In What Patients Should I use LAMA in asthma?

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박 혜 윤

In What Patients Should We Screen Chest CT scan?

The National Lung Screening Trial (NLST)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 4, 2011 VOL. 365 NO. 5

Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team*

53,454 patients at high risk for lung cancer.
Low dose CT vs. PA CXR

In What Patients Should We Screen Chest CT scan?

The National Lung Screening Trial (NLST)

There were 247 deaths from lung cancer per 100,000 person-years in the low-dose CT group and 309 deaths per 100,000 person-years in the radiography group, representing a relative reduction in mortality from lung cancer with low-dose CT screening of 20.0% (95% CI, 6.8 to 26.7; P=0.004). The rate of death from any cause was reduced in the low-dose CT group, as compared with the radiography group, by 6.7% (95% CI, 1.2 to 13.6; P=0.02).

CONCLUSIONS

Screening with the use of low-dose CT reduces mortality from lung cancer. (Funded by the National Cancer Institute; National Lung Screening Trial ClinicalTrials.gov number, NCT00047385.)

In What Patients Should We Screen Chest CT scan?

폐암 검진 권고안 (2015.9.)

- Eligible Participants
  - Age : 55-74 years
  - Smoking status
    - At least 30 pack-years
    - Continue to smoke or have quit within the previous 15 years

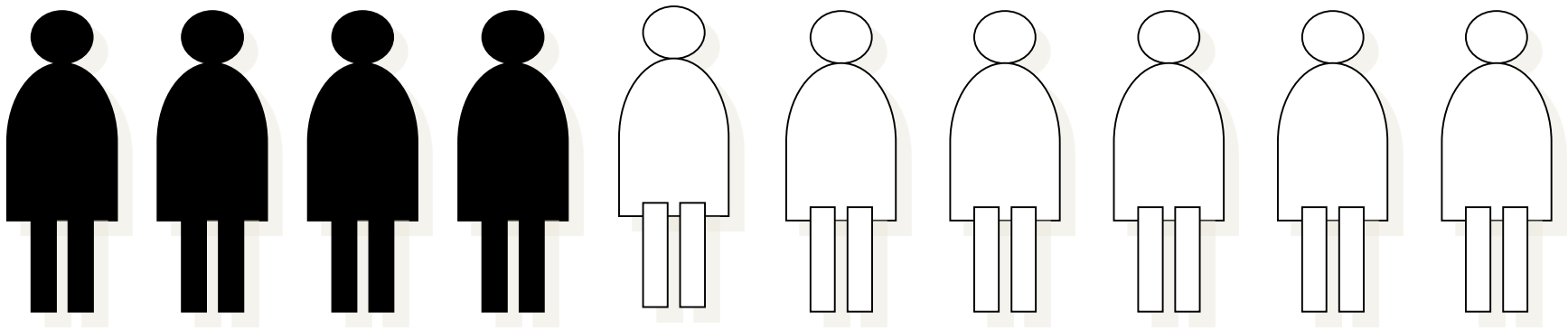
LAMA in asthma?

ICS + LABA

LAMA

Poorly Controlled Asthma: we need more

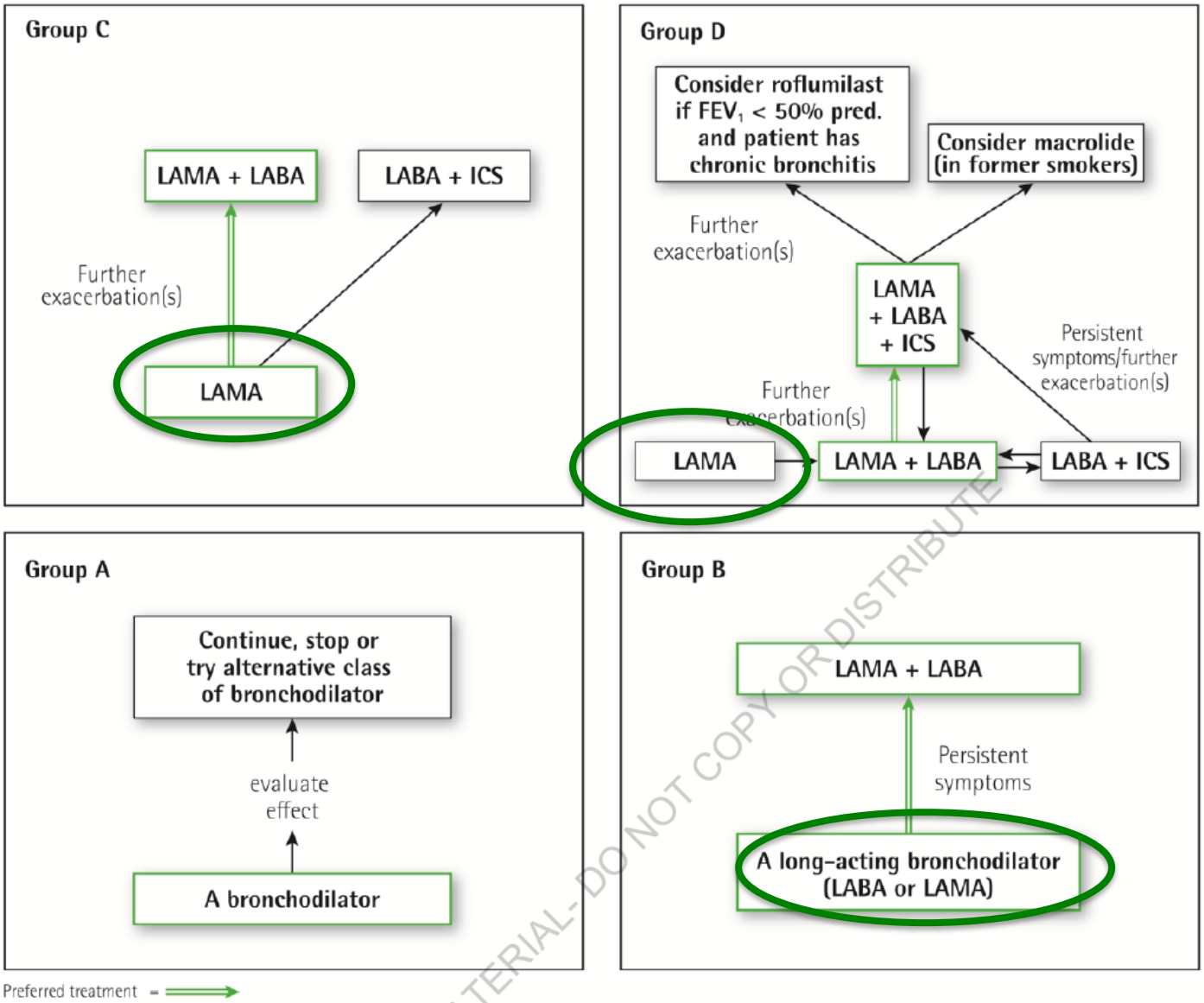
- Many asthma patients remain uncontrolled:
  - **At least 40%** of patients experience asthma symptoms and exacerbations despite treatment with ICS administered as monotherapy or in combination with a LABA

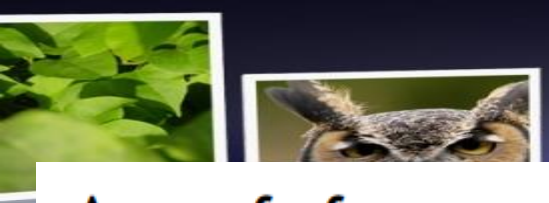


AJRCCM 2004; 170, 836-844
J Allergy Clin Immunol 2004;114:40-47

2017 GOLD guideline

The pivotal role of LAMA in COPD





A proof of concept study to evaluate stepping down the dose of fluticasone in combination with salmeterol and tiotropium in severe persistent asthma

4weeks (n=18)

Tom Fardon, Kay Haggart, Daniel K.C. Lee, Brian J. Lipworth*

2007

Improvements with tiotropium in COPD patients with concon

H. Magnus
F. Gerken , S. Kesten

Lung Function Improvement with Tiotropium

Tiotropium improves lung function in patients with severe uncontrolled asthma: A randomized controlled trial

24weeks (n=107)

Huib A. M. Kerstjens, MD, PhD,[a] Bernd Disse, MD, PhD,[b] Winfried Schröder-Babo, MD,[c] Theo A. Bantje, MD,[d] Martina Gahlemann, MD,[b] Ralf Sigmund, Dipl-Math oec,[b] Michael Engel, MD,[b] and Jan A. van Noord, MD[e] *Groningen, Breda, and Heerlen, The Netherlands, and Biberach and Gelnhausen, Germany*

Boehringer Ingelheim

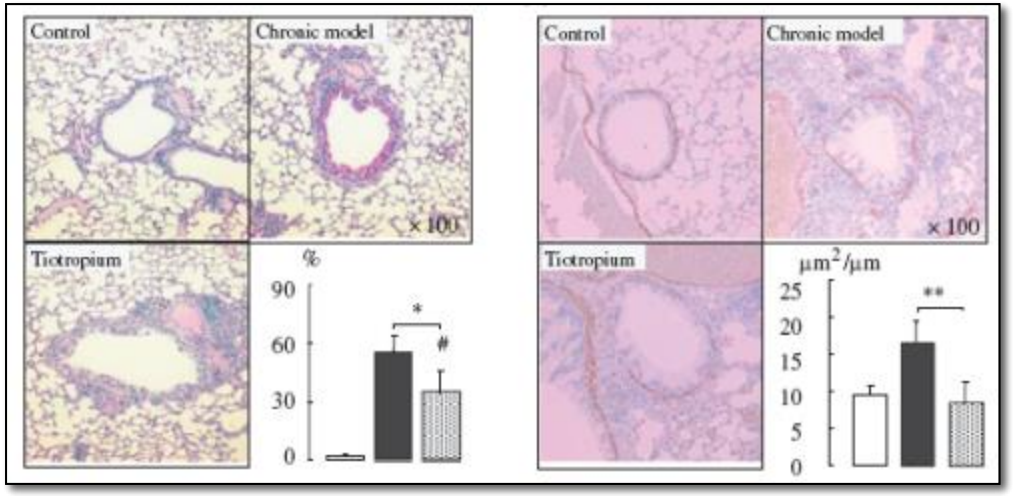
2011

Effect of TIOT on airway inflammation and remodeling in a mouse model of asthma

Effect of Tiotropium on airway remodeling

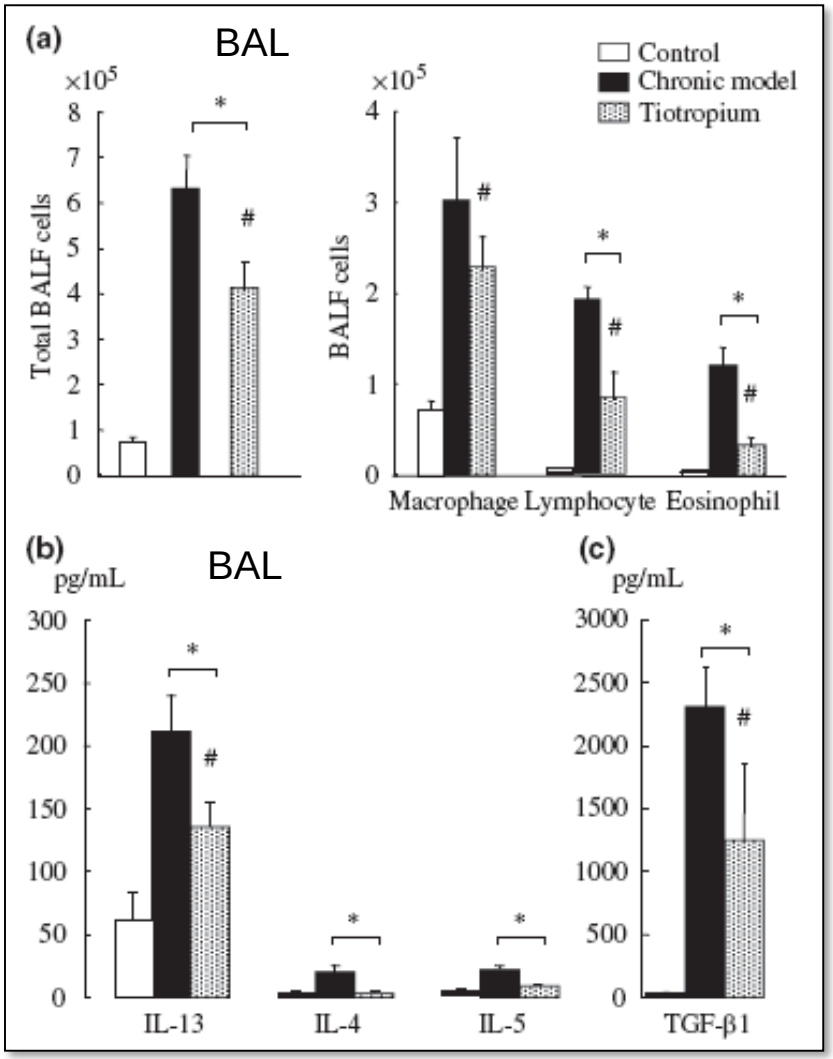
- Inhibit Th2 cytokine production
- Inhibit airway inflammation

Lung section



PAS staining

α-actin staining



Clinical & Experimental Allergy 2010; 40: 1266

ORIGINAL ARTICLE

Primo TinA

Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy

Huib A.M. Kerstjens, M.D., Michael Engel, M.D., Ronald Dahl, M.D., Pierluigi Paggiaro, M.D., Ekkehard Beck, M.D., Mark Vandewalker, M.D., Ralf Sigmund, Dipl.Math., Wolfgang Seibold, M.D., Petra Moroni-Zentgraf, M.D., and Eric D. Bateman, M.D.

Inclusion Criteria

Boehringer Ingelheim

- 18-75 year
- Never smoked, or ex-smoker for more than 1 year (≤10 PY)
- Diagnosed before 40 years, with ≥ 5 year history of asthma
- Poorly controlled asthma
  - Despite stable **high-dose ICS (budesonide ≥ 800 μg or equivalent) + LABA**
  - Symtomatic :**mean ACQ-7 score ≥ 1.5**
  - Postbronchodialtor FEV_1 ≤ 80% predicted & FVC ≤ 70% predicted
  - At least one exacerbation in previous year

Exclusion Criteria

-Dx of COPD, serious coexisting illness, concurrent use of anticholinergics

N Eng J Med 2012; 356(13):1198-207

Daily doses of ICS

Budesonide ≥ 800 µg or equivalent

Adults and adolescents (12 years and older)			
Drug	**Daily dose (mcg)**		
	Low	Medium	High
Beclometasone dipropionate (CFC)*	200–500	>500–1000	>1000
Beclometasone dipropionate (HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100	n.a.	200
Fluticasone propionate(DPI)	100–250	>250–500	>500
Fluticasone propionate (HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000

ACQ-7 score (≥ 1.5: not-fully controlled)

1. On average, during the past week, how often were you **woken by your asthma** during the night?
   0 Never
   1 Hardly ever
   2 A few times
   3 Several times
   4 Many times
   5 A great many times
   6 Unable to sleep because of asthma
2. On average, during the past week, how **bad were your asthma symptoms when you woke** up in the morning?
   0 No symptoms
   1 Very mild symptoms
   2 Mild symptoms
   3 Moderate symptoms
   4 Quite severe symptoms
   5 Severe symptoms
   6 Very severe symptoms
3. In general, during the past week, how **limited were you in your activities** because of your asthma?
   0 Not limited at all
   1 Very slightly limited
   2 Slightly limited
   3 Moderately limited
   4 Very limited
   5 Extremely limited
   6 Totally limited
4. In general, during the past week, how much **shortness of breath** did you experience because of your asthma?
   0 None
   1 A very little
   2 A little
   3 A moderate amount
   4 Quite a lot
   5 A great deal
   6 A very great deal
5. In general, during the past week, how much of the time did you **wheeze**?
   0 Not at all
   1 Hardly any of the time
   2 A little of the time
   3 A moderate amount of the time
   4 A lot of the time
   5 Most of the time
   6 All the time
6. On average, during the past week, how many **puffs of short-acting bronchodilator** (e.g., Ventolin) have you used each day?
   0 None
   1 1–2 puffs most days
   2 3–4 puffs most days
   3 5–8 puffs most days
   4 9–12 puffs most days
   5 13–16 puffs most days
   6 More than 16 puffs most days
7. FEV_1 prebronchodilator: .....
   FEV_1% predicted: .....
   FEV_1% predicted: .....
   (Record actual values on the dotted lines and score the FEV_1% predicted in the next column)

   0 > 95% predicted
   1 95–90%
   2 89–80%
   3 79–70%
   4 69–60%
   5 59–50%
   6 < 50% predicted

ACQ-7 score = Divide sum by 7

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Table 1. Baseline Characteristics of the Patients.*

Characteristic	All Patients (N=912)	Trial 1		Trial 2	
		Tiotropium (N=237)	Placebo (N=222)	Tiotropium (N=219)	Placebo (N=234)
Use of maintenance oral glucocorticoids — %**	5.3	6.8	5.0	3.7	5.6
Use of omalizumab — %	3.9	2.5	4.5	2.7	6.0
Mean daily no. of puffs of short-acting beta-agonists††	3.2	2.8	3.3	3.4	3.3

N Eng J Med 2012; 356(13):1198-207

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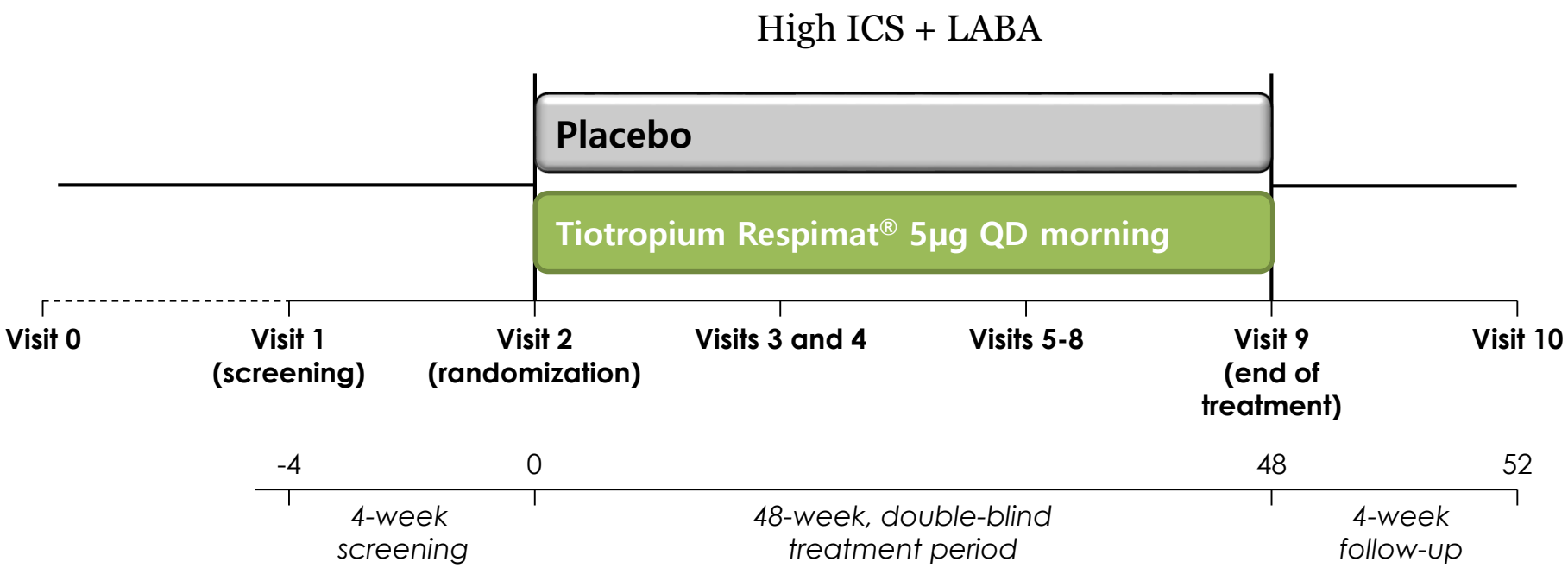
		Tiotropium (N=237)	Placebo (N=222)	Tiotropium (N=219)	Placebo (N=234)
Forced expiratory volume in 1 sec					
Value before bronchodilation — liters**	1.603±0.540	1.596±0.546	1.558±0.537	1.659±0.569	1.598±0.506
Percent of predicted value before bronchodilation	54.8±12.4	54.6±12.2	54.6±12.2	55.1±12.8	55.0±12.6
Percent of predicted value after bronchodilation	62.2±12.7	61.5±12.5	62.7±12.6	62.6±12.5	62.3±13.0
Reversibility — ml	217±217	201±211	230±223	228±206	209±229

Study design

2 Trial, 48 week, Double-blind, Randomized, Placebo-controlled, Parallel group (n=912)

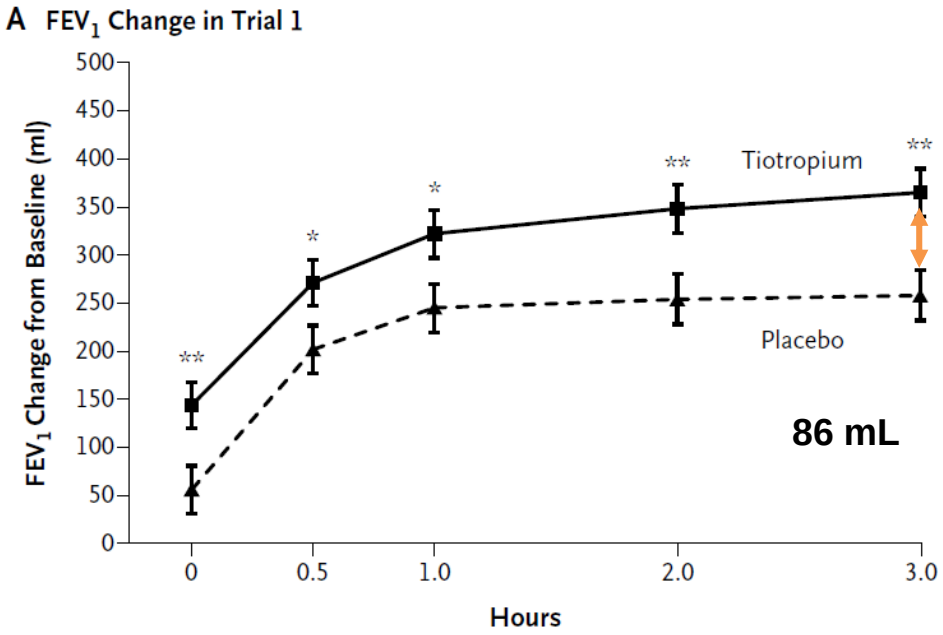


Peak FEV_1 (0-3h) after 24weeks
Trough FEV_1 after 24 weeks
Time to first severe asthma exacerbation in pooled analysis after 48 weeks

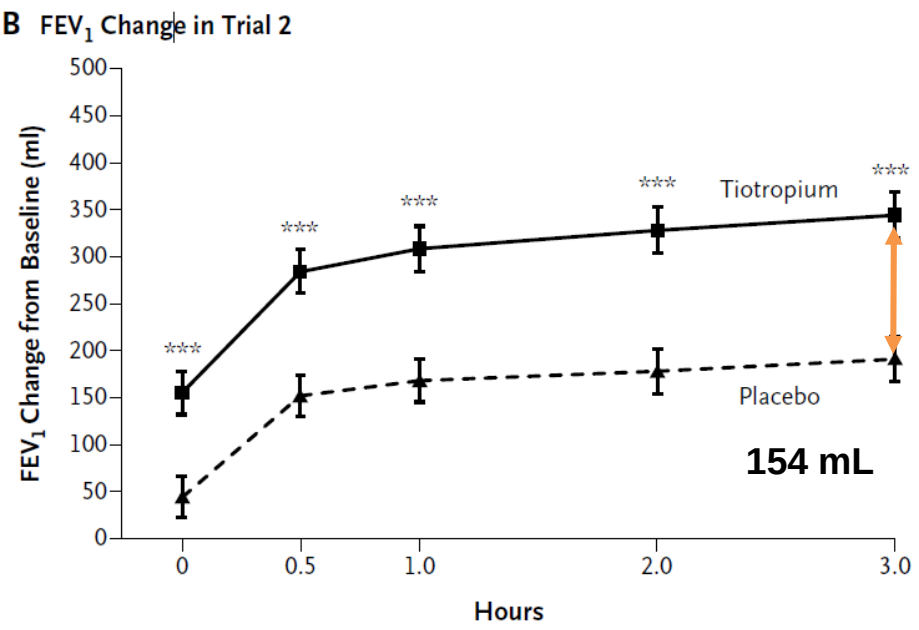
6(13):1198-207

Primary Outcome: Peak FEV_1 at 24 weeks

Trial 1



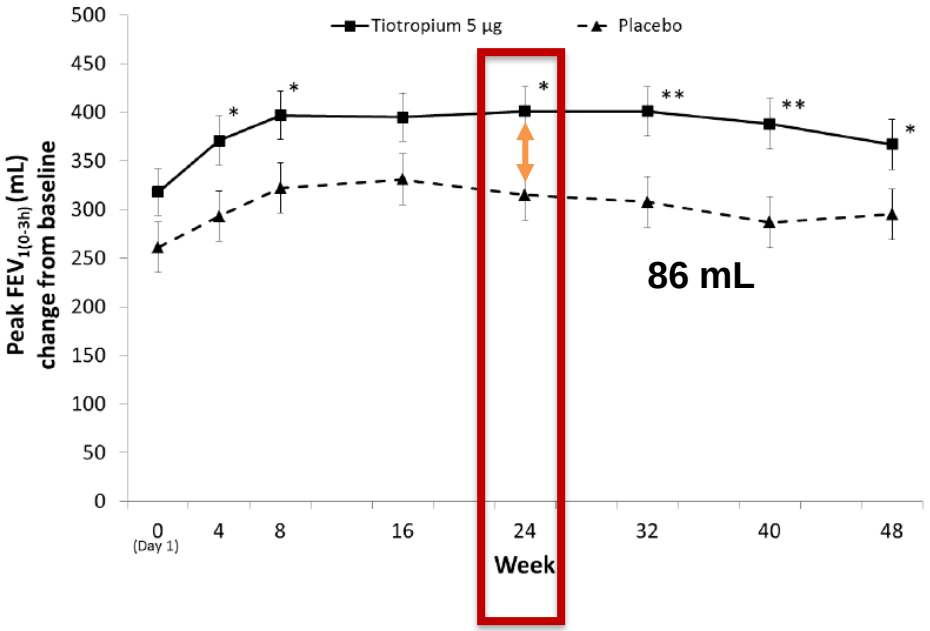
Trial 2



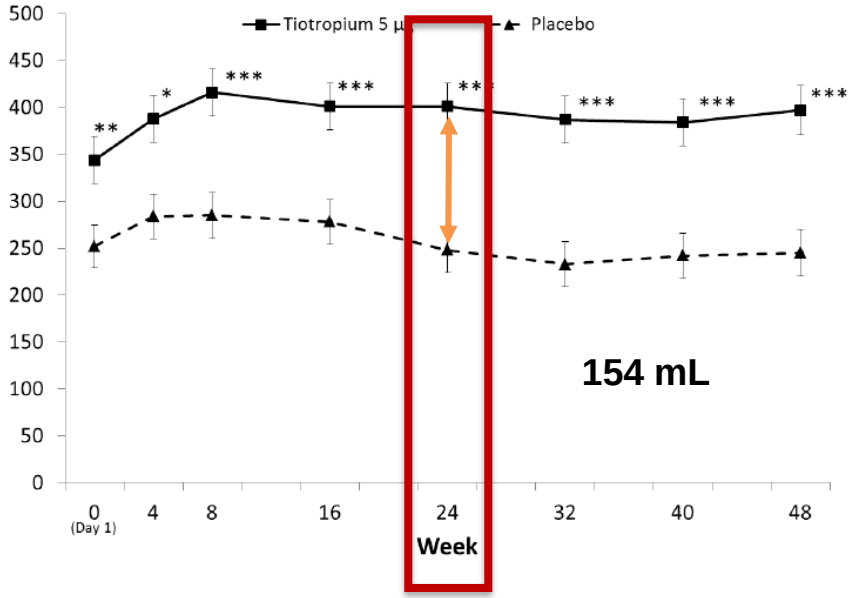
N Eng J Med 2012; 356(13):1198-207

Primary Outcome: Peak FEV_1 at 24 weeks

Trial 1



Trial 2

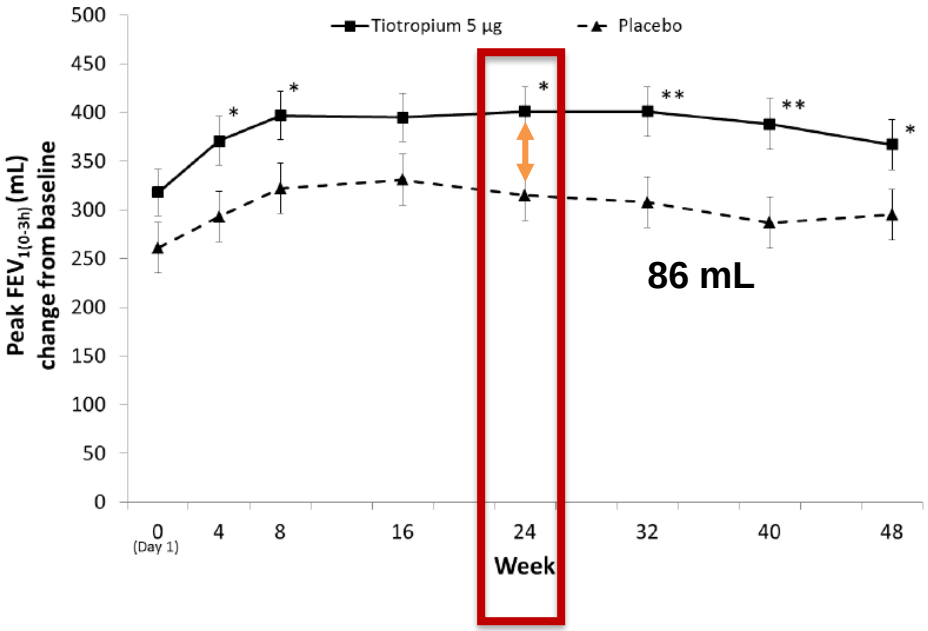


N Eng J Med 2012; 356(13):1198-207

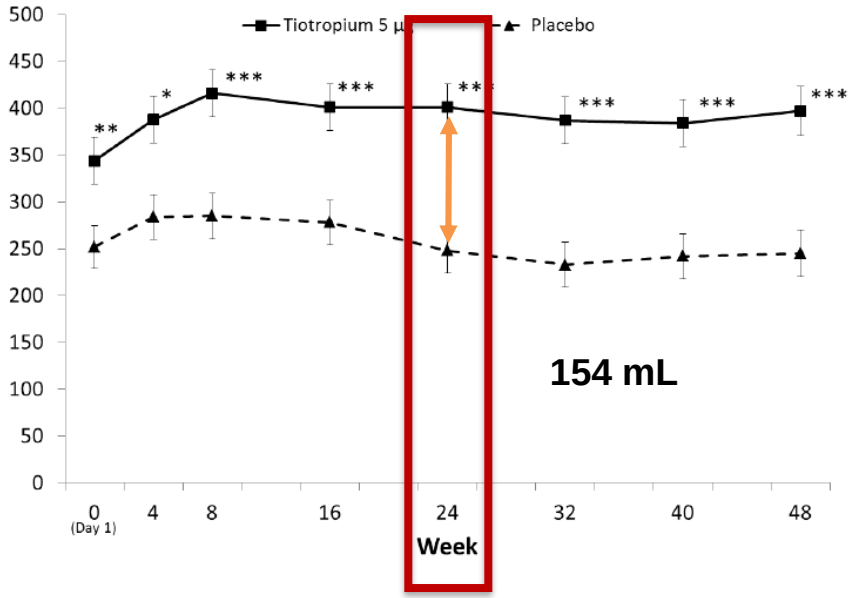
Primary Outcome: Peak FEV_1 at 24 weeks

Subgroup analysis
- Men
- Former smokers with a history of fewer than 10 pack-years
- Lower FEV_1 (% pred)

Trial 1



Trial 2



N Eng J Med 2012; 356(13):1198-207

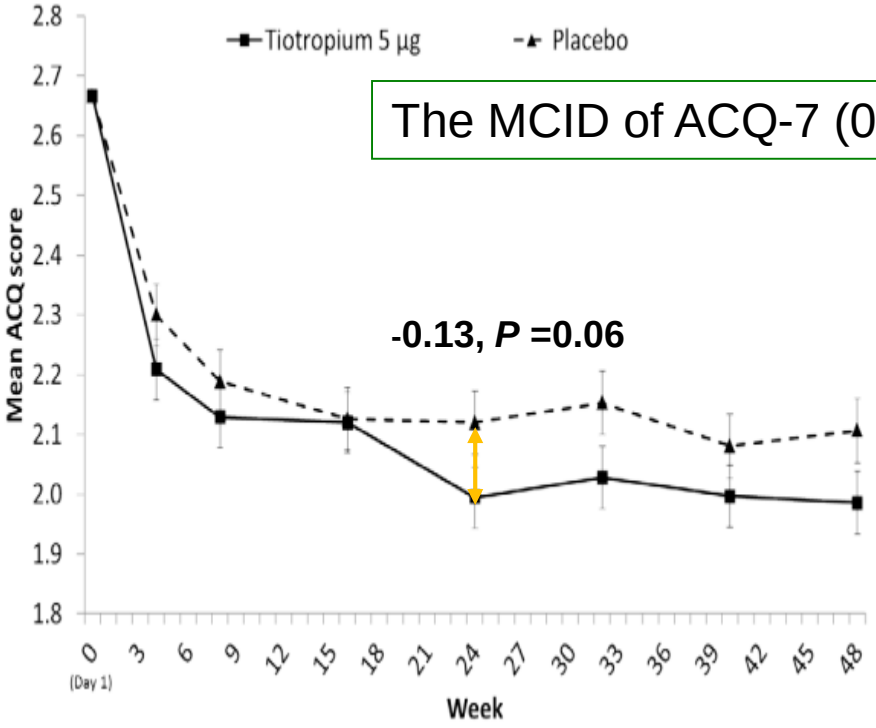
Primary Outcome

Measure and Week	Trial 1		Trial 2	
	No. of Patients	Difference in Change *mean (95% CI)*	No. of Patients	Difference in Change *mean (95% CI)*
Forced expiratory volume in 1 sec				
Peak at 0–3 hr (ml)				
24 wk†	428	86 (20 to 152)‡	423	154 (91 to 217)§
48 wk	417	73 (5 to 140)‡	403	152 (87 to 217)§
Trough (ml)				
24 wk†	428	88 (27 to 149)¶	422	111 (53 to 169)§
48 wk	417	42 (–21 to 104)	402	92 (32 to 151)¶

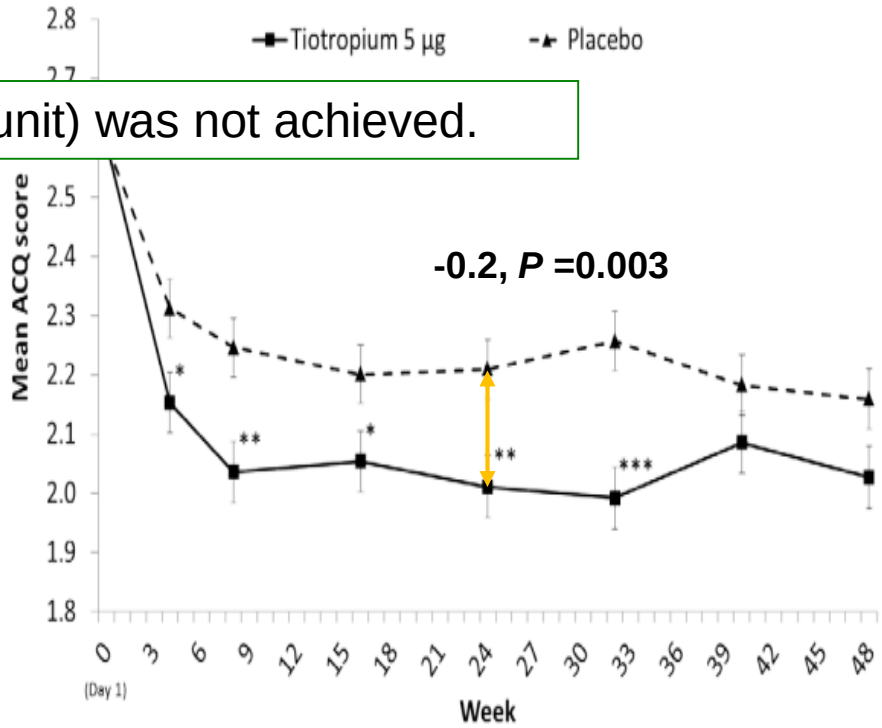
N Eng J Med 2012; 356(13):1198-207

Asthma Control (ACQ-7)

Trial 1



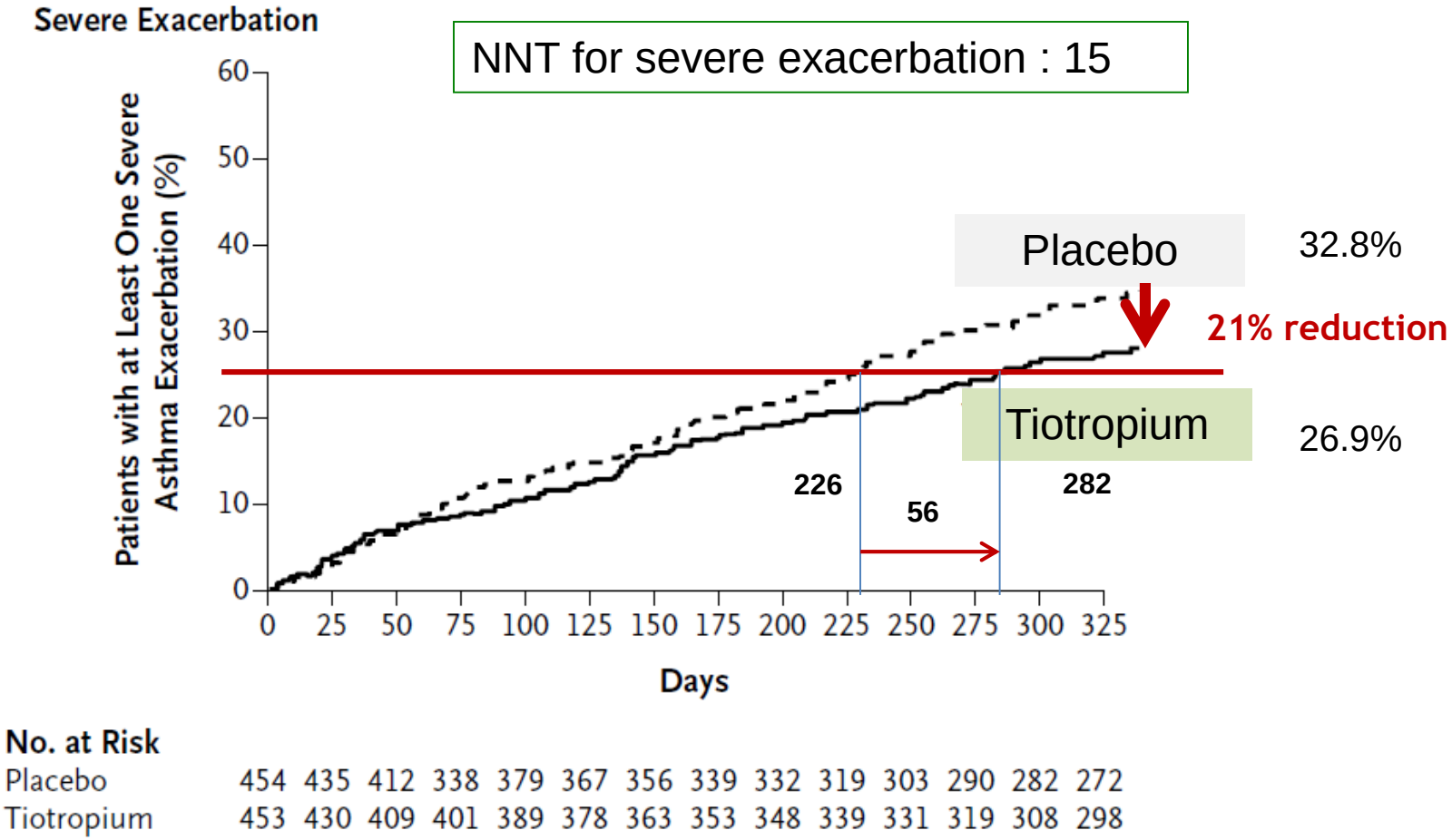
Trial 2



The MCID of ACQ-7 (0.5 unit) was not achieved.

N Eng J Med 2012; 356(13):1198-207

Co-primary Outcome: Severe Exacerbation



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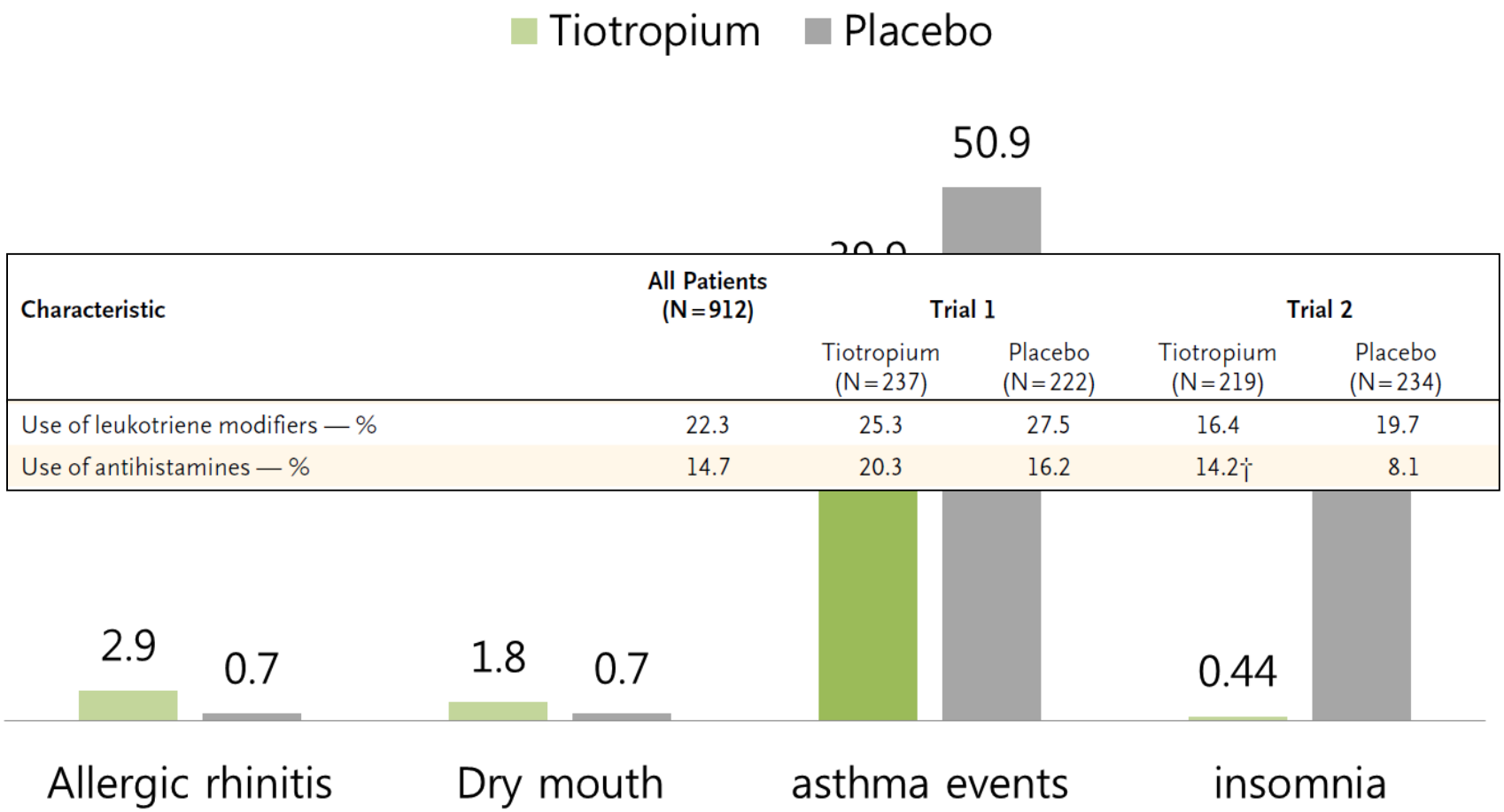
Adverse events



Characteristic	All Patients (N=912)	Trial 1		Trial 2	
		Tiotropium (N=237)	Placebo (N=222)	Tiotropium (N=219)	Placebo (N=234)
Use of leukotriene modifiers — %	22.3	25.3	27.5	16.4	19.7
Use of antihistamines — %	14.7	20.3	16.2	14.2†	8.1

N Eng J Med 2012; 356(13):1198-207

Summary1 (PrimoTinA)

Addition of Tiotropium to high dose ICS+ LABA in patients with

- Asthma > 5 year Hx & diagnosed before 40 yrs
- Never smoker or **< 10 PY, no smoking in the year**
- Poorly controlled asthma
  - ACQ-7 > 1.5, **FEV_1 ≤ 80% & FVC ≤ 70% after BD**
  - At least one severe exacerbation in previous year

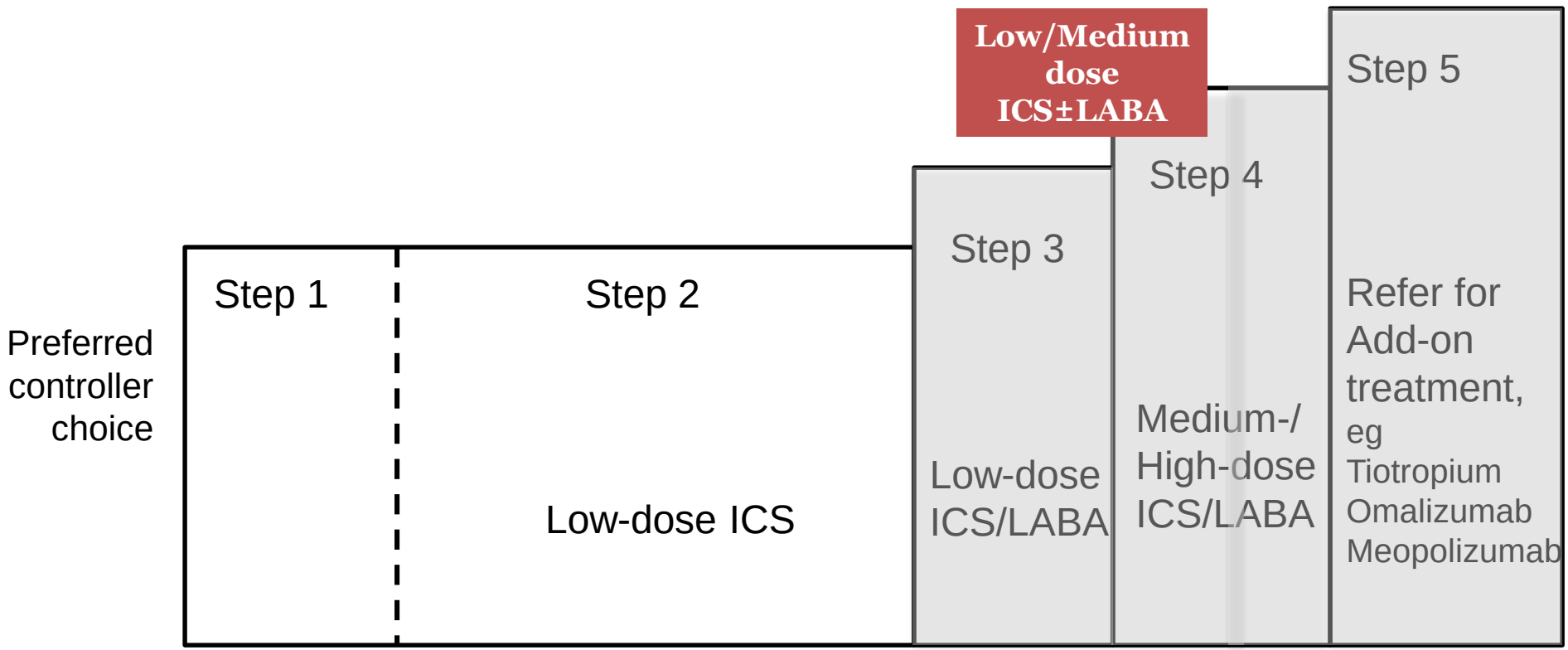
- Improvement in lung function

- Reduction in risk of asthma exacerbation

- Similar safety to placebo

Positioning of TIOT in asthma

Poorly controlled asthma despite high-dose ICS/LABA



Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma

Eric D. Bateman, MD,[a] Oliver Kornmann, MD,[b] Peter Schmidt, PhD,[c] Anna Pivovarova, DiplStat,[c] Michael Engel, MD,[c] and Leonardo M. Fabbri, MD[d] *Cape Town, South Africa, Frankfurt and Biberach, Germany, and Modena, Italy*

Boehringer Ingelheim

Patients aged 18 to 67 years with a history of asthma, with the B16-Arg/Arg genotype and with medium-to-high dose ICS **(budesonide 400-1000 µg or equivalent) ± LABA** (n=388)

Salmeterol

Tiotropium is not inferior to salmeterol.

Both of them are superior to placebo

TABLE II. The primary analysis of efficacy

Mean weekly morning predose PEF (L/min)*				Treatment differences				
	Placebo (n = 125)	Tiotropium (n = 128)	Salmeterol (n = 134)	Comparison	Difference (SE)	95% CI	Noninferiority‡§	Superiority
End of trial	333.3 (4.84)	354.0 (4.87)	354.8 (4.64)	Placebo-tiotropium	−20.70 (6.375)	−33.241 to −8.16	–	0.001
Change from baseline to end of trial†	−24.6 (4.84)	−3.9 (4.87)	−3.2 (4.64)	Placebo-salmeterol	−21.48 (6.319)	−33.912 to −9.06	–	0.001
				Tiotropium-salmeterol	−0.78 (6.261)	−13.096 to 11.53	0.002	–

Weeks of double-blind treatment

Weeks of follow-up with salmeterol

Numbers of patients

Double-blind treatment period:	Placebo n=125	Tiotropium n=128	Salmeterol n=134
Follow-up period:	Placebo n=118	Tiotropium n=121	Salmeterol n=127

J Allergy Clin Immunol 2011;128,315

Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials

*Huib A M Kerstjens, Thomas B Casale, Eugene R Bleecker, Eli O Meltzer, Emilio Pizzichini, Olaf Schmidt, Michael Engel, Loek Bour, Cynthia B Verkleij, Petra Moroni-Zentgraf, Eric D Bateman**

Mezzo TinA

Boehringer Ingelheim

Inclusion Criteria

- 18-75 year
- Never smoked, or ex-smoker for more than 1 year (≤10 PY)
- Diagnosed before 40 years, with ≥ 3-month history of asthma
- Partly controlled asthma
    - Despite stable medium-dose ICS (budesonide **400-800 μg or equivalent) alone or in fixed combination with LABA**
    - Symtomatic :**mean ACQ-7 score ≥ 1.5**
    - Prebronchodilator FEV_1 60-90% predicted
    - Reversibility of 12% and 200 mL (15-30mins after salbutamol)

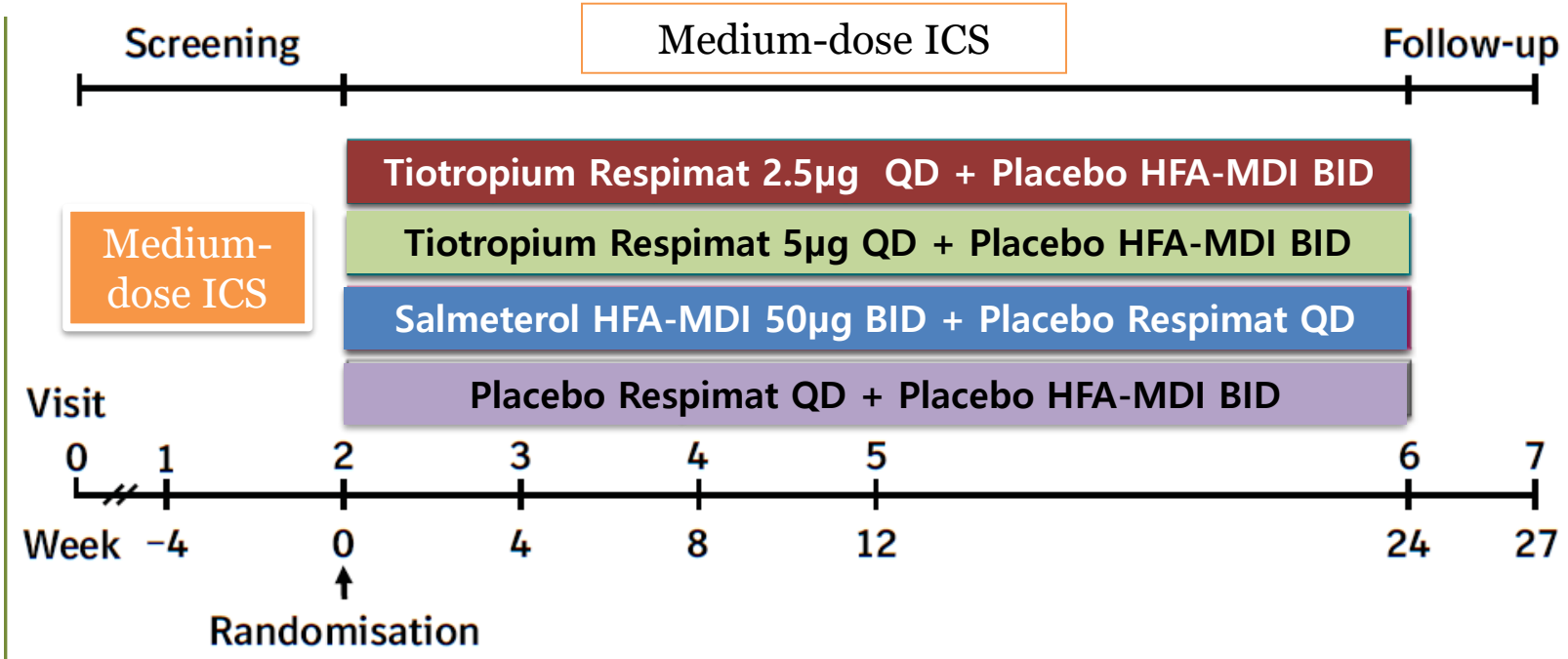
Exclusion Criteria

-Dx of COPD, serious coexisting illness, concurrent use of anticholinergics or beta blockers within 4 weeks before or during screening

Lancet Respir Med 2015, 3 (5) 367

Study design

2 trials, 24 week, Double-blind, Randomized, Placebo- and Active-controlled, Parallel group (n=2103)

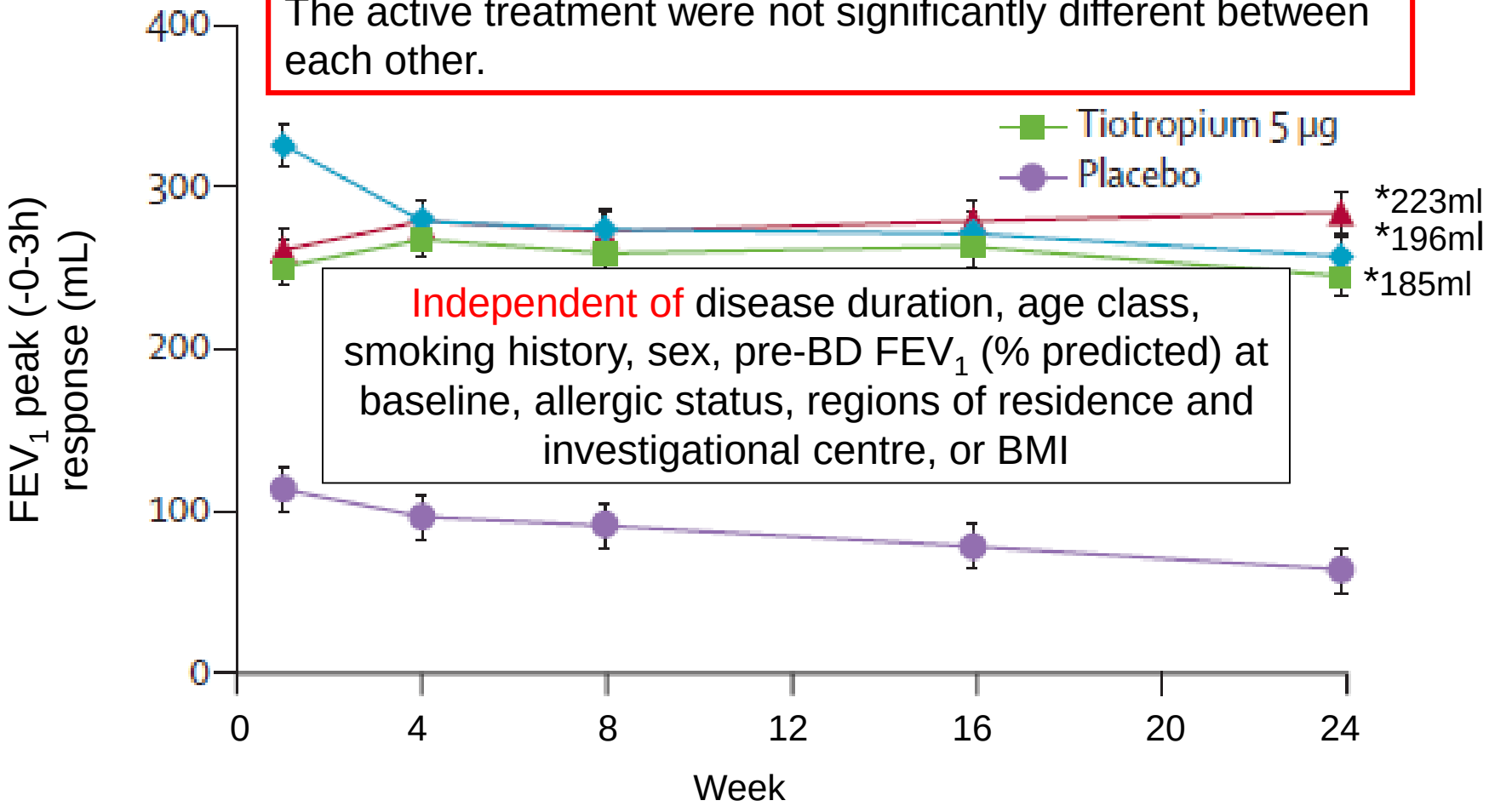


Peak FEV_1 (0-3h) after 24weeks
Trough FEV_1 after 24 weeks
ACQ-7 responder rate after 24 weeks in pooled data

Lancet Respir Med 2015, 3 (5) 367

Primary Outcome: Peak FEV_1 response

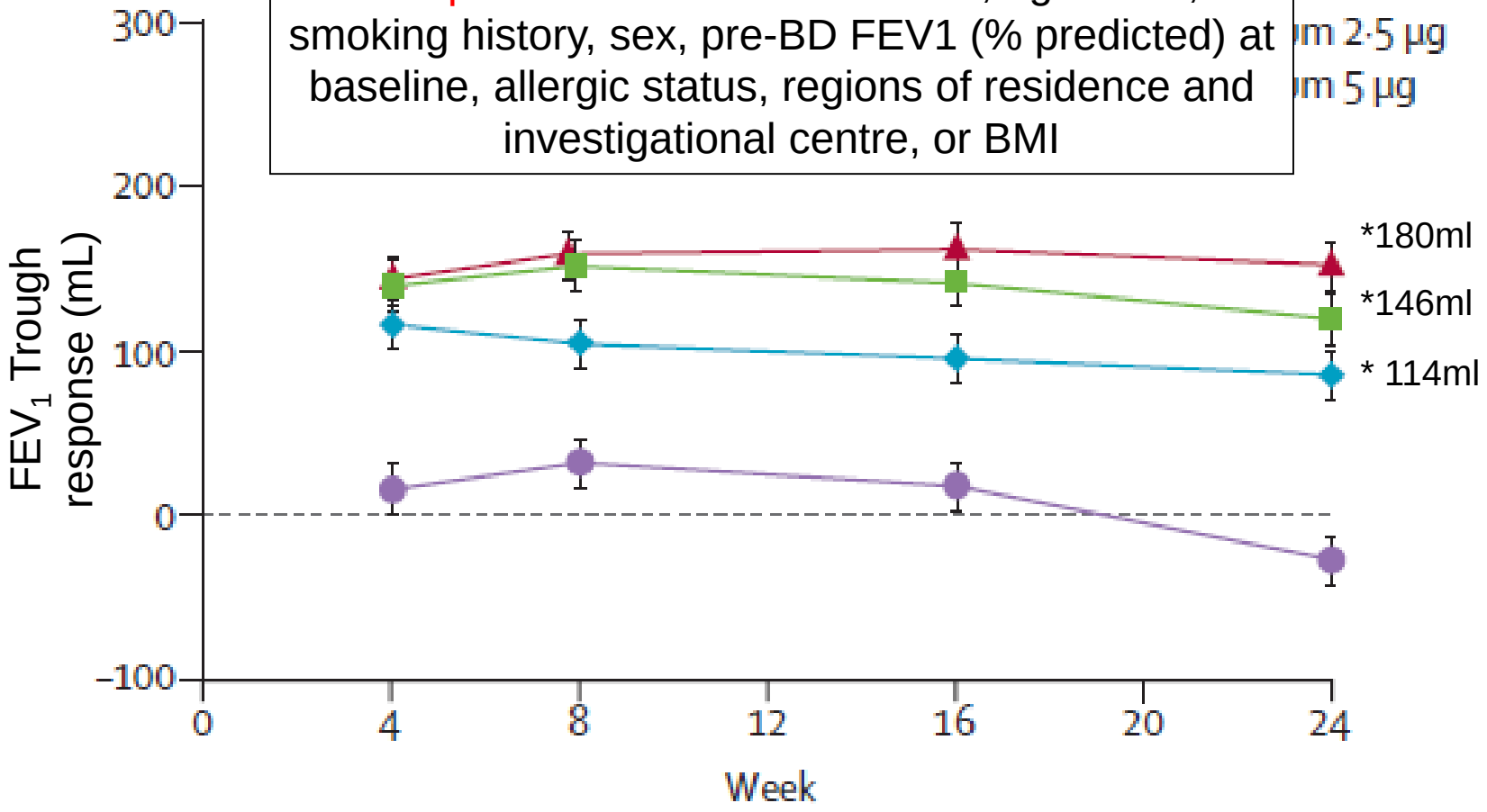
The active treatment were not significantly different between each other.



Lancet Respir Med 2015, 3 (5) 367

Primary Outcome: Tough FEV_1

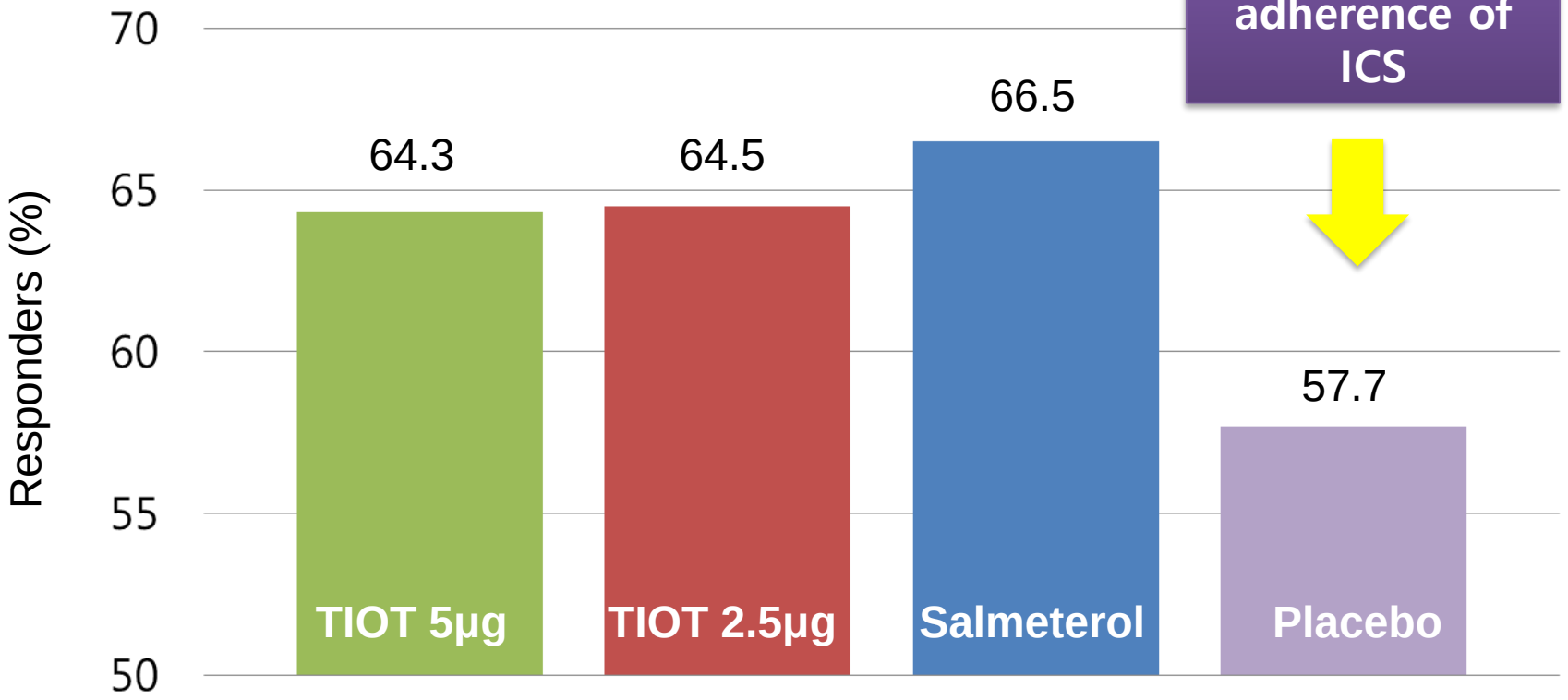
Independent of disease duration, age class, smoking history, sex, pre-BD FEV1 (% predicted) at baseline, allergic status, regions of residence and investigational centre, or BMI



Lancet Respir Med 2015, 3 (5) 367

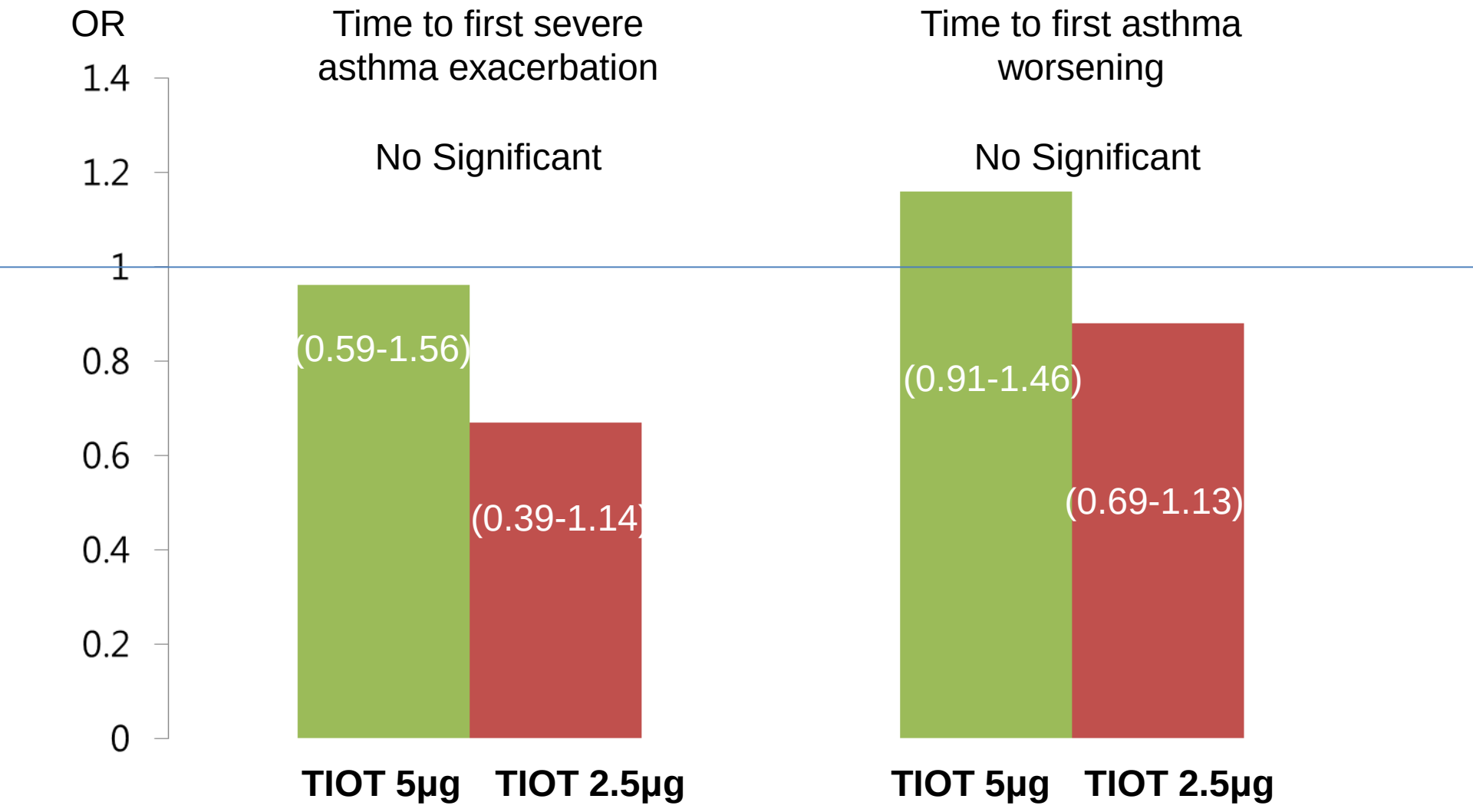
Primary Outcome: ACQ-7 responder (ACQ-7 ≥0.5) rate

Odd Ratio*	**1.32**	**1.33**	**1.45**
95% CI	1.02, 1.71	1.03, 1.72	1.13, 1.89



Lancet Respir Med 2015, 3 (5) 367

Exacerbation Tiotropium vs. Salmeterol



Lancet Respir Med 2015, 3 (5) 367

Summary 2 (Mezzo TinA)

Addition of Tiotropium to medium dose ICS in patients with

- Asthma diagnosed before 40 yrs
- Never smoker or < 10 PY, no smoking in the year
- Partly controlled asthma
  - ACQ-7 > 1.5, prebronchodialtor FEV_1 60-90% predicted
  - Reversibility of 12% and 200 mL (15-30mins after salbutamol)

- Improvement in lung function and asthma control compared with placebo, and similar efficacy and tolerability to salmeterol

Beeh *et al. Respiratory Research* 2014, **15**:61
http://respiratory-research.com/content/15/1/61

RESPIRATORY RESEARCH

RESEARCH Open Access

Tiotropium Respimat® in asthma: a double-blind, randomised, dose-ranging study in adult patients with moderate asthma

Kai-Michael Beeh[1*], Petra Moroni-Zentgraf[2], Othmar Ablinger[3], Zuzana Hollaenderova[4], Anna Unseld[5], Michael Engel[2] and Stephanie Korn[6]

Inclusion Criteria

- 18-75 year
- Never smoked, or ex-smoker for more than 1 year (≤10 PY)
- Diagnosed before 40 years, with ≥ 3-month history of asthma
- Partly controlled asthma
  - Despite stable medium-dose ICS (budesonide **400-800 µg or equivalent) alone or in fixed combination with LABA**
  - Symtomatic :mean ACQ-7 score ≥ 1.5
  - Prebronchodilator FEV_1 60-90% predicted
  - Reversibility of 12% and 200 mL (15-30mins after salbutamol)

Study Design

The randomised, double-blind placebo-controlled, four-way crossover study (n=149)

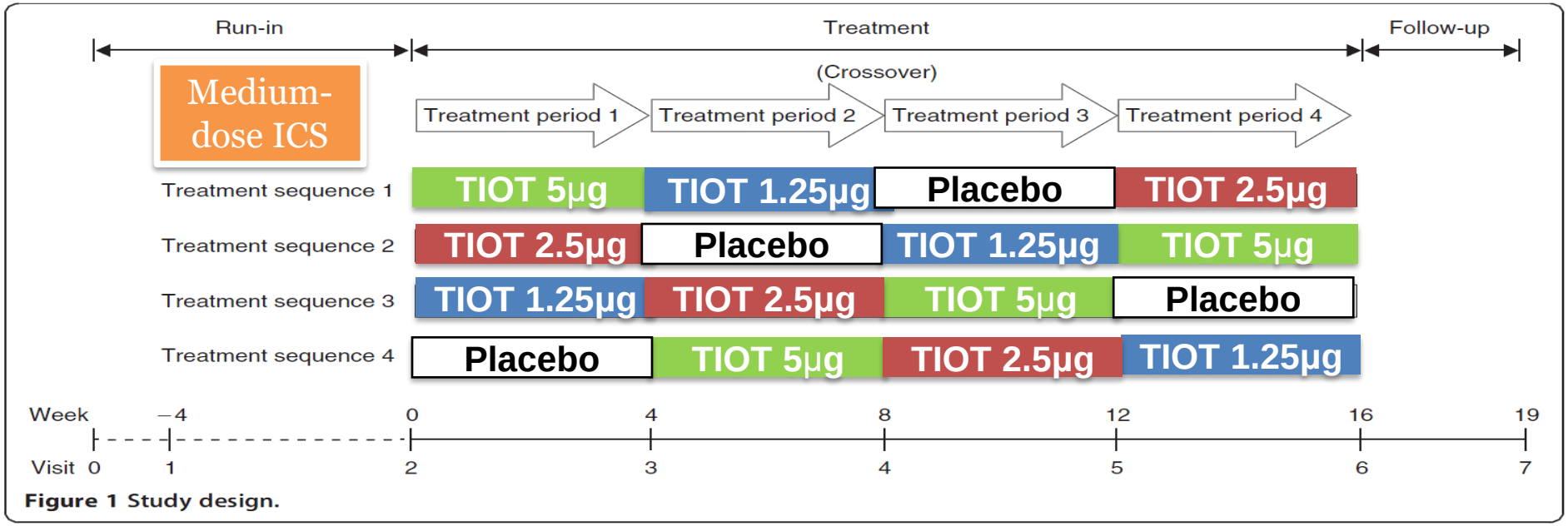


Figure 1 Study design.

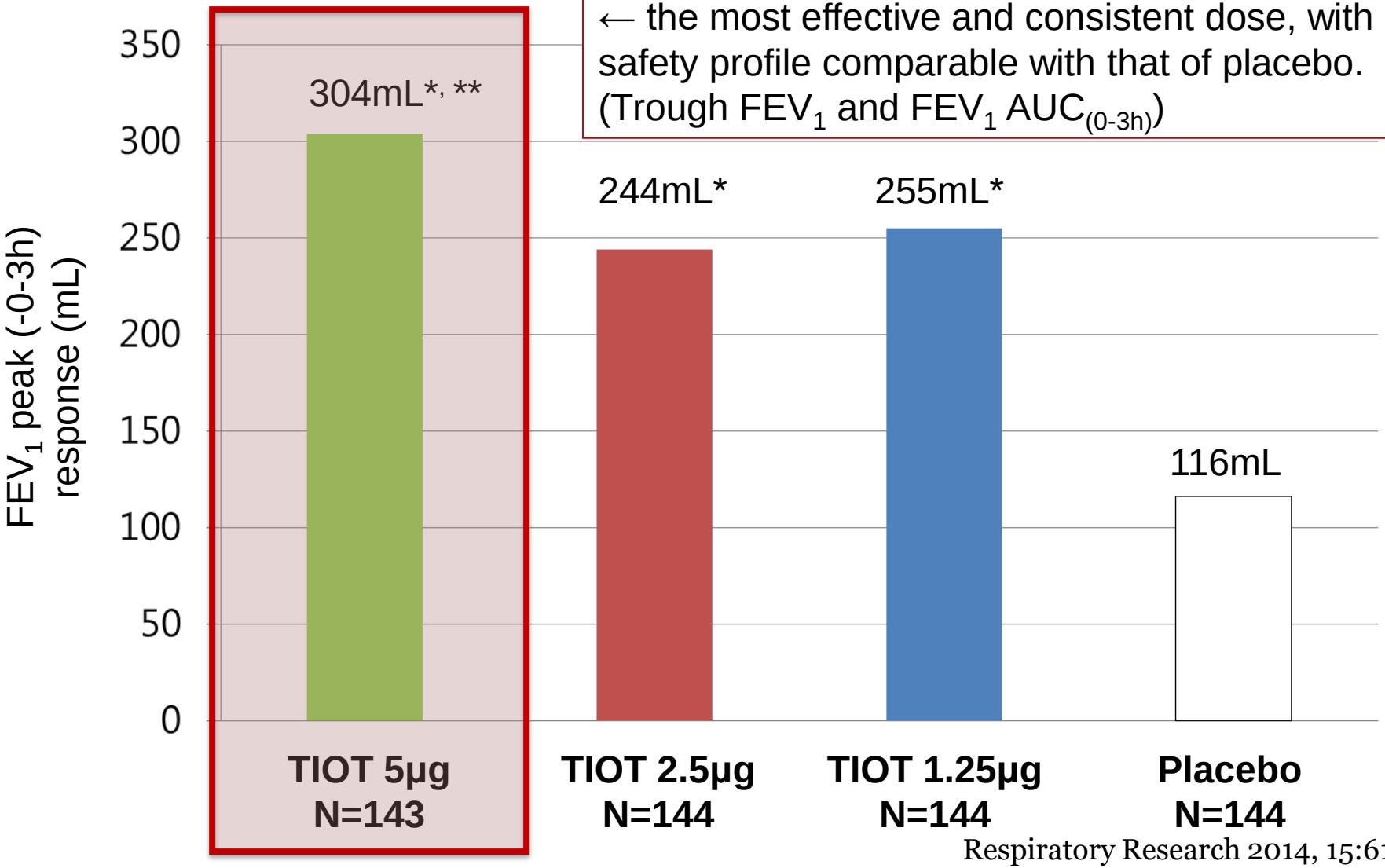
Medium-dose ICS

Peak FEV_1 (0-3h) after 4weeks

Respiratory Research 2014, 15:61

Results (4wks)

← the most effective and consistent dose, with a safety profile comparable with that of placebo. (Trough FEV_1 and FEV_1 $AUC_{(0\text{-}3h)}$)



Respiratory Research 2014, 15:61

PLOS ONE

RESEARCH ARTICLE

Long-Term Once-Daily Tiotropium Respimat® Is Well Tolerated and Maintains Efficacy over 52 Weeks in Patients with Symptomatic Asthma in Japan: A Randomised, Placebo-Controlled Study

Ken Ohta[1]*, Masakazu Ichinose[2], Yuji Tohda[3], Michael Engel[4], Petra Moroni-Zentgraf[4], Satoko Kunimitsu[5], Wataru Sakamoto[6], Mitsuru Adachi[7]

Inclusion Criteria

- 18-75 year
- Never smoked, or ex-smoker for more than 1 year (≤10 PY)
- symptomatic asthma, Diagnosed before 40 years, with ≥ 3-month history of asthma
- Partly controlled asthma
  - Despite stable medium-dose ICS (budesonide **400-800 μg or equivalent) alone or in fixed combination with LABA**
  - Symtomatic :mean ACQ-7 score ≥ 1.5
  - Prebronchodilator FEV_1 60-90% predicted
  - Reversibility of 12% and 200 mL (15-30mins after salbutamol)

Primary outcome: long-term safety

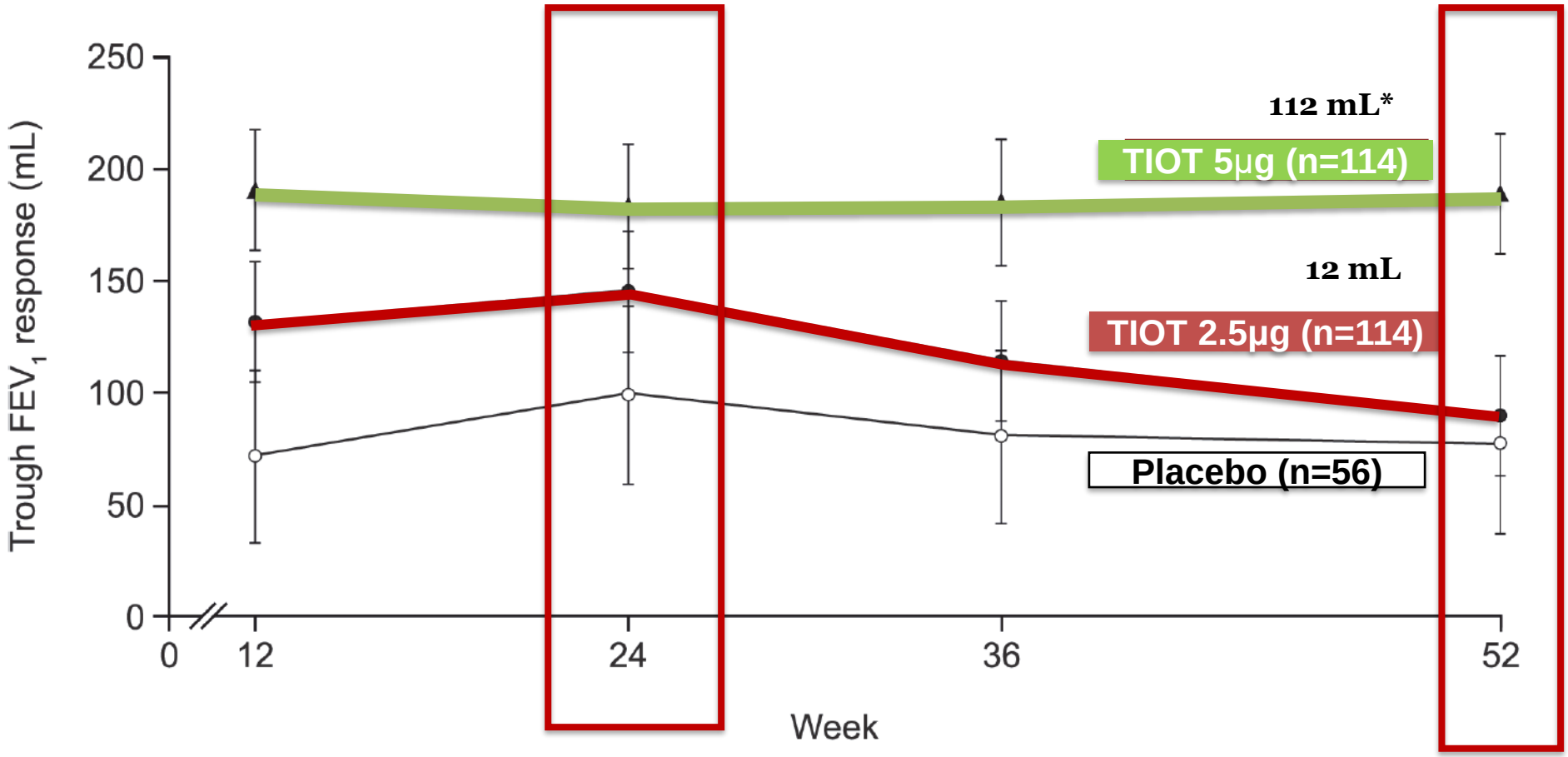
Randomized 2:2:1 **Tio 5 µg vs. Tio 2.5 µg vs. placebo** for 52 weeks

Overall summary of adverse events

n (%)	Tiotropium Respimat 5 µg (n = 114)[a]	Tiotropium Respimat 2.5 µg (n = 114)[a]	Placebo Respimat (n = 57)[a]
Any AE	101 (88.6)	99 (86.8)	51 (89.5)
Severe AEs	2 (1.8)	1 (0.9)	3 (5.3)
Drug-related AEs[b]	10 (8.8)	6 (5.3)	3 (5.3)
AEs leading to discontinuation	2 (1.8)	1 (0.9)	1 (1.8)
Significant (pre-specified) AEs[c]	0	0	0
Serious AEs	4 (3.5)	4 (3.5)	9 (15.8)
Requiring hospitalisation	4 (3.5)	4 (3.5)	7 (12.3)
Drug-related	0	0	1 (1.8)[d]
Fatal	0	0	0
Other	0	0	2 (3.5)

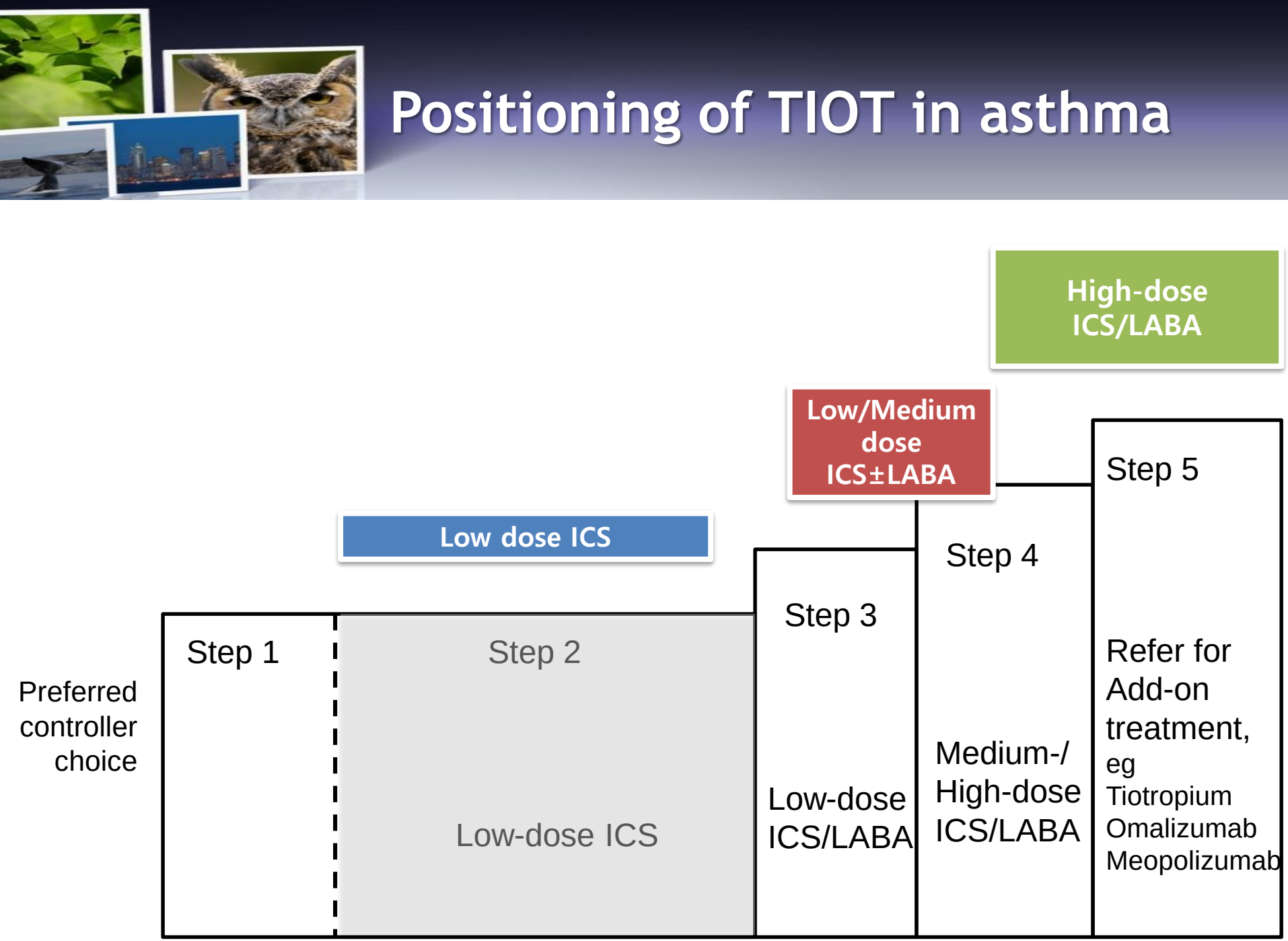
Plos One 2015, April 20

2ndary outcome: Trough FEV_1 response (mL)



Plos One 2015, April 20

Positioning of TIOT in asthma



Daily doses of ICS

Beclometasone dipropionate 160 µg

Adults and adolescents (12 years and older)			
Drug	**Daily dose (mcg)**		
	Low	Medium	High
Beclometasone dipropionate (CFC)*	200–500	>500–1000	>1000
Beclometasone dipropionate (HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100	n.a.	200
Fluticasone propionate(DPI)	100–250	>250–500	>500
Fluticasone propionate (HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000

Tiotropium bromide as an Alternative to increased inhaled glucocorticoid in patients inadequately controlled on a Lower dose of inhaled Corticosteroid (TALC) study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma

Inclusion Criteria

National Heart, Lung, and Blood Institute

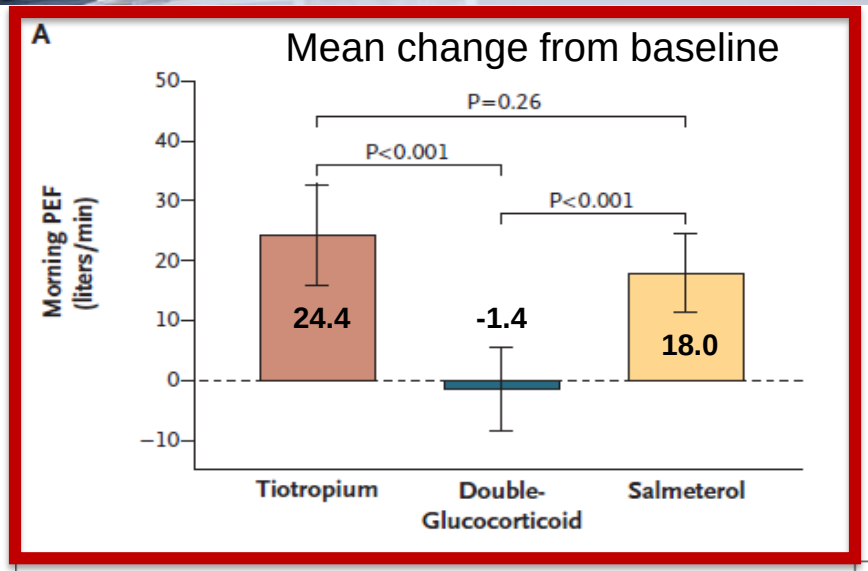
- At least 18 years, history of BA, never smoked, or ex-smoker (≤10 PY) and FEV_1 ≥ 40% predicted (n=210)

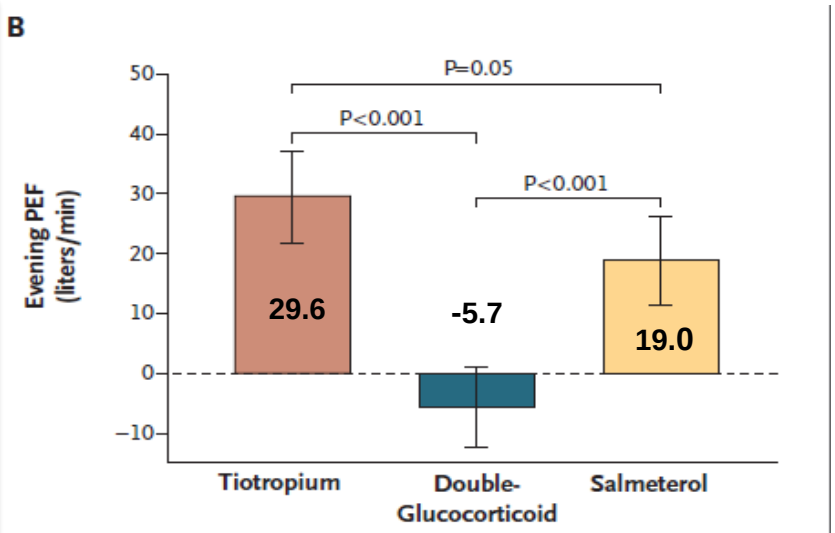
≥6/wk symptoms
≥6/wk rescue Mx
≥2/wk night awakening
FEV_1 < 70% pred

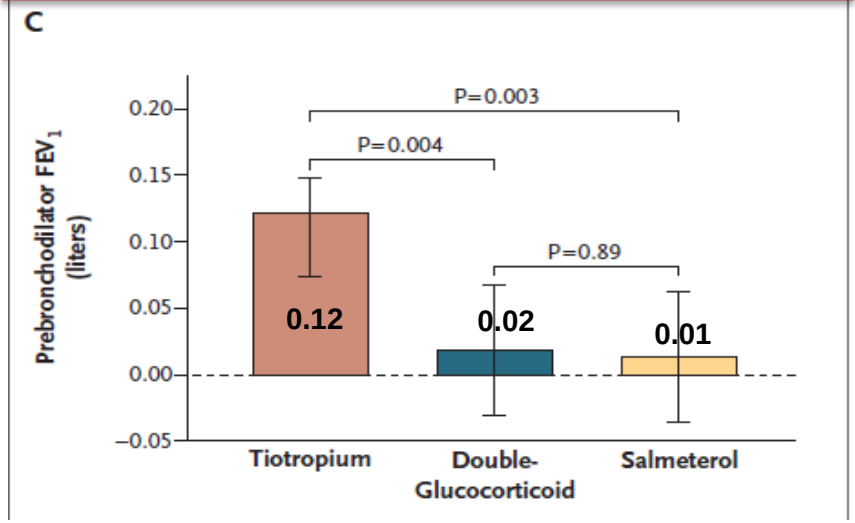
14 week, 3 period, double-blind, triple-dummy cross over

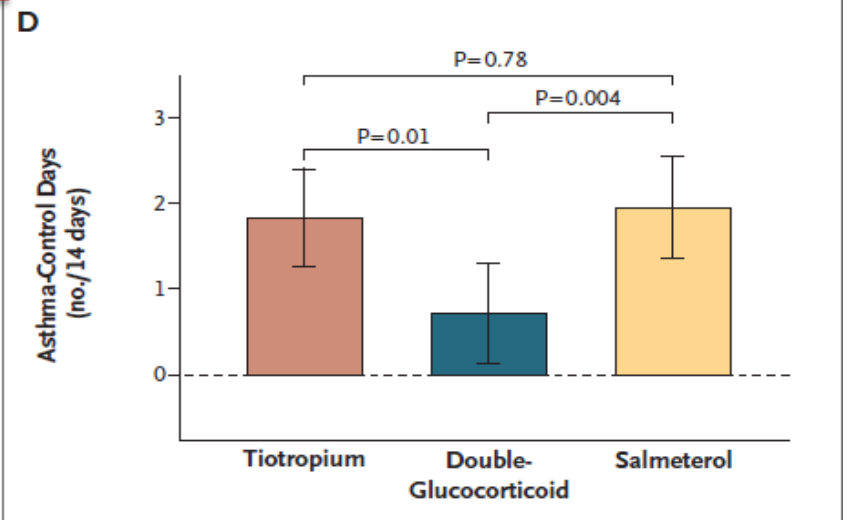
N Eng J Med 2010; 363(18):1715-26

Primary outcome: morning PEF









N Eng J Med 2010; 363(18):1715-26

Grazia TinA

The Effect of Tiotropium in Symptomatic Asthma Despite Low- to Medium-Dose Inhaled Corticosteroids: A Randomized Controlled Trial

Inclusion Criteria

- 18-75 year
- Never smoked, or ex-smoker for more than 1 year (≤10 PY)
- symptomatic asthma, Diagnosed before 40 years, with ≥ 3-month history of asthma
- Partly controlled asthma
    - Despite stable low dose ICS (budesonide **200-400 μg or equivalent) for > 4 weeks prior to screening**
    - Symtomatic :mean ACQ-7 score ≥ 1.5
    - Prebronchodilator FEV_1 60-90% predicted
    - Reversibility of 12% and 200 mL (15-30mins after salbutamol)

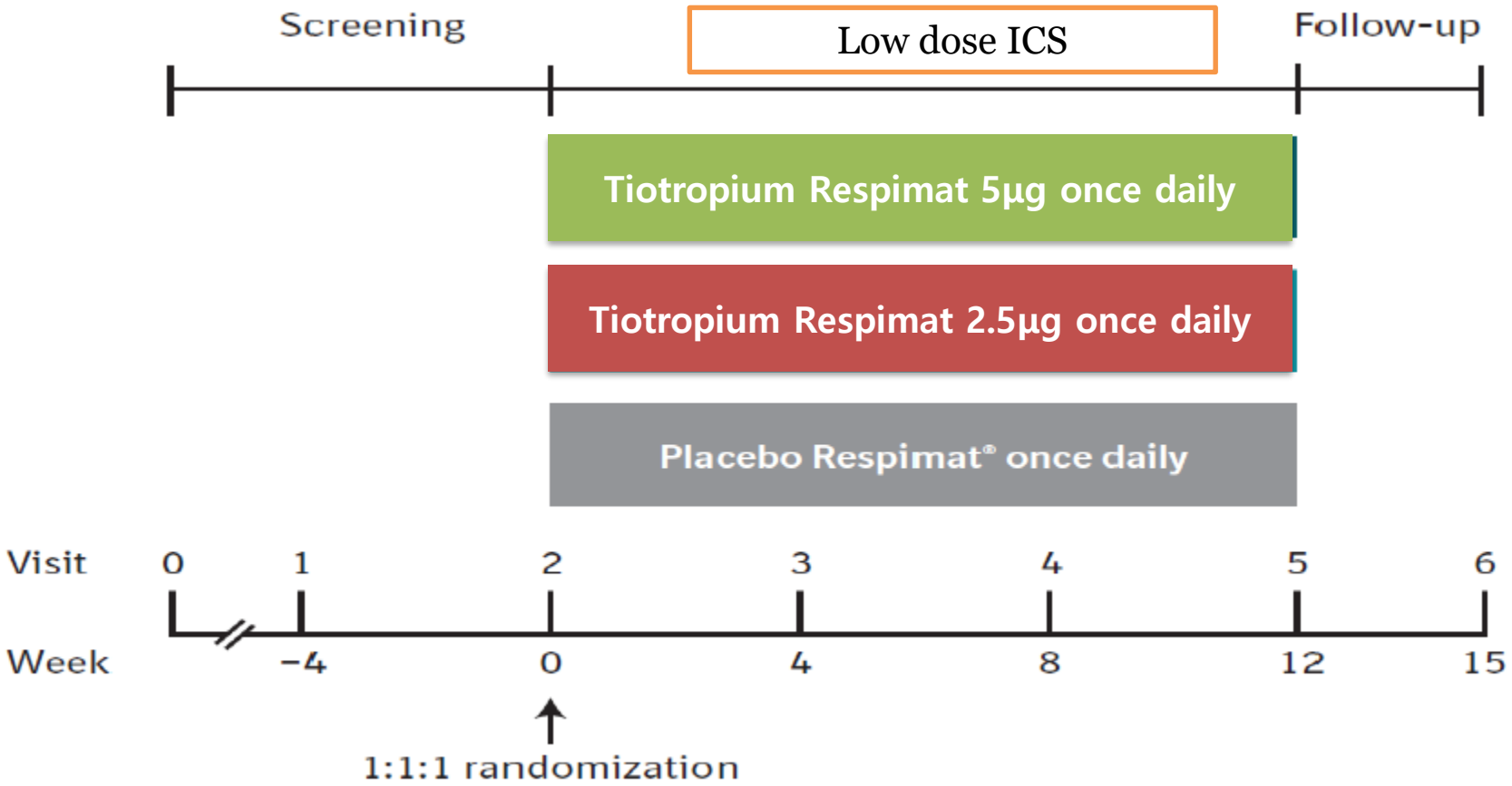
Exclusion Criteria

-Dx of COPD, serious coexisting illness, concurrent use of anticholinergics or beta blockers within 4 weeks before or during screening

J Allegy Clin Immunol Pract 2016 4(1): 104-13

Study Design

12week, Double-blind, Randomized, Placebo-controlled, Parallel group

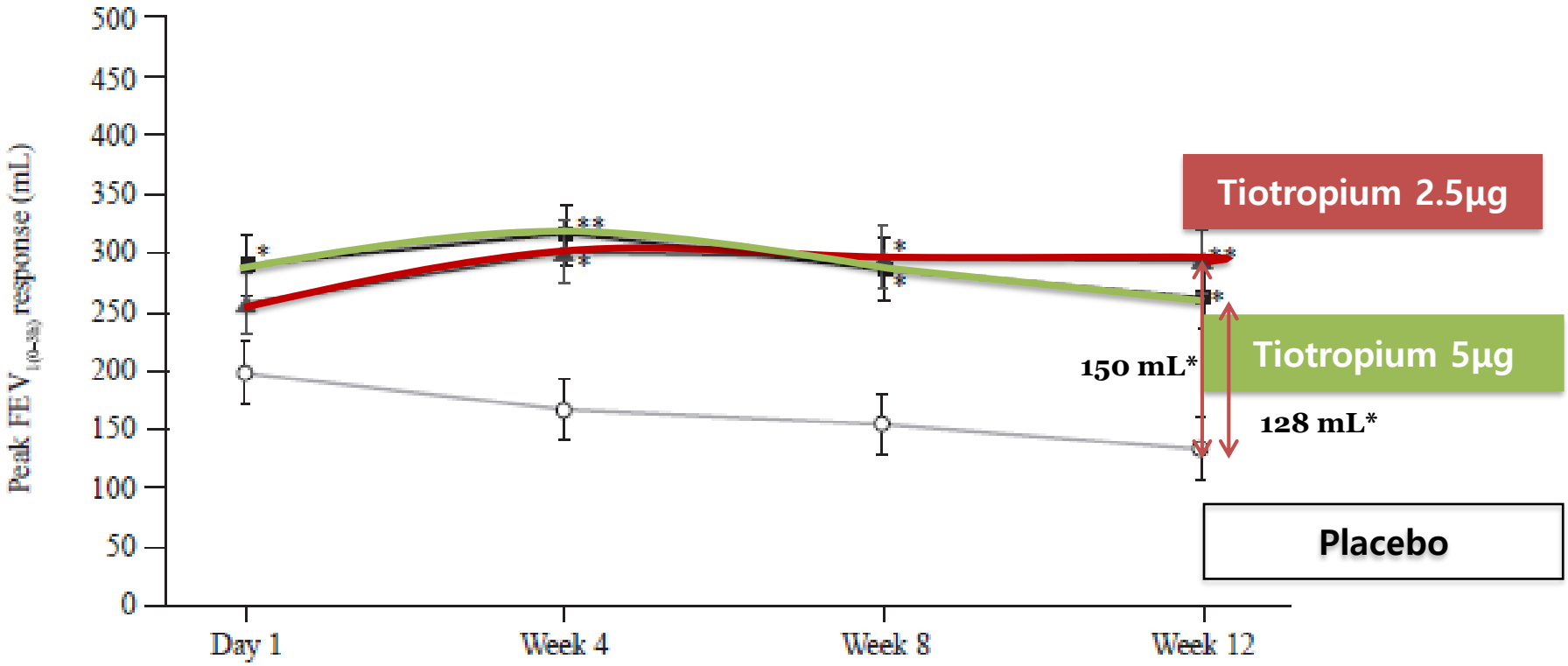


Peak FEV_1 (0-3h) after 12weeks

J Allegy Clin Immunol Pract 2016 4(1): 104-13

Primary Outcome: Peak $FEV_{1(0\text{-}3h)}$ response at 12 weeks

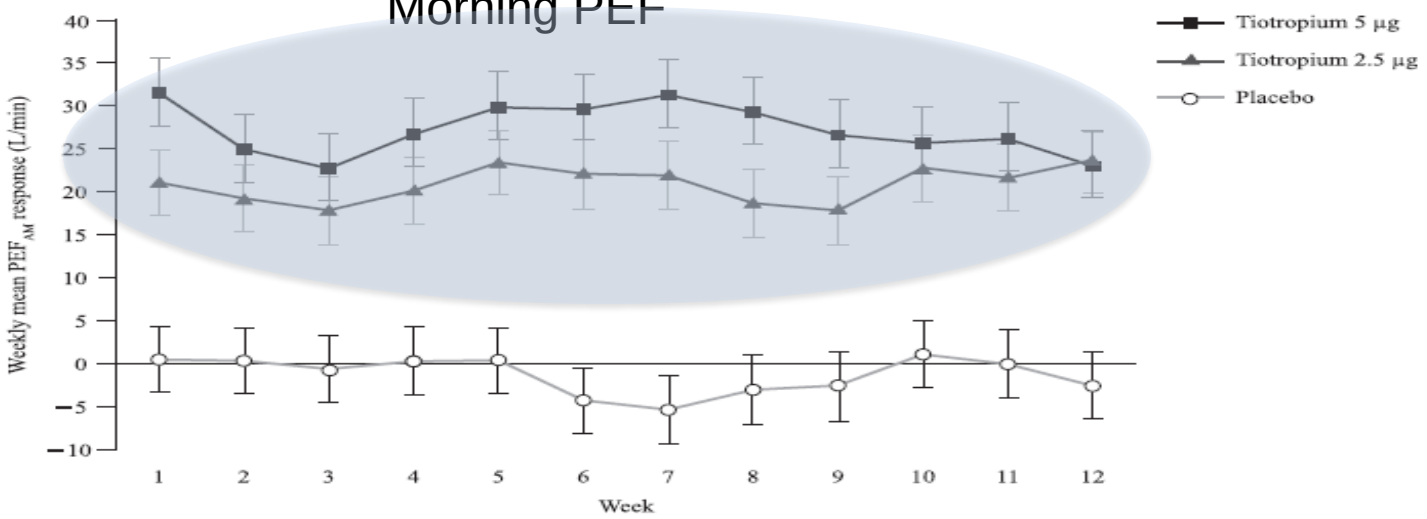
A significant improvement in lung function in Tiotropium compared with placebo after a 12-week treatment period



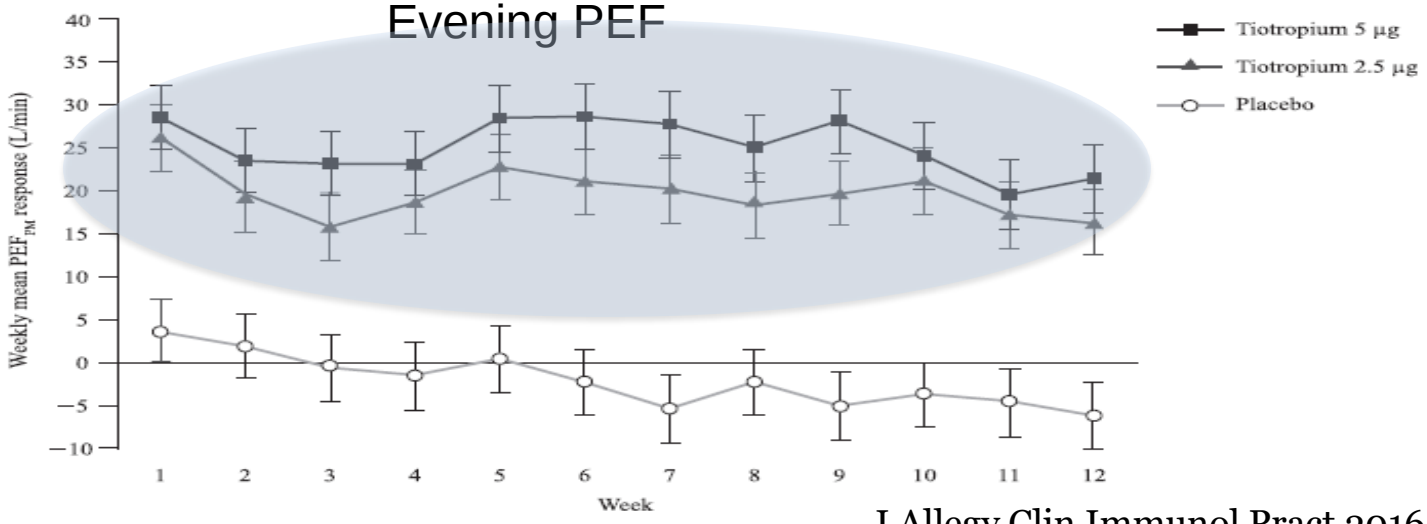
J Allegy Clin Immunol Pract 2016 4(1): 104-13

PEF

Morning PEF



Evening PEF



J Allegy Clin Immunol Pract 2016 4(1): 104-13

Post hoc efficacy analyses

-Gender, smoking status, FEV_1 (% predicted)
: Male, non-smoker, FEV_1 (% predicted) ≥ 80%

Treatment and parameter	Adjusted* mean (SE) (mL)	Active vs placebo		
		Adjusted* mean of difference (SE) (mL)	95% CI	*P* value*
FEV_1 % of predicted normal post-bronchodilator				
Peak $FEV_{1(0\text{-}3h)}$ response				
60% to <80%				
Tiotropium 5 µg (n = 25)	288 (64)	200 (90)	21, 379	.03
Tiotropium 2.5 µg (n = 30)	230 (58)	142 (86)	−28, 311	.10
Placebo (n = 25)	88 (63)			
≥80%				
Tiotropium 5 µg (n = 127)	269 (31)	119 (43)	34, 204	.006
Tiotropium 2.5 µg (n = 121)	316 (31)	166 (44)	81, 252	<.001
Placebo (n = 129)	150 (30)			
Trough FEV_1 response				
60% to <80%				
Tiotropium 5 µg (n = 25)	213 (67)	275 (95)	86, 463	.005
Tiotropium 2.5 µg (n = 30)	37 (61)	99 (90)	−79, 278	.27
Placebo (n = 25)	−62 (67)			
≥80%				
Tiotropium 5 µg (n = 127)	140 (31)	99 (43)	13, 184	.02
Tiotropium 2.5 µg (n = 121)	162 (31)	121 (44)	35, 207	.006
Placebo (n = 129)	42 (31)			

Tiotropium 5µg

Tiotropium 5µg

J Allegy Clin Immunol Pract 2016 4(1): 104-13

Summary 3 (Grazia Tin A)

Addition of Tiotropium to low dose ICS in patients with

- Asthma diagnosed before 40 yrs
- Never smoker or < 10 PY, no smoking in the year
- Symptomatic and partly controlled asthma
  - ACQ-7 > 1.5, prebronchodialtor FEV_1 60-90% predicted
  - Reversibility of 12% and 200 mL (15-30mins after salbutamol)

Addition of tiotropium to low dose ICS with not fully controlled mild symptomatic asthma improves in lung function.

A systematic Review \With Meta-analysis (n=13)

TABLE 1] Characteristics of Included Studies

Study	Design	Duration, wk	Randomized Patients	Age, y	Mean Baseline FEV_1, % Predicted	Asthma Severity	Primary Outcome	Comparisons of Interest
Fardon et al[4]	R, DB, PC, CO	4	25 (29)	54 (35-68)	51	Severe	N/A	ICS high dose + SAL 25 μg bid vs ICS high dose + SAL 25 μg bid + TIO 18 μg HandiHaler OD
Peters et al[6]	R, DB, PC, CO	14	210 (67)	42 (>18)	71.5	Moderate	Morning PEF	ICS medium dose vs ICS low dose + TIO 18 μg HandiHaler OD vs ICS low dose daily + SAL 50 μg bid
Bateman et al[18]	R, DB, PC, PG	16	388 (62)	43 (18-67)	75	Moderate	Morning PEF	ICS moderate-high dose vs ICS moderate-high dose + SAL 25 μg bid vs ICS moderate-high dose + TIO Respimat 5 μg OD
Kerstjens et al[19]	R, DB, PC, CO	8	104 (58)	55 (18-75)	58	Severe	FEV_1 peak	ICS high dose + LABA vs ICS high dose + LABA + TIO 5 μg Respimat OD
Kerstjens et al[20]	R, DB, PC, PG	48	912 (60)	53 (18-75)	55	Severe	FEV_1 peak and trough	ICS high dose + LABA vs ICS high dose + LABA + TIO 5 μg Respimat OD
BI 205.464[21]	R, DB, PC, PG	52	171 (62)	45 (18-75)	80.1	Moderate	Safety	ICS medium-high dose vs ICS medium-high dose + TIO 5 μg Respimat OD
BI 205.420[22]	R, DB, PC, CO	4	94 (59)	44 (18-75)	77	Moderate	FEV_1 AUC 0-24 h	ICS medium dose vs ICS medium dose + TIO 5 μg Respimat OD
Vogelberg et al[23]	R, DB, PC, CO	4	105 (36)	14 (12-17)	N/A	Moderate	FEV_1 peak	ICS medium dose vs ICS medium dose + TIO 5 μg Respimat OD
Beeh et al[24]	R, DB, PC, CO	4	149 (55)	49 (18-75)	71.3	Moderate	FEV_1 peak	ICS medium dose vs ICS medium dose + TIO 5 μg Respimat OD
BI 205.442[25]	R, DB, PC, PG	12	310 (61)	42 (18-75)	77.6	Mild	FEV_1 peak	ICS low dose vs ICS low dose + TIO 5 μg Respimat OD
BI 205.418[26]	R, DB, PC, PG	24	1,070 (59)	43 (18-75)	77.6	Moderate	FEV_1 peak and trough	ICS medium dose vs ICS medium dose + TIO 5 μg Respimat OD vs ICS medium dose + SAL 50 μg bid
BI 205.419[27]	R, DB, PC, PG	24	1,030 (59)	42 (18-75)	75.4	Moderate	FEV_1 peak and trough	ICS medium dose vs ICS medium dose + TIO 5 μg Respimat OD vs ICS medium dose + SAL 50 μg bid
BI 205.444[28]	R, DB, PC, PG	48	398 (65)	14 (12-17)	82.8	Moderate	FEV_1 peak	ICS medium dose vs ICS medium dose + TIO 5 μg Respimat OD

Data are presented as No. (% female sex) or mean (range) unless otherwise indicated. AUC = area under the curve; BI = Boehringer Ingelheim; CO = crossover; ICS = inhaled corticosteroid; DB = double blind; N/A = data not available; OD = once daily; PC = placebo controlled; PEF = peak expiratory flow; PG = parallel group; R = randomized; SAL = salmeterol; TIO = tiotropium

CHEST 2015;147 (2):388-396

A systematic Review \With Meta-analysis (n=13)

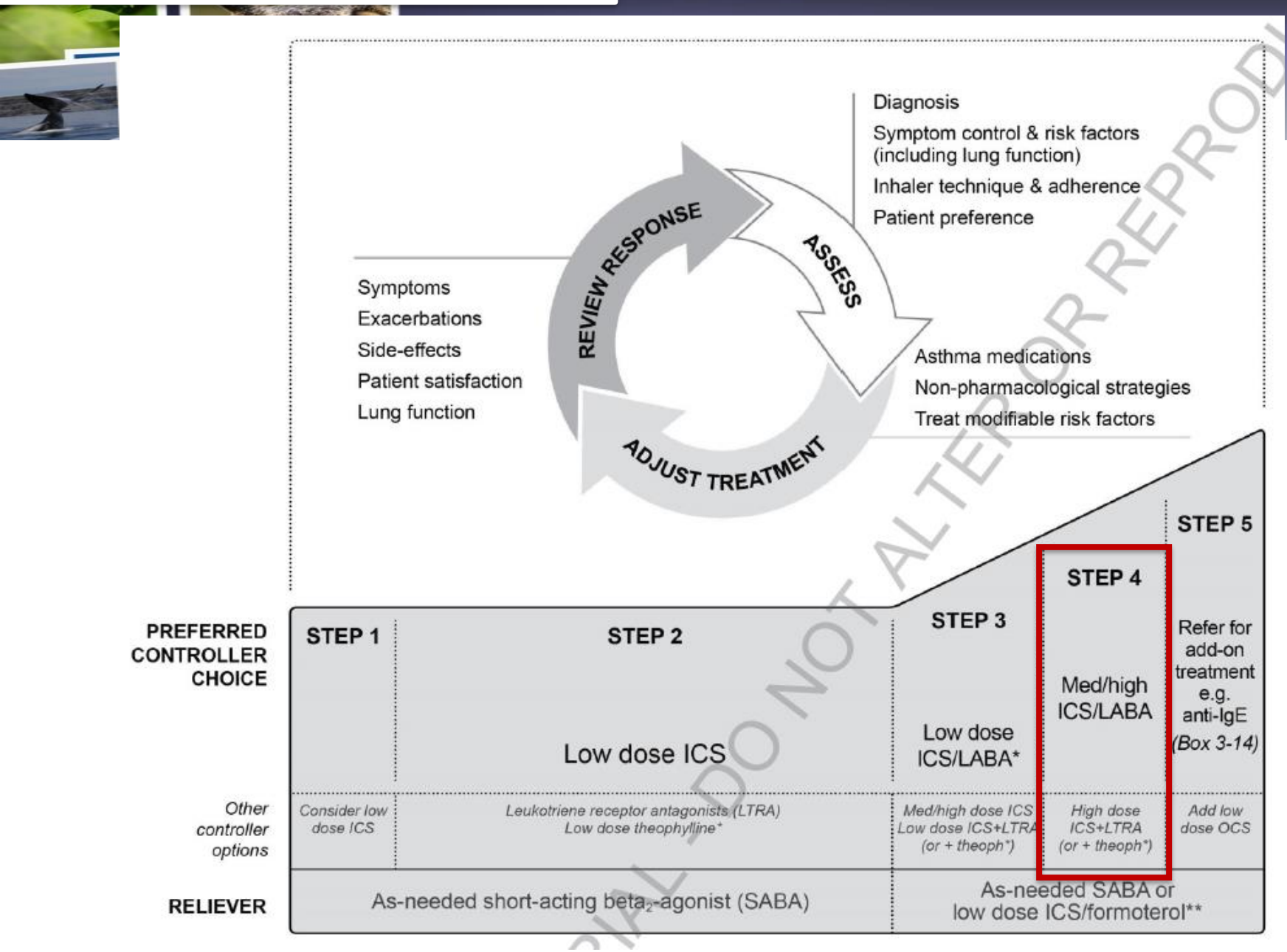
Tiotropium as Add-on to ICS

-Significant improvement in PEF, peak FEV_1, trough FEV_1, AQLQ and ACQ-7
-Significant reduced number of patients with at least one asthma exacerbation with an NNTB 36

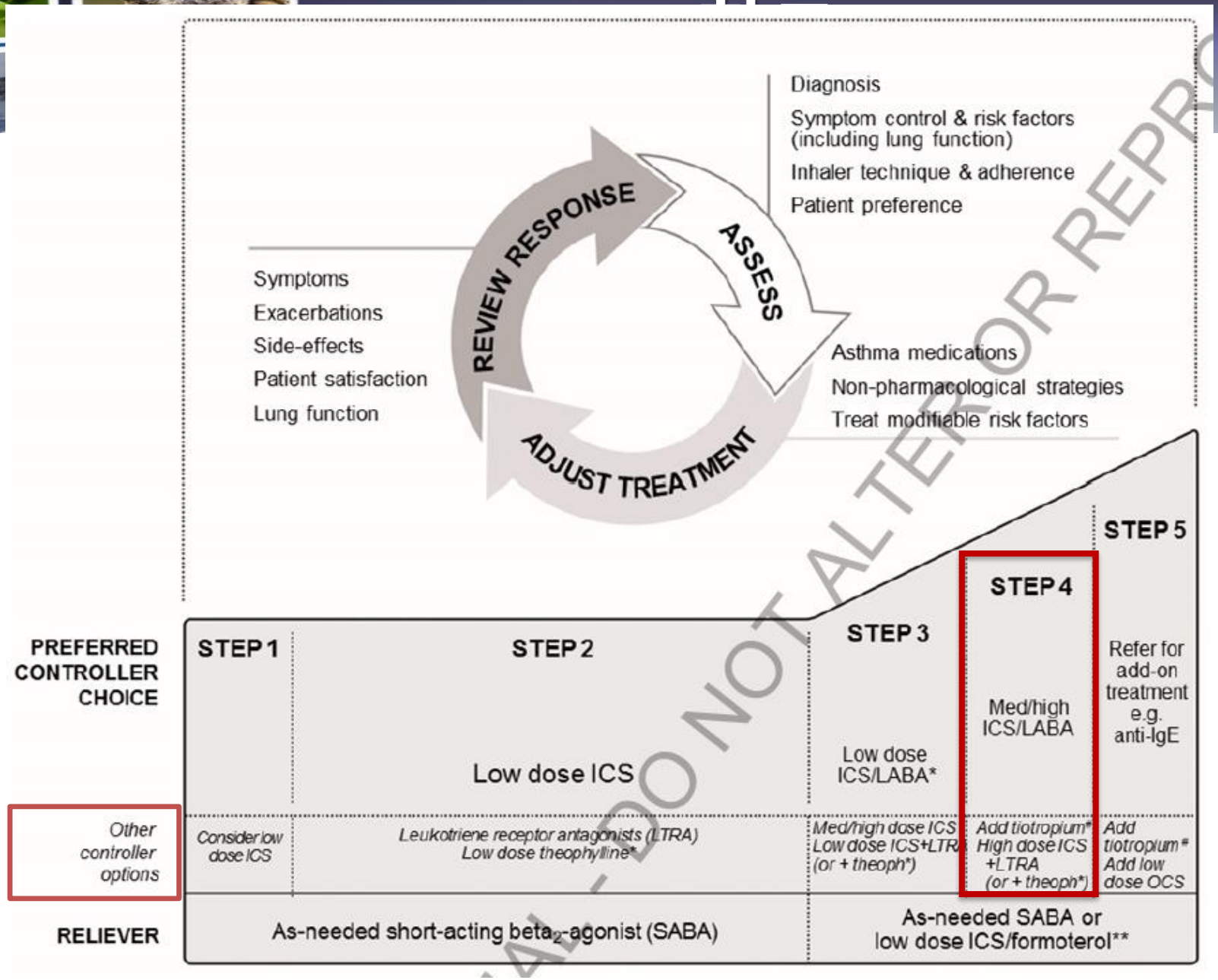
Conclusions: Tiotropium resulted noninferiorly to salmeterol and superiorly to placebo in patients with moderate to severe asthma who were not adequately controlled by ICS or ICS/salmeterol. Major benefits were concentrated in the increase in lung function and in the case of patients with severe asthma, in the reduction of exacerbations.

-Significant improvement in PEF, peak FEV_1, trough FEV_1, AQLQ and ACQ-7
-Significant reduced number of patients with at least one asthma exacerbation with an NNTB 17

2014 GINA guideline



2015 GINA guideline



2016 GINA guideline

Diagnosis

Symptom control & risk factors (including lung function)

Inhaler technique & adherence

STEP 4 Other controller options
STEP 5 Preferred controller choice

Tiotropium by soft-mist inhaler is an added-on treatment for patients with a history of exacerbations: it is not indicated in children < 12 years

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER CHOICE		Low dose ICS	Low dose ICS/LABA**	Med/high ICS/LABA	Refer for add-on treatment e.g. tiotropium,*† omalizumab, mepolizumab*
Other controller options	Consider low dose ICS	Leukotriene receptor antagonists (LTRA) Low dose theophylline*	Med/high dose ICS Low dose ICS+LTRA (or + theoph*)	Add tiotropium*† High dose ICS + LTRA (or + theoph*)	Add low dose OCS
RELIEVER	As-needed short-acting beta$_2$-agonist (SABA)		As-needed SABA or low dose ICS/formoterol#		

In What Patients Should I use TIOTROPIM in asthma?

Summary (Primo TinA)

Addition of Tiotropium to high dose ICS+ LABA in patients with

- Asthma > 5 year Hx of asthma & diagnosed before 40 yrs
- Never smoker or **< 10 PY, no smoking in the year**
- Symptomatic and partly controlled asthma
  - ACQ-7 > 1.5, **FEV_1 ≤ 80% & FVC ≤ 70% after BD**
  - At least one severe exacerbation in previous year

우리 나라 보험 기준 (Tiotropium)

- 각 약제별 허가사항 범위 내에서 아래와 같은 기준으로 투여 시 요양급여를 인정하며, 동 인정기준 이외에는 약값 전액을 환자가 부담토록 함

- - 아 래 -
- 가. 중등도 이상의 만성폐쇄성폐질환[FEV1(1초 강제호기량) 값이 예상 정상치의 80% 미만] 환자의 유지요법

- 나. 고용량의 흡입용 코르티코스테로이드 및 지속성 베타-2 작용제의 병용 유지 요법에도 불구하고 중증의 악화 경험이 있는 천식환자의 병용 유지요법

경청해 주셔서
감사합니다.

Age ?

Tiotropium add-on therapy in adolescents with moderate asthma: A 1-year randomized controlled trial

Eckard Hamelmann, MD,[a] Eric D. Bateman, MD,[b] Christian Vogelberg, MD,[c] Stanley J. Szefler, MD,[d] Mark Vandewalker, MD,[e] Petra Moroni-Zentgraf, MD,[f] Mandy Avis, PhD,[g] Anna Unseld, MSc,[h] Michael Engel, MD,[f] and Attilio L. Boner, MD[i] *Bielefeld, Dresden, Ingelheim am Rhein, and Biberach an der Riss, Germany, Cape Town, South Africa, Aurora, Colo, Columbia, Mo, Alkmaar, The Netherlands, and Verona, Italy*

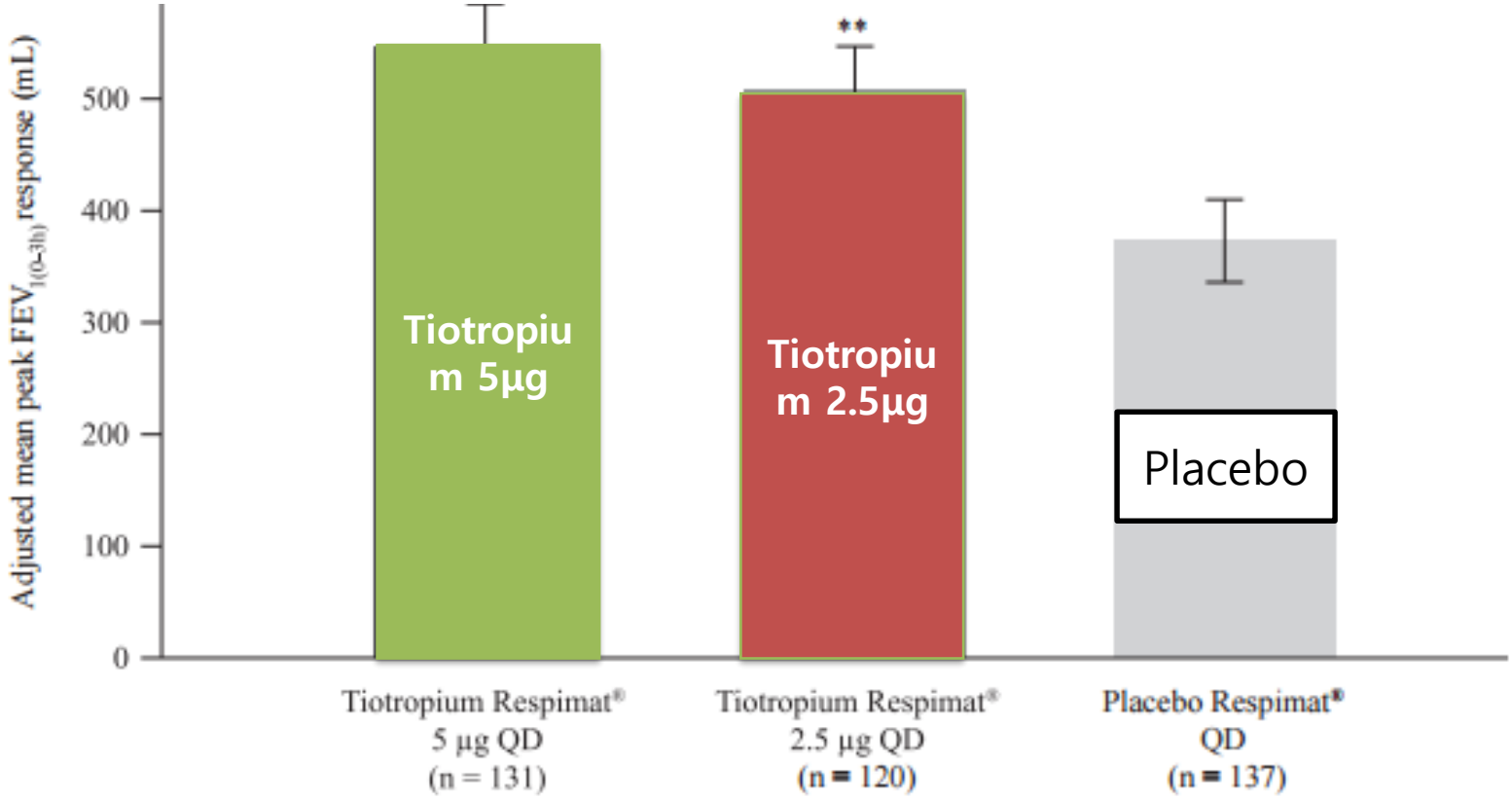
Inclusion Criteria

- **12-17 year**
- symptomatic asthma with ≥ 3-month history of asthma
- Partly controlled asthma
  - Despite stable medium-dose ICS (**budesonide 400-800 µg or equivalent) ± LTRA**
  - Symtomatic :mean ACQ-7 score ≥ 1.5
  - Prebronchodilator FEV_1 60-90% predicted
  - Reversibility of 12% and 200 mL (15-30mins after salbutamol)

J Allergy Clin Immunol 2016 Mar 5

Primary Outcome: Peak $FEV_{1(0-3h)}$ response at 24 weeks

Conclusions: Once-daily tiotropium significantly improved lung function and was safe and well tolerated when added to at least ICS maintenance therapy in adolescent patients with moderate symptomatic asthma. Larger responses were observed with the 5-µg tiotropium dose. (J Allergy Clin Immunol 2016;138:441-50.)



J Allergy Clin Immunol 2016 Mar 5

Asthma Phenotype

Allergic ashtma

Non-allergic asthma

Late-onset asthma

Asthma with fixed airflow limitation

Asthma with obesity

2016 GINA guideline

Post hoc analysis

Grazia TinA

Original Article

The Effect of Tiotropium in Symptomatic Asthma Despite Low- to Medium-Dose Inhaled Corticosteroids: A Randomized Controlled Trial

Mezzo TinA

Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials

Huib A M Kerstjens, Thomas B Casale, Eugene R Bleecker, Eli O Meltzer, Emilio Pizzichini, Olaf Schmidt, Michael Engel, Loek Bour. Cynthia B Verkleij, Pe

Primo TinA

ORIGINAL ARTICLE

Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy

Huib A.M. Kerstjens, M.D., Michael Engel, M.D., Ronald Dahl, M.D., Pierluigi Paggiaro, M.D., Ekkehard Beck, M.D., Mark Vandewalker, M.D., Ralf Sigmund, Dipl.Math., Wolfgang Seibold, M.D., Petra Moroni-Zentgraf, M.D., and Eric D. Bateman, M.D.

Time to first severe exacerbation
Post hoc analysis

ORIGINAL ARTICLE

48 week, primary outome: exacerbation

Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy

Huib A.M. Kerstjens, M.D., Michael Engel, M.D., Ronald Dahl, M.D., Pierluigi Paggiaro, M.D., Ekkehard Beck, M.D., Mark Vandewalker, M.D., Ralf Sigmund, Dipl.Math., Wolfgang Seibold, M.D., Petra Moroni-Zentgraf, M.D., and Eric D. Bateman, M.D.

		Severe asthma exacerbation Number of patients		P value
		Active comparator	Placebo	
PrimoTinA-asthma® (ICS + LABA)	TioR 5 µg	122/453	149/454	0.0343
MezzoTinA-asthma® (ICS)	TioR 5 µg	31/513	43/518	0.1644
	Salmeterol	34/535		0.2149
GraziaTinA-asthma® (ICS)	TioR 5 µg	1/155	4/155	0.2155