Clinical Communications

Tiotropium reduces airflow obstruction in asthma patients, independent of body mass index

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Clinical Implications

- This subgroup analysis on data from 5 phase III clinical trials (12-48 weeks) of tiotropium soft mist inhaler in symptomatic mild, moderate, and severe asthma, stratified by body mass index, demonstrates tiotropium's efficacy in patients across different body mass indexes.

TO THE EDITOR:

Obesity is a major risk factor for asthma, and obese patients tend to have more severe disease than lean patients.[1] One reason for this increased asthma severity might be altered responses to medications.[1] Obese patients with asthma do not respond as well to inhaled corticosteroids (ICSs),[2] to combination therapy with ICSs and long-acting beta-agonists,[3] or to short-acting beta-agonists[4] as lean patients with asthma, and even appear to have worse asthma outcomes when treated with theophylline.[5] Given the increased severity of asthma in obese patients, and their attenuated response to many medications, treatment of this patient population can be challenging.

The long-acting muscarinic antagonist tiotropium, delivered using a soft mist inhaler, is efficacious as an add-on controller therapy in adults with symptomatic asthma of all severities.[6-8] However, the effectiveness of tiotropium specifically in the obese asthma patient population is not known.

The purpose of this *post hoc* analysis was to evaluate the efficacy of tiotropium in patients across different body mass indexes (BMIs). We present subgroup analysis of data from 5 phase III clinical trials of tiotropium soft mist inhaler in patients with differing severities of asthma (2 replicate PrimoTinA-asthma trials, 2 replicate MezzoTinA-asthma trials, and 1 GraziaTinA-asthma trial; Figure 1 provides a schema for these trials, with further information available in this article's Online Repository at www.jaci-inpractice.org). Further details on the study methodology are available in this article's Online Repository at www.jaci-inpractice.org, and details of study designs and treatments have been previously published.[6-8]

The primary efficacy end point was peak forced expiratory volume in 1 second (FEV_1) response 3 hours postdose ($FEV_{1(0\text{-}3h)}$) in all studies. Trough FEV_1 response was a coprimary end point in PrimoTinA-asthma and MezzoTinA-asthma studies, and a secondary end point in the GraziaTinA-asthma study. Data from these 5 clinical trials were stratified according to BMI into underweight (BMI, <18.5 kg/m^2), healthy weight (BMI, 18.5-<25 kg/m^2), overweight (BMI, 25-<30 kg/m^2), and obese (BMI, ≥ 30 kg/m^2). Changes in peak $FEV_{1(0\text{-}3h)}$ and trough FEV_1 compared with baseline were analyzed for each BMI subgroup, as well as modeled across a continuous range of BMI values from 17 to 43 kg/m^2.

A restricted maximum likelihood–based mixed-effect model with repeated measures was performed for *post hoc* analysis for each subgroup ("by-subgroup" analysis). All presented *P* values are nominal.

Post hoc modeling analysis was performed at the time of primary end-point assessment across a continuous range of BMI values from 17 to 43 kg/m^2. The terms "BMI" and "BMI by treatment interaction" were included in the model. Further details on the analysis are available in this article's Online Repository at www.jaci-inpractice.org.

Details of baseline patient demographic and disease characteristics are available in this article's Online Repository at www.jaci-inpractice.org. Tiotropium Respimat provided significant improvements in both peak $FEV_{1(0\text{-}3h)}$ and trough FEV_1 levels in the overall population in PrimoTinA-asthma and MezzoTinA-asthma, where patient numbers were robust (Table I). When stratified by BMI category, tiotropium Respimat significantly improved peak $FEV_{1(0\text{-}3h)}$ and trough FEV_1 in patients categorized as having a BMI of greater than or equal to 18.5 kg/m^2 (although improvements in trough FEV_1 were nonsignificant for patients with symptomatic severe asthma [PrimoTinA-asthma] with a BMI of ≥ 30 kg/m^2 in the 5-μg tiotropium arm). Improvements in patients with a BMI of less than 18.5 kg/m^2 were generally nonsignificant or else could not be calculated because of small patient numbers. For the GraziaTinA-asthma trial, although significant improvements in peak $FEV_{1(0\text{-}3h)}$ and trough FEV_1 responses were observed in the overall population, results were more variable across the BMI categories. Significant improvements in peak and trough $FEV_{1(0\text{-}3h)}$ were observed for patients with a BMI of 25 to less than 30 kg/m^2. There were also significant improvements in trough FEV_1 for patients with a BMI of 18 to less than 25 kg/m^2 in the 5-μg arm and peak $FEV_{1(0\text{-}3h)}$ for patients with a BMI of 18 to less than 25 kg/m^2 in the 2.5-μg arm. This variability may be indicative of the fact that this was an investigative analysis in a small population with mild asthma, whereas the data coming from a larger group of patients with symptomatic severe and moderate asthma show consistent improvements in FEV_1 responses.

In patients with symptomatic severe asthma (PrimoTinA-asthma), significant improvements in peak $FEV_{1(0\text{-}3h)}$ and trough FEV_1 were largest for the BMI category 18.5 to less than 25 kg/m^2, followed by the 25- to less than 30-kg/m^2 subgroup (Table I; see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). In patients with symptomatic moderate asthma (MezzoTinA-asthma), responses were relatively consistent across the BMI categories. In patients with symptomatic mild asthma (GraziaTinA-asthma), significant improvements in peak and trough FEV_1 with both doses of tiotropium were observed in the 25- to less than 30-kg/m^2 subgroup (Table I; Figure E1). For all trials, improvements in peak $FEV_{1(0\text{-}3h)}$ levels and trough FEV_1 levels favoring tiotropium were consistently observed when the data were analyzed across the continuous range of BMI values 17 to 43 kg/m^2 (see Figures E2 and E3, respectively, in this article's Online Repository at www.jaci-inpractice.org).

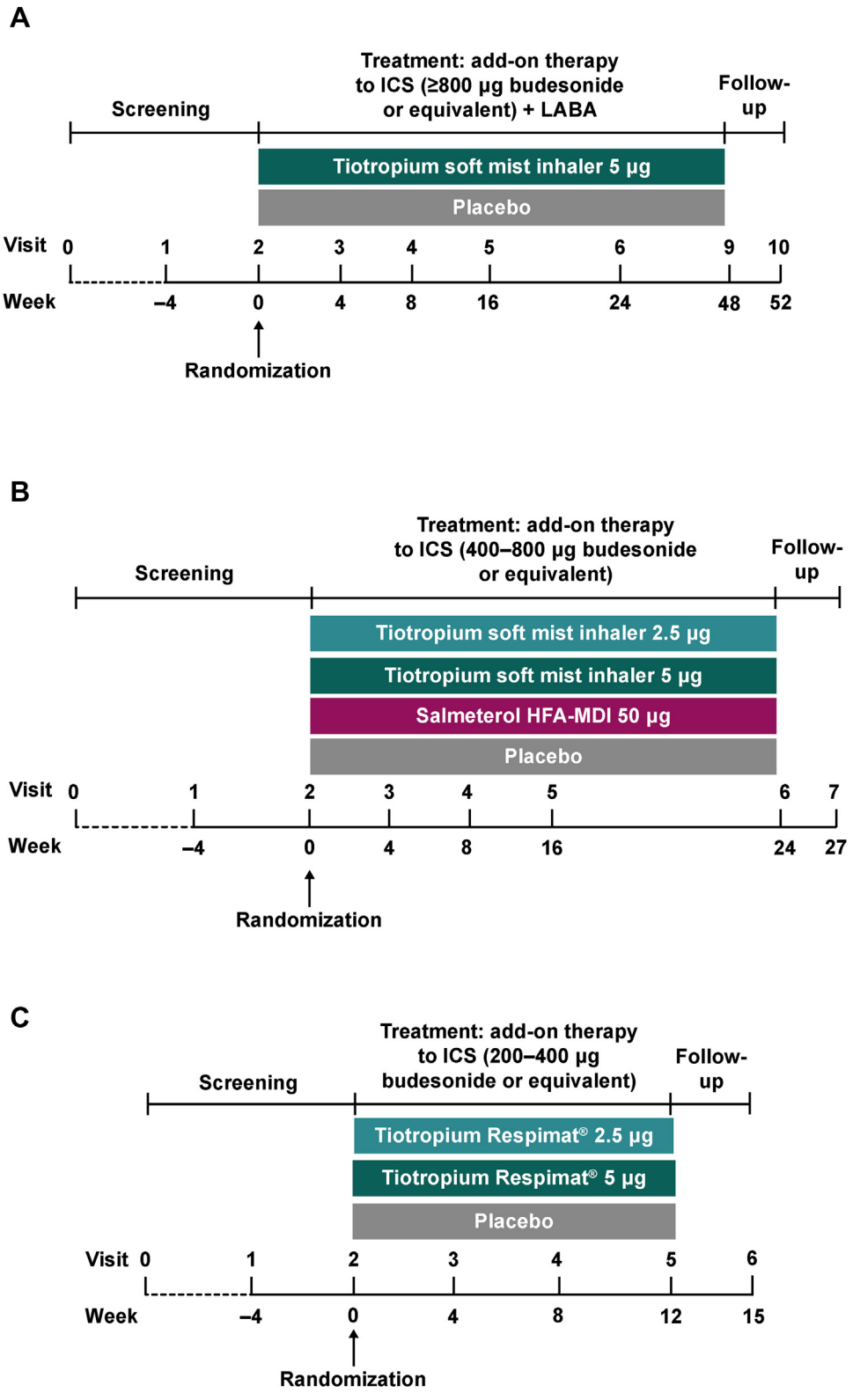

FIGURE 1. Study design for (**A**) PrimoTinA-asthma (**B**) MezzoTinA-asthma, and (**C**) GraziaTinA-asthma. *HFA-MDI*, Hydrofluoroalkane metered-dose inhaler; *ICS*, inhaled corticosteroid; *LABA*, long-acting beta-agonist. The trials included adult patients aged 18 to 75 years. Patients in the 2 PrimoTinA-asthma trials had symptomatic severe asthma, patients in the 2 MezzoTinA-asthma trials had symptomatic moderate asthma, and patients in the GraziaTinA-asthma trial had symptomatic mild asthma.

TABLE I. Changes in peak and trough FEV_1 levels from baseline across categories of BMI

	Adjusted mean change from baseline vs placebo (mL) (95% CI)					
	PrimoTinA-asthma (at week 24)		MezzoTinA-asthma (at week 24)		GraziaTinA-asthma (at week 12)	
BMI categories	$FEV_{1(0\text{-}3h)}$ peak	FEV_1 trough	$FEV_{1(0\text{-}3h)}$ peak	FEV_1 trough	$FEV_{1(0\text{-}3h)}$ peak	FEV_1 trough
Tiotropium Respimat 5 μg						
Overall (n tiotropium/placebo)	110 (63 to 158)	93 (50 to 137)	185 (146 to 223)	146 (105 to 188)	128 (57 to 199)	122 (49 to 194)
	$P < .0001$ (422/429)	$P < .0001$ (421/429)	$P < .0001$ (481/492)	$P < .0001$ (481/492)	$P = .0005$ (152/154)	$P < .0010$ (152/154)
<18.5 kg/m^2 (n tiotropium/placebo)	(NS)	(NS)	307 (93 to 522)	233 (−30 to 495)	(NS)	(NS)
	(5/7)	(5/7)	$P = .0054$ (13/14)	$P = .0822$ (13/14)	(5/3)	(5/3)
18.5-<25 kg/m^2 (n tiotropium/placebo)	147 (60 to 234)	123 (47 to 198)	192 (131 to 254)	160 (94 to 226)	94 (−37 to 225)	138 (8 to 268)
	$P = .0010$ (127/138)	$P = .0015$ (126/138)	$P < .0001$ (194/202)	$P < .0001$ (194/202)	$P = .1597$ (52/63)	$P = .0373$ (52/63)
25-<30 kg/m^2 (n tiotropium/placebo)	108 (26 to 190)	98 (22 to 175)	164 (94 to 235)	108 (32 to 183)	201 (71 to 331)	188 (62 to 315)
	$P = .0104$ (154/160)	$P = .0116$ (154/160)	$P < .0001$ (157/158)	$P = .0051$ (157/158)	$P = .0025$ (58/61)	$P = .0038$ (58/61)
≥30 kg/m^2 (n tiotropium/placebo)	81 (1 to 161)	58 (−17 to 134)	184 (110 to 259)	167 (88 to 247)	48 (−110 to 207)	−48 (−212 to 115)
	$P = .0471$ (136/124)	$P = .1318$ (136/124)	$P < .0001$ (117/118)	$P < .0001$ (117/118)	$P = .5476$ (37/27)	$P = .5602$ (37/27)
Tiotropium Respimat 2.5 μg						
Overall (n tiotropium/placebo)	NA		223 (185 to 262)	180 (138 to 221)	159 (88 to 230)	110 (38 to 182)
			$P < .0001$ (492/492)	$P < .0001$ (492/492)	$P < .0001$ (151/154)	$P = .0028$ (151/154)
<18.5 kg/m^2 (n tiotropium/placebo)	NA		49 (−143 to 240)	−21 (−256 to 214)	(NS)	(NS)
			$P = .6171$ (21/14)	$P = .8578$ (21/14)	(4/3)	(4/3)
18.5-<25 kg/m^2 (n tiotropium/placebo)	NA		235 (174 to 296)	178 (113 to 244)	127 (8 to 246)	94 (−23 to 212)
			$P < .0001$ (200/202)	$P < .0001$ (200/202)	$P = .0359$ (69/63)	$P = .1157$ (69/63)
25-<30 kg/m^2 (n tiotropium/placebo)	NA		200 (130 to 270)	180 (105 to 255)	188 (48 to 328)	168 (31 to 305)
			$P < .0001$ (162/158)	$P < .0001$ (162/158)	$P = .0086$ (43/61)	$P = .0162$ (43/61)
≥30 kg/m^2 (n tiotropium/placebo)	NA		266 (190 to 342)	215 (134 to 296)	110 (−45 to 266)	13 (−147 to 173)
			$P < .0001$ (109/118)	$P < .0001$ (109/118)	$P = .1632$ (35/27)	$P = .8727$ (35/27)

BMI, Body mass index; *CI*, confidence interval; *FEV_1*, forced expiratory volume in 1 second; *$FEV_{1(0\text{-}3h)}$*, forced expiratory volume in 1 second 3 hours postdose; *n*, number of patients with measurements at the respective time point; *NA*, not applicable; *NS*, not shown due to low patient numbers.

Safety and tolerability of tiotropium in all trials were comparable with placebo, and the details are reported elsewhere.[9] Further information and a table detailing adverse events are available in this article's Online Repository at www.jaci-inpractice.org.

This study is the first to evaluate the effects of a long-acting muscarinic antagonist, namely, tiotropium, across different BMI subgroups and asthma severities. Our results confirm that tiotropium Respimat is effective as add-on therapy in obese patients with symptomatic moderate or severe asthma receiving a range of different asthma medications, whereas data in patients with symptomatic mild asthma were more variable. However, this observed variability may be due to the small study population and the shorter study duration in the trial involving patients with mild asthma. In general, greatest improvements in lung function were seen in patients with moderate asthma enrolled in MezzoTinA-asthma trials,[7] with similar improvement seen across all BMI categories. These patients were receiving ICSs as background controller therapy. Improvements in lung function across all BMI categories were also seen in symptomatic severe asthma patients enrolled in the PrimoTinA-asthma study.[8] Although the improvements in FEV_1 were smaller in this study, it is important to note that these patients were already receiving at least ICSs and a long-acting bronchodilator and had fixed airflow obstruction. The additive effects of a third controller therapy may, therefore, not be as pronounced as those seen in patients receiving tiotropium as a second therapy.[8]

We acknowledge some limitations of our study. This was a *post hoc* analysis of previously prospectively completed trials. The number of patients in the subgroups with BMI less than 18.5 kg/m^2 and BMI greater than or equal to 30 kg/m^2 was small. Assessment of the effects of tiotropium across different asthma phenotypes and on exacerbation frequency in obese patients could not be made because of the infrequency of events during the study period. Despite these limitations, we believe that this study is significant because it provides much-needed data on the efficacy of long-acting muscarinic antagonists in asthma across different BMIs.

Obesity has been associated with more severe forms of asthma and an impaired response to controller medication in this patient population. Efficacious treatment options for these patients can be challenging. Tiotropium has been found to work well in adult patients independent of asthma severity, and our data show this to be true across BMI categories. We conclude that tiotropium Respimat is effective and safe as an add-on therapy in patients with asthma, independent of BMI and severity.

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ONLINE REPOSITORY METHODS

Study design and treatment

Data from 5 phase III clinical trials evaluating the efficacy of tiotropium soft mist inhaler in persistent asthma were included.[E1-E3] PrimoTinA-asthma 1 and 2 (NCT00772538/NCT00776984) were 2 replicate 48-week, randomized, placebo-controlled trials studying the efficacy and safety of tiotropium soft mist inhaler at 5-μg dose as add-on therapy to inhaled corticosteroids (ICSs) and long-acting beta-agonists (LABAs) in adult patients with poorly controlled severe asthma.[E2] Data from these 2 studies were pooled for analysis. MezzoTinA-asthma 1 and 2 (NCT01172808/NCT01172821) were 2 replicate 24-week, randomized, placebo- and active-controlled studies evaluating the efficacy and safety of tiotropium soft mist inhaler (2.5-μg or 5-μg dose) as add-on therapy in patients whose asthma was not well controlled on medium-dose ICS.[E1] Patients were randomized 1:1:1:1 to receive tiotropium 2.5 μg once daily, tiotropium 5 μg once daily, salmeterol 50 μg twice daily, or placebo. Data were also pooled from these 2 studies. GraziaTinA-asthma (NCT01316380) was a 12-week, randomized, placebo-controlled study evaluating the efficacy and safety of add-on therapy with tiotropium soft mist inhaler (2.5-μg or 5-μg dose) in patients with symptomatic asthma receiving low- to medium-dose ICSs.[E3] Following a 4-week screening period, patients were randomly assigned to active treatment or placebo (per each study protocol) as add-on therapy to their existing treatment regimens. Details of study designs and treatments have been previously published.[E1-E3]

Written informed consent was obtained from all patients enrolled in the clinical studies. All studies were approved by ethical committees and registered on clinicaltrials.gov. For the PrimoTinA-asthma, MezzoTinA-asthma, and GraziaTinA-asthma studies reported here, before the start of the study, the clinical trial protocol, patient information leaflet, informed consent form, and other locally required documents were reviewed by the independent ethics committees or institutional review boards, or both, of the participating centers. All studies were performed in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonization's Harmonized Tripartite Guideline for Good Clinical Practice.

Study population

The trials included adult patients between the ages of 18 and 75 years with a documented history of asthma at the time of enrollment, and who were symptomatic as defined by a 7-question Asthma Control Questionnaire score of 1.5 or more. Patients in the 2 PrimoTinA-asthma trials had severe asthma with persistent airflow limitation, as defined by post-bronchodilator forced expiratory volume in 1 second (FEV_1) of less than or equal to 80% of predicted value and 70% or less of forced vital capacity, despite daily therapy with inhaled glucocorticoids (≥800 μg of budesonide or equivalent) and LABAs.[E2] Patients were also required to have had at least 1 exacerbation that was treated with systemic glucocorticoids in the previous year. MezzoTinA-asthma trials enrolled patients with asthma who were symptomatic (7-question Asthma Control Questionnaire score of ≥1.5) despite a stable treatment regimen of medium-dose ICSs (400-800 μg budesonide or equivalent) alone or in fixed combination with a LABA.[E1] The GraziaTinA-asthma trial included patients who were symptomatic (7-question Asthma Control Questionnaire score of ≥1.5) on stable maintenance low- to medium-dose ICSs (200-400 μg budesonide or equivalent dose).[E3] The main exclusion criteria were chronic obstructive pulmonary disease, current smoker or greater than or equal to 10 pack-years smoking history, serious unstable coexisting illnesses, and concurrent use of long-acting anticholinergic bronchodilators. Full details of inclusion and exclusion criteria have been published previously.[E1-E3]

Analysis

The restricted maximum likelihood–based mixed-effect model included the fixed, categorical effects of "treatment," "center" ("trial" in pooled analysis), "visit," and "treatment-by-visit interaction," as well as the continuous fixed covariates of "baseline" and "baseline-by-visit interaction." "Patient" was included as a random effect. Adjusted means (with SEs) and treatment contrasts were calculated together with 95% CIs.

RESULTS

Patients

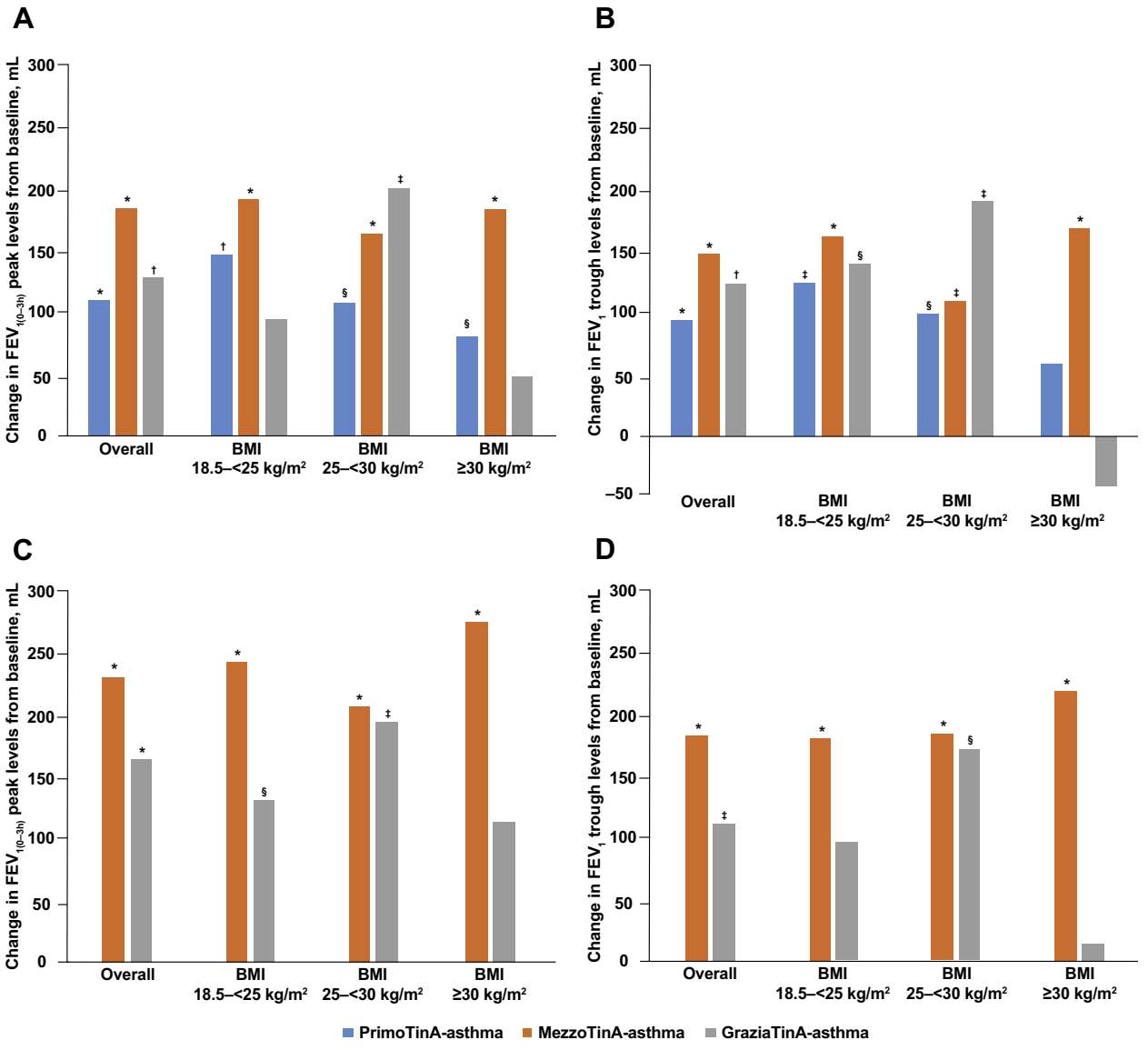
A total of 3,476 patients were treated in the 5 trials. Of these, 912 patients had severe asthma (PrimoTinA-asthma), 2,100 had moderate asthma (MezzoTinA-asthma), and 464 had mild asthma (GraziaTinA-asthma). Table E1 includes the baseline characteristics of the cohorts in these trials. The overall numbers of patients in the body mass index (BMI) categories were as follows: BMI less than 18.5 kg/m^2 (n = 96; 2.8%), BMI 18.5 to less than 25 kg/m^2 (n = 1,340; 38.6%), BMI 25 to less than 30 kg/m^2 (n = 1,160; 33.4%), and BMI greater than or equal to 30 kg/m^2 (n = 880; 25.3%). This investigative analysis generated some small subgroups in some of the studies; of particular note, the number of patients in the subgroups with BMI less than 18.5 kg/m^2 was very small. Most patients in the trials were female. A greater proportion of patients with severe asthma were overweight or obese (n = 615; 67.4%) in comparison with patients with moderate (n = 1,160; 55.2%) and mild (n = 265; 57.1%) asthma. There was a higher proportion of former smokers in the severe asthma group. Mean age of asthma onset was similar across the BMI categories.

Efficacy

The *post hoc* analysis of efficacy across BMI ranges was based on data from the full analysis set (severe, n = 907; moderate, n = 2,081 [including salmeterol arm]; mild, n = 464). Patients receiving salmeterol in the original studies were included in the statistical model, but we present efficacy results for tiotropium-treated patients versus placebo-treated patients only. Figure E1 shows placebo-adjusted changes from baseline for patients with severe, moderate, and mild asthma across the BMI categories 18.5 kg/m^2 through greater than or equal to 30 kg/m^2; the BMI less than 18.5 kg/m^2 groups were not included in this graph because of the very small numbers.

Safety

In this analysis, adverse event rates were similar between the treatment groups (Table E2).



*$P < .0001$; †$P \leq .001$; ‡$P \leq .01$; §$P \leq .05$.

FIGURE E1. $FEV_{1(0\text{-}3h)}$ peak and FEV_1 trough adjusted placebo-corrected mean change from baseline. **A**, Tiotropium 5 μg $FEV_{1(0\text{-}3h)}$ peak levels. **B**, Tiotropium 5 μg FEV_1 trough levels. **C**, Tiotropium 2.5 μg $FEV_{1(0\text{-}3h)}$ peak levels. **D**, Tiotropium 2.5 μg FEV_1 trough levels. *BMI*, Body mass index; *FEV_1*, forced expiratory volume in 1 second; *$FEV_{1(0\text{-}3h)}$*, forced expiratory volume in 1 second 3 hours postdose.

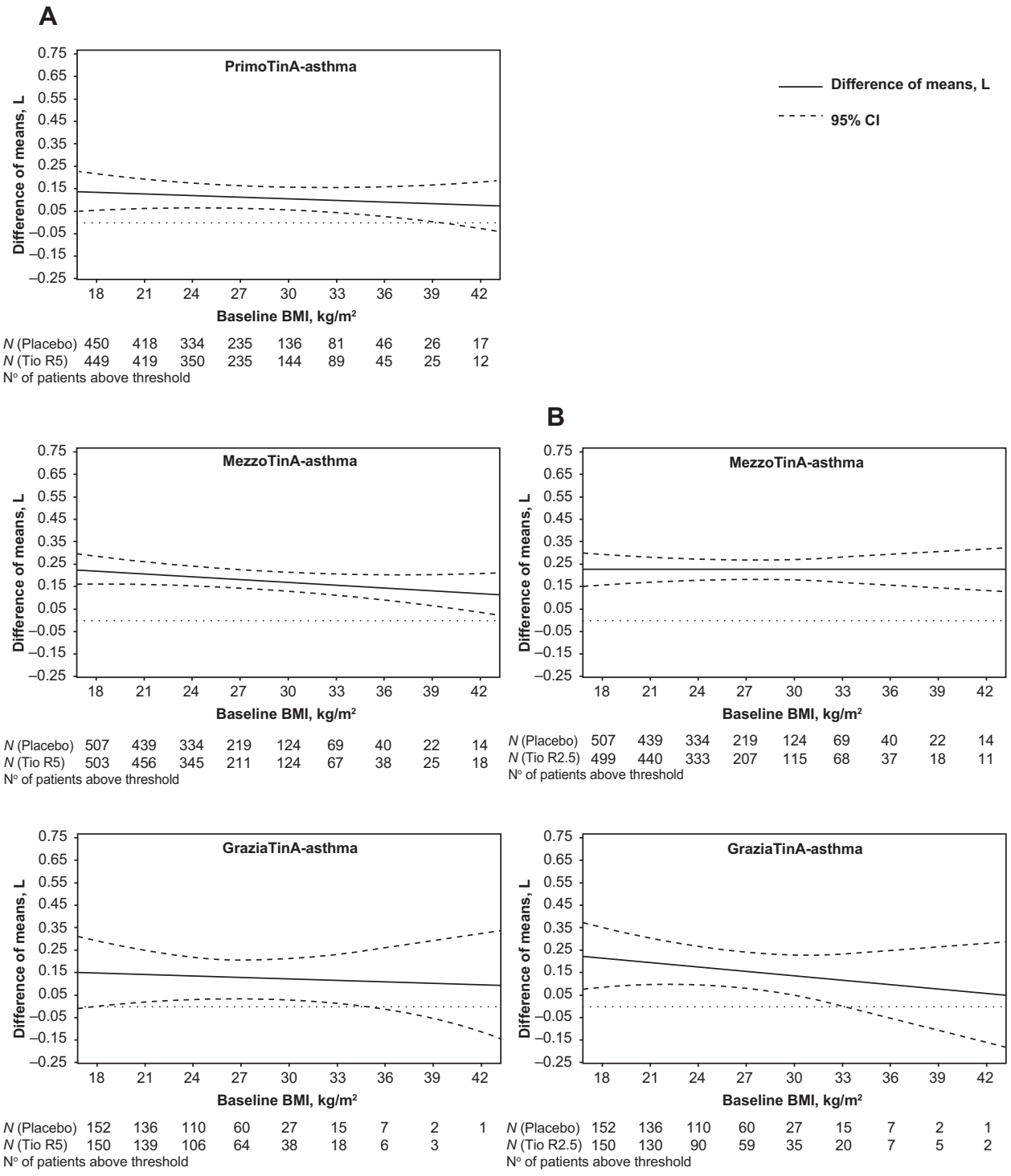


FIGURE E2. $FEV_{1(0\text{-}3h)}$ peak adjusted mean change from baseline vs placebo across the continuous range of BMI values for (**A**) tiotropium 5 μg vs placebo and (**B**) tiotropium 2.5 μg vs placebo. *BMI*, Body mass index; *CI*, confidence interval; *FEV_1*, forced expiratory volume in 1 second; *$FEV_{1(0\text{-}3h)}$*, forced expiratory volume in 1 second 3 hours postdose; *Tio*, tiotropium.

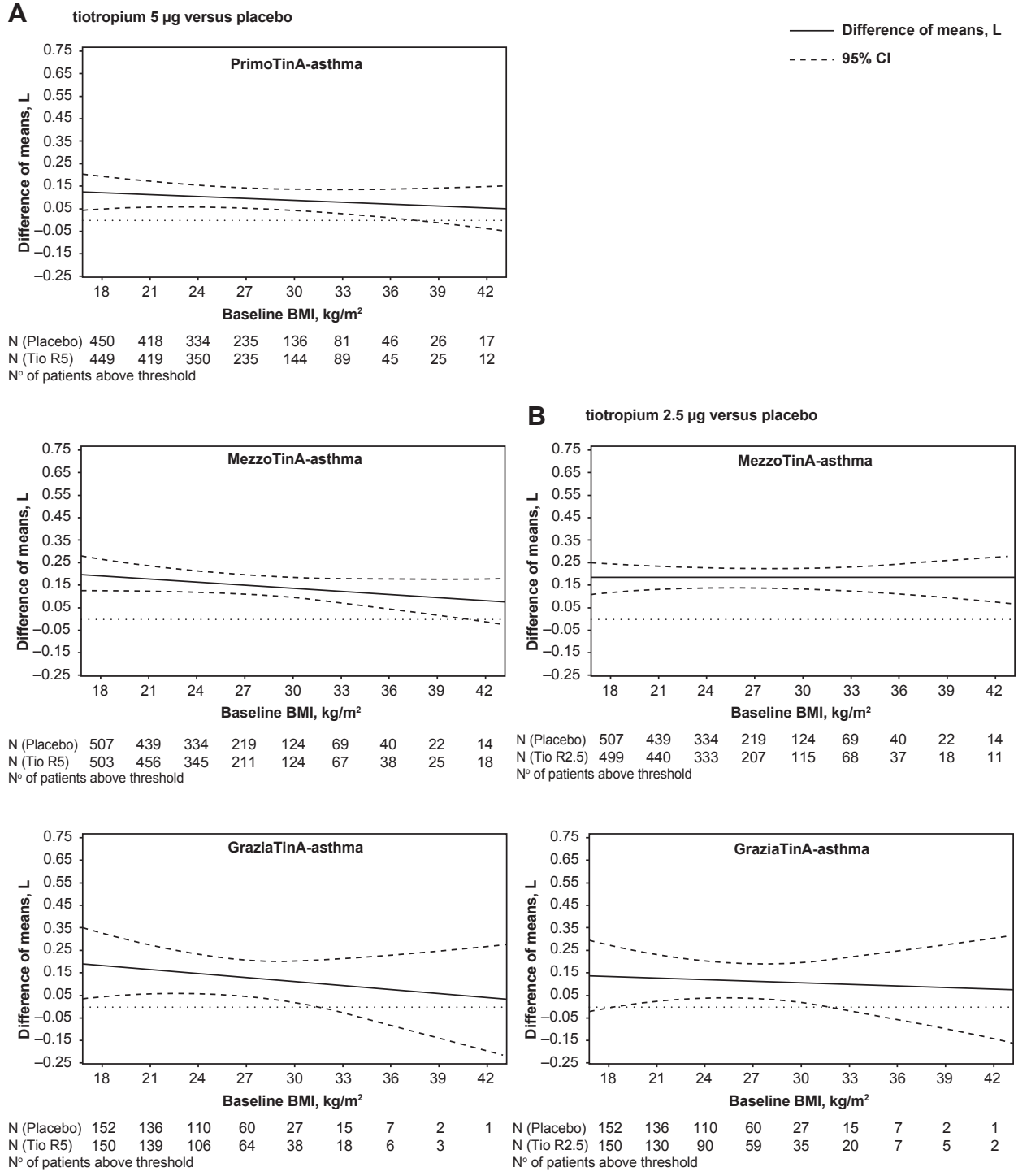


FIGURE E3. FEV_1 trough adjusted mean change from baseline vs placebo across the continuous range of BMI values for (**A**) tiotropium 5 µg vs placebo and (**B**) tiotropium 2.5 µg vs placebo. *BMI*, Body mass index; *CI*, confidence interval; *FEV_1*, forced expiratory volume in 1 second; *Tio*, tiotropium.

TABLE E1. Baseline patient demographic and disease characteristics for the 5 tiotropium trials, across categories of BMI

Characteristic	Trial											
	PrimoTinA-asthma				MezzoTinA-asthma				GraziaTinA-asthma			
BMI subgroup (kg/m^2)	<18.5	18.5-<25	25-<30	≥30	<18.5	18.5-<25	25-<30	≥30	<18.5	18.5-<25	25-<30	≥30
No. of patients, n (%)	15 (1.6)	282 (30.9)	334 (36.6)	281 (30.8)	69 (3.3)	871 (41.5)	661 (31.5)	499 (23.8)	12 (2.6)	187 (40.3)	165 (35.6)	100 (21.6)
Sex: male, %	13.3	39.7	44.9	34.5	37.7	40.3	48.1	33.3	58.3	41.7	40.6	31.0
Race, n (%)												
Am. Ind./Alaska native	0	0	0	1 (0.4)	0	38 (4.4)	45 (6.8)	35 (7.0)	0	7 (3.7)	5 (3.0)	4 (4.0)
Asian	4 (26.7)	53 (18.8)	32 (9.6)	14 (5.0)	58 (84.1)	541 (62.1)	238 (36.0)	56 (11.2)	7 (58.3)	54 (28.9)	22 (13.3)	2 (2.0)
Black/African American	0	12 (4.3)	13 (3.9)	22 (7.8)	1 (1.4)	13 (1.5)	25 (3.8)	42 (8.4)	0	0	1 (0.6)	0
Hawaiian/Pacific Islander	0	0	1 (0.3)	1 (0.4)	0	1 (0.1)	1 (0.2)	1 (0.2)	0	0	0	0
White	11 (73.3)	217 (77.0)	288 (86.2)	243 (86.5)	10 (14.5)	278 (31.9)	352 (53.3)	365 (73.1)	5 (41.7)	126 (67.4)	137 (83.0)	94 (94.0)
Age (y), mean ± SD	48.7 ± 15.9	51.7 ± 13.6	54.2 ± 11.9	52.9 ± 11.2	34.6 ± 10.8	40.9 ± 12.8	45.1 ± 12.7	45.6 ± 12.4	30.5 ± 10.0	39.8 ± 13.7	45.1 ± 12.2	46.4 ± 11.2
Age at onset of asthma (y), mean ± SD	24.5 ± 12.2	22.1 ± 13.2	24.1 ± 12.2	21.5 ± 13.4	22.5 ± 10.3	21.9 ± 12.6	21.8 ± 12.9	19.8 ± 13.0	22.4 ± 8.7	25.0 ± 11.6	27.9 ± 9.7	28.4 ± 10.8
Age at onset of asthma classes (y), n (%)												
<18	5 (33.3)	103 (36.5)	93 (27.8)	100 (35.6)	18 (26.1)	317 (36.4)	248 (37.5)	221 (44.3)	2 (16.7)	53 (28.3)	29 (17.6)	20 (20.0)
≥18	10 (66.7)	179 (63.5)	241 (72.2)	181 (64.4)	51 (73.9)	554 (63.6)	413 (62.5)	278 (55.7)	10 (83.3)	134 (71.7)	136 (82.4)	80 (80.0)
Smoking status, %												
Never smoked	66.7	74.5	76.3	77.2	91.3	87.4	81.8	78.4	91.7	84.5	78.8	83.0
Ex-smoker	33.3	25.5	23.7	22.8	8.7	12.6	18.2	21.6	8.3	15.5	21.2	17.0
Smoking history (pack years), mean ± SD	3.8 ± 2.9	5.0 ± 2.6	5.1 ± 2.9	5.2 ± 2.8	4.9 ± 3.5	4.0 ± 2.5	4.3 ± 2.8	4.2 ± 3.1	0.6* (NA)	4.5 ± 3.2	5.0 ± 2.7	4.8 ± 3.0
Duration of asthma (y), mean ± SD	24.1 ± 14.4	29.7 ± 14.1	30.1 ± 13.8	31.5 ± 13.6	12.2 ± 10.9	18.9 ± 13.8	23.4 ± 14.5	25.9 ± 13.7	8.1 ± 8.7	14.8 ± 11.3	17.2 ± 12.4	18.0 ± 11.8
FEV_1 % predicted, mean ± SD	49.4 ± 13.9	57.0 ± 13.9	55.9 ± 12.8	55.4 ± 12.7	76.5 ± 10.2	75.5 ± 11.6	74.4 ± 11.8	75.0 ± 11.1	79.3 ± 10.5	79.0 ± 11.9	75.9 ± 12.2	77.9 ± 11.5
Potentially allergic asthma, n (%)												
IgE ≤ 430 μg/L	5 (33.3)	108 (38.3)	127 (38.0)	113 (40.2)	19 (27.5)	316 (36.3)	245 (37.1)	208 (41.7)	5 (41.7)	75 (40.1)	73 (44.2)	57 (57.0)
IgE > 430 μg/L	8 (53.3)	125 (44.3)	152 (45.5)	106 (37.7)	48 (69.6)	550 (63.1)	420 (62.0)	289 (57.9)	7 (58.3)	107 (57.2)	91 (55.2)	43 (43.0)
Missing	2 (13.3)	49 (17.4)	55 (16.5)	62 (22.1)	2 (2.9)	5 (0.6)	6 (0.9)	2 (0.4)	0	5 (2.7)	1 (0.6)	0

Am. Ind., American Indian; *BMI*, body mass index; *FEV_1*, forced expiratory volume in 1 second; *IgE*, immunoglobulin E; *NA*, not applicable; *SD*, standard deviation.
*N = 1 subject.

TABLE E2. Adverse events across BMI categories*

	BMI subgroup (kg/m^2)											
Adverse events	**<18.5**			**18.5–<25**			**25–<30**			**≥30**		
PrimoTinA-asthma												
No. of patients	Pbo (n = 8)	Tio 5 μg (n = 7)	Tio 2.5 μg (NA)	Pbo (n = 145)	Tio 5 μg (n = 137)	Tio 2.5 μg (NA)	Pbo (n = 166)	Tio 5 μg (n = 168)	Tio 2.5 μg (NA)	Pbo (n = 137)	Tio 5 μg (n = 144)	Tio 2.5 μg (NA)
Total patients with adverse events, n (%)	5 (62.5)	5 (71.4)	NA	109 (75.2)	103 (75.2)	NA	143 (86.1)	117 (69.6)	NA	109 (79.6)	110 (76.4)	NA
Total patients with serious adverse events, n (%)	1 (12.5)	1 (14.3)	NA	11 (7.6)	11 (8.0)	NA	12 (7.2)	14 (8.3)	NA	16 (11.7)	11 (7.6)	NA
MezzoTinA-asthma												
No. of patients	Pbo (n = 14)	Tio 5 μg (n = 13)	Tio 2.5 μg (n = 21)	Pbo (n = 219)	Tio 5 μg (n = 210)	Tio 2.5 μg (n = 213)	Pbo (n = 164)	Tio 5 μg (n = 170)	Tio 2.5 μg (n = 170)	Pbo (n = 126)	Tio 5 μg (n = 124)	Tio 2.5 μg (n = 115)
Total patients with adverse events, n (%)	9 (64.3)	7 (53.8)	14 (66.7)	130 (59.4)	117 (55.7)	118 (55.4)	103 (62.8)	96 (56.5)	108 (63.5)	67 (53.2)	76 (61.3)	62 (53.9)
Total patients with serious adverse events, n (%)	1 (7.1)	1 (7.7)	1 (4.8)	7 (3.2)	4 (1.9)	1 (0.5)	3 (1.8)	3 (1.8)	3 (1.8)	3 (2.4)	3 (2.4)	7 (6.1)
GraziaTinA-asthma												
No. of patients	Pbo (n = 3)	Tio 5 μg (n = 5)	Tio 2.5 μg (n = 4)	Pbo (n = 63)	Tio 5 μg (n = 53)	Tio 2.5 μg (n = 71)	Pbo (n = 62)	Tio 5 μg (n = 59)	Tio 2.5 μg (n = 44)	Pbo (n = 27)	Tio 5 μg (n = 38)	Tio 2.5 μg (n = 35)
Total patients with adverse events, n (%)	0 (0)	0 (0)	1 (25.0)	18 (28.6)	19 (35.8)	26 (36.6)	20 (32.3)	21 (35.6)	11 (25.0)	7 (25.9)	10 (26.3)	10 (28.6)
Total patients with serious adverse events, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.9)	0 (0)	1 (1.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

NA, Not applicable; *Pbo*, placebo; *Tio*, tiotropium.

*By BMI, treatment and system organ class and preferred term, treated set.

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