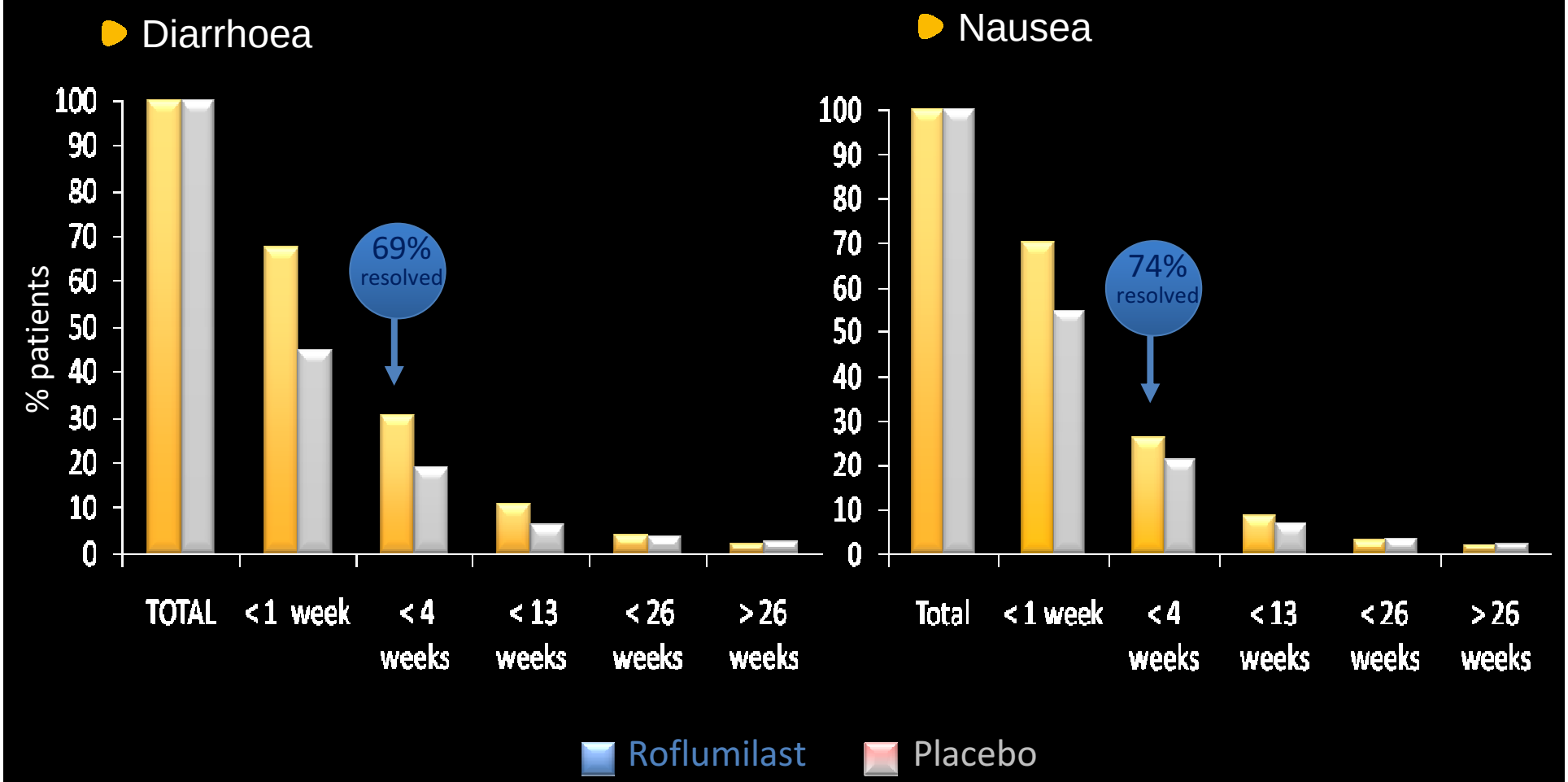
Diarrhoea	5.9%
Weight decrease	3.4%
Nausea	2.9%
Abdominal pain	1.9%
Headache	1.7%

- Changes in weight, and neuropsychiatric events should be monitored

Daxas® EU SmPC. Available at www.ema.europa.eu

*Expressed as percent of total study population

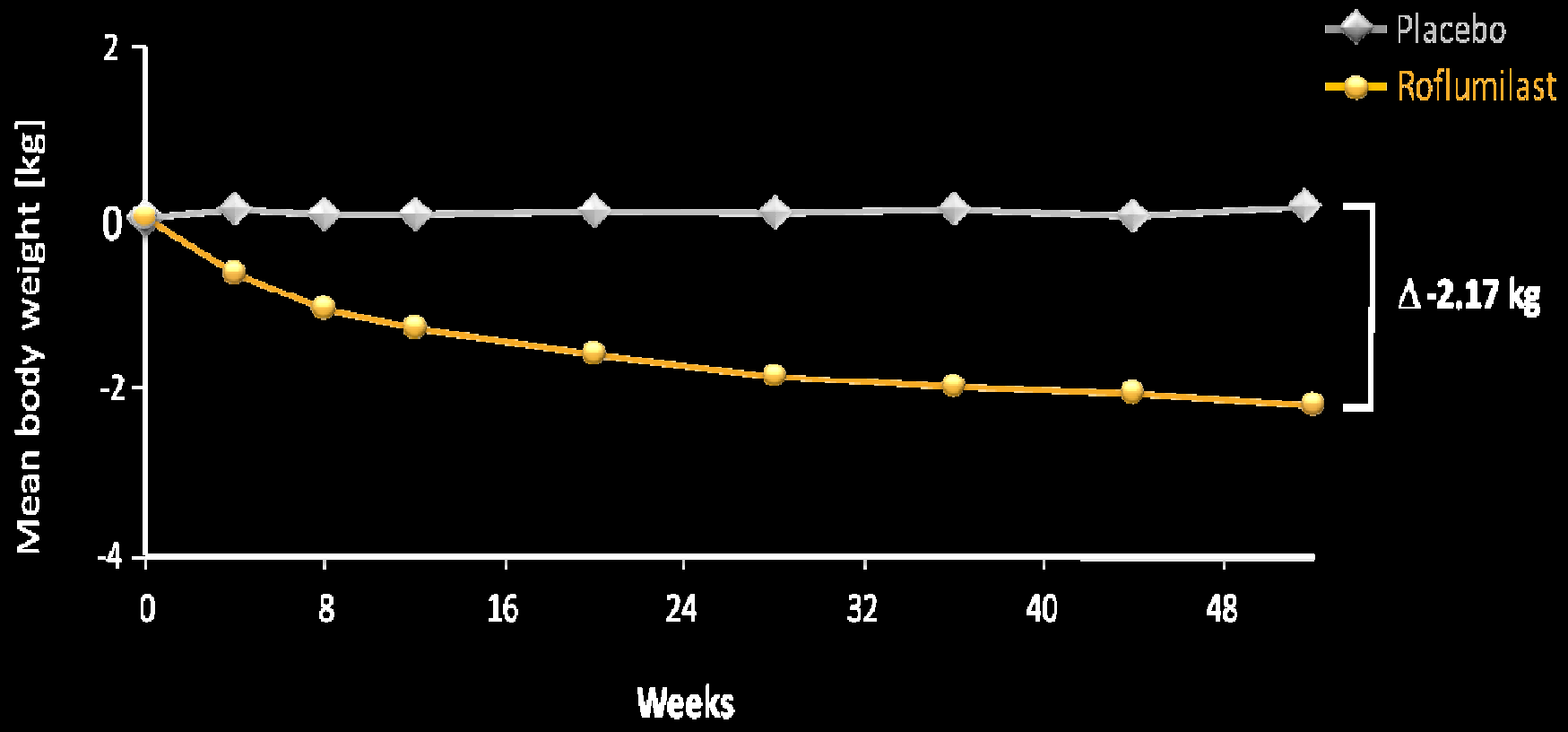
The majority of GI-related adverse events resolved within 4 weeks



Adapted from Gross N, Calverley P, Fabbri LM, et al. *Chest*. **2010**; 138:466A (Abstract+ Poster).

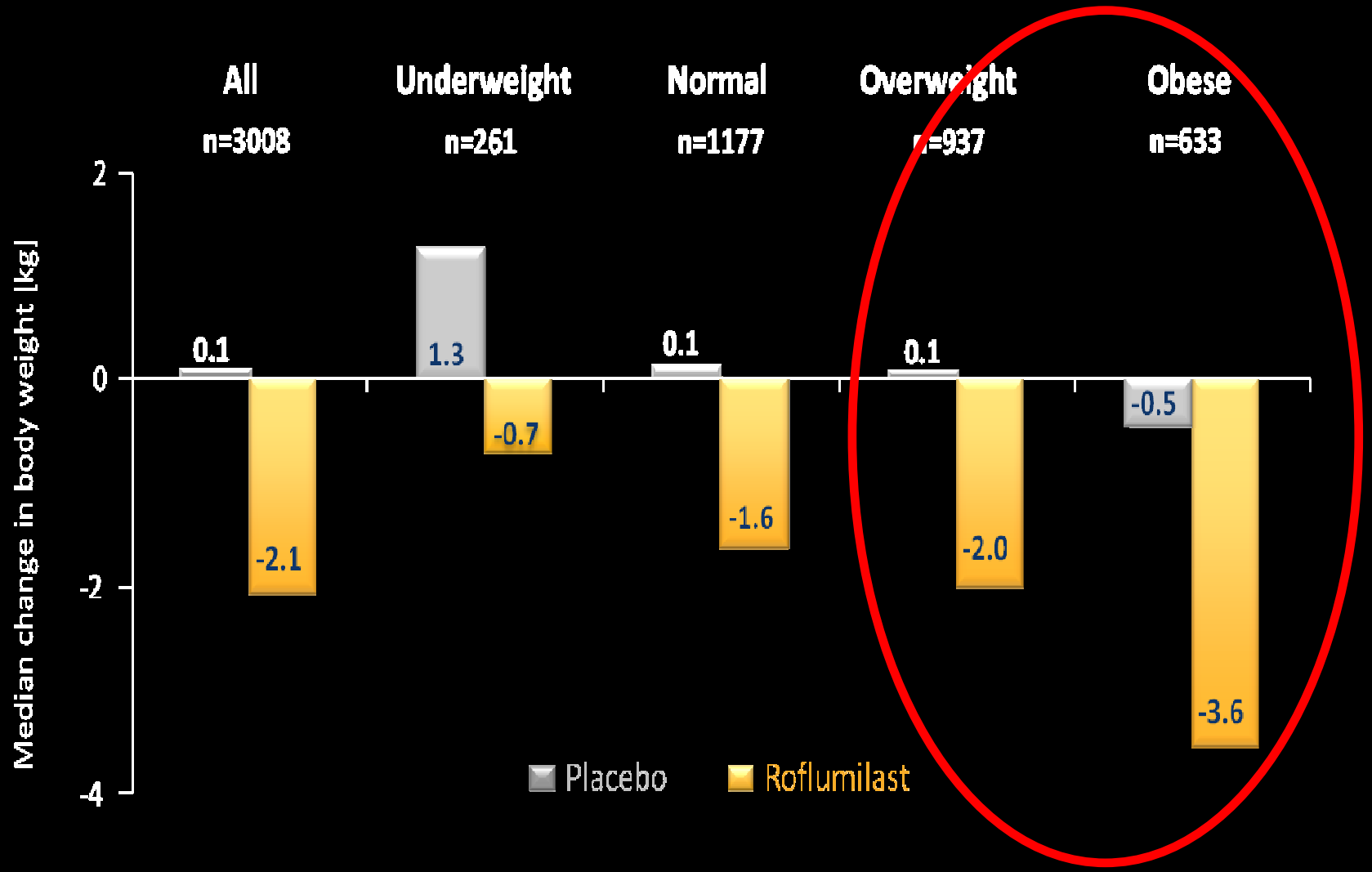
GI=Gastrointestinal

Weight decrease associated with Roflumilast occurred mainly in the first 6 months of treatment



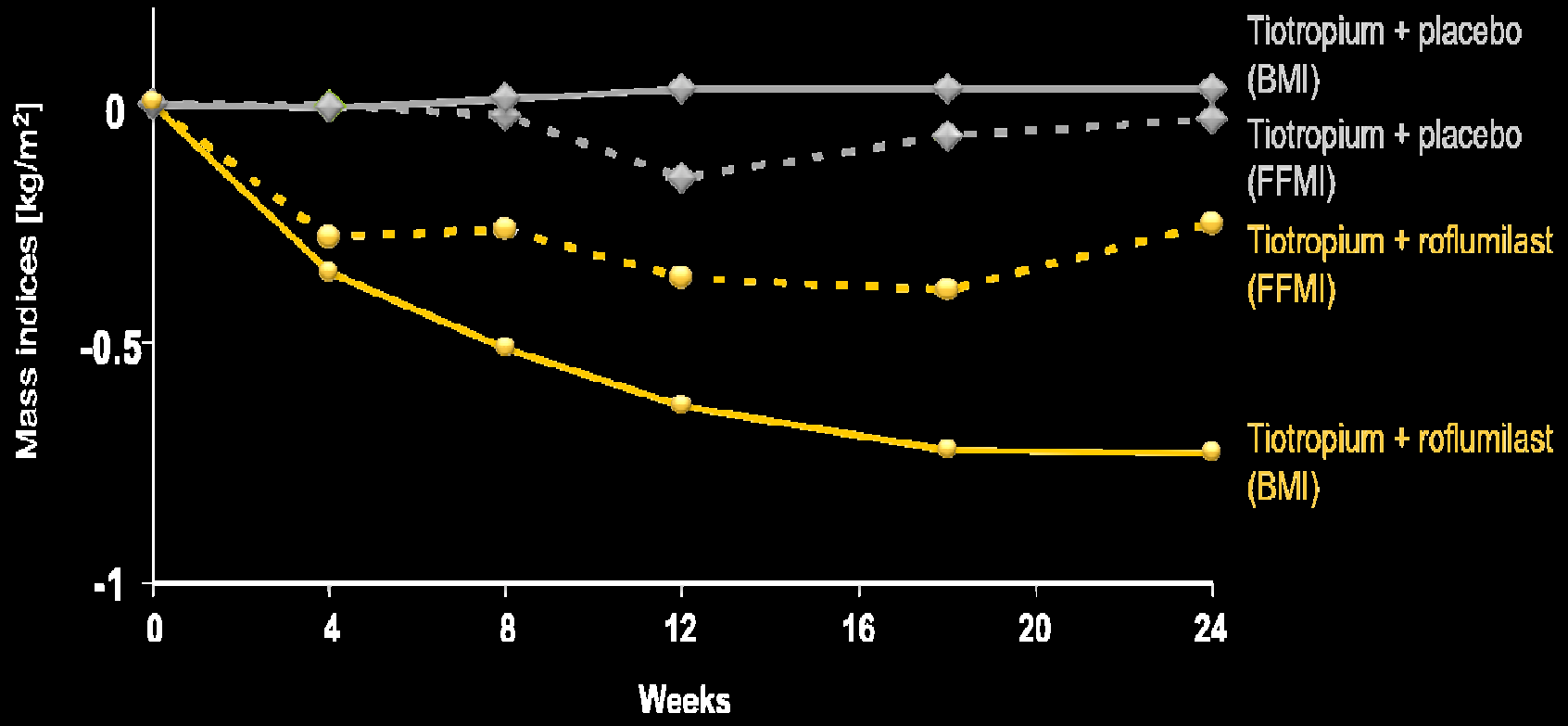
Calverley PMA, Rabe KF, Goehring UM, et al. *Lancet* **2009**;374:685–694.

The largest weight decrease was observed in obese patients



Calverley PMA, Rabe,KF, Goehring, UM, et al. *Lancet* **2009**;374:685–694. (supplementary webappendix).

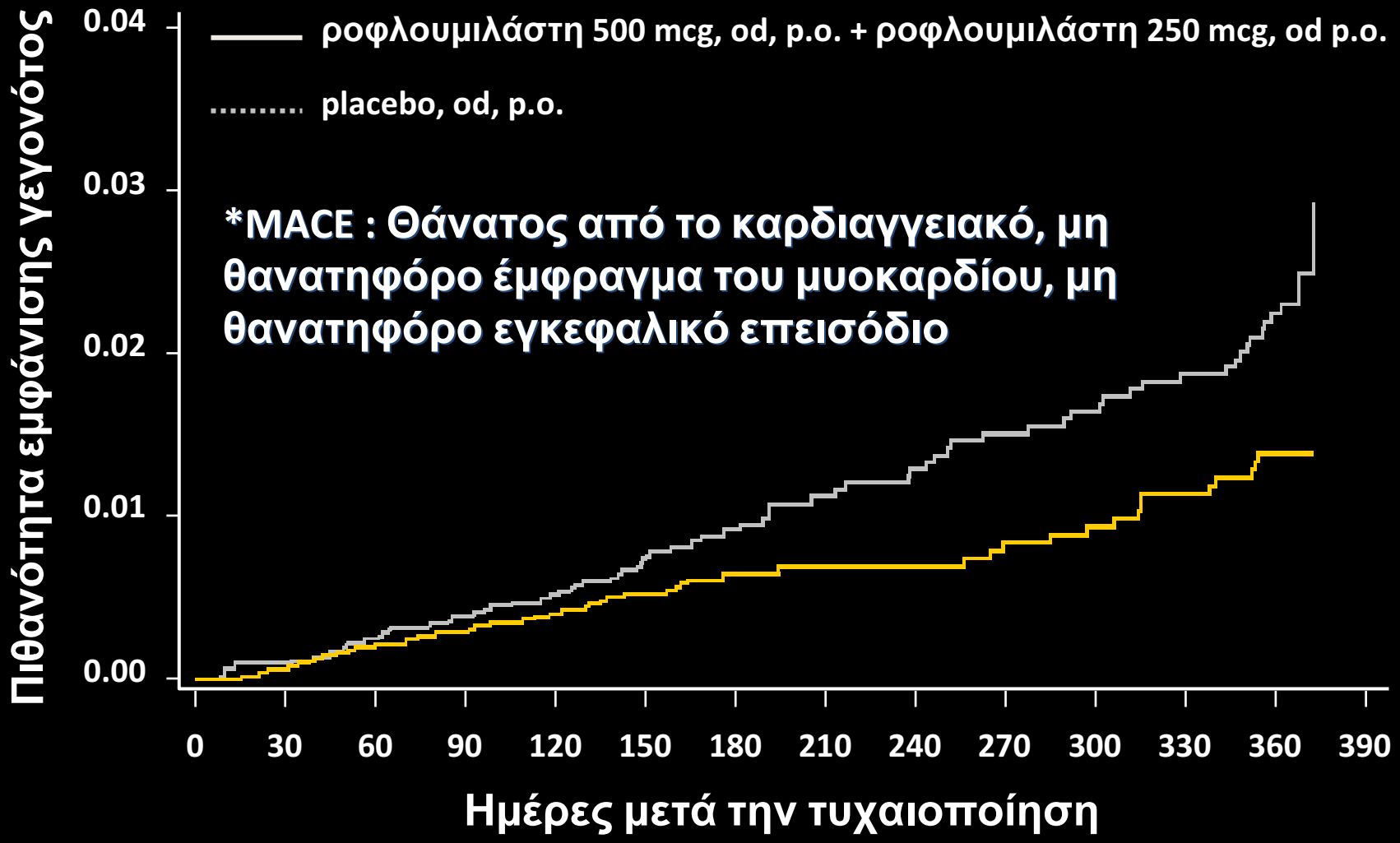
WEIGHT DECREASE ASSOCIATED WITH ROFLUMILAST WAS PRIMARILY FAT MASS



Wouters EFM, Teichmann P, Brose M, et al. *Am J Respir Crit Care Med* **2010**;181:A4473.

FFMI = Fat Free Mass Index
BMI = Body Mass Index

Χρόνος μέχρι την έναρξη του πρώτου σημαντικού ανεπιθύμητου γεγονότος από το Καρδιαγγειακό Σύστημα [major adverse CV event (MACE*)]

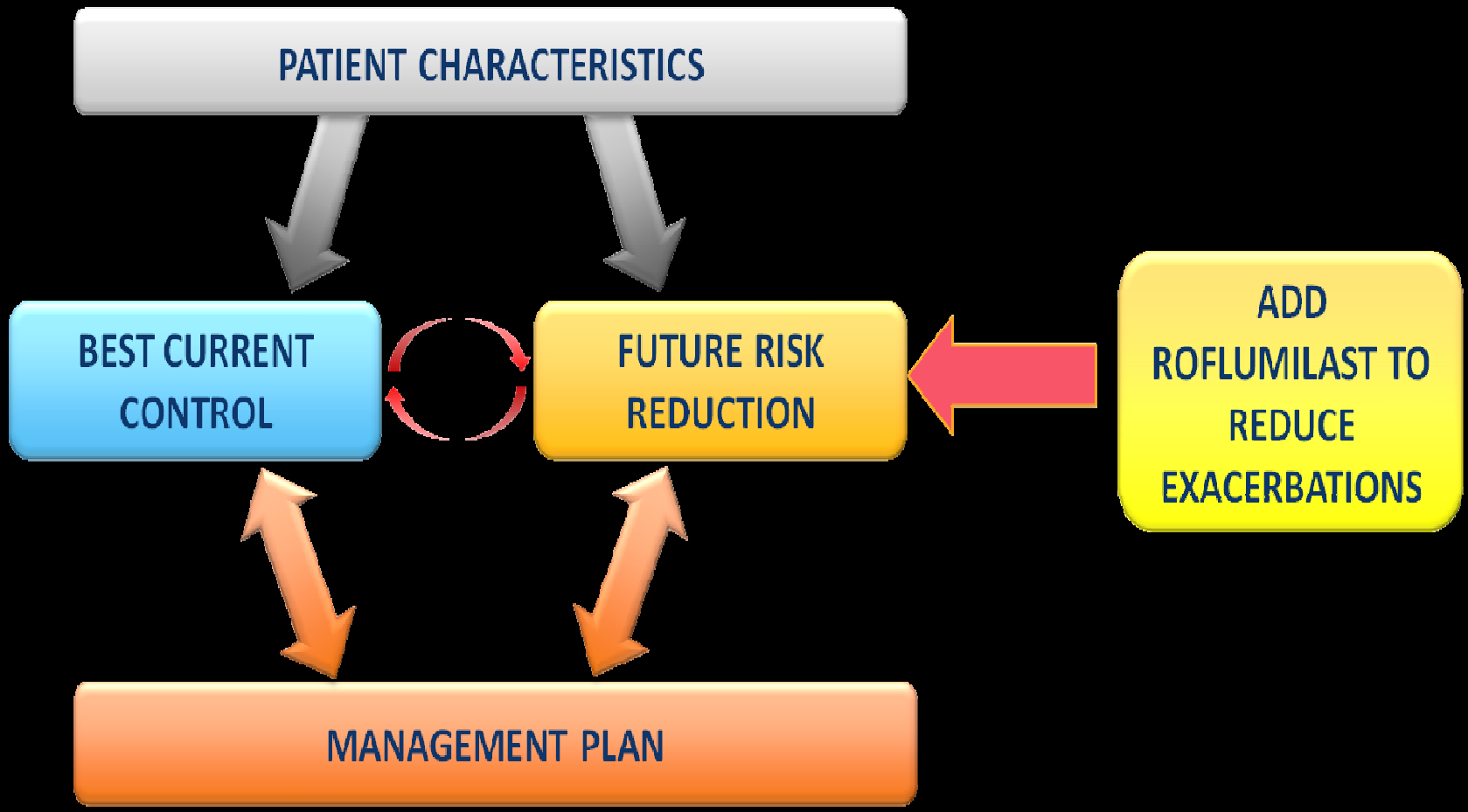


ROFLUMILAST IS INCLUDED IN THE GOLD 2010 UPDATE

- The principle action of PDE-4 inhibitors is to reduce inflammation through inhibition of the breakdown of intracellular cyclic AMP
- Roflumilast is a once daily oral medication with no direct bronchodilator activity although it has been shown to improve FEV_1 in patients treated with salmeterol or tiotropium
- In patients with Stage III: Severe COPD or Stage IV: Very Severe COPD and a history of exacerbations and chronic bronchitis, Roflumilast reduces exacerbations. These effects are also seen when roflumilast is added to long-acting bronchodilators

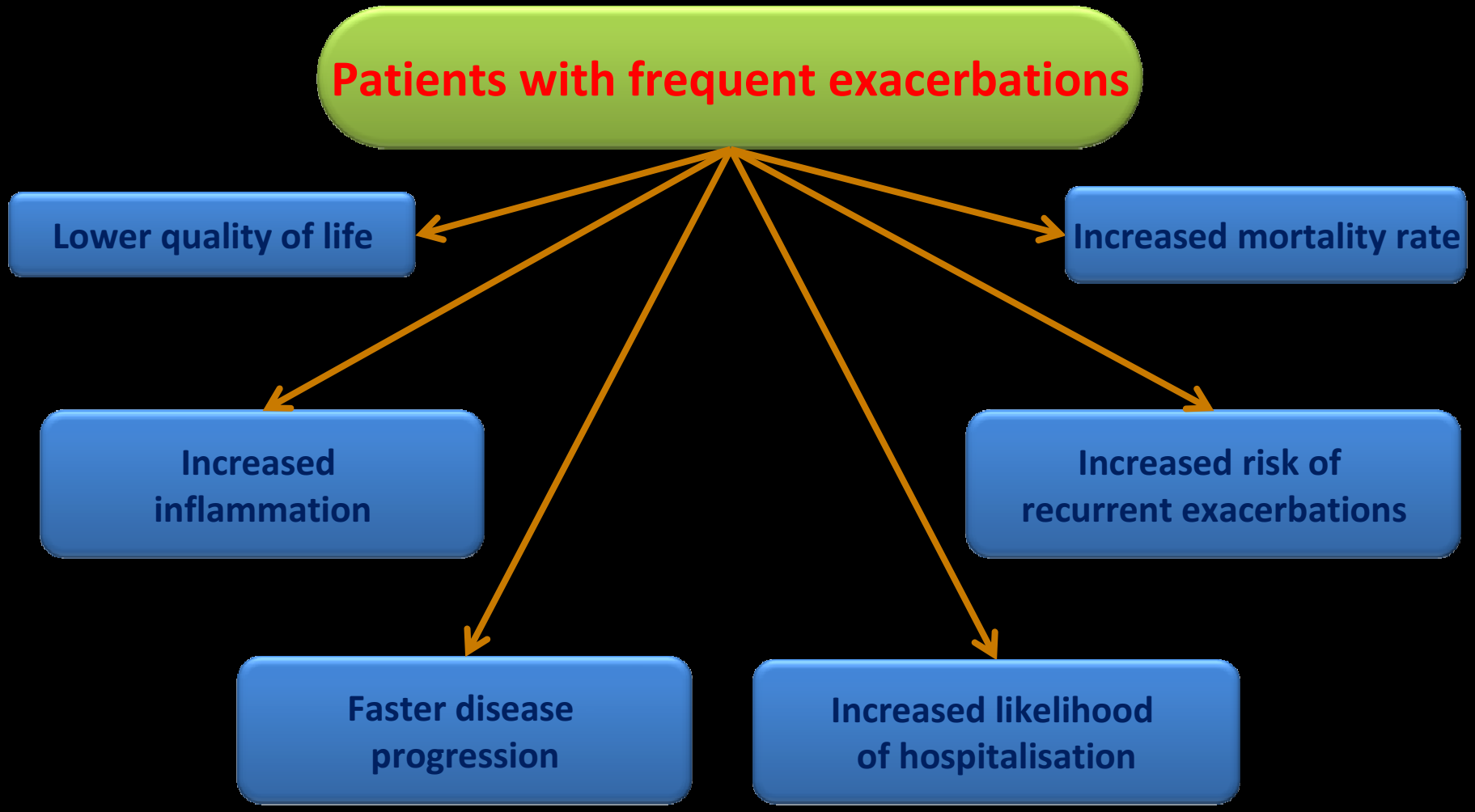
Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, Global Initiative for Chronic Obstructive Lung Disease (GOLD) **2010**
Available from www.goldcopd.org

A new perspective on ‘optimal care’ for patients with COPD



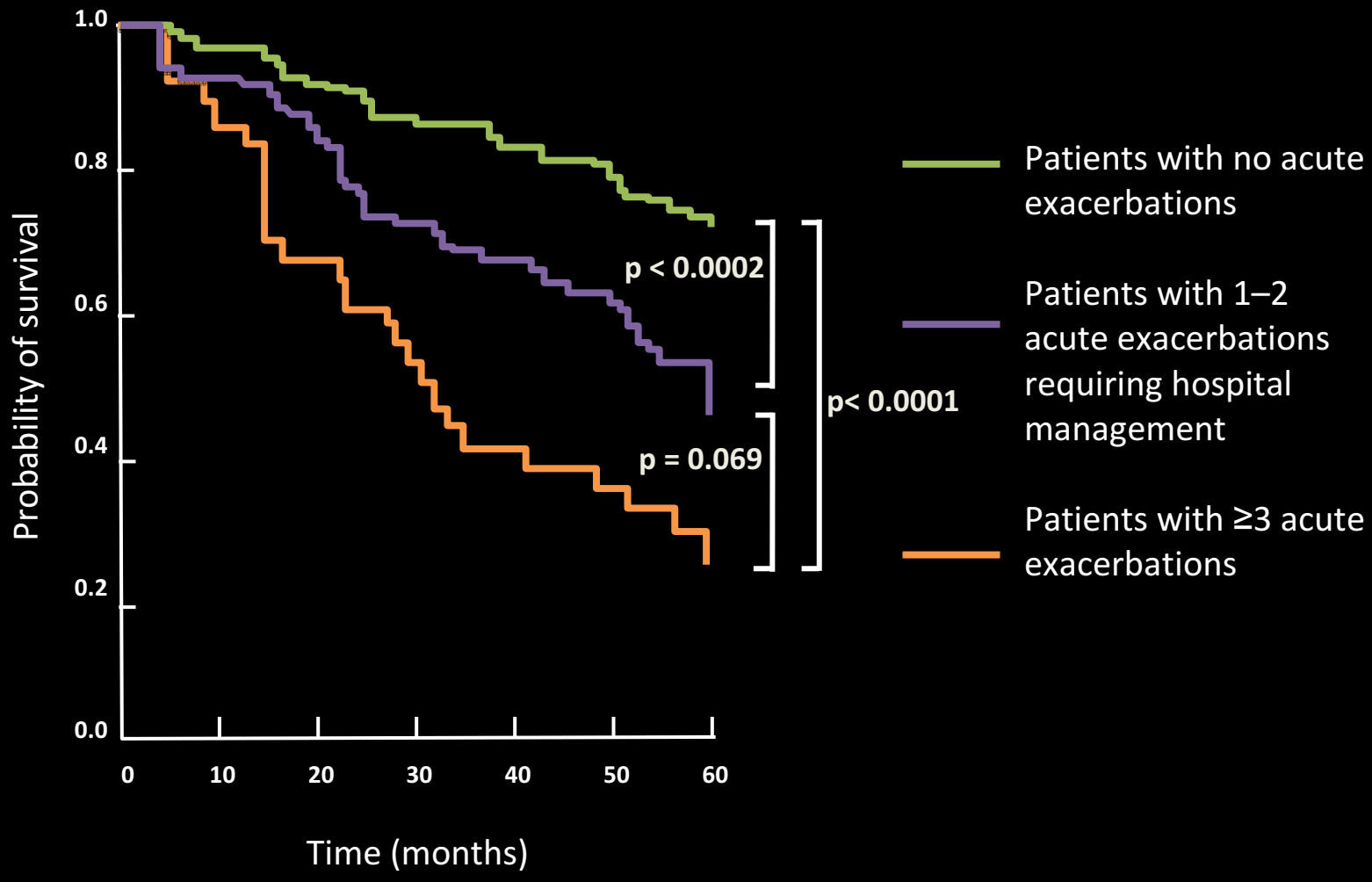
Postma D, Anzueto A, Calverley P et al. *Prim Care Respir J* **2011**; 20: 205-209.

Frequent exacerbations drive disease progression



Adapted from Wedzicha JA and Seemungal TA. *Lancet* **2007**;370:786-796.; and Donaldson GC and Wedzicha JA. *Thorax* **2006**;61:164-168.

Exacerbation Frequency and Severity Both Increase Mortality Risk



Soler-Cataluna JJ, Martinez-Garcia MÁ, Román Sánchez P, et al. *Thorax* **2005**;60:925-931.

Frequent exacerbators are found at all stages of COPD severity

GOLD stage	Base-line therapy		Exacerbation rate in year 1 (number/ patient)	% of patients who were 'Frequent exacerbators'
	% Patients on long-acting bronchodilators	% Patients on inhaled corticosteroids		
II	67	60	0.85	22
III	83	80	1.34	33
IV	86	86	2.00	47

Adapted from Hurst JR, Vestbo J, Anzueto A et al. *N Engl J Med* **2010**;363:1128-1138.

The ‘frequent exacerbator phenotype’: ECLIPSE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease

John R. Hurst, M.B., Ch.B., Ph.D., Jørgen Vestbo, M.D., Antonio Anzueto, M.D., Nicholas Locantore, Ph.D., Hana Müllerova, Ph.D., Ruth Tal-Singer, Ph.D., Bruce Miller, Ph.D., David A. Lomas, Ph.D., Alvar Agusti, M.D., Ph.D., William MacNee, M.B., Ch.B., M.D., Peter Calverley, M.D., Stephen Rennard, M.D., Emiel F.M. Wouters, M.D., Ph.D., and Jadwiga A. Wedzicha, M.D., for the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators*

ABSTRACT

BACKGROUND

Although we know that exacerbations are key events in chronic obstructive pulmonary disease (COPD), our understanding of their frequency, determinants, and effects is incomplete. In a large observational cohort, we tested the hypothesis that there is a frequent-exacerbation phenotype of COPD that is independent of disease severity.

METHODS

We analyzed the frequency and associations of exacerbation in 2138 patients enrolled in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study. Exacerbations were defined as events that led a care provider to prescribe antibiotics or corticosteroids (or both) or that led to hospitalization (severe exacerbations). Exacerbation frequency was observed over a period of 3 years.

RESULTS

Exacerbations became more frequent (and more severe) as the severity of COPD increased; exacerbation rates in the first year of follow-up were 0.85 per person for patients with stage 2 COPD (with stage defined in accordance with Global Initiative for Chronic Obstructive Lung Disease [GOLD] stages), 1.34 for patients with stage 3, and 2.00 for patients with stage 4. Overall, 22% of patients with stage 2 disease, 33% with stage 3, and 47% with stage 4 had frequent exacerbations (two or more in the first year of follow-up). The single best predictor of exacerbations, across all GOLD stages, was a history of exacerbations. The frequent-exacerbation phenotype appeared to be relatively stable over a period of 3 years and could be predicted on the basis of the patient's recall of previous treated events. In addition to its association with more severe disease and prior exacerbations, the phenotype was independently associated with a history of gastroesophageal reflux or heartburn, poorer quality of life, and elevated white-cell count.

CONCLUSIONS

Although exacerbations become more frequent and more severe as COPD progresses, the rate at which they occur appears to reflect an independent susceptibility phenotype. This has implications for the targeting of exacerbation-prevention strategies across the spectrum of disease severity. (Funded by GlaxoSmithKline; ClinicalTrials.gov number, NCT00292552.)

From the Academic Unit of Respiratory Medicine, Royal Free Campus, UCL Medical School, London (J.R.H., J.A.W.); Cardiology and Respiratory Medicine, Hvidovre Hospital and University of Copenhagen, Copenhagen (J.V.); the Respiratory Research Group, School of Translational Medicine, Manchester Academic Health Science Centre, University of Manchester, Manchester (J.V.), the Department of Medicine, University of Cambridge, Cambridge Institute for Medical Research, Cambridge (D.A.L.), and the Department of Respiratory Medicine, School of Clinical Science, University of Liverpool, Liverpool (P.C.) — all in the United Kingdom; the Pulmonary Section, University of Texas Health Science Center, San Antonio (A. Anzueto); GlaxoSmithKline, Research Triangle Park, NC (N.L.), London (H.M.), and King of Prussia, PA (R.T.-S., B.M.); Institut del Tòrax, Hospital Clínic, CIBER Enfermedades Respiratorias and Fundación Caubet-Cimera, Barcelona (A. Agustí); ELEGI Colt Research Labs, University of Edinburgh/MRC Centre for Inflammation Research, Queen's Medical Research Institute, Edinburgh (W.M.); the Department of Pulmonary and Critical Care Medicine, Nebraska Medical Center, Omaha (S.R.); and the Department of Respiratory Medicine, Maastricht University Medical Center, Maastricht, the Netherlands (E.F.M.W.). Address reprint requests to Dr. Vestbo at the Department of Cardiology and Respiratory Medicine 253, Hvidovre Hospital, Kettegaard Alle 30, 2650 Hvidovre, Denmark, or at jorgen.vestbo@manchester.ac.uk.

*Members of the ECLIPSE steering and scientific committees and the study investigators are listed in the Appendix.

N Engl J Med 2010;363:1128-38.

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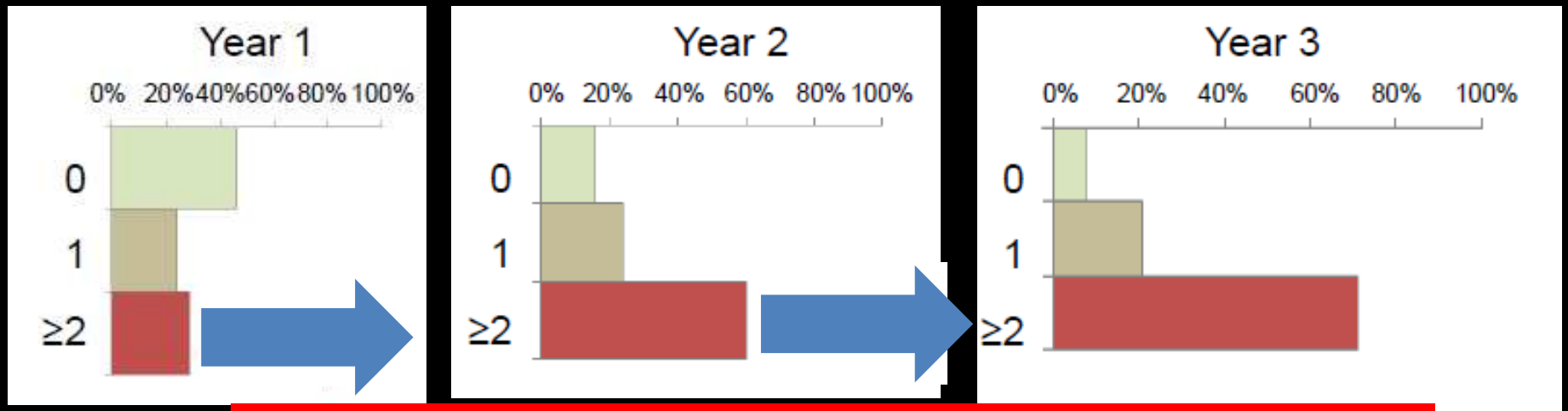
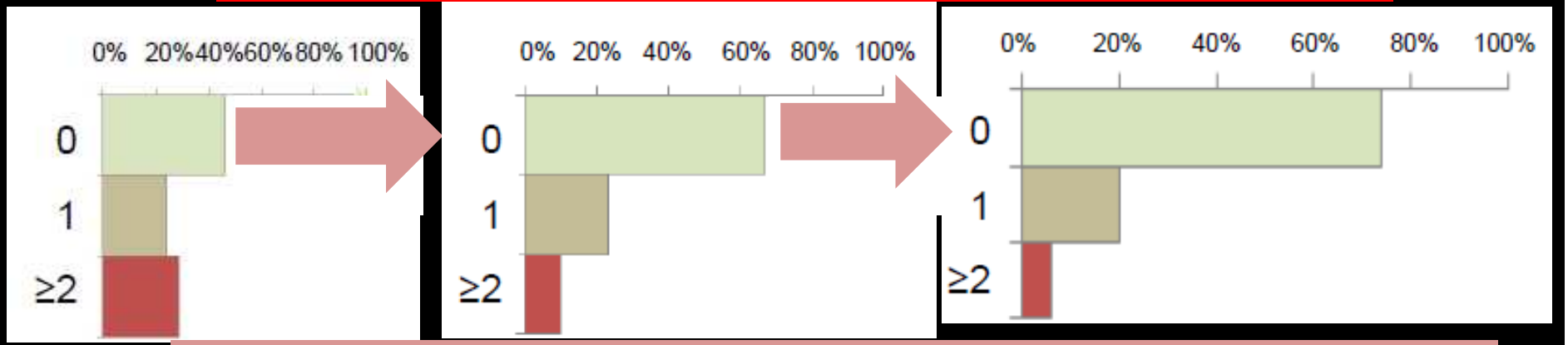
New England Journal of Medicine

2010;363:1128-38

The 'frequent exacerbator phenotype': ECLIPSE Stability of the Exacerbator Phenotype

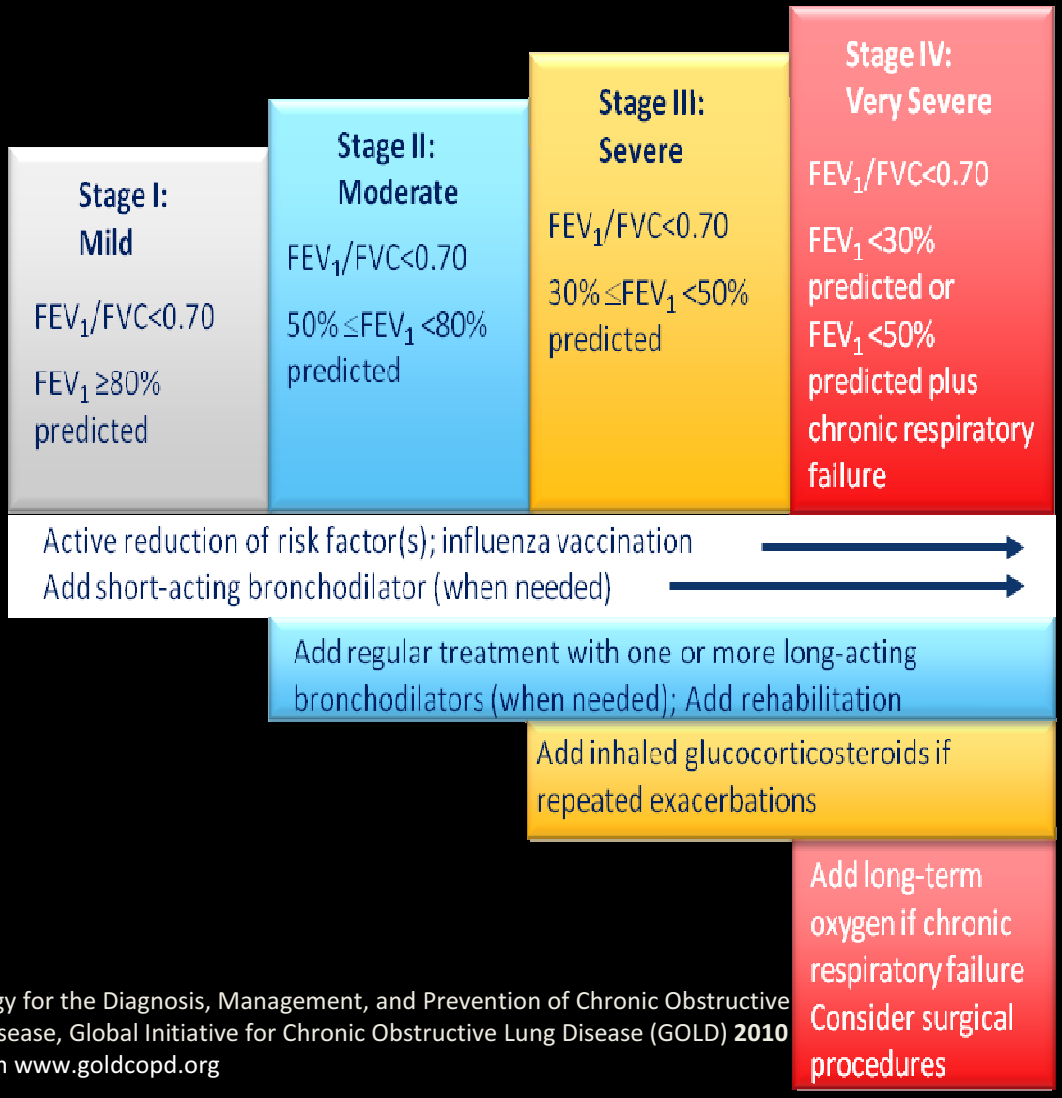


71% of Frequent Exacerbators in Year 1 and Year 2 were Frequent Exacerbators in Year 3



74% of patients having no exacerbations in Years 1 and Year 2 had no exacerbations in Year 3

Pharmacological treatments should be added stepwise as copd progresses



ADD ROFLUMILAST

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, Global Initiative for Chronic Obstructive Lung Disease (GOLD) **2010** Available from www.goldcopd.org

Mills EJ. Pharmacotherapies for COPD: a multiple treatment comparison meta-analysis. *Clin Epidemiol 2011*

- 26 RCTs evaluating LABA, LAMA, ICS, Roflumilast and combinations of these inteventions in moderate-to-severe COPD populations
- 36312 patients
- The primary outcome was the event rate of exacerbations

- Compared with all the 15 treatment combinations, the combination of Roflumilast+LAMA exhibited the largest treatment effects and had the highest probability (45%) of being the best 1st-line treatment

Primary Analysis (10 treatments)

Treatment	Exacerbations/pt/yr	95% CI
Placebo	1.21	1.17, 1.24
Roflumilast	1.03	0.87, 1.21
LABA	1.01	0.90, 1.11
LAMA	0.89	0.80, 0.98
ICS	0.96	0.85, 1.08
Roflumilast+LABA	0.81	0.58, 1.10
Roflumilast+LAMA	0.75	0.53, 1.02
LABA+LAMA	0.97	0.67, 1.34
ICS+LABA	0.83	0.73, 0.93
ICS+LABA+LAMA	0.82	0.57, 1.15

Mills EJ. Clin Epidemiol 2011

Secondary Analysis (10 combinations)

Treatment	Exacerb./pt/yr	95% CI
Roflumilast+LABA	0.87	0.75, 1.01
Roflumilast+LAMA	0.75	0.64, 0.87
Roflumilast+ICS	0.82	0.71, 0.95
LABA+LAMA	0.77	0.67, 0.87
LABA+ICS	0.85	0.77, 0.94
LAMA+ICS	0.73	0.64, 0.82
Roflumilast+LABA+LAMA	0.65	0.54, 0.77
Roflumilast+LABA+ICS	0.71	0.61, 0.83
LABA+LAMA+ICS	0.63	0.54, 0.73
Roflumilast+LABA+LAMA+ICS	0.53	0.43, 0.64

Mills EJ. Clin Epidemiol 2011