Who can get most **benefit** from **tiotropium** in **asthma?**

Y-M. Oh
Asan Medical Center
Univ. of Ulsan College of Medicine
Seoul, Korea

New in GINA 2015

Add-on **tiotropium** by soft-mist inhaler

- for **steps 4 & 5**
- as a new 'other controller option'
- age ≥ 18 yrs
- with history of exacerbations

Spiriva Respimat should **NOT** be used in asthma status below

should NOT

① as first-line monotherapy

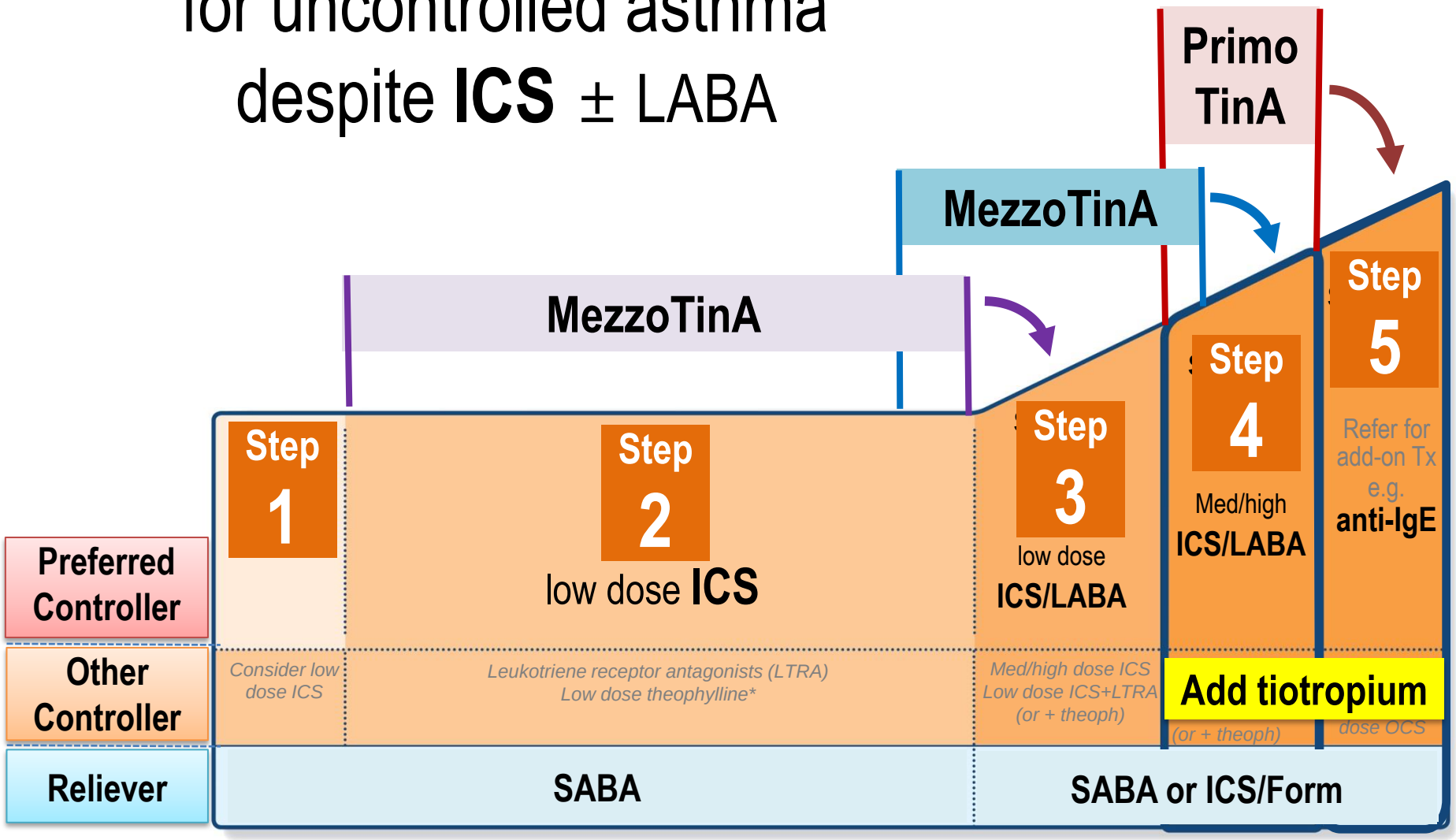
② as a reliever for acute symptoms

③ for acute exacerbation

NICE advice [ESNM55] Published date: March 2015

http://www.nice.org.uk/advice/esnm55/chapter/key-points-from-the-evidence

Tiotropium as an **add-on Tx** for uncontrolled asthma despite **ICS** ± LABA



Tiotropium Respimat for **uncontrolled asthma despite ICS** ±LABA

RCTs	PrimoTinA	MezzoTinA	GraziaTinA
Add-on	medium/**high ICS + LABA**	low/**medium ICS ± LABA**	**low ICS**
Pri. End Points	FEV_1, Exacerb'n ***Success***	FEV_1, ACQ ***Success***	FEV_1 ***Success***
Sec. End Points	ACQ ***Partial Success***	FVC, PEF ***Success***	ACQ ***Fail***
Number of Pts	**912**	**2103**	**4206**
Duration	48 wks	24 wks	12 wks
Comparator	Placebo	Salmeterol, Placebo	Placebo

Tiotropium Respimat

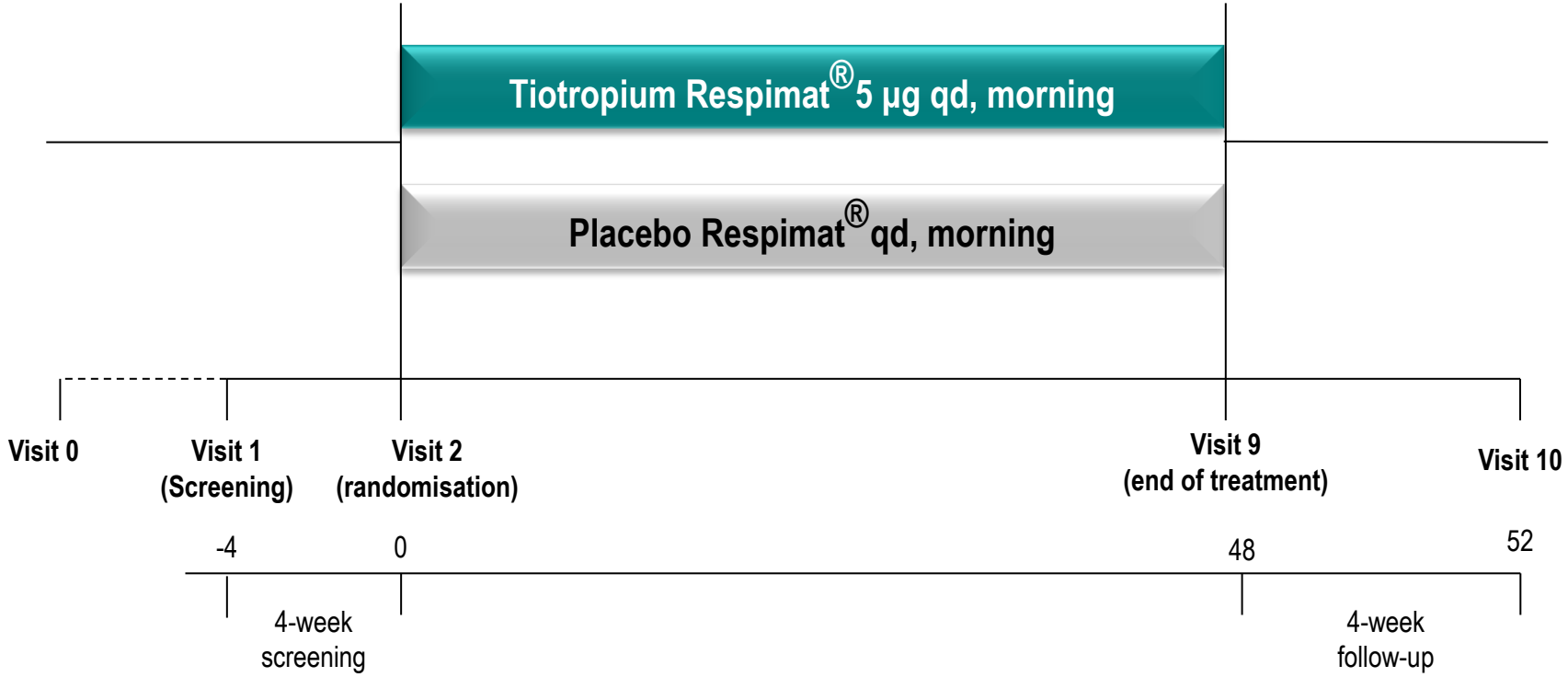
for uncontrolled asthma despite **Step 4** Tx

- 912 uncontrolled asthma
  - ACQ-7 ≥ 1.5
  - despite medium/**high ICS + LABA**
- Age ≥ 18 yrs
- Lung fxn : moderate obstructive
- Hx of exacerbation ≤ 12 months

Tiotropium improved lung function & delayed severe exacerbation compared with placebo.

Kerstjens, …, Bateman. NEJM 2012

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



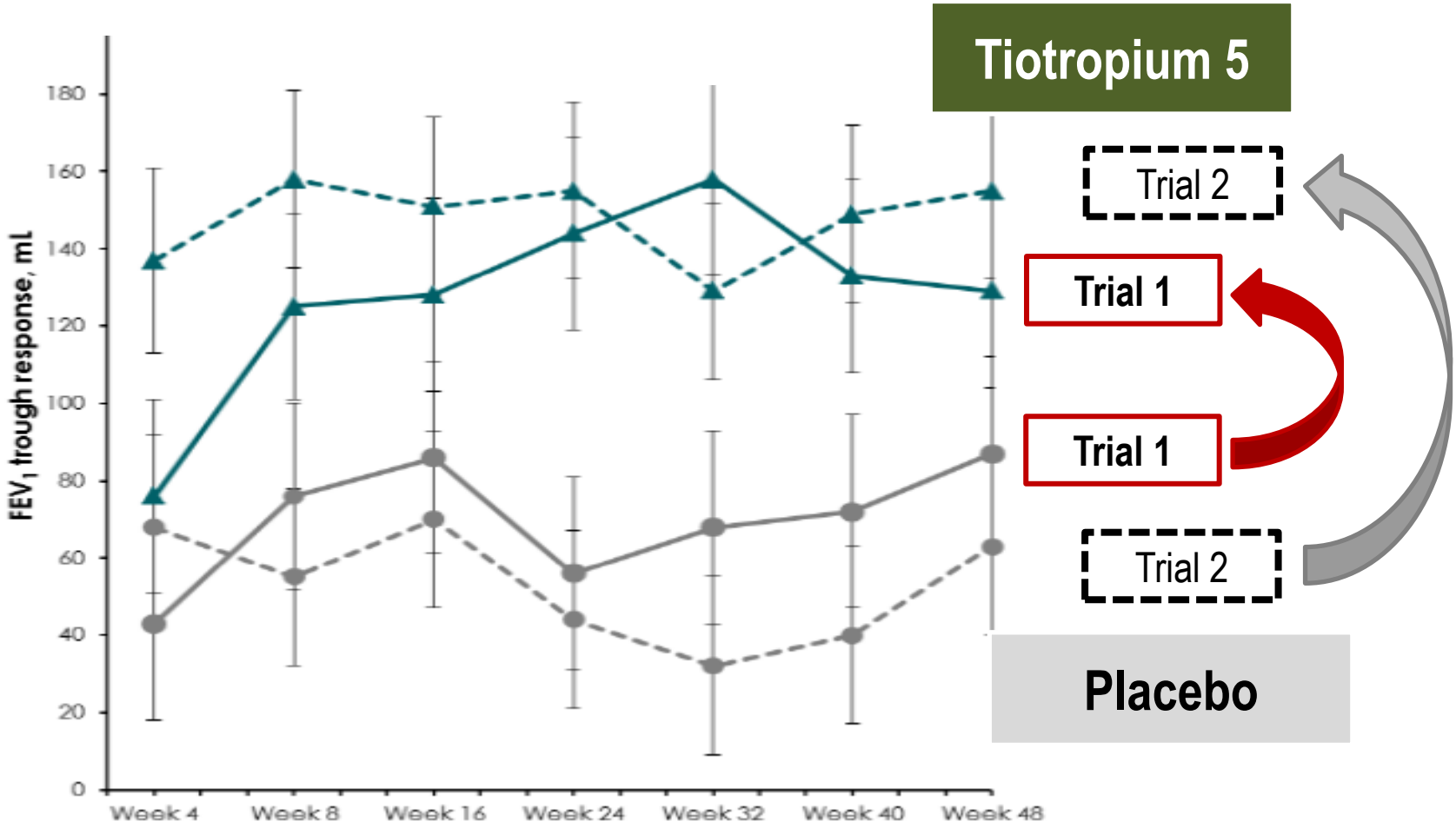
Three co-primary endpoints: hierarchical testing

1. FEV1 peak (0-3 h) after 24 weeks
2. FEV1 trough after 24 weeks
3. Time to first severe asthma exacerbation in pooled* analysis after 48 weeks

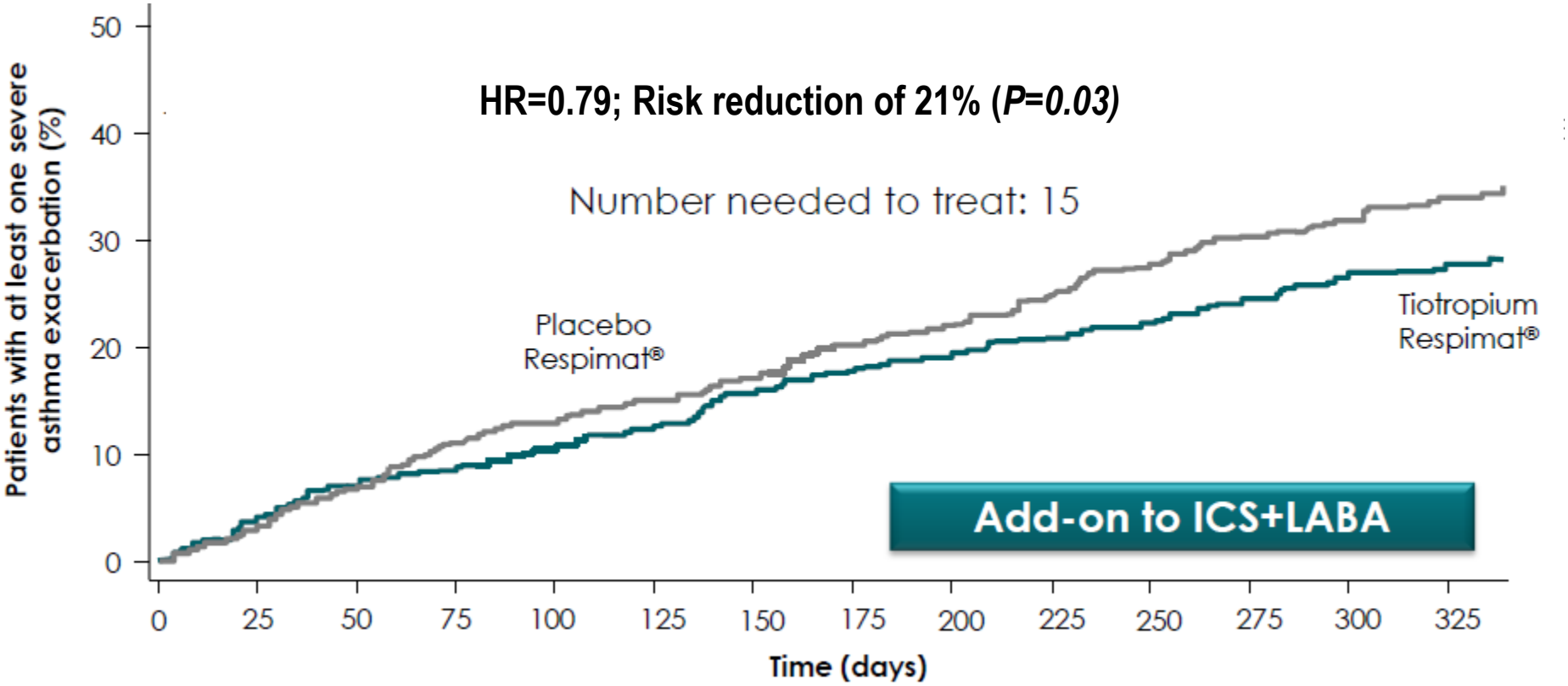
All patients at least on ICS maintenance therapy (≥800 µg budesonide or equivalent/day)+LABA

148 centres, 5 continents

Tio. Improved Lung Function



Reduced Severe Exacerbation

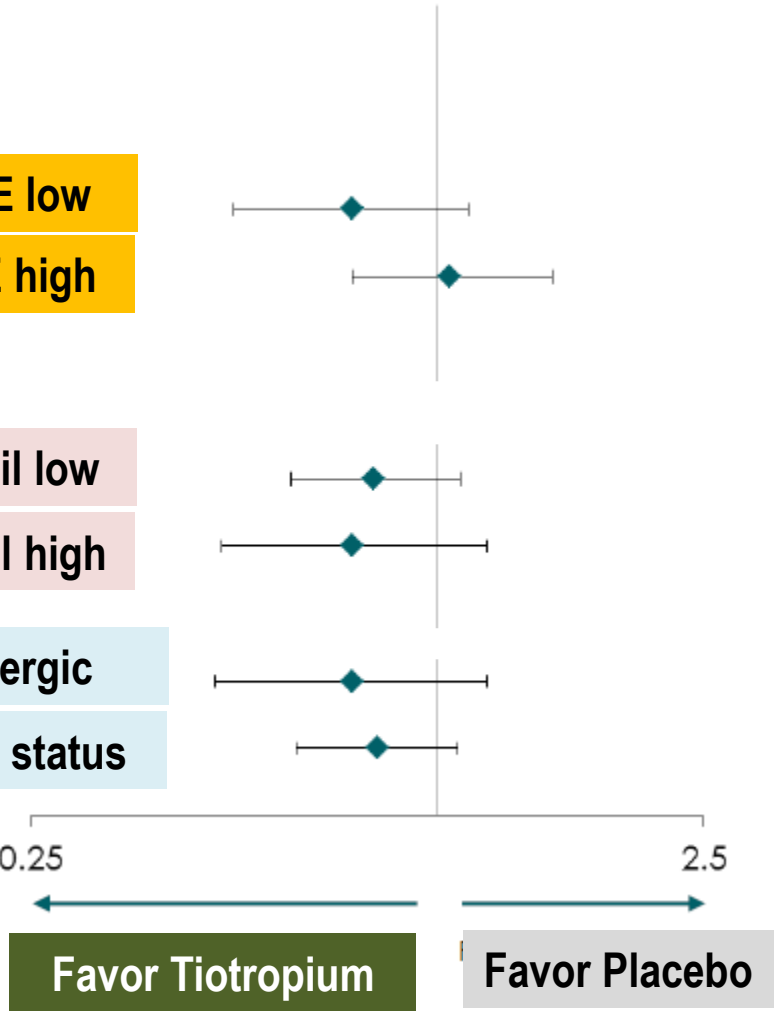


Tiotropium Respimat® n=122 (26.9%) vs.
Placebo Respimat® n=149 (32.8%)

Kerstjens, …, Bateman. NEJM 2012

Tiotropium Respimat may reduce risk of severe asthma exacerbations 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])		
≤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])		
≤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

Tiotropium Respimat

for uncontrolled asthma despite **Step 3** or 4 Tx

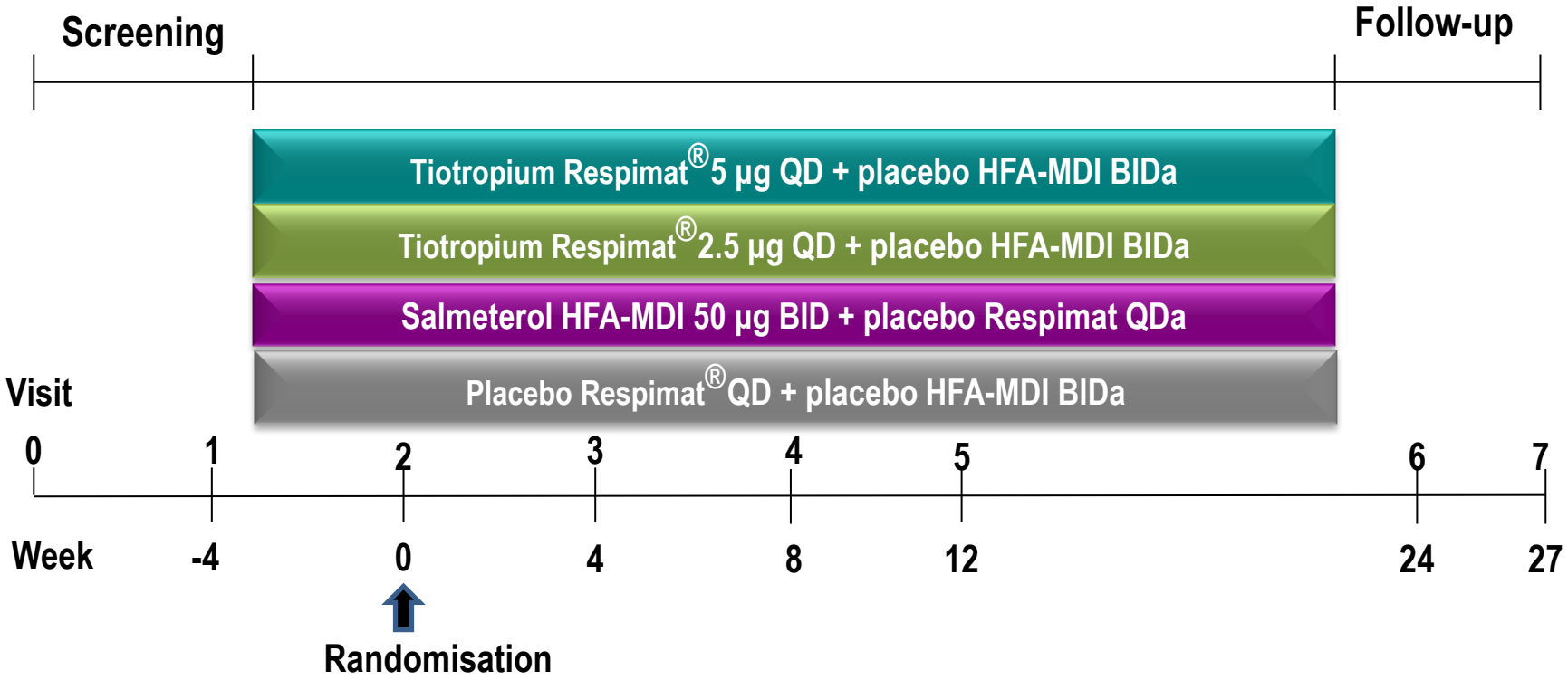
- **2103** uncontrolled asthma
  - – ACQ-7 ≥ 1.5
    cf. controlled < 0.5 vs. uncontrolled ≥ 1.0
  - – despite low/**medium ICS** ± LABA
- Age 18 ~ 75 yrs
- FEV_1 60–90% pred.

Tiotropium improved lung function & asthma control compared with placebo.

MezzoTinA, 400–800 μg budesonide

Lancet Respir Med 2015

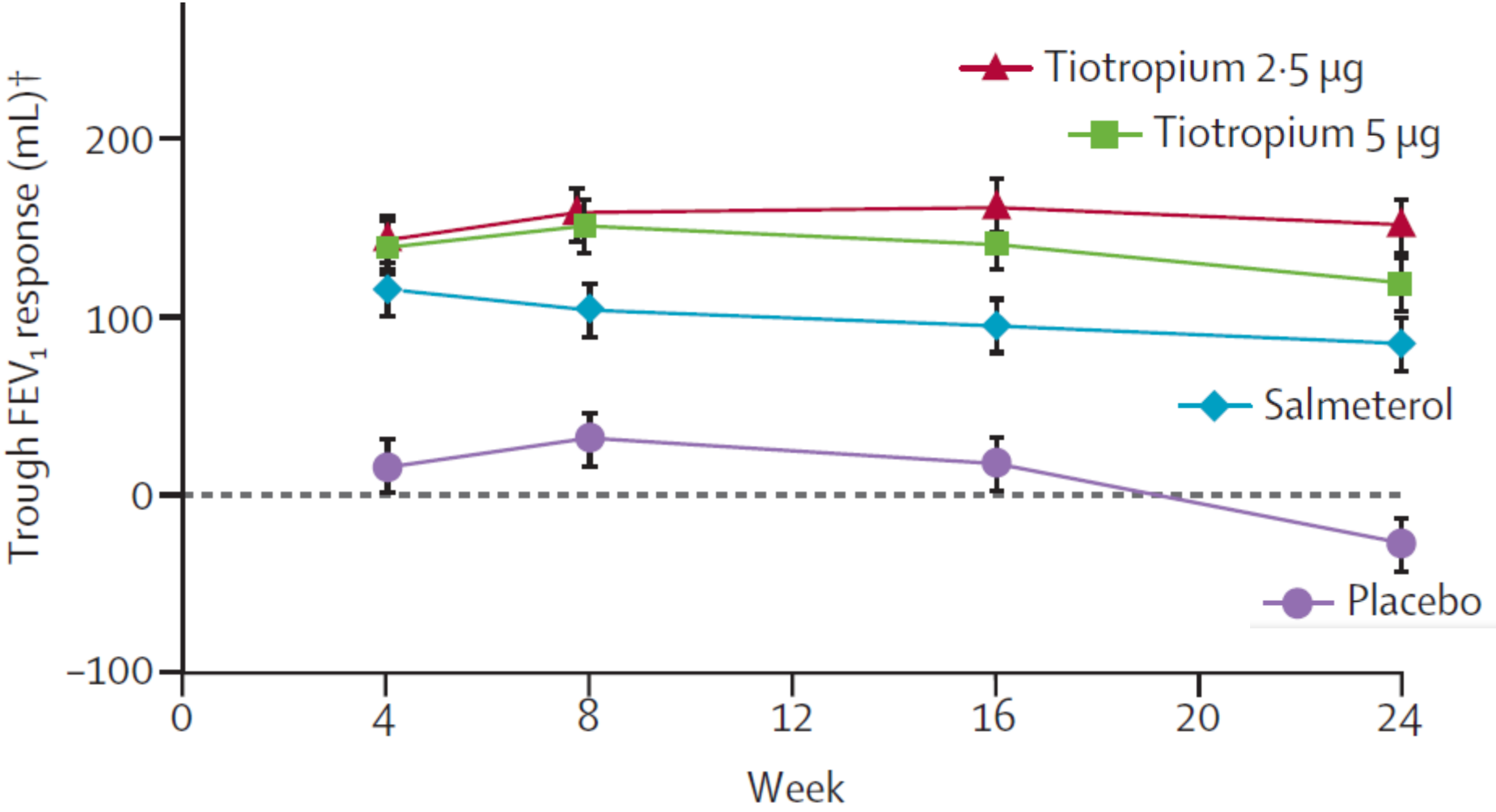
Study design



• Double-blind, randomised, placebo- and active-controlled, parallel-group **(two identical trials)**

Three coprimary endpoints:
1. Peak FEV1 (0-3h) after 24 weeks
2. Trough FEV1 after 24 weeks
3. ACQ responder rate after 24 weeks in pooled data

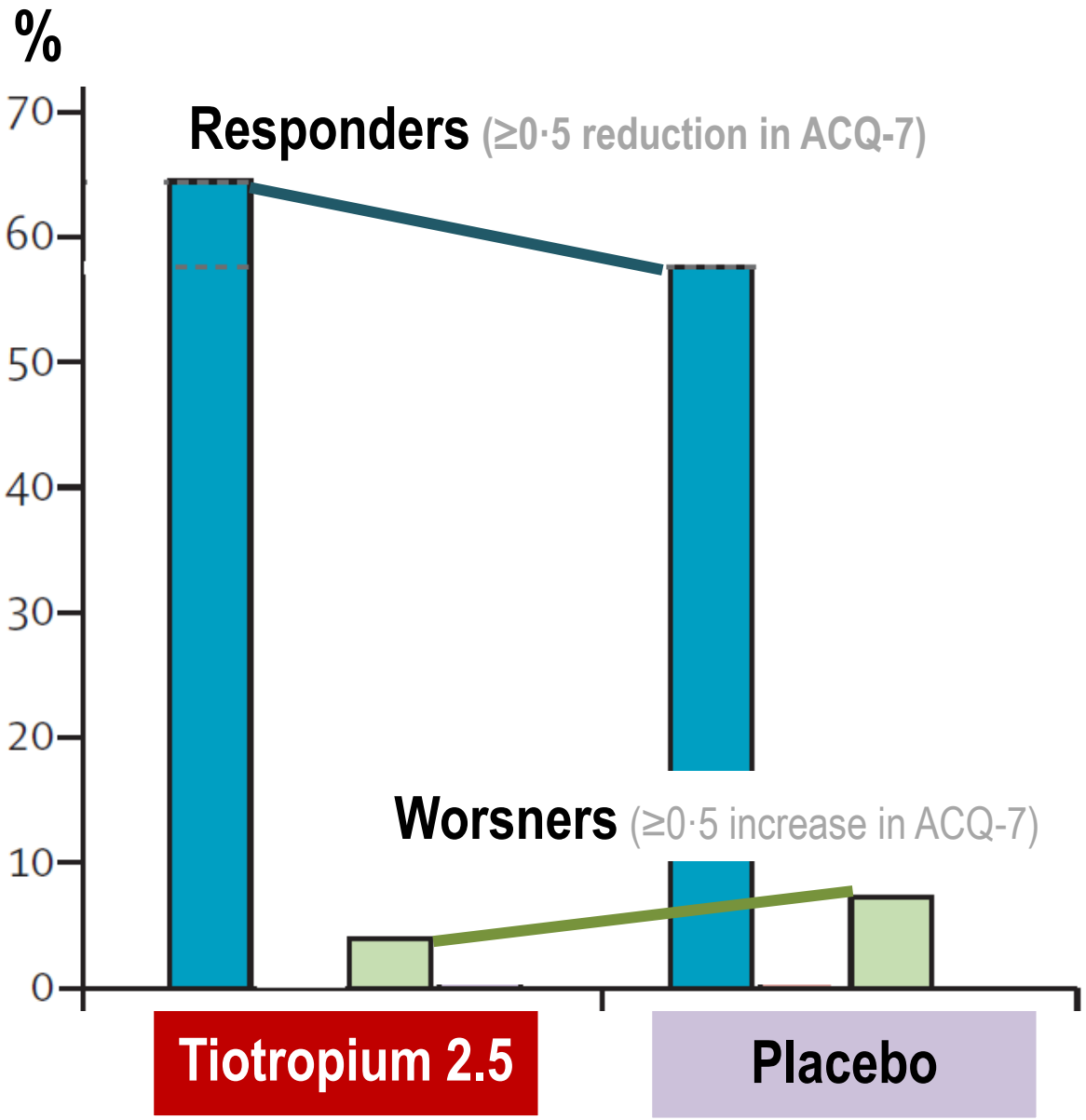
FEV1 improvement with Tiotropium



Lancet Respir Med 2015

MezzoTinA

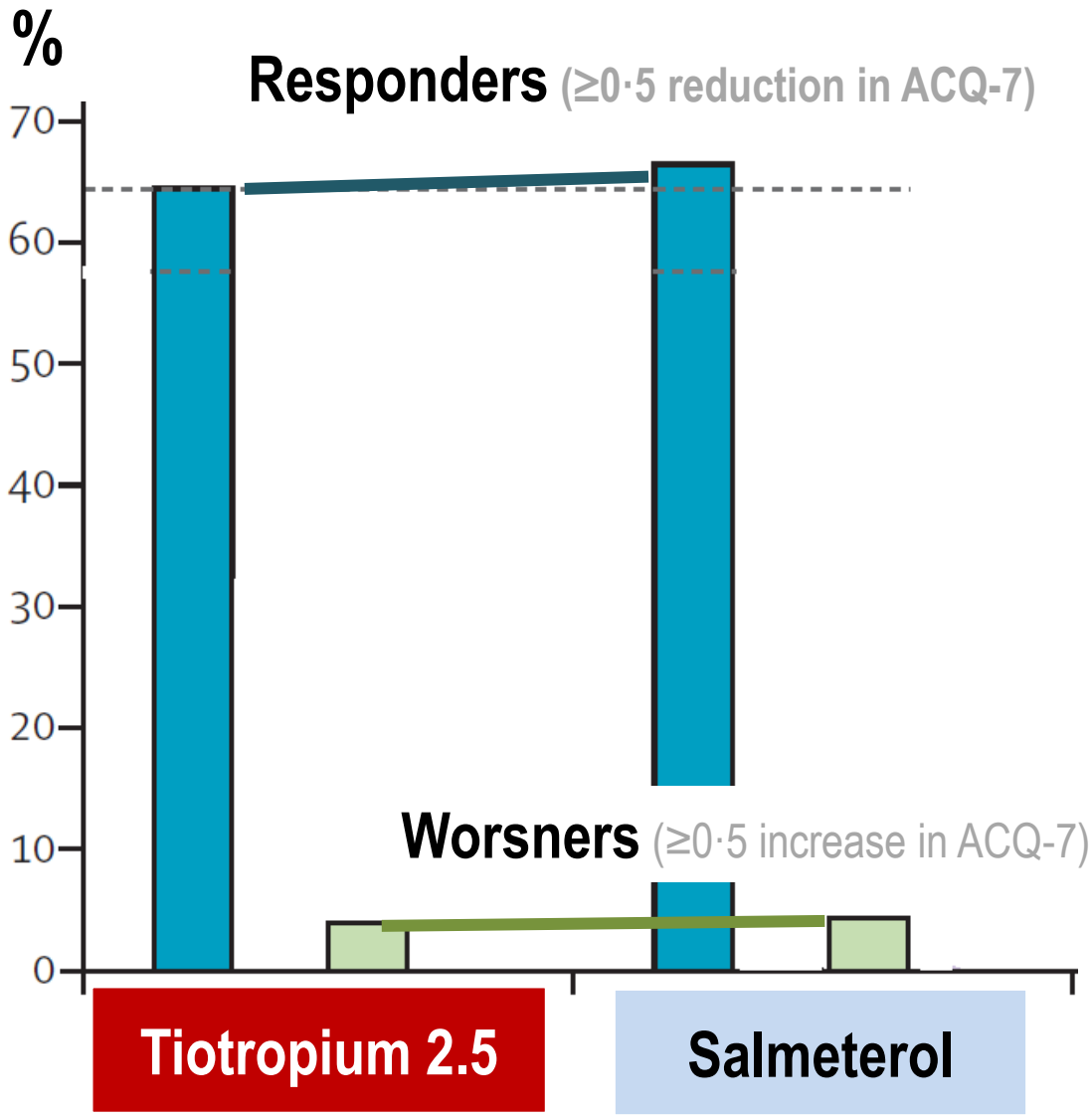
Asthma Control



P = 0.03

Lancet Respir Med 2015

Asthma Control



Lancet Respir Med 2015

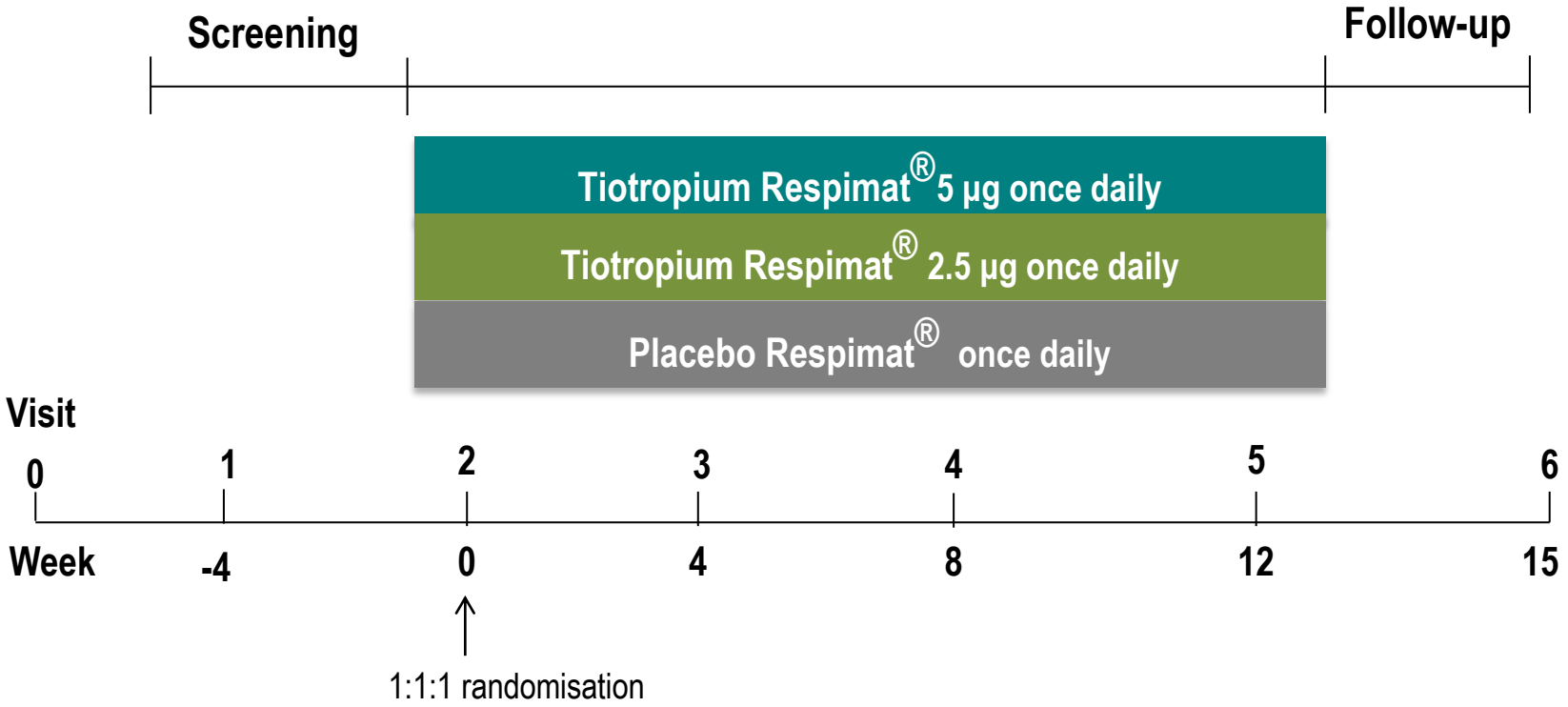
Tiotropium Respimat

for symptomatic asthma despite **Step 2** Tx

- 4206 symptomatic asthma
  despite Step 2 Tx
  - mean ACQ = 1.5
  - FEV_1 60~90% pred.
  - 18~75 yrs

Tiotropium improved lung function compared with placebo.

Study design

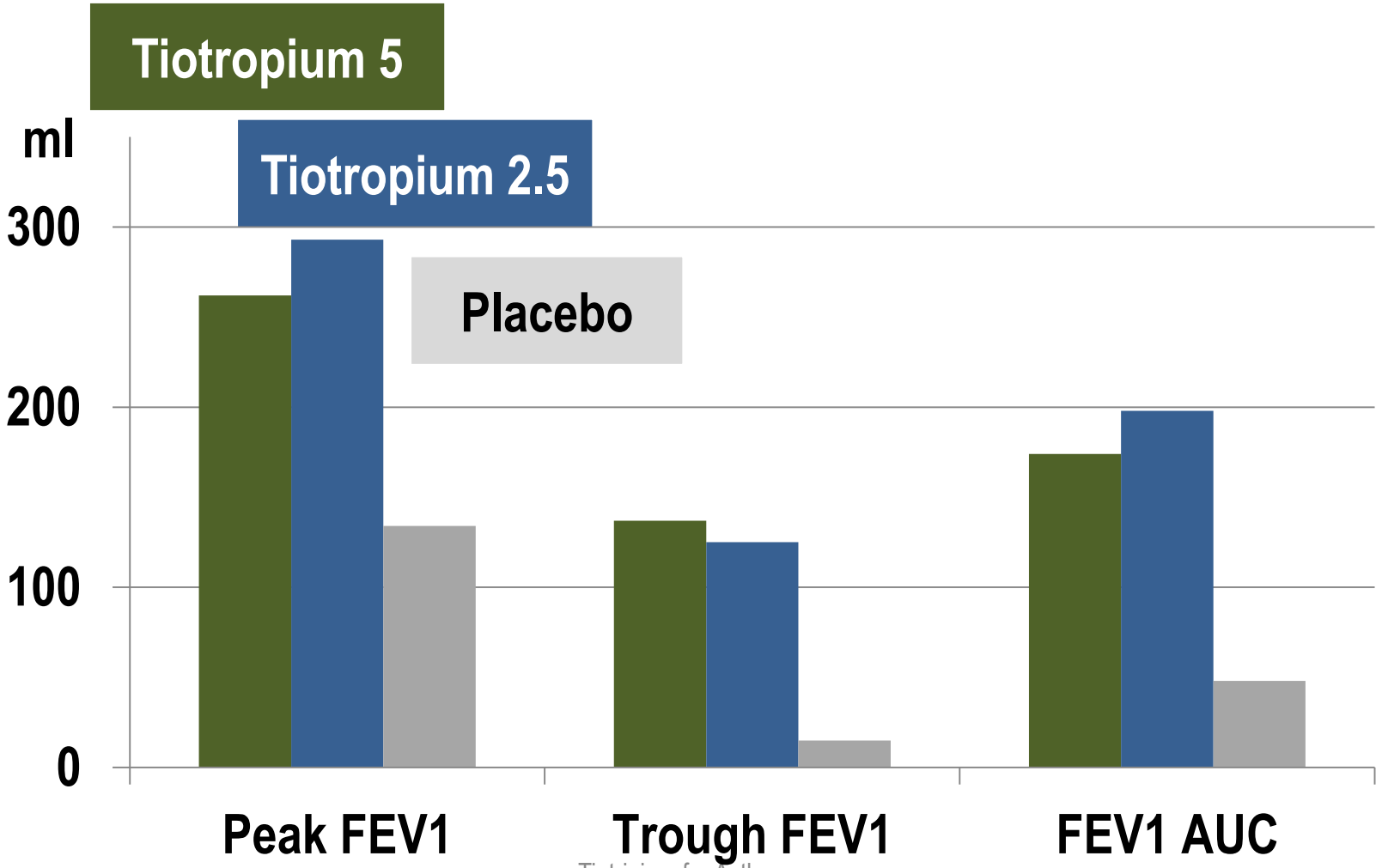


- Double-blind, randomised, placebo- controlled, parallel-group

Primary endpoint : Peak FEV1(0-3h) response at Week 12

Secondary endpoints : Trough FEV1, FEV1 AUC(0-3h), Peak FVC (0-3h), Trough FVC, FVC AUC(0-3h), PEF(am), PEF(pm), ACQ-7 total score

FEV1 improvement with Tiotropium



P<0.001

Safety

Safety
Adverse events

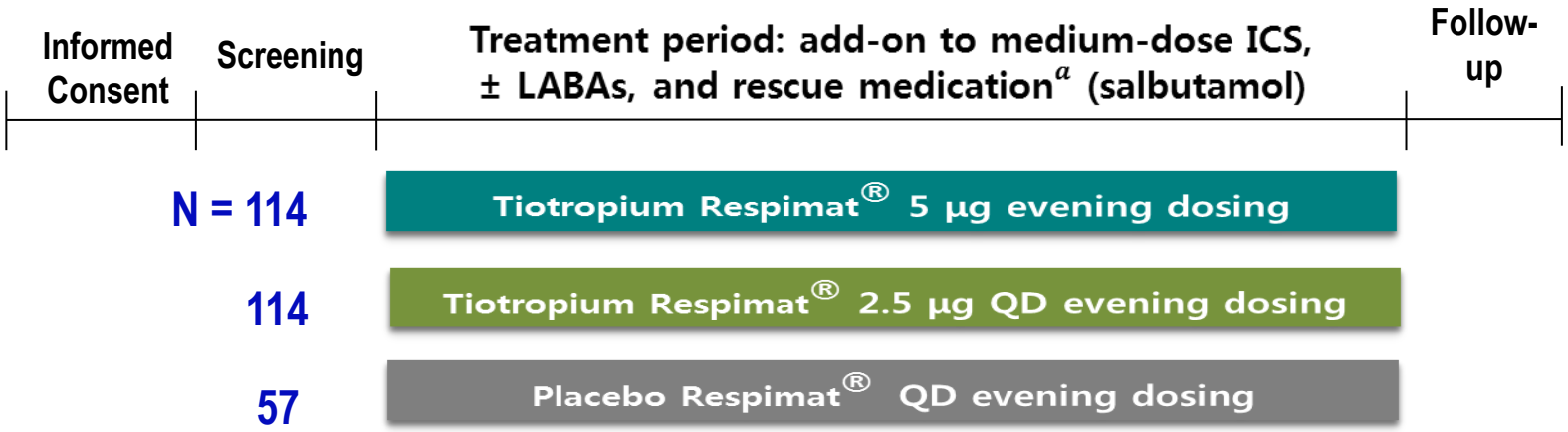
	Tiotropium Respimat® n (%)	Placebo Respimat® n (%)
Number of patients	456 (100.0)	456 (100.0)
Total with any Adverse Event	335 (73.5)	366 (80.3)
Drug-related adverse event as defined by Investigator	26 (5.7)	21 (4.6)
Serious adverse event	37 (**8.1**)	40 (**8.8**)

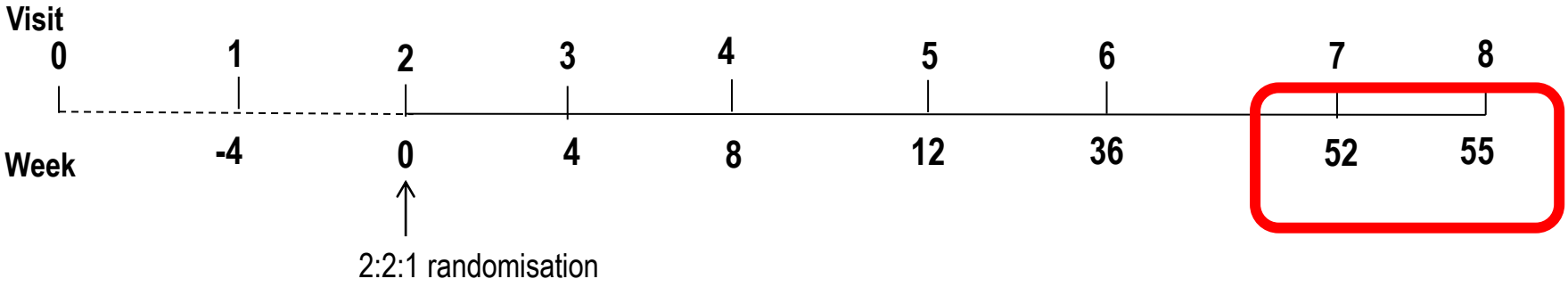
No deaths occurred.

Kerstjens, …, Bateman. NEJM 2012

CadenTinA

Japan "Safety" Study





- RCT across 54 Japanese centers
- Tiotropium Respimat 5ug (n=114), 2.5ug (n=114), or placebo (n=57), for 52 weeks

Primary end point : long term safety

Secondary end point : long term efficacy (trough FEV1 & trough PEFR)

Long term safety

N(%)	Tiotropium Respimat 5ug (n=114)	Tiotropium Respimat 2.5ug (n=114)	Placebo (n=57)
Total number of patients with AE	101 (88.6)	99 (86.8)	51 (89.5)
Severe AE	2 (**1.8**)	1 (**0.9**)	3 (**5.3**)
Drug-related AE*	10 (8.8)	6 (5.3)	3 (5.3)
AE leading to discontinuation	2 (1.8)	1 (0.9)	1 (1.8)
Significant (pre-specified) AE**	0	0	0
SAE	4 (3.5)	4 (3.5)	9 (15.8)
Requiring hospitalization	4 (**3.5**)	4 (**3.5**)	7 (**12.3**)
Drug-related	0	0	1 (1.8)***
Fatal	0	0	0
Other	0	0	2 (3.5)

Long term safety

- Incidence of **AE was similar** across Tx groups.
- Most AE were **mild to moderate**
- **No deaths** or life-threatening events

Overall, **10 cardiac** events occurred:

- 9 events (in 5) in **Tiotropium 5ug** group (4.4%)
- 1 in **Tiotropium 2.5ug** (0.9%)
- 0 in **placebo**

Who may **use** tiotropium **with caution** in **asthma?**

Concomitant Diseases	
Myocardial infarction	≤ 6 months
Cardiac arrhythmia, unstable or life-threatening	≤ 12 months
Hospitalized for **heart failure** NYHA class III or IV	≤ 12 months

NICE advice [ESNM55] Published date: March 2015

http://www.nice.org.uk/advice/esnm55/chapter/key-points-from-the-evidence

Summary
Tiotropium for Asthma Control

- Add-on **tiotropium** for **steps 4 & 5**
  - **—"a new controller option"**

- Should **NOT**
  1. first-line monotherapy
  2. as a reliever for acute symptoms
  3. for acute exacerbation

Thank You