Le evidenze di Tiotropio respimat nel trattamento dell'asma nel paziente adulto

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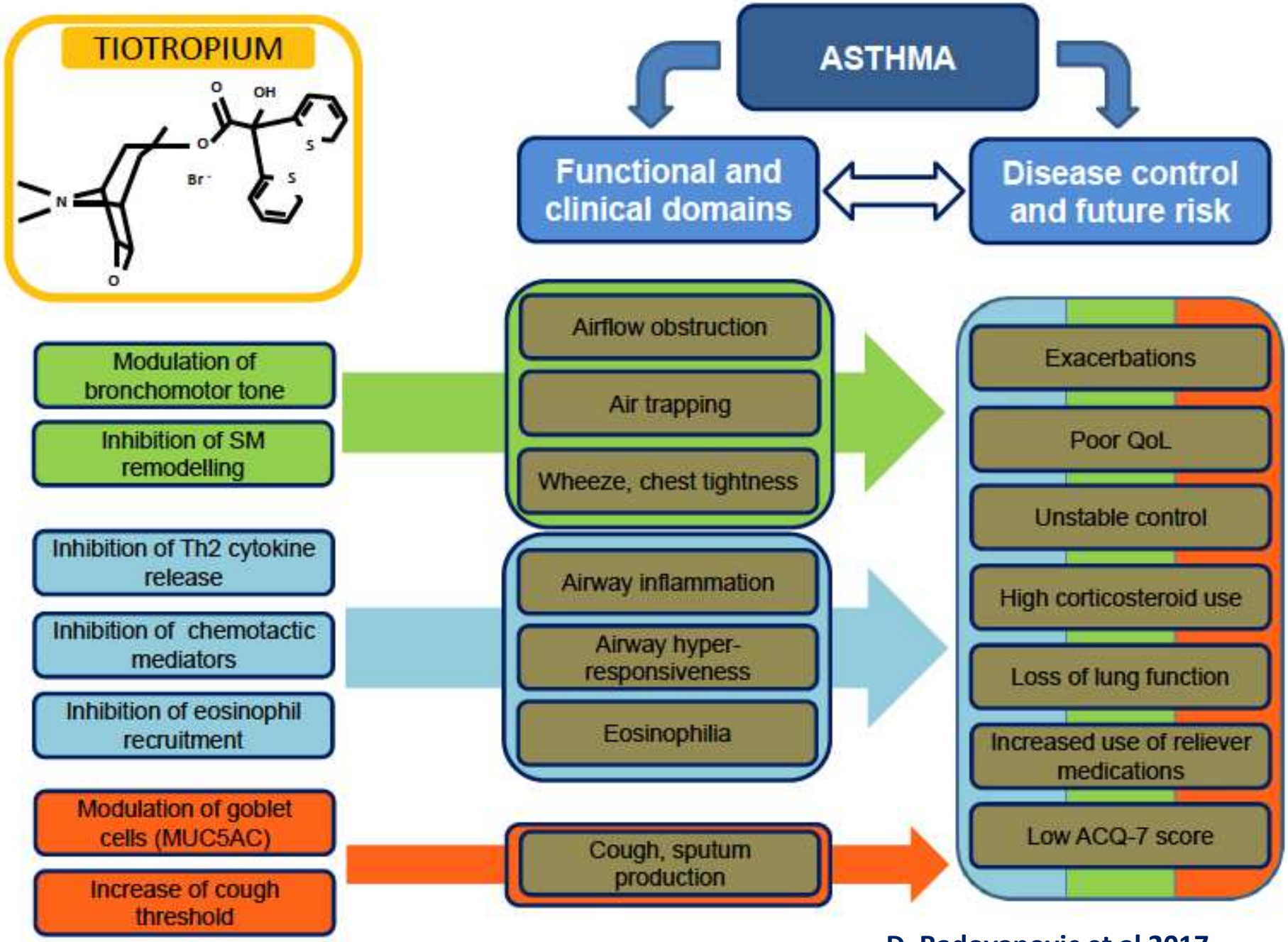
Disclosures

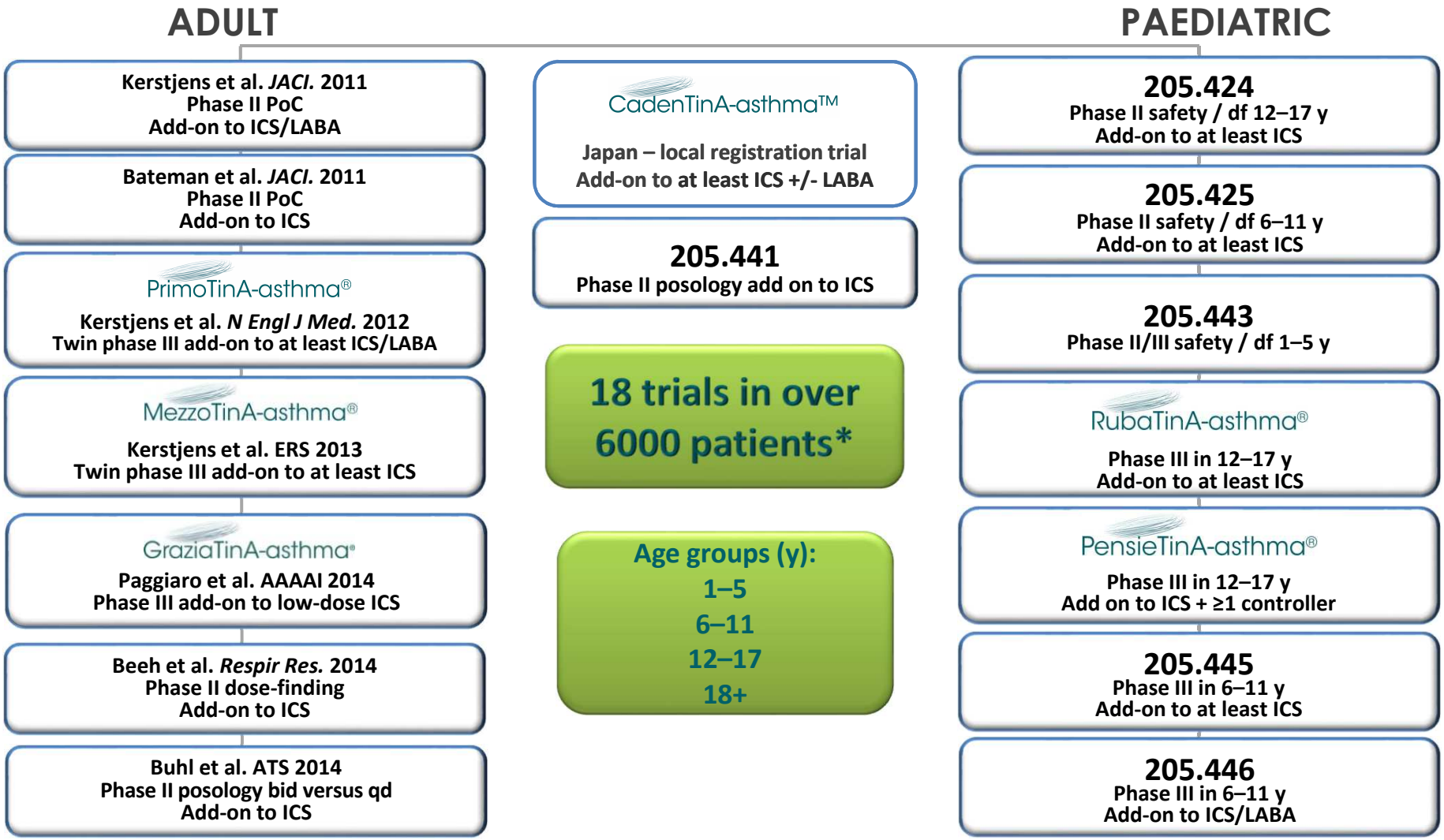
- I have accepted grants, speaking and conference invitations from Angelini, AstraZeneca, Almirall, Bayer, Chiesi, Dompé, GSK, Guidotti-Malesci, Menarini, Novartis, Pfizer, Sanofi, Teva and Zambon

- I have had recent or ongoing consultancy with Angelini, AstraZeneca, Chiesi, GSK, Menarini, Mundipharma, Novartis, Teva and Zambon



D. Radovanovic et al 2017

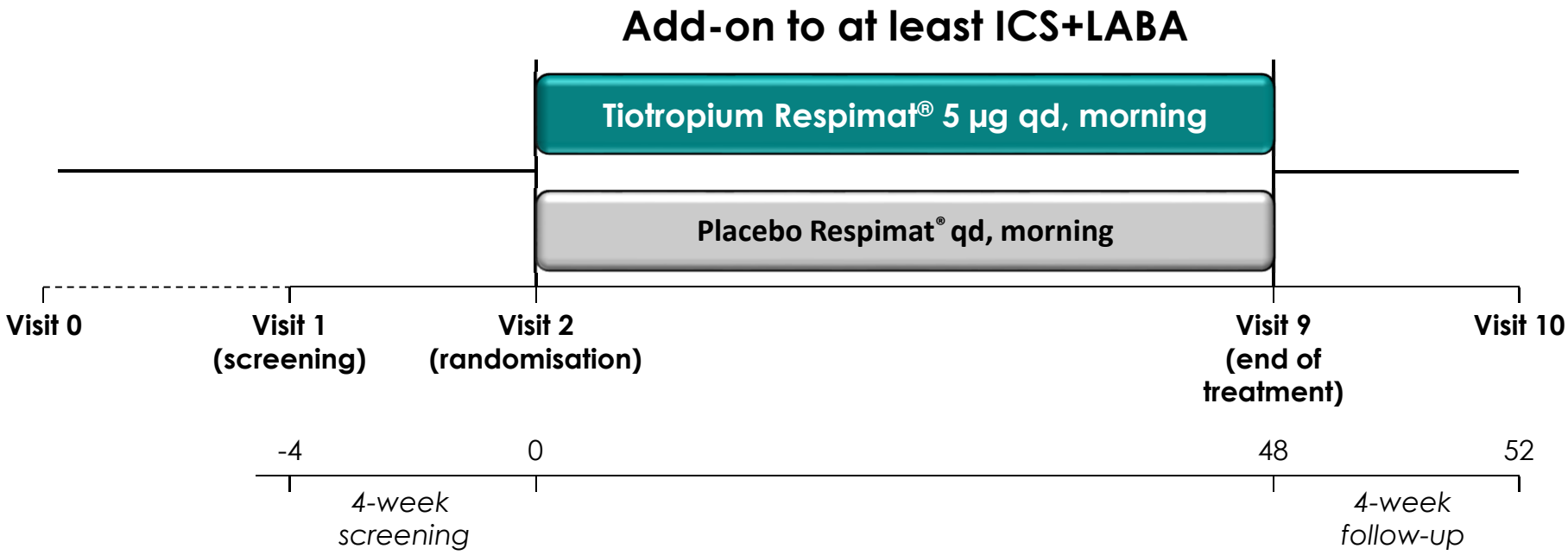
Tiotropium Respimat® in Asthma clinical development programme



bid, twice daily; df, dose finding; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; PoC, proof of concept; qd, once daily

***In the full clinical development programme**

Study design: double-blind, randomised, placebo-controlled, parallel-group (twin trials)



Three co-primary endpoints:
hierarchical testing

1. FEV_1 peak (0-3 h) after 24 weeks
2. FEV_1 trough after 24 weeks
3. Time to first severe asthma exacerbation in pooled* analysis after 48 weeks

All patients at least on ICS maintenance therapy (≥800 µg budesonide or equivalent/day)+LABA

148 centres, 5 continents

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FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; qd, once daily
* Pre-specified dataset of trial 1 + trial 2

Kerstjens et al. NEJM 2012;367:1198-1207

Main inclusion criteria

- **Asthma diagnosis**
  - **Asthma diagnosed at age <40 years, documented by BHR, PEF variability, or SABA or OCS response**
  - **5-year history of asthma**
  - **18–75 years**
  - **Never-smoker or ex-smoker ≥1 year cessation and <10 pack-years**
- **Symptomatic asthma**
  - **Uncontrolled despite ICS+LABA and potential other controllers**
    - **Mandatory: high-dose ICS (≥800 µg budesonide equivalent)+LABA**
    - **Permitted: stable theophylline, leukotriene modifiers, omalizumab, oral steroids (≤5 mg/day)**
  - **ACQ ≥1.5 at screening and baseline visit**
- **Lung function**
  - **Persistent obstruction**
    - **Post-bronchodilator FEV_1 ≤80% predicted; FEV_1/FVC ≤70% at screening**
- **Exacerbations**
  - **At least one severe asthma exacerbation in previous year treated with systemic steroids**

Kerstjens et al. *NEJM* 2012;367:1198-1207.
ACQ, asthma control questionnaire; BHR, bronchial hyper-responsiveness; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; OCS, oral corticosteroids; PEF, peak flow; SABA, short-acting β_2-agonist

Demographics at baseline: Pooled

Total treated[a]	Tiotropium Respimat® (n=456)	Placebo Respimat® (n=456)	Total (n=912)
Gender, n (%)			
Female	273 (59.9)	278 (61.0)	551 (60.4)
Race, n (%)			
White	376 (82.5)	383 (84.0)	759 (83.2)
Black	22 (4.8)	25 (5.5)	47 (5.2)
Asian	56 (12.3)	47 (10.3)	103 (11.3)
Other	2 (0.4)	1 (0.2)	3 (0.3)
Mean age, years (SD)	52.2 (12.5)	53.8 (12.2)	53.0 (12.4)
Mean BMI (SD)[b]	28.2 (5.9)	28.2 (6.1)	28.2 (6.0)
Never smoked, n (%)	340 (74.6)	352 (77.2)	692 (75.9)
Median duration of asthma, years (range)	28.0 (5.3-72.0)	28.0 (5.0-69.0)	28.0 (5.0-72.0)
Median age of onset, years (range)	26 (0-44)	26 (0-39)	26 (0-44)

Kerstjens et al. *NEJM* 2012;367:1198-1207.
[a]Treated set; Visit 2 (randomisation); [b]BMI, body mass index (= weight in kilogrammes divided by the square of the height in meters);
SD, standard deviation

Demographics at baseline

	PrimoTinA-asthma® 1	PrimoTinA-asthma® 2	Pooled
Total treated, N (%)	459 (100.0)	453 (100.0)	912 (100.0)
Female, N (%)	289 (63.0)	262 (57.8)	551 (60.4)
Mean age, years (min, max)	53.4 (18, 75)	52.5 (19, 75)	53.0 (18, 75)
Median BMI (min, max)	27.3 (15, 62)	27.0 (16, 47)	27.2 (15, 62)
Smoking status, N (%)			
Never smoked	356 (77.6)	336 (74.2)	692 (75.9)
Ex-smoker	103 (22.4)	117 (25.8)	220 (24.1)
Mean age onset asthma, years	21.9	23.4	22.7
Mean duration of asthma, years	31.5	29.1	30.3
Mean ACQ total score	2.7	2.6	2.6

Data on file

Kerstjens et al. NEJM 2012;367:1198-1207

ACQ, Asthma Control Questionnaire; BMI, body mass index

Disease characteristics at baseline: Pooled

Total treated	Tiotropium Respimat® (n=456)	Placebo Respimat® (n=456)	Total (n=912)
FEV_1, L mean (pre-bronchodilator)	1.63	1.58	1.60
FEV_1, % predicted mean (pre-bronchodilator)	54.9	54.8	54.8
FEV_1, % predicted mean (post-bronchodilator)	62.0	62.5	62.2
**FEV_1 bronchodilator rev mean, L (%)*, ** **	0.21 (14.7)	0.22 (15.6)	0.22 (15.2)
FVC, % predicted mean (post-bronchodilator)	87.3	88.1	87.7
FEV_1/FVC % mean (post-bronchodilator)	59.4	59.0	59.2
FEV_1 % predicted classes (post-bronchodilator), n (%)			
<60%	179 (39.3)	183 (40.1)	362 (39.7)
≥60% to <80%	274 (60.1)	264 (57.9)	538 (59.0)
≥80% to <90%	3 (0.7)	9 (2.0)	12 (1.3)

*Performed 30 minutes after four puffs of 100 µg salbutamol.

**Mean absolute (L) and mean percentage(%) change in FEV_1 pre-/post-bronchodilator

Kerstjens et al. *NEJM* 2012;367:1198-1207.

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity

rev, reversibility

Kerstjens et al. NEJM 2012;367:1198-1207.

Medications at baseline: Pooled

	Treatment arms, n (%)		
	Tiotropium Respimat®	Placebo Respimat®	Total
Total treated	456 (100.0)	456 (100.0)	912 (100.0)
Inhaled corticosteroids	456 (100.0)	450 (98.7)	906 (99.3)
Oral corticosteroids	24 (5.3)	24 (5.3)	48 (5.3)
Anticholinergics	7 (1.5)	6 (1.3)	13 (1.4)
Long-acting	0 (0.0)	0 (0.0)	0 (0.0)
Short-acting	5 (1.1)	4 (0.9)	9 (1.0)
LABA	444 (97.4)	449 (98.5)	893 (97.9)
Antibiotics	5 (1.1)	7 (1.5)	12 (1.3)
Mucolytics	10 (2.2)	6 (1.3)	16. (1.8)
Theophyllines	75 (16.4)	72 (15.8)	147 (16.1)
Antihistamines	81 (17.8)	55 (12.1)	136 (14.9)
Leukotriene modifiers	92 (20.2)	108 (23.7)	200 (21.9)
Omalizumab	13 (2.9)	24 (5.3)	37 (4.1)

Kerstjens et al. *NEJM* 2012;367:1198-1207.
LABA, long-acting β_2-agonist.

Significant lung function improvement in FEV_1 peak and trough: Trial 1

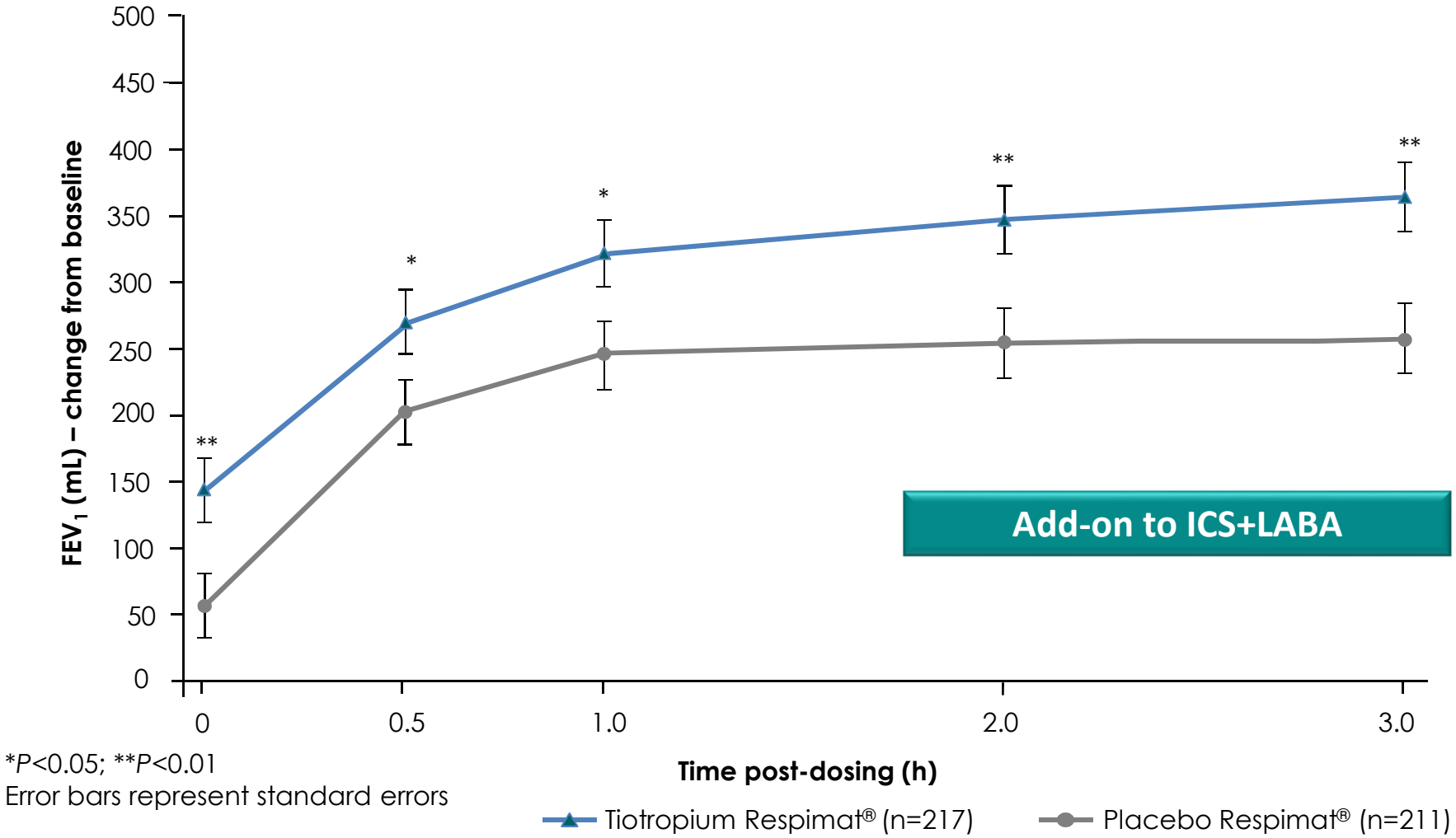
	Baseline, mL	Adjusted mean change (SE), mL	Difference from placebo		
			Adjusted mean (SE), mL	95% CI, mL	*P*-value
FEV_1 peak$_{(0\text{-}3h)}$					
Tiotropium Respimat® (n=217)	1578	401 (25)	86 (34)	20, 152	<0.05
Placebo Respimat® (n=211)		315 (26)			
FEV_1 trough					
Tiotropium Respimat® (n=217)	1578	144 (24)	88 (31)	27, 149	<0.01
Placebo Respimat® (n=211)		56 (25)			

Kerstjens et al. *NEJM* 2012;367:1198-1207.

CI, confidence interval; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; SE, standard error

Kerstjens et al. NEJM 2012;367:1198-1207

FEV_1 response 0–3 hours at week 24: Trial 1



*P<0.05; **P<0.01
Error bars represent standard errors

Kerstjens et al. *NEJM* 2012;367:1198-1207.
FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist

Significant lung function improvement in FEV_1 peak and trough: Trial 2

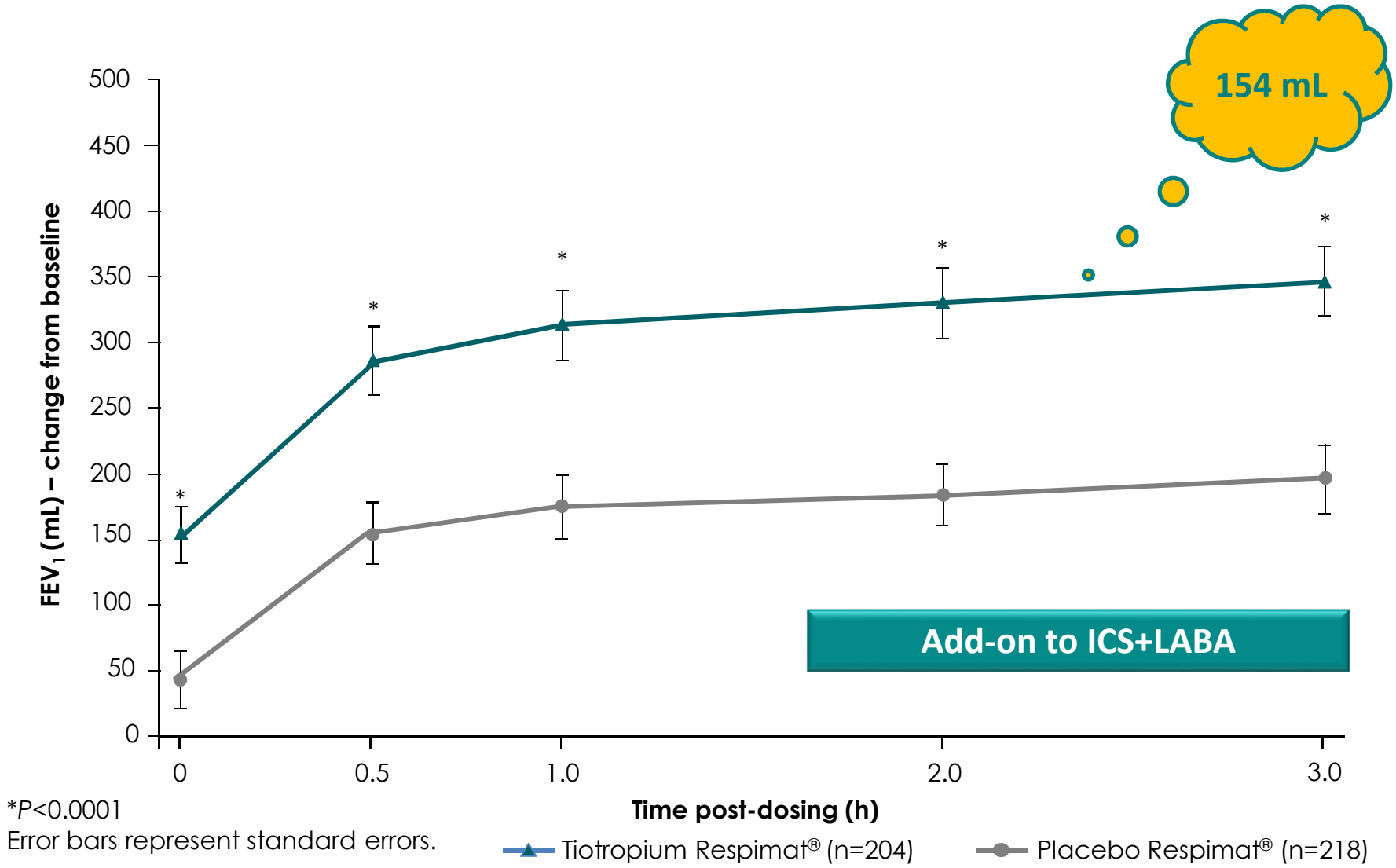
	Baseline, mL	Adjusted mean change (SE), mL	Difference from placebo		
			Adjusted mean (SE), mL	95% CI, mL	*P*-value
FEV_1 peak$_{(0\text{-}3h)}$					
Tiotropium Respimat® (n=205)	1628	401 (25)	**154 (32)**	91, 217	<0.0001
Placebo Respimat® (n=218)		248 (24)			
FEV_1 trough					
Tiotropium Respimat® (n=204)	1628	155 (23)	111 (30)	53, 169	<0.001
Placebo Respimat® (n=218)		44 (22)			

Kerstjens et al. *NEJM* 2012;367:1198-1207.

CI, confidence interval; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; SE, standard error

Kerstjens et al. NEJM 2012;367:1198-1207

FEV_1 response 0–3 hours at week 24: Trial 2



*P<0.0001
Error bars represent standard errors.

Kerstjens et al. *NEJM* 2012;367:1198-1207.
FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist

Definition of any asthma exacerbation

Symptoms

- **Episode of progressive increase in one or more asthma symptoms, e.g. shortness of breath, cough, wheezing or chest tightness**
- **Must have been outside the patient's usual range of day-to-day asthma**
- **Must have had a duration of at least two consecutive days**

and/or

PEF

- **Decrease of patient's best morning PEF of 30% or more from the patient's mean screening morning PEF for at least two consecutive days**

Kerstjens et al. *NEJM* 2012;367:1198-1207.
PEF, peak expiratory flow

Definition of severe asthma exacerbation

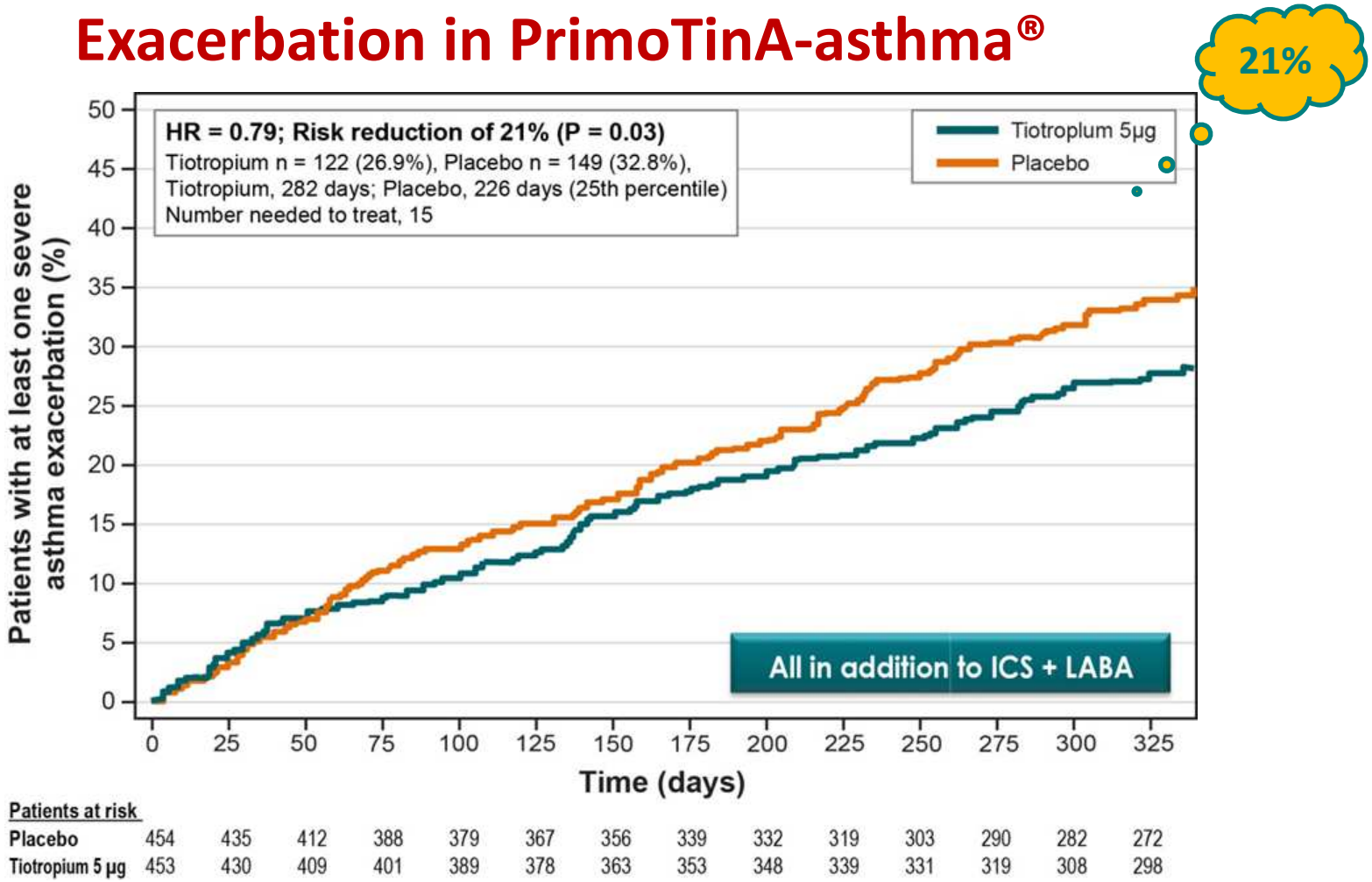
- **All exacerbations (as defined previously) that required**
  - **Treatment with systemic corticosteroids for at least 3 days**

  OR

  - **At least a doubling of the previous daily dose of systemic corticosteroids for at least 3 days – in case of ongoing and pre-existing systemic corticosteroid therapy**

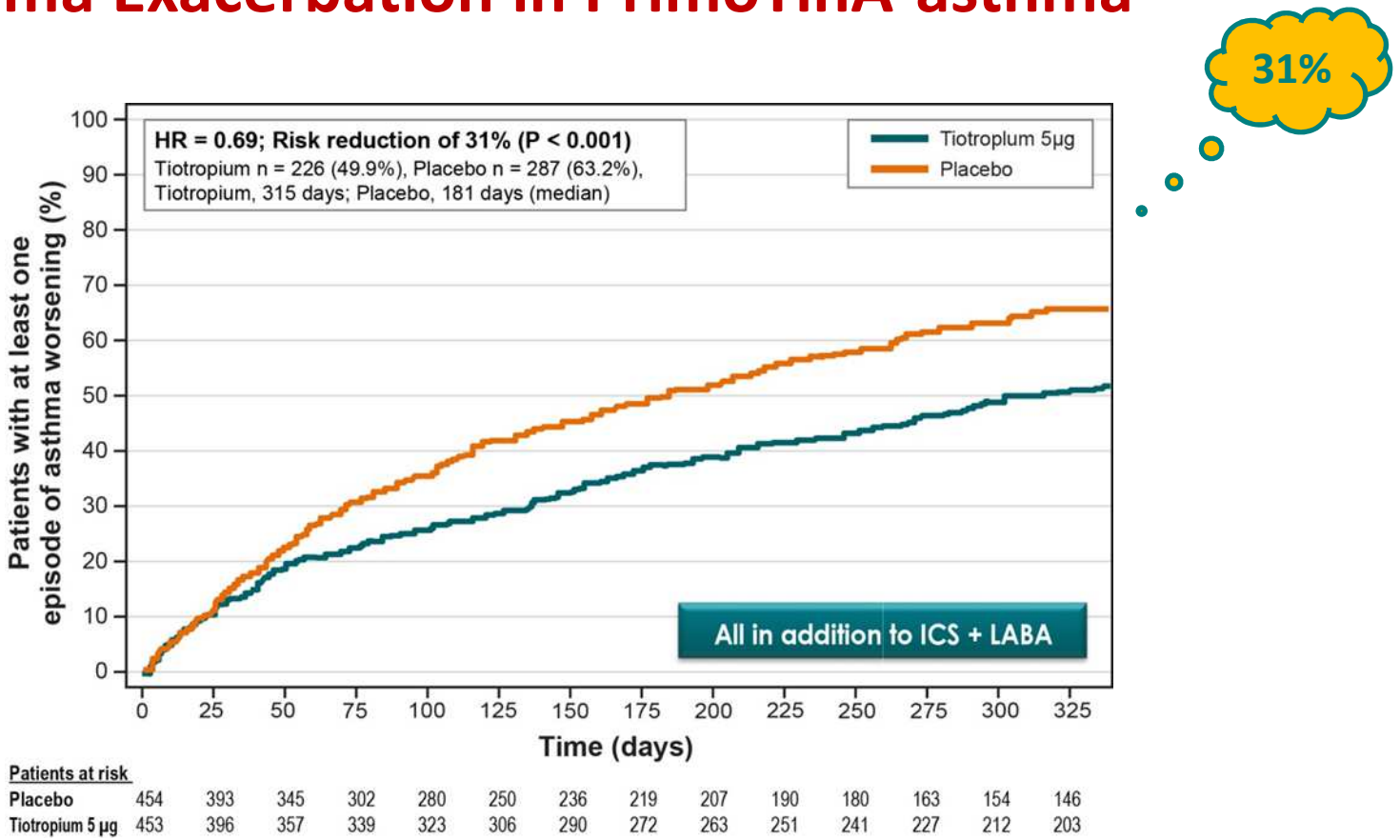
Kerstjens et al. NEJM 2012;367:1198-1207

Kaplan-Meier Plot of the Cumulative Percentage of Patients With at Least One Severe Asthma Exacerbation in PrimoTinA-asthma®



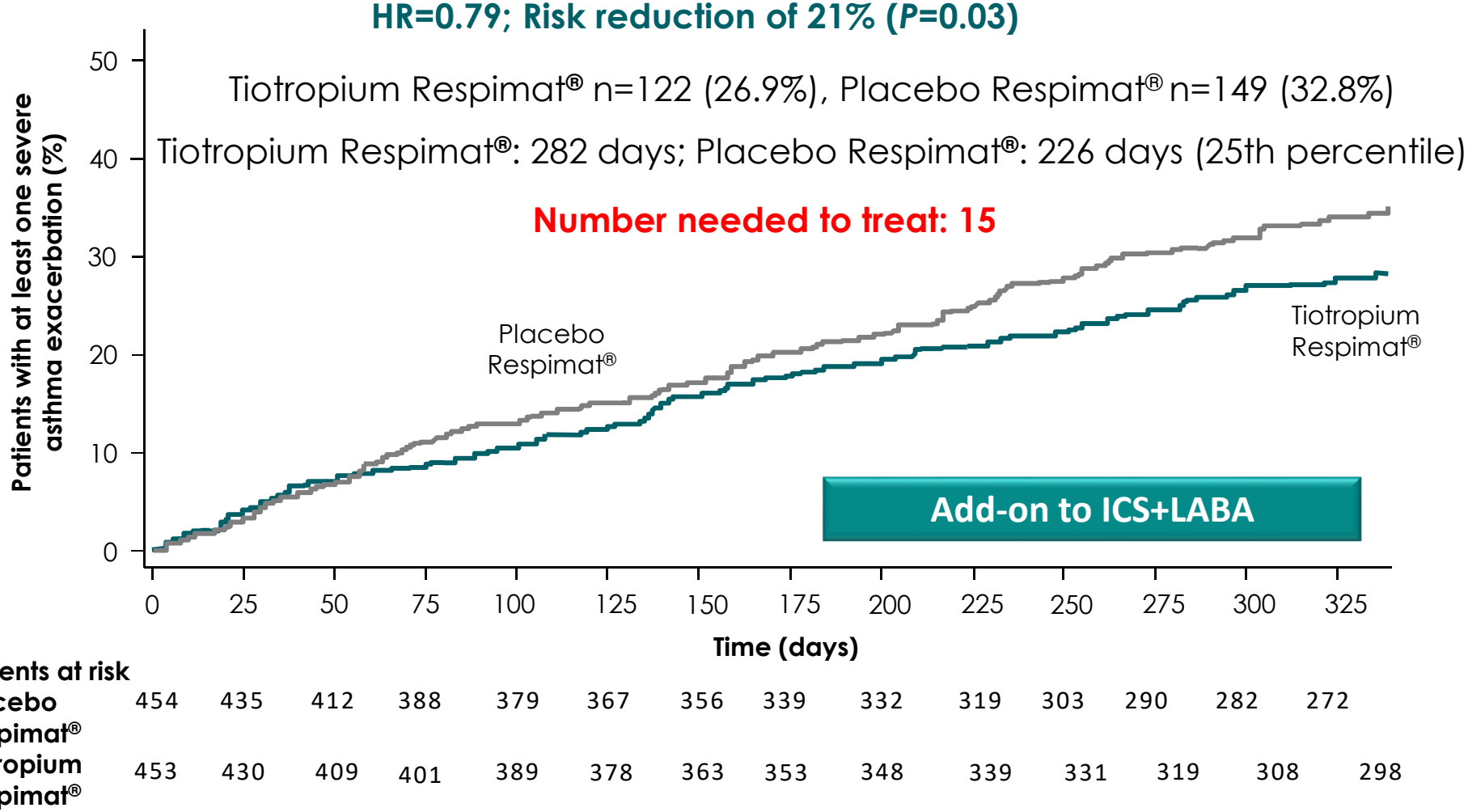
Kerstjens et al. NEJM 2012;367:1198-1207

Cumulative Percentage of Patients With at Least 1 Asthma Exacerbation in PrimoTinA-asthma®



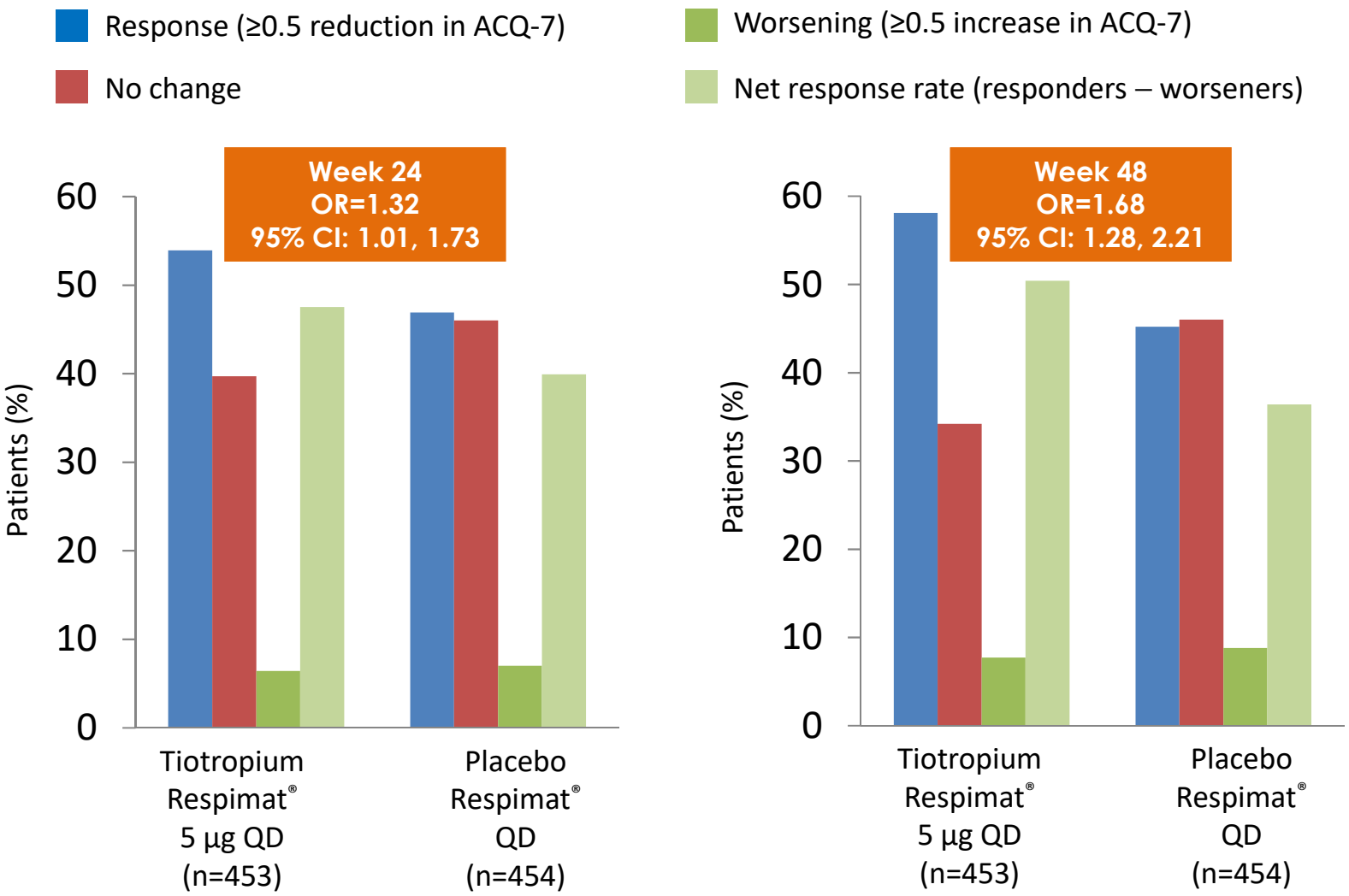
Kerstjens et al. NEJM 2012;367:1198-1207

Significant reduction in time to first severe asthma exacerbation – pooled



Kerstjens et al. NEJM 2012;367:1198-1207

68% of tiotropium Respimat® patients had an improvement in asthma control at 48 weeks



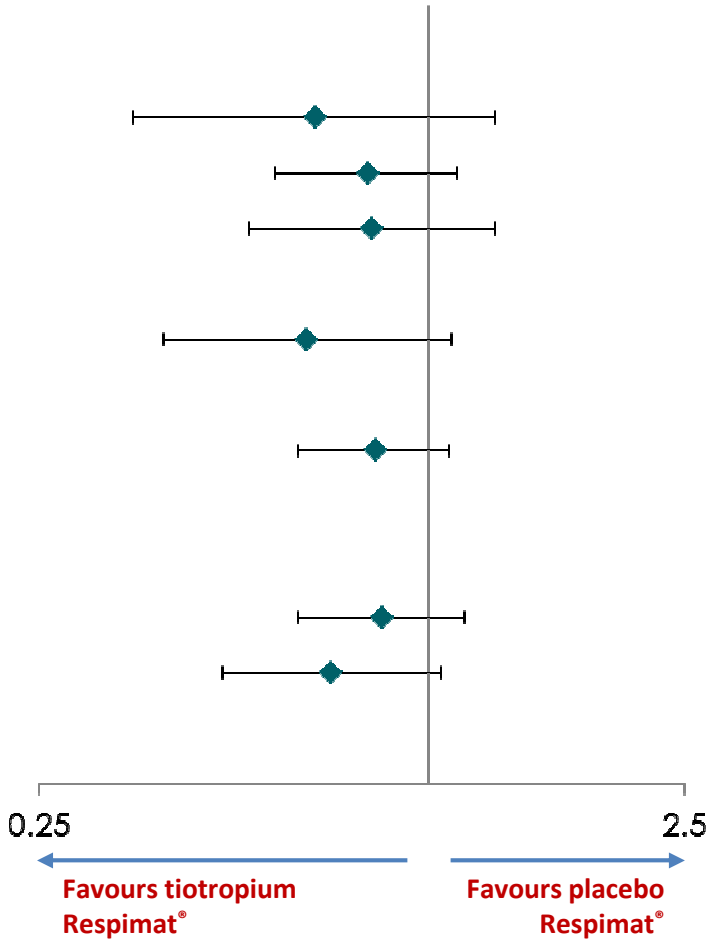
[a]Full analysis set, pooled data, add-on to high-dose ICS + LABA
ACQ, Asthma Control Questionnaire; OR, odds ratio active versus placebo; CI, confidence interval; QD, once daily. Data on File

Pooled subgroup analysis

TIME TO FIRST SEVERE ASTHMA EXACERBATION BY BASELINE CHARACTERISTICS

Tiotropium Respimat® is effective independent of baseline demographics

Baseline characteristics	Events[a]: placebo Respimat®/ Tiotropium Respimat®	Hazard ratio[b] (95% CI)
Age class, years (*P*=0.841)		
<40 (n=136)	23/16	0.67 (0.35, 1.27)
40–60 (n=494)	78/71	0.81 (0.58, 1.11)
>60 (n=277)	48/35	0.82 (0.53, 1.27)
Smoking status (*P*=0.423)		
Ex-smoker >2–10 pack-years (n=179)	32/26	0.65 (0.39, 1.09)
Never smoked and ex-smoker ≤2 pack-years (n=728)	117/96	0.83 (0.63, 1.08)
Sex (*P*=0.493)		
Female (n=549)	93/78	0.85 (0.63, 1.14)
Male (n=358)	56/44	0.71 (0.48, 1.05)



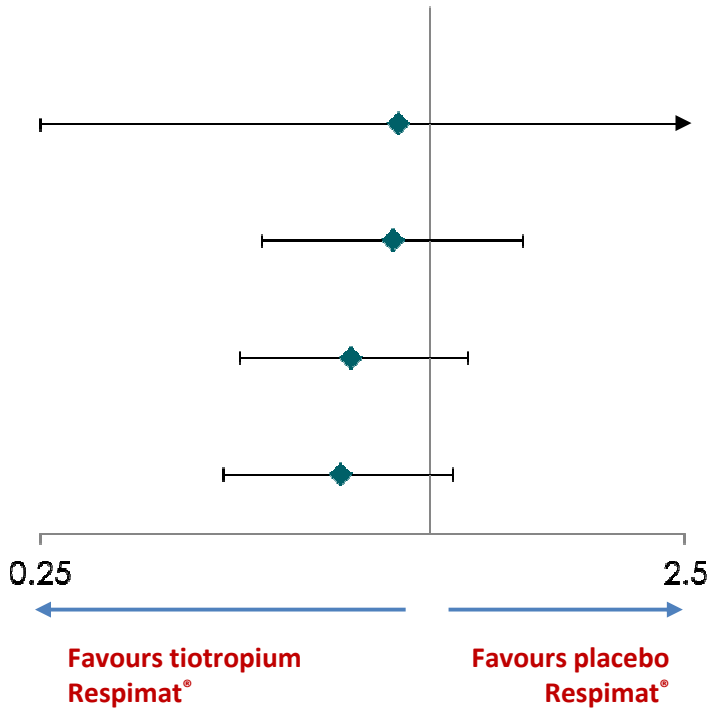
Kerstjens et al. *AJRCCM* 2013; 187:A4217

[a]Only the first occurrence of an event; [b]Tiotropium Respimat® versus placebo Respimat®. Cox regression adjusted for treatment, (pooled) centre, visit, baseline, treatment visit and baseline visit

CI, confidence interval

Tiotropium Respimat® is effective independent of BMI

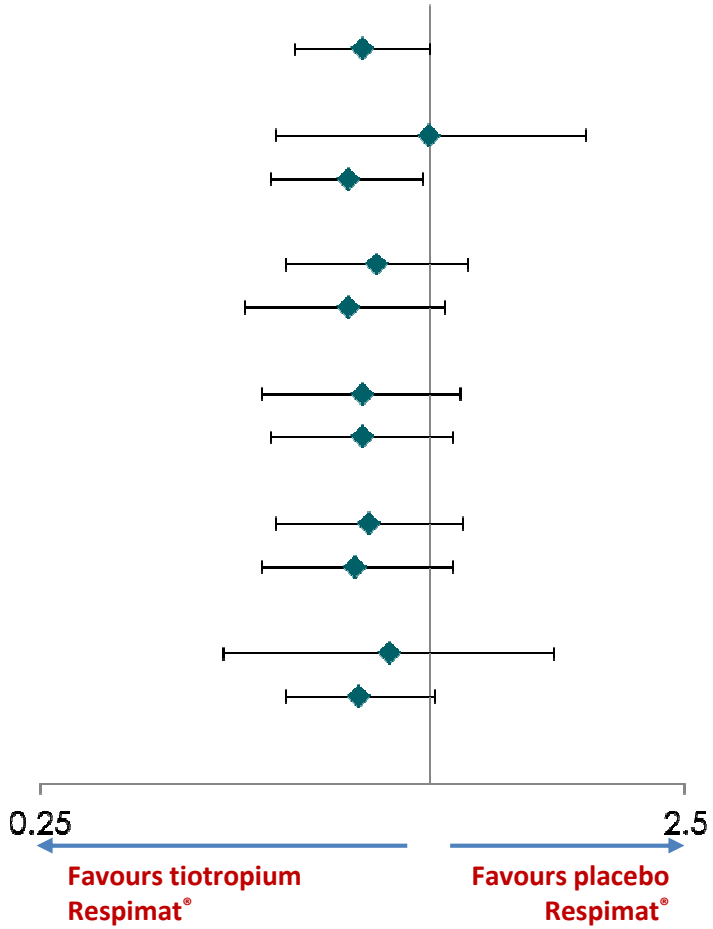
Baseline characteristics	Events[a]: placebo Respimat®/ tiotropium Respimat®	Hazard ratio[b] (95% CI)
BMI class (*P*=0.942)		
<20 (n=35)	**6/4**	**0.90 (0.25, 3.21)**
20-<25 (n=260)	**39/33**	**0.88 (0.55, 1.40)**
25-<30 (n=332)	**53/42**	**0.76 (0.51, 1.15)**
≥30 (n=280)	**51/43**	**0.73 (0.48, 1.09)**



Kerstjens et al. *AJRCCM* 2013; 187:A4217
[a]Only the first occurrence of an event; [b]Tiotropium Respimat® versus placebo Respimat®; Cox regression adjusted for treatment, (pooled) centre, visit, baseline, treatment visit and baseline visit
BMI, body mass index; CI, confidence interval

Tiotropium Respimat® is effective independent of disease characteristics

Baseline characteristics	Events[a]: placebo Respimat®/ Tiotropium Respimat®	Hazard ratio[b] (95% CI)
Overall population		
Overall(N=907)	149/122	0.79 (0.62, 1.00)
Number of hospital admissions in past year (*P*=0.375)		
≥1 (n=162)	23/27	1.00 (0.58, 1.75)
0 (n=745)	126/95	0.75 (0.57, 0.98)
FEV_1 reversibility (≥12% and 200 mL) at screening (*P*=0.656)		
No (n=473)	75/70	0.83 (0.60, 1.15)
Yes (n=434)	74/52	0.75 (0.52, 1.06)
FEV_1 (% predicted) post-bronchodilation at screening (*P*=0.988)		
<60% (n=360)	68/55	0.79 (0.55, 1.12)
≥60% (n=547)	81/67	0.79 (0.57, 1.09)
ACQ at randomisation relative to mean (*P*=0.853)		
<mean (n=477)	74/63	0.81 (0.58, 1.13)
≥mean (n=430)	75/59	0.77 (0.55, 1.09)
Disease duration, years (*P*=0.733)		
5-20 (n=214)	23/22	0.87 (0.48, 1.56)
≥20 (n=693)	126/100	0.78 (0.60, 1.02)



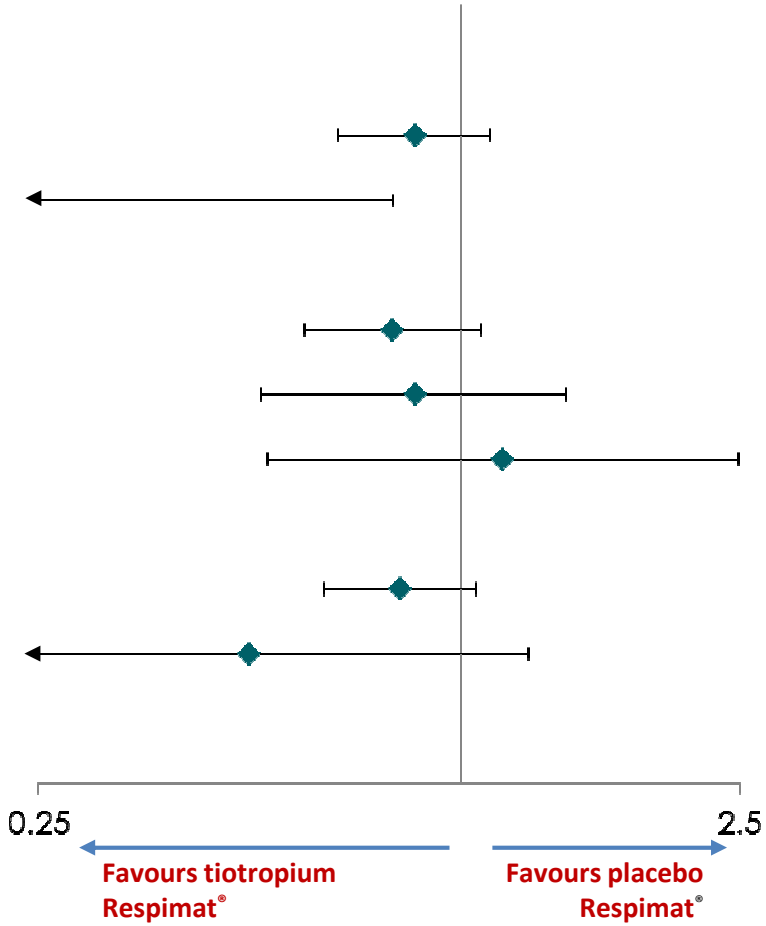
Kerstjens et al. *AJRCCM* 2013; 187:A4217

[a]Only the first occurrence of an event; [b]Tiotropium Respimat® versus placebo Respimat®. Cox regression adjusted for treatment, (pooled) centre, visit, baseline, treatment visit and baseline visit

ACQ, Asthma Control Questionnaire; CI, confidence interval; FEV_1, forced expiratory volume in 1 second

Tiotropium Respimat® is effective independent of omalizumab and steroid medication

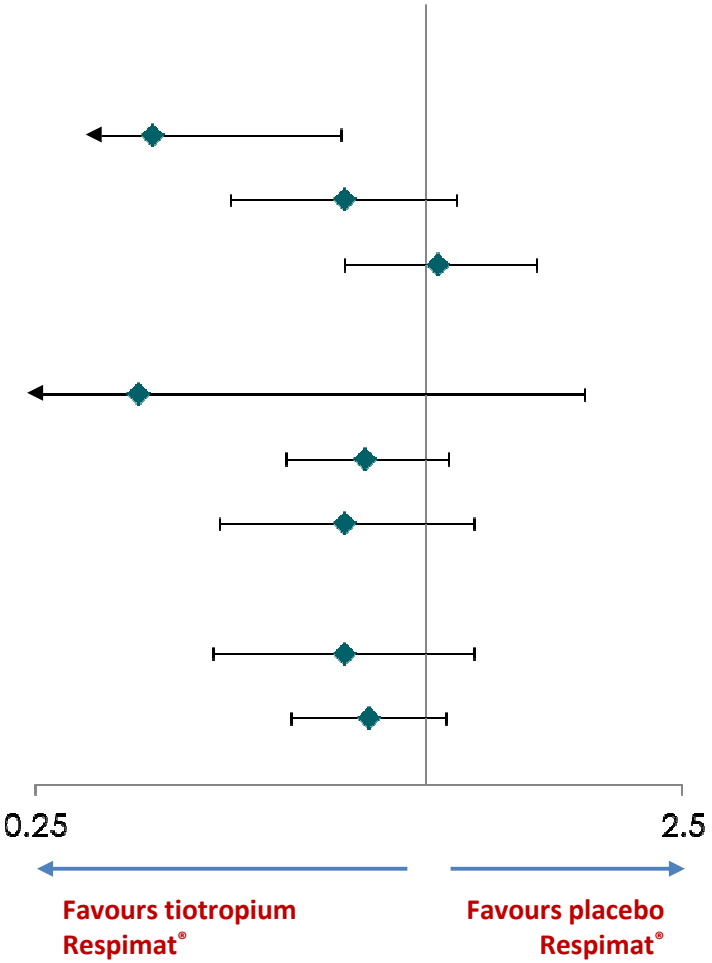
Baseline characteristics	Events[a]: placebo Respimat® / tiotropium Respimat®	Hazard ratio[b] (95% CI)
Omalizumab at baseline (*P*=0.032)		
No (n=870)	133/119	0.86 (0.67, 1.10)
Yes (n=37)	16/3	0.23 (0.07, 0.80)
Number of systemic steroid courses in past year (*P*=0.720)		
<3 (n=734)	97/84	0.80 (0.60, 1.07)
3-5 (n=128)	36/27	0.86 (0.52, 1.41)
>5 (n=45)	16/11	1.15 (0.53, 2.49)
Oral steroid at baseline (*P*=0.262)		
No (n=862)	136/115	0.82 (0.64, 1.05)
Yes (n=45)	13/7	0.50 (0.20, 1.25)



Kerstjens et al. *AJRCCM* 2013; 187:A4217
[a]Only the first occurrence of an event; [b]Tiotropium Respimat® versus placebo Respimat®. Cox regression adjusted for treatment, (pooled) centre, visit, baseline, treatment visit and baseline visit
CI, confidence interval

Tiotropium Respimat® is effective independent of allergic status

Baseline characteristics	Events[a]: placebo Respimat®/ tiotropium Respimat®	Hazard ratio[b] (95% CI)
IgE class (Harrison reference) (*P*=0.21[c])		
Missing (n=161)	37/12	0.38 (0.20, 0.74)
≤430 µg/L (n=352)	52/41	0.75 (0.50, 1.12)
>430 µg/L (n=394)	60/69	1.05 (0.75, 1.49)
Blood eosinophilia (Harrison reference) (*P*=0.748[c])		
Missing (n=25)	6/2	0.36 (0.07, 1.76)
≤0.6 × 10^9/L (n=696)	104/85	0.81 (0.61, 1.09)
>0.6 × 10^9/L (n=186)	39/35	0.75 (0.48, 1.19)
Clinician judgement of allergic status (*P*=0.745[c])		
No (n=352)	40/33	0.75 (0.47, 1.19)
Yes (n=555)	109/89	0.82 (0.62, 1.08)



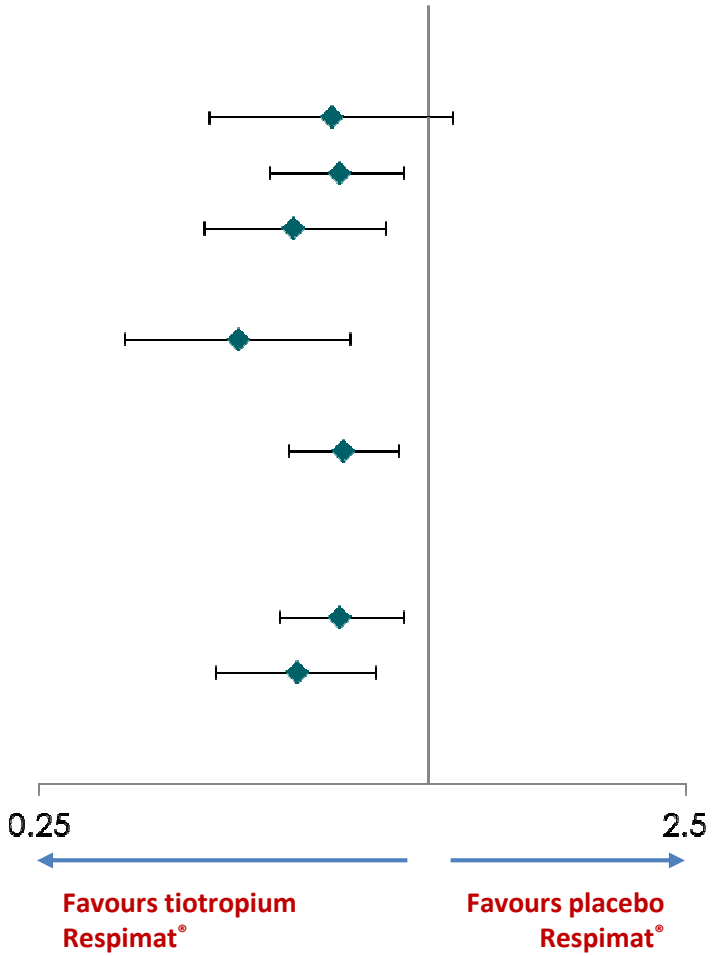
Kerstjens et al. AJRCCM 2013; 187:A4217
[a]Only the first occurrence of an event; [b]Tiotropium Respimat® versus placebo Respimat®; [c]Interaction *P* values only calculated between nonmissing categories
CI, confidence interval; IgE, immunoglobulin E

Pooled subgroup analysis

TIME TO FIRST ASTHMA WORSENING BY BASELINE CHARACTERISTICS

Tiotropium Respimat® is effective independent of baseline demographics

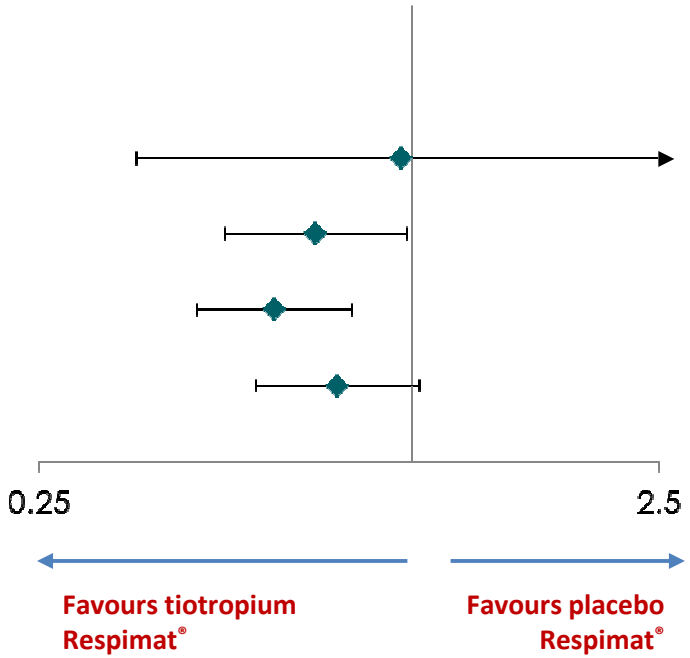
Baseline characteristics	Events[a]: placebo Respimat®/ tiotropium Respimat®	Hazard ratio[b] (95% CI)
Age class, years (*P*=0.711)		
<40 (n=136)	46/38	0.71 (0.46, 1.09)
40-60 (n=494)	148/129	0.73 (0.57, 0.92)
>60 (n=277)	93/59	0.62 (0.45, 0.86)
Smoking status (*P*=0.132)		
Ex-smoker >2-10 pack-years (n=179)	56/45	0.51 (0.34, 0.76)
Never smoked and ex-smoker ≤2 pack-years (n=728)	231/181	0.74 (0.61, 0.90)
Sex (*P*=0.395)		
Female (n=549)	174/139	0.73 (0.59, 0.92)
Male (n=358)	113/87	0.63 (0.47, 0.83)



Kerstjens et al. *AJRCCM* 2013; 187:A4217
[a]Only the first occurrence of an event; [b]Tiotropium Respimat® versus placebo Respimat®. Summary results: full analysis set. Cox regression adjusted for treatment.
CI, confidence interval

Tiotropium Respimat® is effective independent of BMI

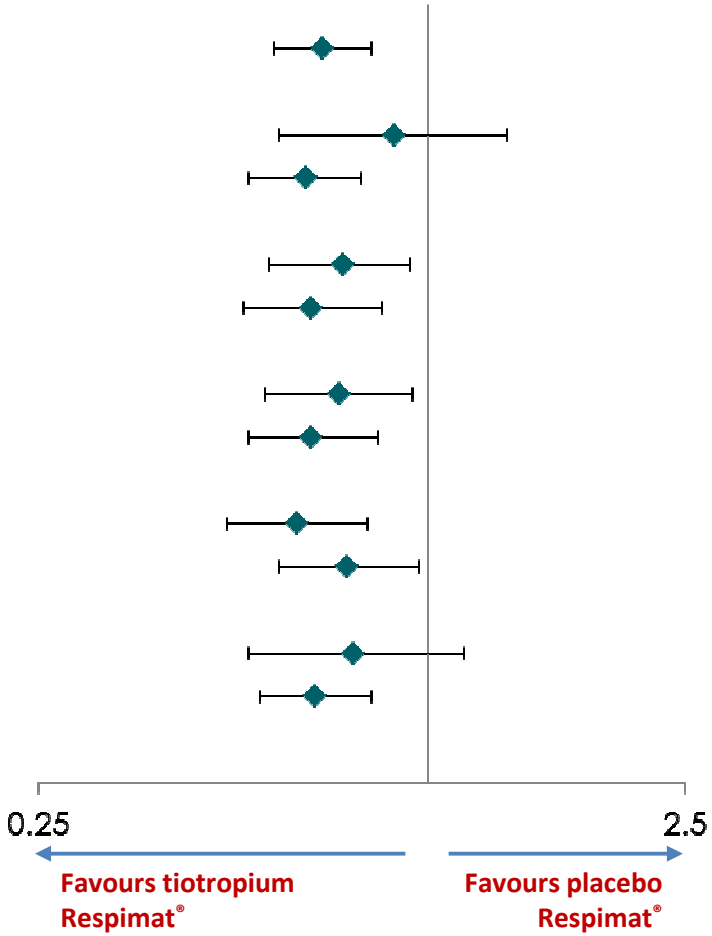
Baseline characteristics	Events[a]: placebo Respimat®/ tiotropium Respimat®	Hazard ratio[b] (95% CI)
BMI class (*P*=0.542)		
<20 (n=35)	9/7	0.96 (0.36, 2.58)
20–<25 (n=260)	79/60	0.70 (0.50, 0.98)
25–<30 (n=332)	112/79	0.60 (0.45, 0.80)
≥30 (n=280)	87/80	0.76 (0.56, 1.03)



Kerstjens et al. *AJRCCM* 2013; 187:A4217.
[a]Only the first occurrence of an event; [b]Tiotropium Respimat® versus placebo Respimat®; Summary results: full analysis set. Cox regression adjusted for treatment.
BMI, body mass index; CI, confidence interval

Tiotropium Respimat® is effective independent of disease characteristics

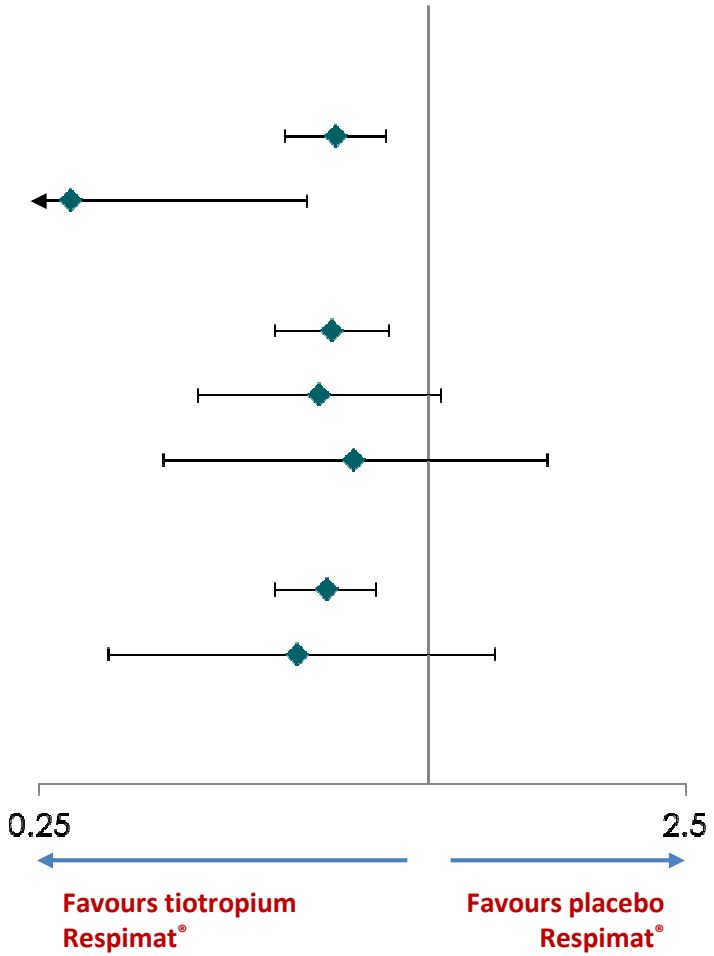
Baseline characteristics	Events[a]: placebo Respimat® / tiotropium Respimat®	Hazard ratio[b] (95% CI)
Overall Population		
Overall(N=907)	287/226	0.69 (0.58, 0.82)
Number of hospital admissions in past year (*P*=0.211)		
≥1 (n=162)	44/49	0.89 (0.59, 1.33)
0 (n=745)	243/177	0.65 (0.53, 0.79)
FEV_1 reversibility (≥12% and 200 mL) at screening (*P*=0.5)		
No (n=473)	133/119	0.74 (0.57, 0.94)
Yes (n=434)	154/107	0.66 (0.52, 0.85)
FEV_1 (% predicted) post-bronchodilation at screening (*P*=0.676)		
<60% (n=360)	120/96	0.73 (0.56, 0.95)
≥60% (n=547)	167/130	0.66 (0.53, 0.84)
ACQ at randomisation relative to mean (*P*=0.352)		
<mean (n=477)	149/112	0.63 (0.49, 0.81)
≥mean (n=430)	138/114	0.75 (0.59, 0.97)
Disease duration, years (*P*=0.563)		
5-20 (n=214)	56/50	0.77 (0.53, 1.14)
≥20 (n=693)	231/176	0.67 (0.55, 0.82)



Kerstjens et al. AJRCCM 2013; 187:A4217
[a]Only the first occurrence of an event; [b]Tiotropium Respimat® versus placebo Respimat®. Summary results: full analysis set. Cox regression adjusted for treatment
ACQ, Asthma Control Questionnaire; CI, confidence interval; FEV_1, forced expiratory volume in 1 second

Tiotropium Respimat® is effective independent of omalizumab and steroid medication

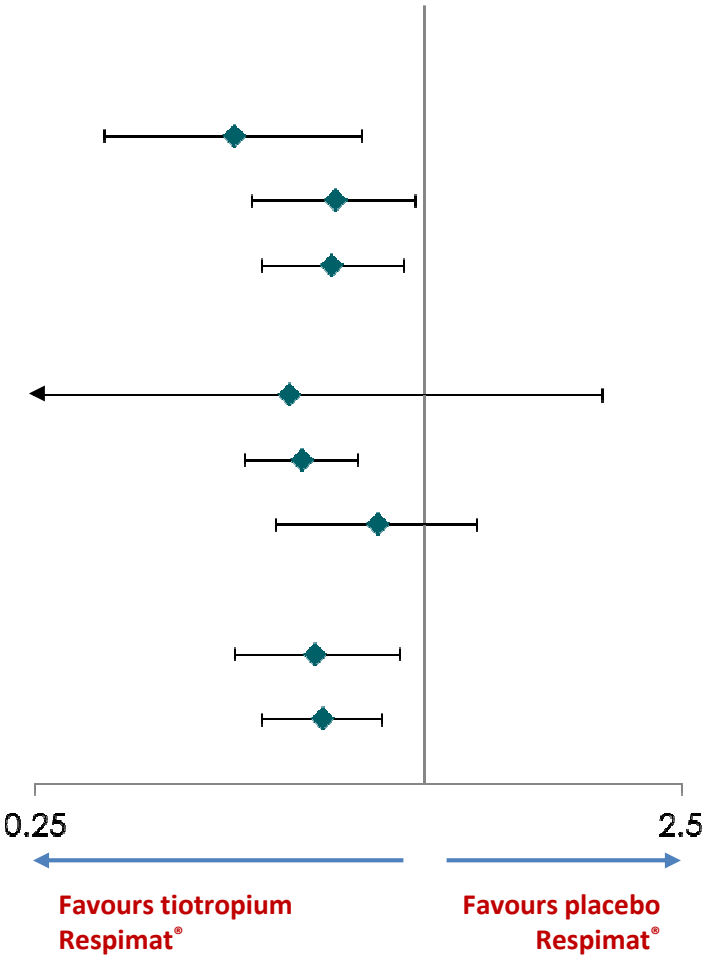
Baseline characteristics	Events[a]: placebo Respimat®/ tiotropium Respimat®	Hazard ratio[b] (95% CI)
Omalizumab at baseline (*P*=0.104)		
No (n=870)	263/217	0.72 (0.60, 0.86)
Yes (n=37)	24/9	0.28 (0.12, 0.65)
Number of systemic steroid courses in past year (*P*=0.961)		
<3 (n=734)	211/178	0.71 (0.58, 0.87)
3-5 (n=128)	52/35	0.68 (0.44, 1.05)
>5 (n=45)	24/13	0.77 (0.39, 1.53)
Oral steroid at baseline (*P*=0.637)		
No (n=862)	267/212	0.70 (0.58, 0.83)
Yes (n=45)	20/14	0.63 (0.32, 1.27)



Kerstjens et al. *AJRCCM* 2013; 187:A4217
[a]Only the first occurrence of an event; [b]Tiotropium Respimat® versus placebo Respimat®. Summary results: full analysis set. Cox regression adjusted for treatment.
CI, confidence interval

Tiotropium Respimat® is effective independent of allergic status

Baseline characteristics	Events[a]: placebo Respimat®/ tiotropium Respimat®	Hazard ratio[b] (95% CI)
IgE class (Harrison reference) (*P*=0.913[c])		
Missing (n=161)	59/29	0.51 (0.32, 0.80)
≤430 µg/L (n=352)	103/82	0.73 (0.54, 0.97)
>430 µg/L (n=394)	125/115	0.72 (0.56, 0.93)
Blood eosinophilia (Harrison reference) (*P*=0.250[c])		
Missing (n=25)	8/5	0.62 (0.20, 1.89)
≤0.6 × 10^9/L (n=696)	221/160	0.65 (0.53, 0.79)
>0.6 × 10^9/L (n=186)	58/61	0.85 (0.59, 1.21)
Clinician judgement of allergic status (*P*=0.905[c])		
No (n=352)	96/77	0.68 (0.51, 0.92)
Yes (n=555)	191/149	0.70 (0.56, 0.86)



Kerstjens et al. AJRCCM 2013; 187:A4217
[a]Only the first occurrence of an event; [b]Tiotropium Respimat® versus placebo Respimat®; [c]Interaction *P*-values only calculated between non-missing categories. Summary results: full analysis set. Eosinophil blood count was included to characterise patients' atopic immune status. Cox regression adjusted for treatment.
CI, confidence interval; IgE, immunoglobulin E

Adverse events: Overall summary

	Tiotropium Respimat® n (%)	Placebo Respimat® n (%)
Number of patients	456 (100.0)	456 (100.0)
Total with any adverse event	335 (73.5)	366 (80.3)
Drug-related adverse event as defined by Investigator	26 (5.7)	21 (4.6)
Serious adverse event	37 (8.1)	40 (8.8)

No deaths occurred.

Kerstjens et al. NEJM 2012;367:1198-1207

Serious adverse events: Overall summary

	Tiotropium Respimat® 5 µg, n (%)	Placebo Respimat® n (%)
Patients with serious AEs	37 (8.1)	40 (8.8)
Fatal	0 (0.0)	0 (0.0)
Immediately life threatening	3 (0.7)	0 (0.0)
Disability/incapacity	2 (0.4)	0 (0.0)
Requires hospitalisation	35 (7.7)	39 (8.6)
Prolonged hospitalisation	3 (0.7)	1 (0.2)
Congenital anomaly	0 (0.0)	0 (0.0)
Other	3 (0.7)	0 (0.0)

A patient may be counted in more than one seriousness criterion. Percentages are calculated using total number of patients per treatment as the denominator.

AE, adverse event

Kerstjens et al. NEJM 2012;367:1198-1207

Adverse events reported by >2% of randomised patients in pooled groups

	Tiotropium Respimat® n (%)	Placebo Respimat® n (%)
Patients with any AE, n (%)	335 (73.5)	366 (80.3)
Asthma	182 (39.9)	232 (50.9)*
Nasopharyngitis	51 (11.2)	56 (12.3)
Peak expiratory flow rate decreased	93 (20.4)	122 (26.8)
Headache	29 (6.4)	33 (7.2)
Bronchitis	25 (5.5)	20 (4.4)
Sinusitis	16 (3.5)	22 (4.8)
Upper respiratory tract infection	21 (4.6)	16 (3.5)
Influenza	20 (4.4)	14 (3.1)
Cough	13 (2.9)	13 (2.9)
Rhinitis allergic	13 (2.9)*	3 (0.7)
Pneumonia	12 (2.6)	7 (1.5)
Back pain	11 (2.4)	12 (2.6)
Arthralgia	10 (2.2)	9 (2.0)
Dysphonia	10 (2.2)	8 (1.8)
Oropharyngeal pain	9 (2.0)	11 (2.4)
Diarrhoea	8 (1.8)	10 (2.2)
Respiratory tract infection	7 (1.5)	11 (2.4)
Hypertension	6 (1.3)	10 (2.2)
Insomnia	2 (0.4)	10 (2.2)*

Kerstjens et al. *NEJM* 2012;367:1198-1207. Dry mouth reported in 3 (0.7%) placebo Respimat® and 8 (1.8%) tiotropium Respimat® patients; *$P<0.05$.

Kerstjens et al. NEJM 2012;367:1198-1207

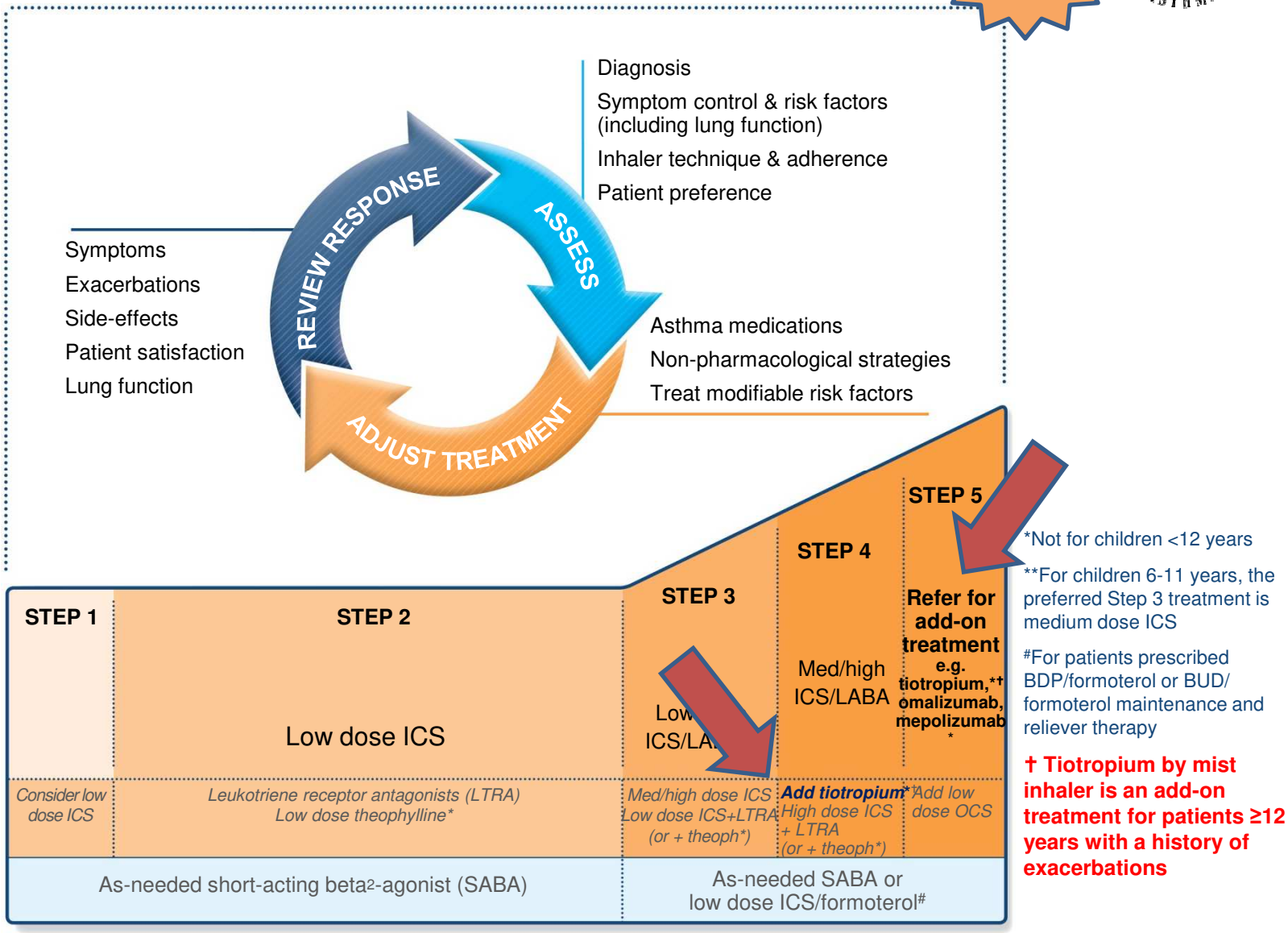
Summary: Primary analysis

- **Tiotropium Respimat® added on to at least ICS+LABA resulted in:**
  - **Up to154 mL improvement in lung function,**
  - **68% more likely to improve asthma control,**
  - **21% risk reduction for severe asthma exacerbation,**
  - **31% risk reduction for asthma worsening,**
  - **Safety profile comparable to placebo**

Kerstjens et al. *NEJM* 2012;367:1198-1207 and data on file
ACQ, Asthma Control Questionnaire; AQLQ, Asthma Qualify of Life Questionnaire;
ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist

Stepwise management - pharmacotherapy

UPDATED!



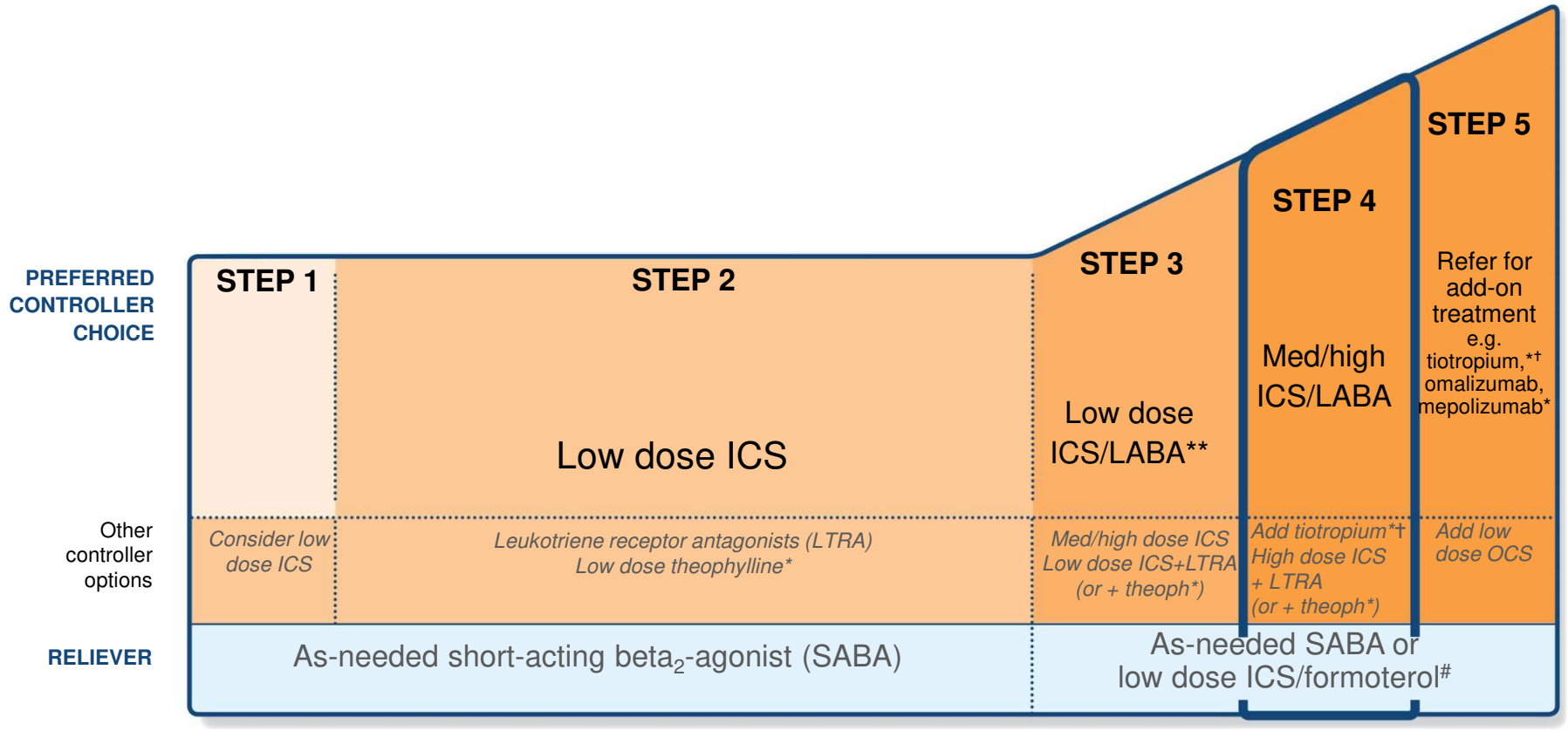
*Not for children <12 years

**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS

#For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

Step 4 – two or more controllers + as-needed inhaled reliever



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**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS
#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy
† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

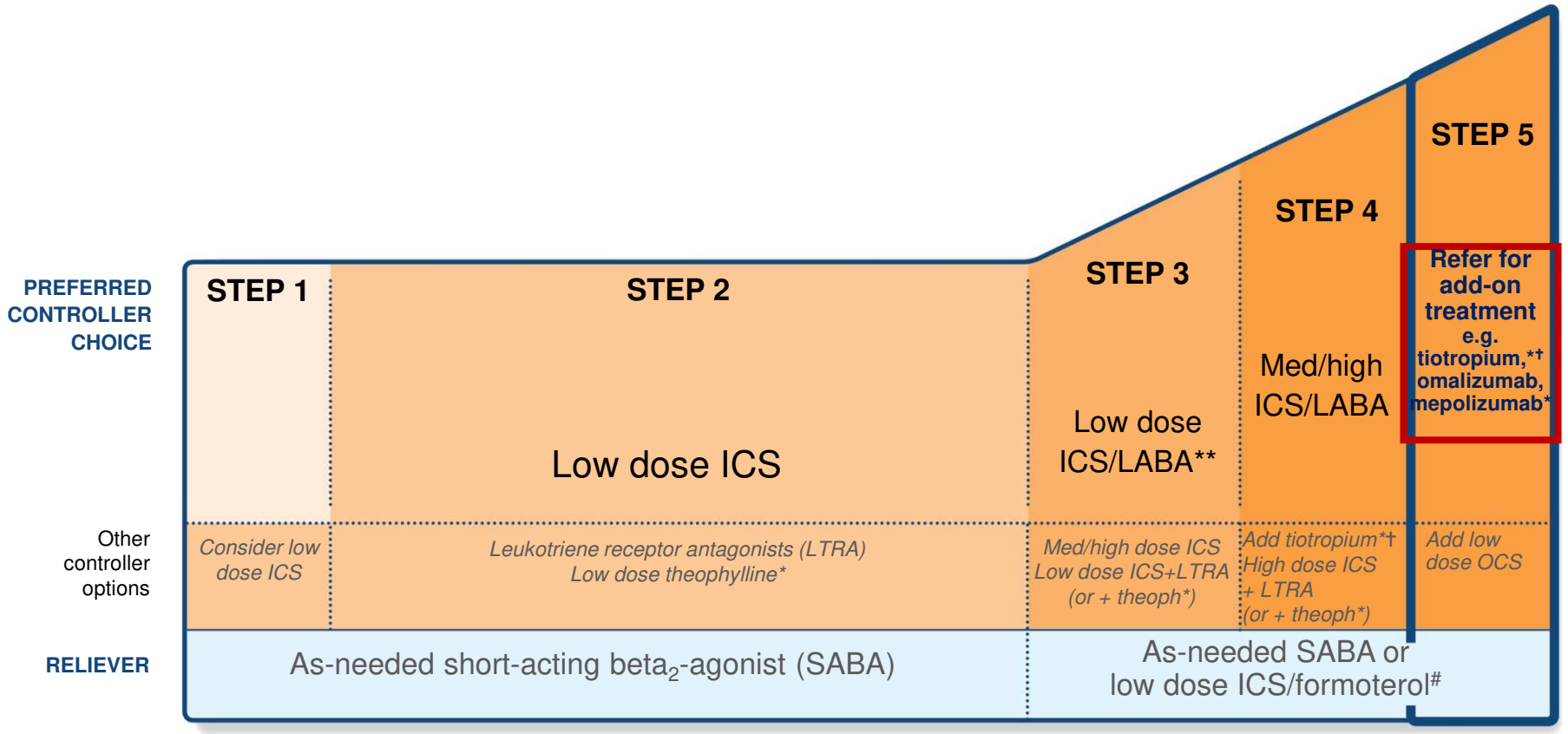
Step 4 – two or more controllers + as-needed inhaled reliever

- Before considering step-up
  - Check inhaler technique and adherence
- Adults or adolescents: preferred option is combination low dose ICS/formoterol as maintenance and reliever regimen*, OR combination medium dose ICS/LABA with as-needed SABA
- Children 6–11 years: preferred option is to refer for expert advice
- Other options (adults or adolescents)
  - **Tiotropium by mist inhaler may be used as add-on therapy for patients aged ≥12 years with a history of exacerbations**
  - Trial of high dose combination ICS/LABA, but little extra benefit and increased risk of side-effects
  - Increase dosing frequency (for budesonide-containing inhalers)
  - Add-on LTRA or low dose theophylline

*Approved only for low dose beclometasone/formoterol and low dose budesonide/formoterol

Step 5 – higher level care and/or add-on treatment

UPDATED!



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**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS
#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy
† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

Step 5 – higher level care and/or add-on treatment

UPDATED!

- Preferred option is referral for specialist investigation and consideration of add-on treatment
  - If symptoms uncontrolled or exacerbations persist despite Step 4 treatment, check inhaler technique and adherence before referring
  - **Add-on tiotropium for patients ≥12 years with history of exacerbations**
  - Add-on omalizumab (anti-IgE) for patients with severe allergic asthma
  - Add-on mepolizumab (anti-IL5) for severe eosinophilic asthma (≥12 yrs)
- Other add-on treatment options at Step 5 include:
  - Sputum-guided treatment: this is available in specialized centers; reduces exacerbations and/or corticosteroid dose
  - Add-on low dose oral corticosteroids (≤7.5mg/day prednisone equivalent): this may benefit some patients, but has significant systemic side-effects. Assess and monitor for osteoporosis
  - See ERS/ATS Severe Asthma Guidelines (Chung et al, ERJ 2014) for more detail

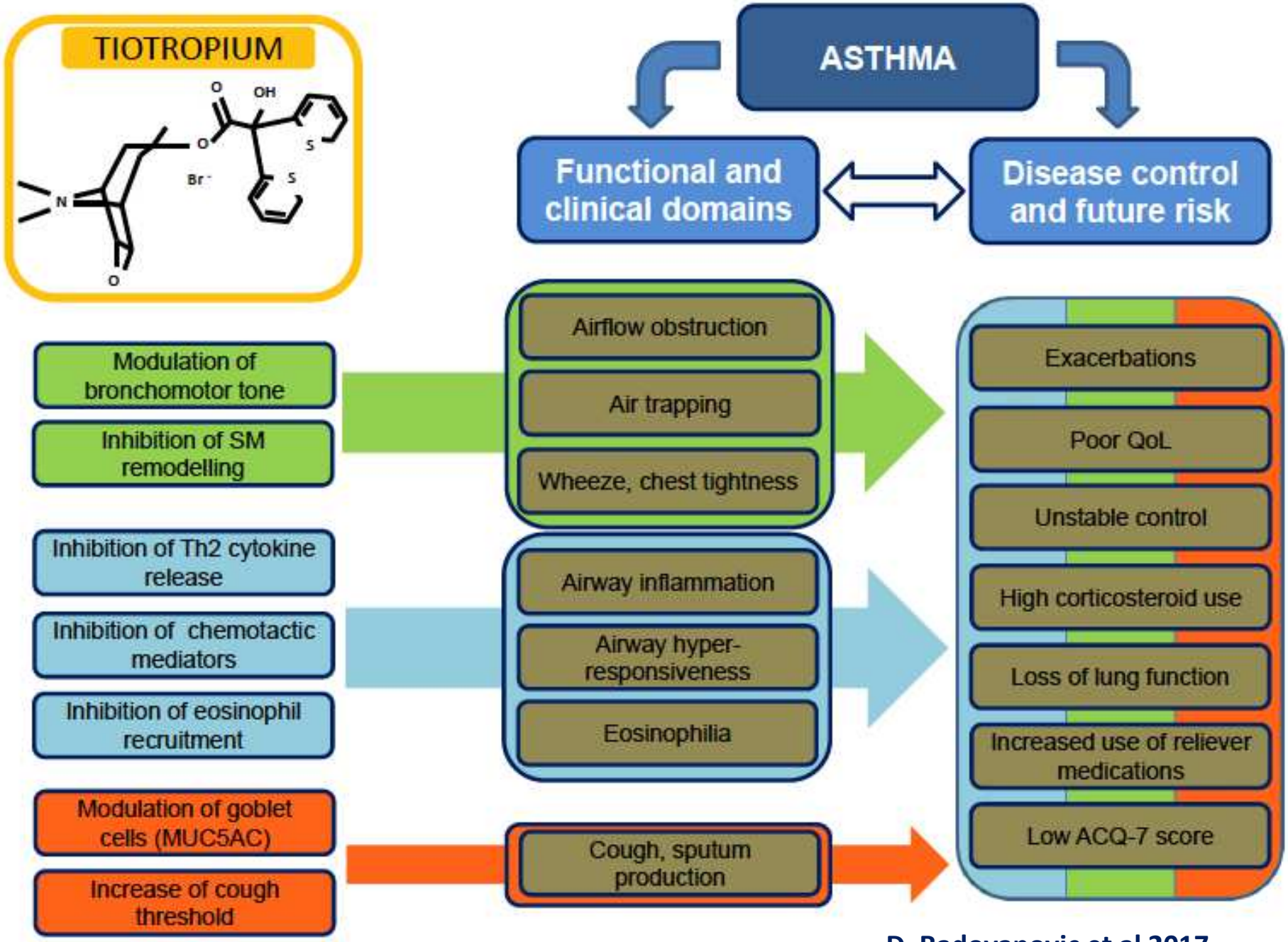
Conclusion

Tiotropium Respimat® as add-on to ICS+LABA has been shown to be efficacious in all subgroups tested compared to placebo Respimat®

Exploratory sub-analyses were not powered for low patient numbers, and variation in results may be high for subgroups containing a low number of patients

Safety profile comparable to placebo

ACQ, Asthma Control Questionnaire; FEV_1, forced expiratory volume in 1 second;
ICS, inhaled corticosteroid



D. Radovanovic et al 2017