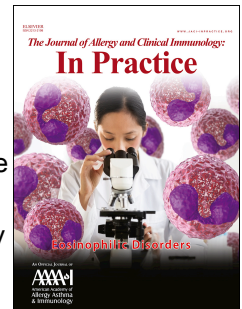


Accepted Manuscript

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PII: S2213-2198(19)30283-1

DOI: <https://doi.org/10.1016/j.jaip.2019.03.019>

Reference: JAIP 2168

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 11 December 2018

Revised Date: 7 March 2019

Accepted Date: 12 March 2019

Please cite this article as: Szefer SJ, Vogelberg C, Bernstein JA, Goldstein S, Mansfield L, Zaremba-Pechmann L, Engel M, Hamelmann E, Tiotropium is efficacious in 6–17-year-olds with asthma, independent of T2 phenotype, *The Journal of Allergy and Clinical Immunology: In Practice* (2019), doi: <https://doi.org/10.1016/j.jaip.2019.03.019>.

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Tiotropium is efficacious in 6–17-year-olds with asthma, independent of T2 phenotype

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Funding statement: This work was supported by Boehringer Ingelheim.

Conflicts of interest

S.J. Szefer has potential conflicts of interest with Aerocrine, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, GlaxoSmithKline, Genentech, Novartis, Propeller Health, Regeneron and Sanofi, and has received research support from GlaxoSmithKline.

J.A. Bernstein is a principal investigator for Boehringer Ingelheim, principal investigator and consultant for AstraZeneca, Merck, GlaxoSmithKline, Genentech, Novartis, Teva and Sanofi-Regeneron, and a speaker for AstraZeneca.

L. Mansfield has received funding from Boehringer Ingelheim for contributions to clinical studies.

S. Goldstein has potential conflicts of interest with Genentech, GlaxoSmithKline, Novartis, Regeneron and Sanofi.

C. Vogelberg reports study-related payments to his institution from Boehringer Ingelheim during the conduct of the study, and personal fees for advisory boards and lectures from Boehringer Ingelheim and Novartis outside the submitted work.

E. Hamelmann has consulted for Allergopharma, ALK, Bencard, Boehringer Ingelheim, GlaxoSmithKline, HAL Allergy, Novartis, Nutricia and Stallergenes, and has received research support from the German Society of Research (DFG), the State Ministry of Education and Research of Nordrhein-Westfalen (LMBF) and the German Ministry of Education and Research (BMBF).

52 L. Zaremba-Pechmann is employed as a contractor by Boehringer Ingelheim, both during the conduct
53 of this study and outside the submitted work. M. Engel is an employee of Boehringer Ingelheim.

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Abstract

BACKGROUND: Tiotropium add-on therapy has demonstrated efficacy and safety in 6–17-year-olds with symptomatic asthma despite treatment with inhaled corticosteroids (ICS), with or without additional controllers. Pediatric patients often have a significant allergic component to their asthma.

OBJECTIVE: To explore whether responses to tiotropium add-on were influenced by patients' type 2 (T2) status, assessed by serum immunoglobulin E (IgE) levels and blood eosinophil counts.

METHODS: Data from two Phase III trials in symptomatic moderate asthma (CanoTinA-asthma®; RubaTinA-asthma®) and two Phase III trials in symptomatic severe asthma (VivaTinA-asthma®; PensieTinA-asthma®) were pooled by severity. Patients were treated with tiotropium 5 µg, 2.5 µg or placebo (two puffs once daily via Respimat® inhaler), as add-on to ICS, with or without additional controllers. Modeling of efficacy outcomes was performed over the whole range of baseline IgE levels and blood eosinophil counts, and the treatment effect of the tiotropium doses was presented graphically.

RESULTS: Improvements with tiotropium in peak forced expiratory volume in 1 second (FEV₁) within 3 hours post-dose, trough FEV₁, forced expiratory flow at 25–75% of the pulmonary volume and FEV₁/forced vital capacity responses were generally consistent across the range of baseline IgE levels and blood eosinophil counts. Risk of exacerbations and improvement in Asthma Control Questionnaire responder rates with tiotropium were also largely independent of IgE levels or eosinophil counts.

CONCLUSIONS: This exploratory analysis suggests that improvements with tiotropium as add-on to ICS, with or without additional controllers, in 6–17-year-olds with symptomatic asthma do not vary according to systemic markers of T2 inflammation, namely total IgE and blood eosinophil counts.

Highlights

What is already known about this topic? Current research in asthma is directed towards identifying endotypes/phenotypes that predict response to asthma therapies, including biologics. T2 phenotypes are defined by their differing inflammatory cell composition and biomarkers.

What does this article add to our knowledge? This exploratory analysis of four large randomized trials in children and adolescents suggests that the efficacy of tiotropium is irrespective of T2 phenotype, as defined by IgE level or eosinophil count, in patients with asthma.

How does this study impact current management guidelines? Our data suggest that children and adolescents being considered for the addition of tiotropium Respimat® for symptomatic asthma do not require prior phenotyping by T2 status.

Key words: adolescents; allergy; asthma; children; eosinophil; IgE; T2 phenotype; tiotropium Respimat®

89 **Abbreviations used**

ACQ	Asthma Control Questionnaire
ACQ-IA	investigator-administered Asthma Control Questionnaire
CI	confidence interval
FEF _{25–75%}	forced expiratory flow at 25–75% of the pulmonary volume
FEV ₁	forced expiratory volume in 1 second
FEV _{1(0–3h)}	forced expiratory volume in 1 second within 3 hours post-dose
FVC	forced vital capacity
GINA	Global Initiative for Asthma
HR	hazard ratio
ICS	inhaled corticosteroids
IgE	immunoglobulin E
IL	interleukin
LABA	long-acting β_2 -agonist
MMRM	restricted maximum likelihood-based repeated measures
OR	odds ratio
PFT	pulmonary function test
T2	type 2
TALC	Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid

Introduction

Asthma is the most common chronic disease in children,¹ and despite currently available therapies and detailed guidelines, more than 38% of children and adolescents with asthma still suffer from symptomatic, uncontrolled disease.^{2,3} This results in greater impairment in quality of life, decreased school attendance and productivity while at school, as well as increased healthcare resource use and costs to the family.⁴

Treatment with the long-acting anticholinergic bronchodilator tiotropium, as add-on to maintenance therapy, has been demonstrated to improve lung function in children and adolescents aged 6–17 years whose asthma is symptomatic despite treatment with inhaled corticosteroids (ICS), with or without additional controllers.^{5–8}

Tiotropium is recommended as an add-on option in the Global Initiative for Asthma (GINA) “Global Strategy for Asthma Management and Prevention” (Step 4 or 5) for patients aged ≥ 12 years with a history of exacerbations.² Tiotropium 2.5 μg is approved for the maintenance treatment of asthma in patients aged ≥ 6 years in the US.⁹ More recently, in the EU, tiotropium 5 μg has been included for use as an add-on bronchodilator for patients aged ≥ 6 years with severe asthma who experienced one or more severe asthma exacerbations in the past year.¹⁰

A large proportion of asthma patients, especially pediatric patients, have a significant allergic component,² and allergic asthma is recognized as the most common asthma phenotype.¹¹ One feature of allergic asthma is elevated type 2 (T2) inflammatory cytokines, classified as T2_{high} asthma. These patients may be identified by elevations in particular biomarkers of allergic inflammation, such as sputum and blood eosinophils, as well as in elevated serum-specific immunoglobulin E (IgE) levels.¹² Treatment options for patients with T2_{high} asthma include biologics that target IgE and the Th2-interleukins (IL) IL-4/IL-13 and IL-5,¹² and it is a future goal to adjust asthma therapy to the specific underlying disease mechanism of the individual patient (the “endotype”). However, identification of patients suitable for these treatments requires phenotyping, which is demanding

and involves additional clinic visits or invasive assessments and significant costs. It is important to understand whether asthma therapies work well for specific endotypes/ phenotypes, and especially according to the predominant T2 status.

Anticholinergic bronchodilators have been shown to reduce acetylcholine-induced inflammatory responses, and tiotropium has shown anti-inflammatory properties in animal models. Acetylcholine is released from airway neurons, airway epithelial cells and inflammatory cells. It binds to muscarinic receptors, triggering smooth muscle contraction and mucus secretion.¹³ It is of interest, therefore, to consider whether the antimuscarinic action of tiotropium shows specific or even enhanced anti-inflammatory activities in a population of patients with significant T2 inflammation.

Here, we present the results of an exploratory analysis to assess whether treatment with tiotropium added to ICS, with or without other controllers, is effective in children and adolescents with symptomatic asthma in respect of their T2 status and phenotype, as indicated by baseline serum IgE levels and blood eosinophil counts. Data from four Phase III trials in children and adolescents with symptomatic asthma were included in the analysis.⁵⁻⁸

Methods

Full details of the individual study designs, methodologies and prespecified efficacy outcomes from these four Phase III trials have been reported previously.^{5–8} The trials were carried out in accordance with the Declaration of Helsinki and Good Clinical Practice, and all participating patients provided written, informed consent.

Study design and treatment

Data from four Phase III, randomized, double-blind, placebo-controlled, parallel-group trials were pooled by asthma severity, namely symptomatic moderate asthma (CanoTinA-asthma® [NCT01634139; 6–11-year-olds⁵] and RubaTinA-asthma® [NCT01257230; 12–17-year-olds⁶]), and symptomatic severe asthma (VivaTinA-asthma® [NCT01634152; 6–11-year-olds⁷] and PensieTinA-asthma® [NCT01277523; 12–17-year-olds⁸]). Treatment with tiotropium 5 µg, 2.5 µg or placebo (delivered by Respimat® as two puffs once daily) was added onto ICS, with or without other maintenance therapy, as detailed in Table E1.

Study population

All participants were aged 6–17 years, with a documented history of symptomatic asthma. Baseline disease characteristics varied according to the trial design and included patients with symptomatic moderate and severe asthma (Table 1). Patients with a significant disease other than asthma were excluded.

Study endpoints

The primary endpoint in each study was peak forced expiratory volume in 1 second (FEV₁) within 3 hours post-dose (FEV_{1(0–3h)}), measured as response (i.e. change from baseline) at Week 24 for those with symptomatic moderate asthma, and at Week 12 for those with symptomatic severe asthma.

Secondary and further endpoints included trough FEV₁ response (pre-dose measured at the end of the dosing interval, 10 minutes before the next dose of trial medication) at Week 24 (symptomatic moderate asthma) or Week 12 (symptomatic severe asthma); forced expiratory flow at 25–75% of the pulmonary volume (FEF_{25–75%}) response; Asthma Control Questionnaire (ACQ) and investigator-

administered ACQ (ACQ-IA, in children aged 6–11 years) responder rate (defined as an improvement [decrease] in ACQ total score of ≥ 0.5 from baseline); and time to first asthma exacerbation (defined as an episode of progressive increase in one or more asthma symptoms [shortness of breath, cough, wheezing or chest tightness, or some combination of these symptoms, lasting for 2 or more consecutive days]). Further post hoc endpoints included FEV₁/forced vital capacity (FVC) ratio response (%).

Analysis of data by T2 status

In order to evaluate whether the improvements in lung function, exacerbations and asthma control provided by tiotropium versus placebo were seen in patients regardless of their allergic status, treatment effects were analyzed according to serum IgE levels and blood eosinophil counts. Since there is little consensus on the most appropriate cut-off values for these parameters, modeling of their influence on the treatment effect was carried out over the whole range of IgE and eosinophil values.

Post hoc modeling was performed on the mean treatment differences between tiotropium and placebo at Weeks 24 and 12 for symptomatic moderate and symptomatic severe asthma, respectively, and represented graphically across the range of baseline IgE levels and blood eosinophil counts.

Statistical analysis

This exploratory analysis was not powered for inferential conclusions; *P* values presented must be considered nominal at the 5% alpha level, and conclusions are exploratory in nature.

Analysis of treatment differences for peak FEV_{1(0–3h)}, trough FEV₁, FEF_{25–75%} and FEV₁/FVC were performed using a restricted maximum likelihood-based repeated measures (MMRM) model, with the variables “treatment”, “study”, “visit”, “pulmonary function test (PFT) endpoint baseline”, “treatment-by-visit interaction”, “PFT endpoint baseline-by-visit interaction”, “baseline serum IgE or

blood eosinophil counts (log values)” and “baseline serum IgE or blood eosinophil counts (log values)-by-treatment”.¹⁴

For the analysis of ACQ responders (i.e. with an improvement in mean score of ≥ 0.5 , the minimum clinically important difference) a logistic regression model was applied with the variables “treatment”, “baseline serum IgE or blood eosinophil counts (log values)” and “baseline IgE or blood eosinophil counts (log values)-by-treatment” throughout the range of serum IgE levels and blood eosinophil counts (log values). The odds ratios (ORs) and 95% confidence interval (CI) categories are plotted.

Time to first asthma exacerbation was modeled using a Cox proportional hazards model with “treatment”, “baseline serum IgE or blood eosinophil count (log values)” and “baseline serum IgE or blood eosinophil count (log values)-by-treatment”. Hazard ratios (HRs) and respective 95% CI are plotted.

All analyses were conducted using SAS® v9.4 (SAS Institute Inc, Cary, NC).

Results

Patients

Baseline demographics and disease characteristics for the individual trials have been previously reported^{5–8} and were comparable between treatment groups within each trial. The majority of patients were male; most patients had never smoked or been exposed to second-hand smoke. Median age was 9.0 years (studies including 6–11-year-olds) and 14.0 years (studies including 12–17-year-olds). Median total IgE levels were higher in 12–17-year-olds with symptomatic moderate or symptomatic severe asthma compared with those aged 6–11 years, and were also higher in 6–11-year-olds with symptomatic severe asthma compared with those in the same age group with symptomatic moderate asthma. Mean ICS dose of stable maintenance treatment was 310 µg and 539 µg for patients with symptomatic moderate asthma aged 6–11 years and 12–17 years, respectively, and 457 µg and 747 µg (budesonide or equivalent) for patients with symptomatic severe asthma aged 6–11 years and 12–17 years, respectively. Long-acting β_2 -agonist (LABA) use at baseline for patients with symptomatic moderate asthma aged 6–11 years and 12–17 years was 18% and 29%, respectively, and 79% and 83% for patients with symptomatic severe asthma aged 6–11 years and 12–17 years, respectively. Median eosinophil levels were similar in the different age groups (Table 1). No patients had previously received treatment with a long-acting anticholinergic bronchodilator.

Lung function efficacy

Greater improvements in peak $FEV_{1(0-3h)}$ response were observed with both doses of tiotropium versus placebo (Table 2). Improvements were also seen with tiotropium versus placebo in trough FEV_1 , FEV_1/FVC ratio and $FEF_{25-75\%}$ at Weeks 24 and 12 for patients with symptomatic moderate and symptomatic severe asthma, respectively. These improvements were statistically significant for all measures except for trough FEV_1 response with the 2.5 µg dose of tiotropium in patients with symptomatic severe asthma (Table 2).

Influence of baseline IgE and blood eosinophils on lung function efficacy

Modeling of the mean differences from placebo in peak $FEV_{1(0-3h)}$ showed consistent responses across the range of baseline IgE levels and blood eosinophil counts, favoring tiotropium versus placebo, for both tiotropium 5 μ g and 2.5 μ g and in both symptomatic severe or symptomatic moderate asthma (Figures 1A and 1B).

Responses were also generally consistent for trough FEV_1 and $FEF_{25-75\%}$ across the range of IgE and eosinophil counts, and greater than zero (indicating greater response with tiotropium vs placebo) in patients with symptomatic moderate or symptomatic severe asthma (Figures 2A, 2B, 3A and 3B).

However, for trough FEV_1 , the response with tiotropium 2.5 μ g in patients with symptomatic moderate asthma shows a minor decline with increasing eosinophil count. For $FEF_{25-75\%}$, a slight decline in response towards the higher levels of eosinophils was observed in patients with symptomatic moderate asthma treated with tiotropium 2.5 μ g and with increased IgE in patients with symptomatic severe asthma treated with tiotropium 5 μ g (Figures 3A and 3B).

Responses according to FEV_1/FVC ratio showed improvements with both doses of tiotropium versus placebo, declining slightly (but still above 0, indicating improvement with tiotropium) at the higher ranges of baseline IgE levels in both symptomatic moderate and symptomatic severe patients (Figures E1A and E1B). A similar pattern was seen with blood eosinophil counts with tiotropium 2.5 μ g versus placebo in patients with symptomatic moderate asthma (Figure E1A). Conversely, the modeling indicates slightly improved responses at the higher end of the range of blood eosinophil counts for both doses of tiotropium versus placebo in patients with symptomatic severe asthma (Figure E1B).

ACQ response and time to first exacerbation

ACQ responder rates improved with both doses of tiotropium versus placebo for both symptomatic moderate and symptomatic severe asthma, reaching statistical significance in patients with

symptomatic moderate asthma who were treated with tiotropium 5 µg (OR 1.81 [95% CI 1.19, 2.77]; $P = 0.0048$) (Table 2).

Time to first asthma exacerbation also improved with both doses of tiotropium versus placebo in symptomatic moderate and symptomatic severe asthma, reaching statistical significance in the population with severe asthma with both tiotropium 5 µg and 2.5 µg (HR 0.67 [95% CI 0.47, 0.96]; $P = 0.0294$; HR 0.61 [95% CI 0.42, 0.89]; $P = 0.0091$, respectively) (Table 2).

Influence of baseline IgE and blood eosinophils on ACQ response and time to first exacerbation

In patients with symptomatic moderate asthma, the improvements in ACQ with tiotropium 5 µg or 2.5 µg versus placebo were observed across the whole range of IgE and blood eosinophil counts (Figure E2A). Improvements were seen in patients with symptomatic severe asthma, but these decreased slightly with higher values of IgE (both doses) and blood eosinophils (2.5 µg only). For the 5 µg dose, the improvement increased slightly with higher blood eosinophil counts (Figure E2B).

For time to first exacerbation, there was no consistent improvement with tiotropium 2.5 µg in patients with symptomatic moderate asthma across the range of IgE values and blood eosinophil levels. However, with tiotropium 5 µg, the treatment effect was greater with higher eosinophil counts (Figure E3A). In patients with symptomatic severe asthma, results generally favored tiotropium treatment reducing the risk of exacerbation and were consistent across the range of IgE levels and eosinophil counts (Figure E3B).

Discussion

Asthma is widely recognized to be a heterogeneous disease encompassing multiple subgroups or phenotypes, often with a significant allergic component.¹⁵ In children and adolescents, and in more severe disease, asthma is mostly, but certainly not always, associated with an allergic status. It is, therefore, important to note that tiotropium – now indicated for treatment of children and adolescents with symptomatic asthma – is effective regardless of the allergic status. The mechanism of action of tiotropium is predominantly via antagonism of muscarinic (M3) receptors, leading to airway smooth muscle relaxation and, consequently, a reduction in the airflow obstruction, with efficacy observed across a number of different asthma phenotypes.¹⁶ Anticholinergics can also reduce the acetylcholine-induced inflammatory response by blocking neutrophil migration.¹⁷ Studies have shown that most children aged >5 years are able to perform correct inhalation with the Respimat Soft Mist™ Inhaler (SMI) used in our studies to deliver tiotropium.¹⁸ A further handling study demonstrated that the Respimat SMI is suitable for inhalation therapy in young children (aged <5 years).¹⁹

We have carried out a comprehensive exploratory analysis of the influence of baseline counts of eosinophils and serum-specific IgE levels (which are recognized to be indicators of allergic status and T2 inflammatory status) on the treatment effect of tiotropium in children and adolescents. Our findings suggest that the improvements in lung function, asthma control and exacerbation risk seen with once-daily tiotropium versus placebo when added to ICS (with or without other maintenance therapies) are generally independent of the T2 phenotype.

The results presented here are consistent with a similar exploratory study carried out in adult patients with symptomatic moderate or symptomatic severe asthma despite maintenance therapy. Those analyses suggested that the improvements seen with tiotropium as add-on to ICS, with or without LABAs, on lung function, exacerbation risk and symptom control are also independent of T2 phenotype.¹⁴ Additionally, results from the 'Tiotropium Bromide as an Alternative to Increased

Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid (TALC)' study, which investigated selected patient baseline characteristics for their predictive potential for a response to tiotropium treatment, indicated that response to tiotropium was independent of atopy, IgE level and sputum eosinophil count.²⁰

Tiotropium is the only long-acting anticholinergic bronchodilator approved for maintenance therapy of asthma, and is recommended as an add-on therapy in the GINA recommendations, with no requirement for prior phenotyping.² Biologic agents that target T2 factors such as eosinophils or IgE, however, require phenotyping of patients to assess the potential of a positive response to treatment. This is associated with additional costs and resources; thus, it may be appropriate in many patients to prescribe tiotropium before introducing biologic agents. The data presented here provide reassurance regarding the efficacy of tiotropium for patients and that the treatment effect is largely consistent across the range of IgE and eosinophil counts. It is important to note, however, that these data are the result of an exploratory analysis, and do not provide head-to-head comparisons of tiotropium and biologic agents. In case other treatment options such as biologics are considered, phenotyping remains warranted.

The strengths of the analysis presented here are in the large number of patients (more than 1500) and the inclusion of patients with symptomatic moderate and symptomatic severe asthma. In addition, the duration of the study in patients with symptomatic moderate asthma (Week 24 data presented) allows for the confirmation of a sustained response to treatment. Conversely, this study has some limitations. As it is an exploratory analysis, the studies were not powered for such analyses. Some patients had values at the extreme ends of the IgE- and eosinophil-level spectrum, and the range of the CIs is wide; thus, the effect sizes at either end of the ranges should be interpreted with caution and are prone to being chance findings. The slight decline in response towards the higher levels of eosinophils seen in the modeling of the response for FEF_{25-75%} in patients with symptomatic moderate asthma treated with tiotropium 2.5 µg and by IgE level for

patients with symptomatic severe asthma treated with tiotropium 5 µg may be chance findings. The studies in patients with symptomatic severe asthma were perhaps too short to see strong signals in ACQ response and exacerbation risk, although trends can be seen despite low numbers of patients being included in some analyses. The ACQ responder rates were not significantly higher with tiotropium versus placebo in patients with symptomatic severe asthma. Speculation suggests that this may be due to the large placebo effect seen in these and other studies for these endpoints, and are presumed to relate to improved adherence in the clinical trial environment and/or the subjective nature of this endpoint.²¹ Alternatively, it may be that the minimum clinically important difference in mean ACQ score of ≥ 0.5 , which is based on improvements in adults, is not as relevant or applicable in children.

Optimization of treatment decisions for individual patients is reliant on scientific evidence and in line with GINA guidance. Our analysis supports the positioning of tiotropium as an add-on therapy option in pediatric patients with symptomatic asthma, with no requirement for prior phenotyping, thus enabling physicians to make educated and individualized treatment decisions.

Conclusion

The results of this exploratory analysis indicate that the improvements in lung function, exacerbation risk and symptom control seen with tiotropium when given as add-on therapy in children and adolescents aged 6–17 years with symptomatic asthma are largely independent of systemic markers of T2 inflammation, that is total IgE and blood eosinophil counts. These findings support the use of tiotropium add-on therapy in pediatric patients with symptomatic asthma, with no requirement for phenotyping of these parameters before treatment.

Acknowledgments

This work was supported financially by Boehringer Ingelheim. Medical writing assistance, in the form of the preparation and revision of the manuscript, was supported financially by Boehringer Ingelheim and provided by Jonathan Brennan, PhD, at MediTech Media, under the authors' conceptual direction and based on feedback from the authors. The authors would like to thank all the patients and their families for participating in these trials, and they also extend their thanks to the investigators.

Role of the funding source

This work was supported by Boehringer Ingelheim. The sponsor was involved in the study design, analysis, interpretation and writing of the manuscript, and the decision to submit the manuscript for publication in conjunction with the authors.

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404 Tables and Figures

405 Table 1. Baseline demographics and disease characteristics

Demographic/characteristic	CanoTinA-asthma® (N = 401)	RubaTinA-asthma® (N = 397)	VivaTinA-asthma® (N = 400)	PensieTinA-asthma® (N = 392)
Population	6–11 years old; symptomatic moderate asthma	12–17 years old; symptomatic moderate asthma	6–11 years old; symptomatic severe asthma	12–17 years old; symptomatic severe asthma
Male, n (%)	264 (65.8)	258 (65.0)	279 (69.8)	242 (61.7)
Age, years, median (range)	9.0 (6–11)	14.0 (11*–17)	9.0 (6–11)	14.0 (12–17)
Never smoked, n (%)	–	396 (99.7)	–	392 (100)
No exposure to second-hand smoke, n (%)	372 (92.8)	353 (88.9)	369 (92.3)	367 (93.6)
Age at onset of asthma, years, median (range)	4.6 (0–10.0)	6.1 (0–17.0)	3.9 (0–10.0)	6.0 (0–17.0)
Duration of asthma, years, median (range)	4.0 (0.5–11.0)	8.0 (0.3–16.3)	4.8 (0.6–11.0)	8.0 (0.3–16.5)
Concomitant diagnoses [†] , n (%)				
Allergic rhinitis	284 (70.8)	301 (75.8)	302 (75.5)	302 (77.0)
Atopic dermatitis	230 (57.4)	219 (55.2)	238 (59.5)	225 (57.4)
Atopic dermatitis	55 (13.7)	37 (9.3)	38 (9.5)	38 (9.7)
Concomitant medications, n (%)				
LABA	72 (18.0)	115 (29.0)	315 (78.8)	326 (83.2)
Systemic antihistamines	58 (14.5)	97 (24.4)	66 (16.5)	98 (25.0)
Leukotriene modifiers	122 (30.4)	47 (11.8)	340 (85.0)	315 (80.4)
FEV ₁ % predicted, mean ± SD	84.055 ± 10.788	82.788 ± 10.561	81.641 ± 11.450	79.524 ± 11.488
ACQ score, mean ± SD [‡]	1.87 ± 0.31	2.03 ± 0.43	1.97 ± 0.36	2.13 ± 0.43
ICS dose of stable maintenance treatment, µg; budesonide or equivalent dose, mean ± SD	310.0 ± 112.0	539.4 ± 292.7	457.4 ± 236.0	747.0 ± 357.7
Total IgE [§] , µg/L, median (Q1, Q3)	492.2 (161.5, 1484.2)	1065.4 (360.3, 2510.8)	696.8 (203.4, 1756.0)	1001.9 (337.5, 2691.0)
Eosinophils, absolute [§] , 10 ⁹ /L, median (Q1, Q3)	0.37 (0.21, 0.69)	0.37 (0.22, 0.68)	0.42 (0.22, 0.68)	0.43 (0.21, 0.80)

406 Treated set.

407 *One patient aged 11 years at enrollment.

408 [†]Within the last 3 months before screening.409 [‡]ACQ-IA in CanoTinA-asthma® and VivaTinA-asthma®.410 [§]At screening visit.

411 ACQ, Asthma Control Questionnaire; ACQ-IA, interviewer-administered Asthma Control Questionnaire;

412 FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; IgE, immunoglobulin E;413 LABA, long-acting β₂-agonist; Q, quartile; SD, standard deviation.

414 **Table 2. Efficacy in the overall population with tiotropium in trials pooled by asthma severity**

		Adjusted* mean difference to placebo (SE)	95% CI	P value
	Number of patients (active/placebo)	Peak FEV _{1(0-3h)} response, mL†		
Moderate asthma (Week 24)				
Tiotropium 5 µg	265/263	168 (30)	109, 228	<0.0001
Tiotropium 2.5 µg	251/263	159 (31)	98, 219	<0.0001
Severe asthma (Week 12)				
Tiotropium 5 µg	258/262	117 (34)	51, 183	0.0005
Tiotropium 2.5 µg	261/262	74 (33)	8, 140	0.0273
		Trough FEV ₁ , mL†		
Moderate asthma (Week 24)				
Tiotropium 5 µg	265/263	118 (33)	53, 182	0.0004
Tiotropium 2.5 µg	250/263	105 (33)	39, 170	0.0017
Severe asthma (Week 12)				
Tiotropium 5 µg	258/262	71 (34)	3, 139	0.0395
Tiotropium 2.5 µg	261/262	64 (34)	-3, 132	0.0617
		FEV ₁ /FVC, ratio		
Moderate asthma (Week 24)				
Tiotropium 5 µg	265/263	3.006 (0.645)	1.740, 4.271	<0.0001
Tiotropium 2.5 µg	250/263	1.393 (0.654)	0.110, 2.676	0.0334
Severe asthma (Week 12)				
Tiotropium 5 µg	258/262	1.921 (0.666)	0.614, 3.229	0.0040
Tiotropium 2.5 µg	261/262	1.930 (0.666)	0.623, 3.236	0.0038
		FEF _(25-75%) , L/sec‡		
Moderate asthma (Week 24)				
Tiotropium 5 µg	265/263	0.287 (0.061)	0.166, 0.407	<0.0001
Tiotropium 2.5 µg	250/263	0.193 (0.062)	0.071, 0.315	0.0019
Severe asthma (Week 12)				
Tiotropium 5 µg	258/262	0.192 (0.063)	0.068, 0.317	0.0024
Tiotropium 2.5 µg	261/262	0.175 (0.063)	0.051, 0.299	0.0057
		ACQ responder rate‡		
	Number of responders (active/placebo)	OR (active versus placebo)	95% CI	P value
Moderate asthma (Week 24)				
Tiotropium 5 µg	218/189	1.81	1.19, 2.77	0.0048
Tiotropium 2.5 µg	203/189	1.51	1.00, 2.28	0.0506
Severe asthma (Week 12)				
Tiotropium 5 µg	200/202	1.11	0.73, 1.68	0.6962
Tiotropium 2.5 µg	203/202	1.12	0.74, 1.71	0.6425
		Time to first exacerbation§		
	Number of patients with exacerbations (active/placebo)	HR (active versus placebo)	95% CI	P value
Moderate asthma				
Tiotropium 5 µg	87/103	0.81	0.61, 1.07	0.1370
Tiotropium 2.5 µg	97/103	0.97	0.73, 1.27	0.8066
Severe asthma				
Tiotropium 5 µg	50/72	0.67	0.47, 0.96	0.0294
Tiotropium 2.5 µg	47/72	0.61	0.42, 0.89	0.0091

*Adjusted for treatment, trial, visit, treatment-by-visit interaction, baseline and baseline-by-visit interaction, and the interaction term "treatment by trial".

†Change from baseline.

‡Fisher's exact test.

§Cox proportional hazards model with treatment as a covariate.

420 ACQ, Asthma Control Questionnaire (ACQ-IA in children aged 6–11 years); CI, confidence interval;
421 $FEF_{(25-75\%)}$, forced expiratory flow at 25–75% of the pulmonary volume; FEV_1 , forced expiratory volume in
422 1 second; $FEV_{1(0-3h)}$, forced expiratory volume in 1 second within 3 hours post-dose; FVC, forced vital
423 capacity; HR, hazard ratio; OR, odds ratio; SE, standard error of the mean.

Figure legends

Figure 1. Peak $FEV_{1(0-3h)}$ responses in (A) patients with moderate asthma (RubaTinA-asthma®/CanoTinA-asthma®) and in (B) patients with severe asthma (VivaTinA-asthma®/PensieTinA-asthma®) according to baseline serum IgE levels and blood eosinophil counts

*Number of patients above threshold. Full analysis set. Difference of means, L (solid line) and 95% CIs (dotted line) are presented.

A flat line indicates that the response to tiotropium is not affected by IgE levels or eosinophil counts.

A rising line would indicate a greater response to tiotropium in patients with higher IgE levels or eosinophil counts; conversely, a falling line would indicate a reduced response to tiotropium with higher IgE levels or eosinophil counts.

CI, confidence interval; $FEV_{1(0-3h)}$, forced expiratory volume in 1 second within 3 hours post-dose; IgE, immunoglobulin E; Tio, tiotropium.

Figure 2. Trough FEV_1 responses in (A) patients with moderate asthma (RubaTinA-asthma®/CanoTinA-asthma®) and in (B) patients with severe asthma (VivaTinA-asthma®/PensieTinA-asthma®) according to baseline serum IgE levels and blood eosinophil counts

*Number of patients above threshold. Full analysis set. Difference of means, L (solid line) and 95% CIs (dotted line) are presented.

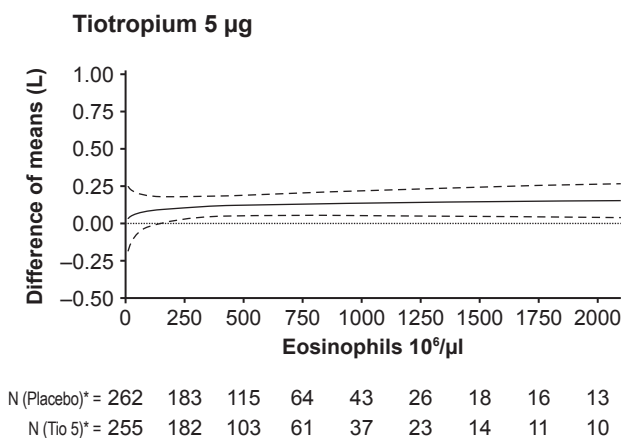
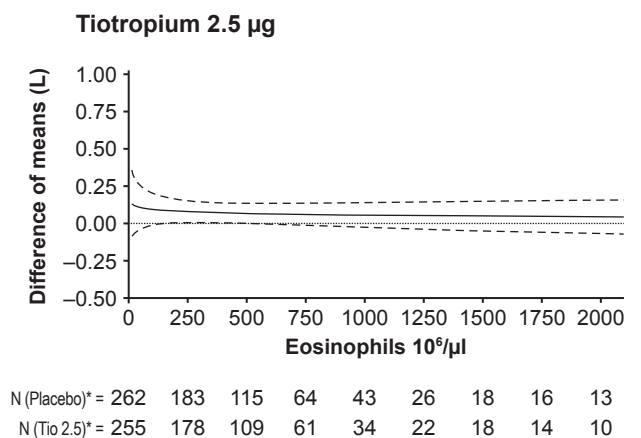
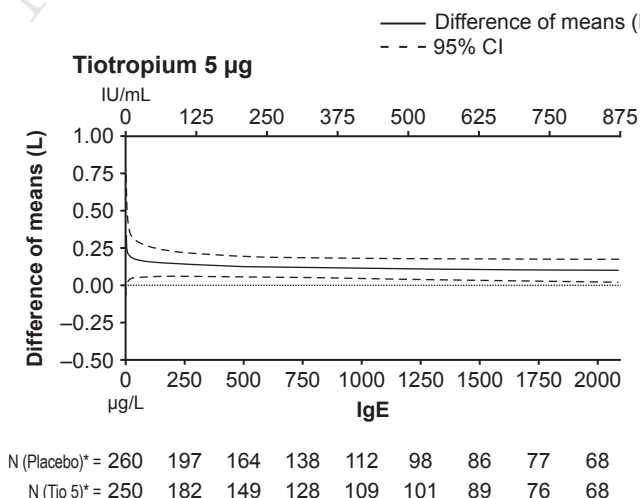
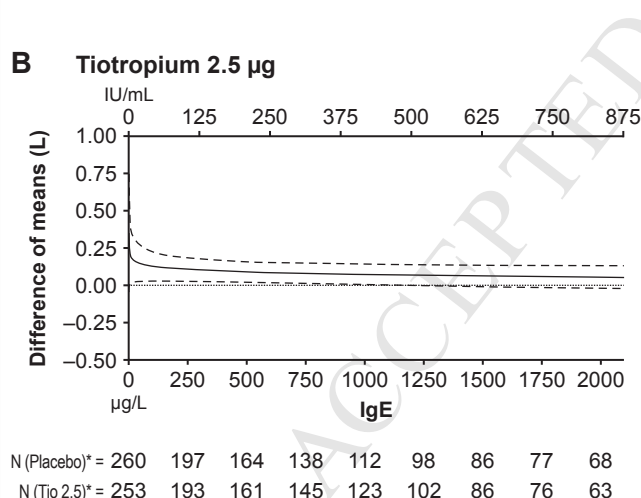
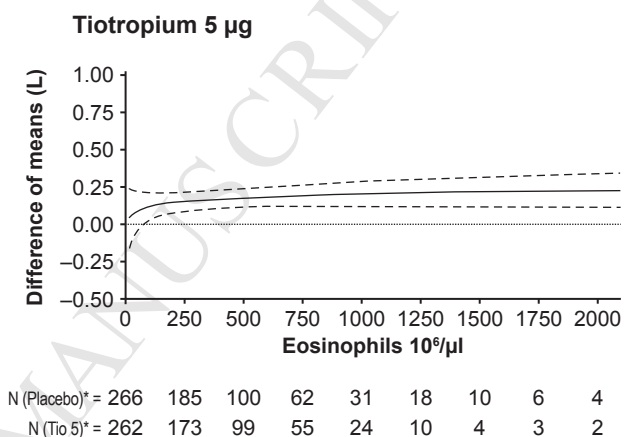
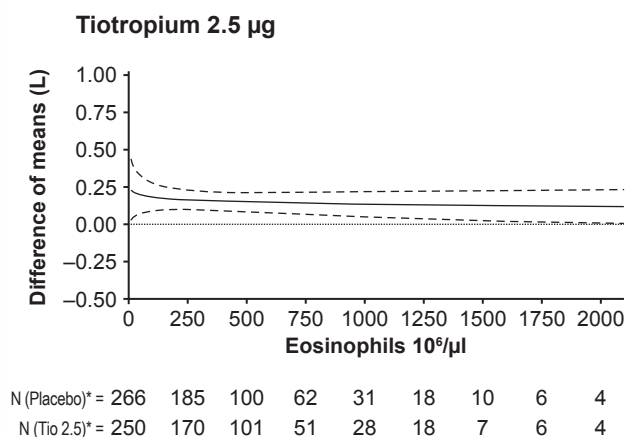
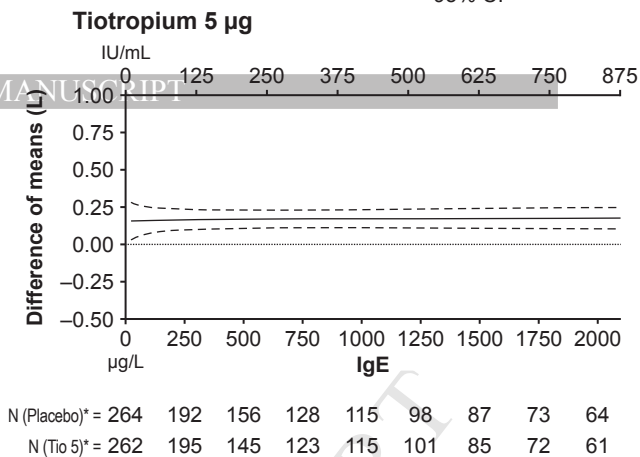
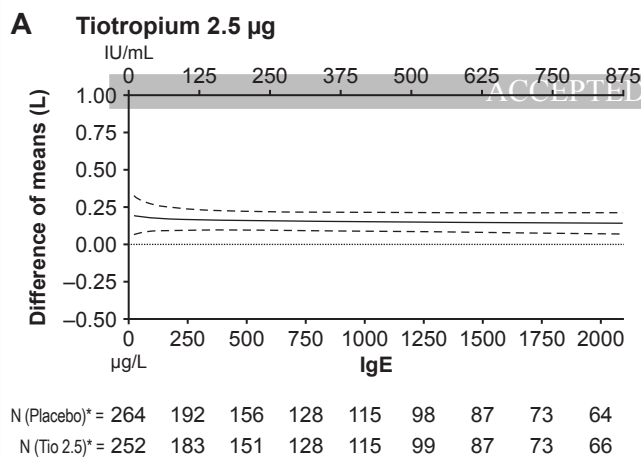
CI, confidence interval; FEV_1 , forced expiratory volume in 1 second; IgE, immunoglobulin E.

Figure 3. $FEF_{25-75\%}$ responses in (A) patients with moderate asthma (RubaTinA-asthma®/CanoTinA-asthma®) and in (B) patients with severe asthma (VivaTinA-asthma®/PensieTinA-asthma®) according to baseline serum IgE levels and blood eosinophil counts

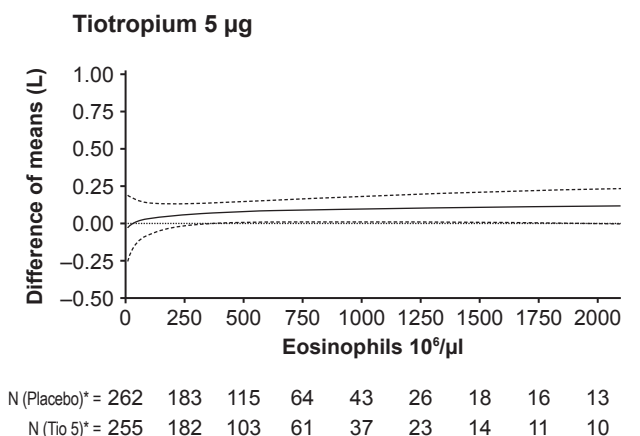
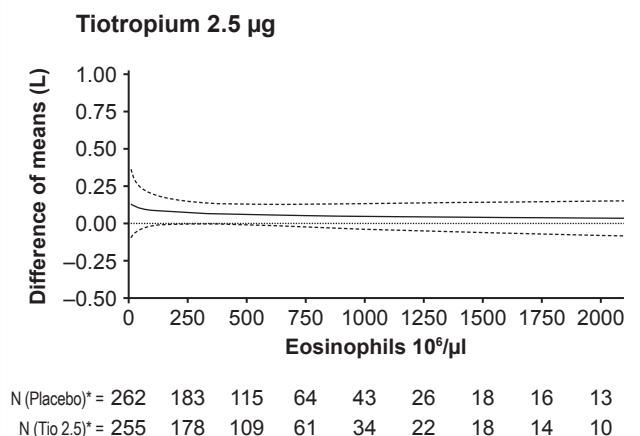
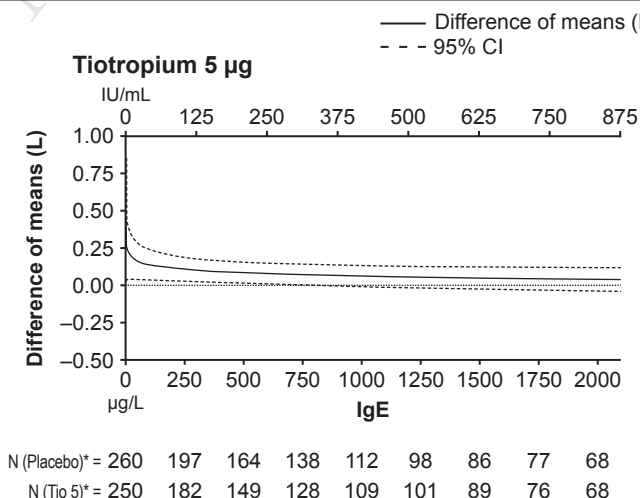
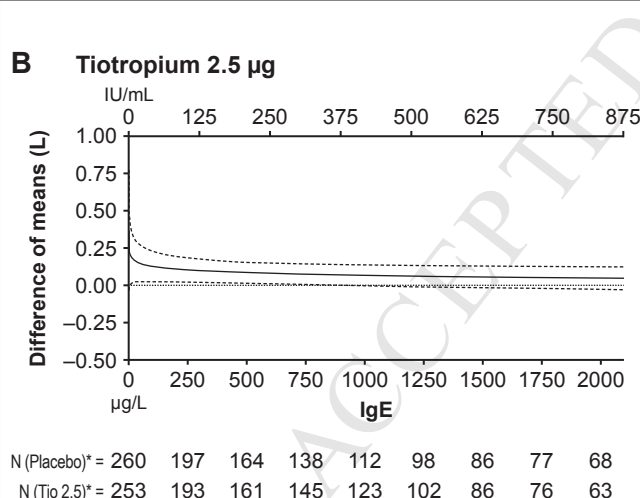
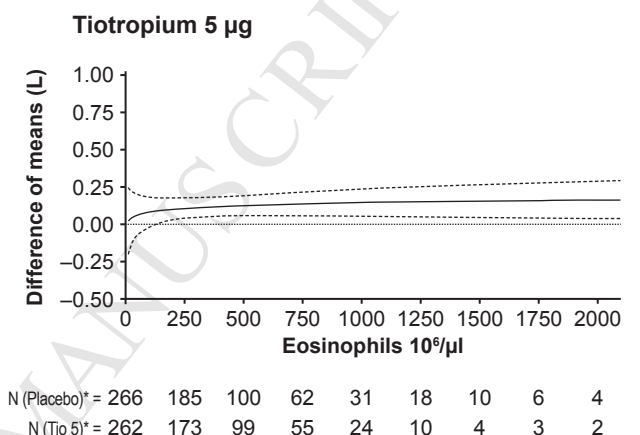
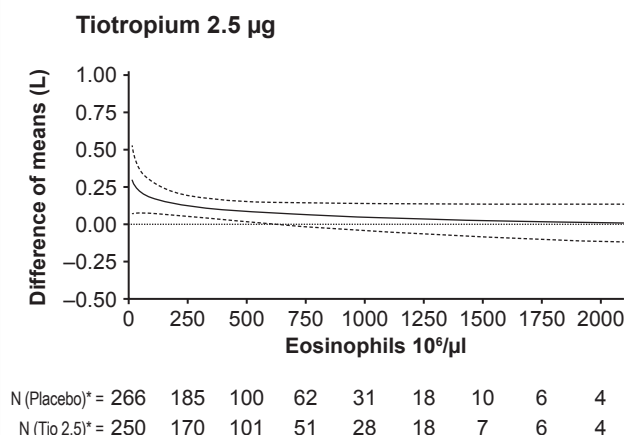
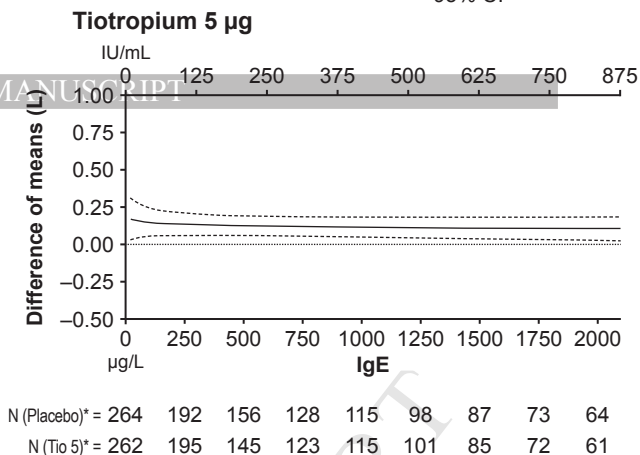
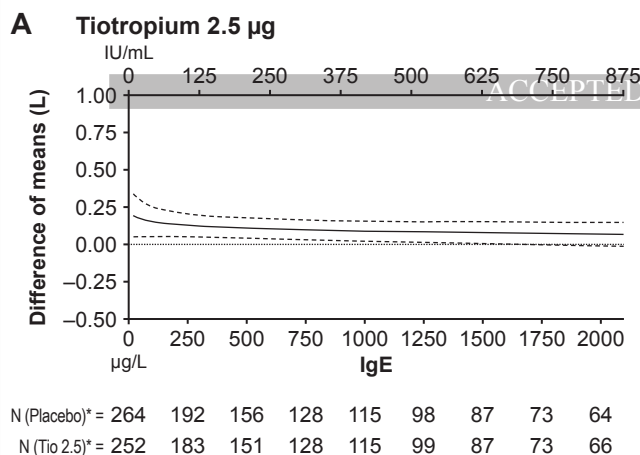
*Number of patients above threshold. Full analysis set. Difference of means, L/sec (solid line) and 95% CIs (dotted line) are presented.

- 447 CI, confidence interval; FEF_{25–75%}, forced expiratory flow at 25–75% of the pulmonary volume;
448 IgE, immunoglobulin E.

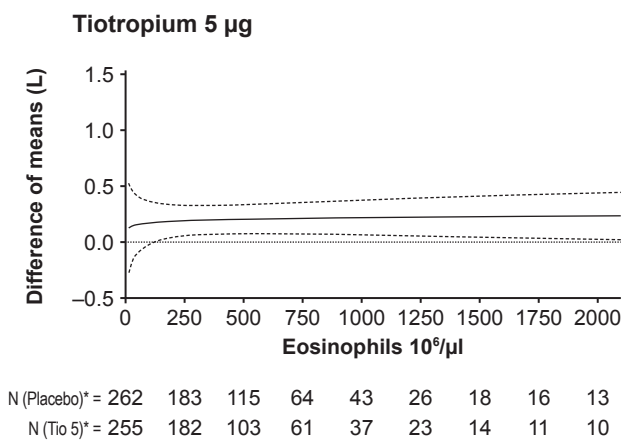
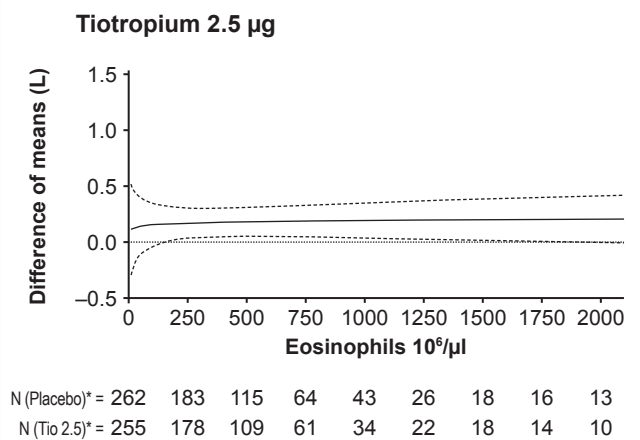
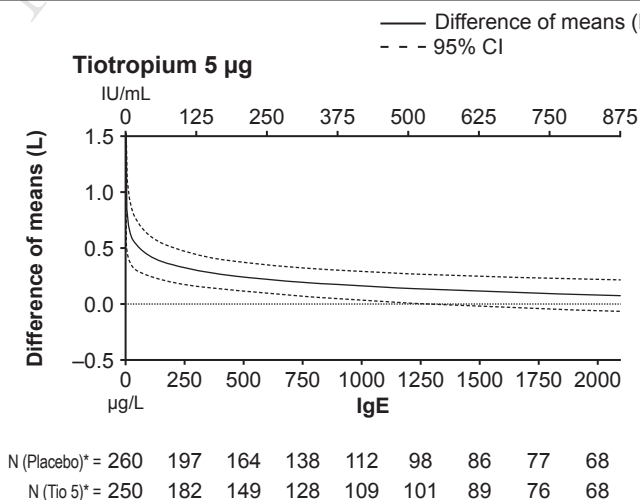
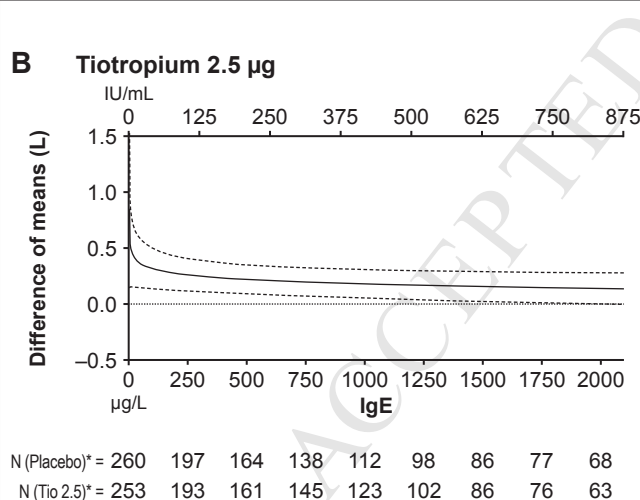
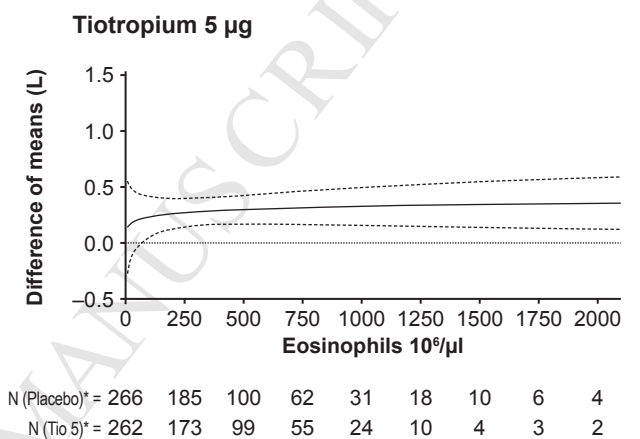
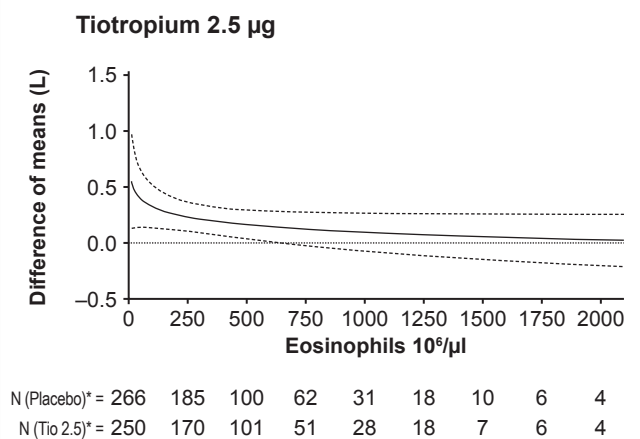
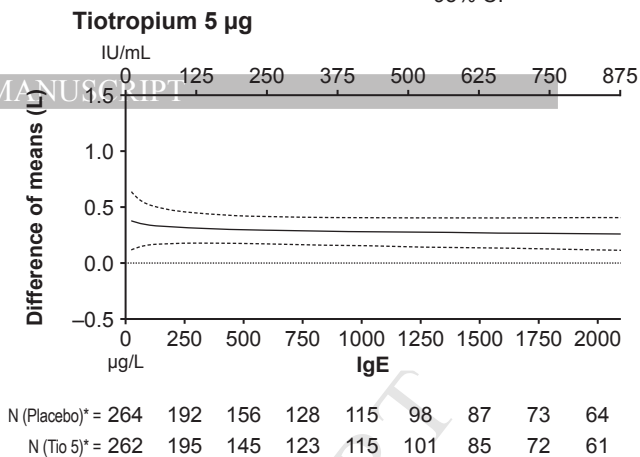
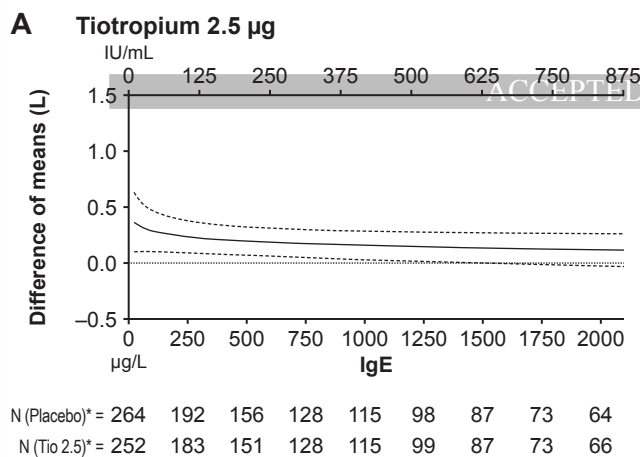
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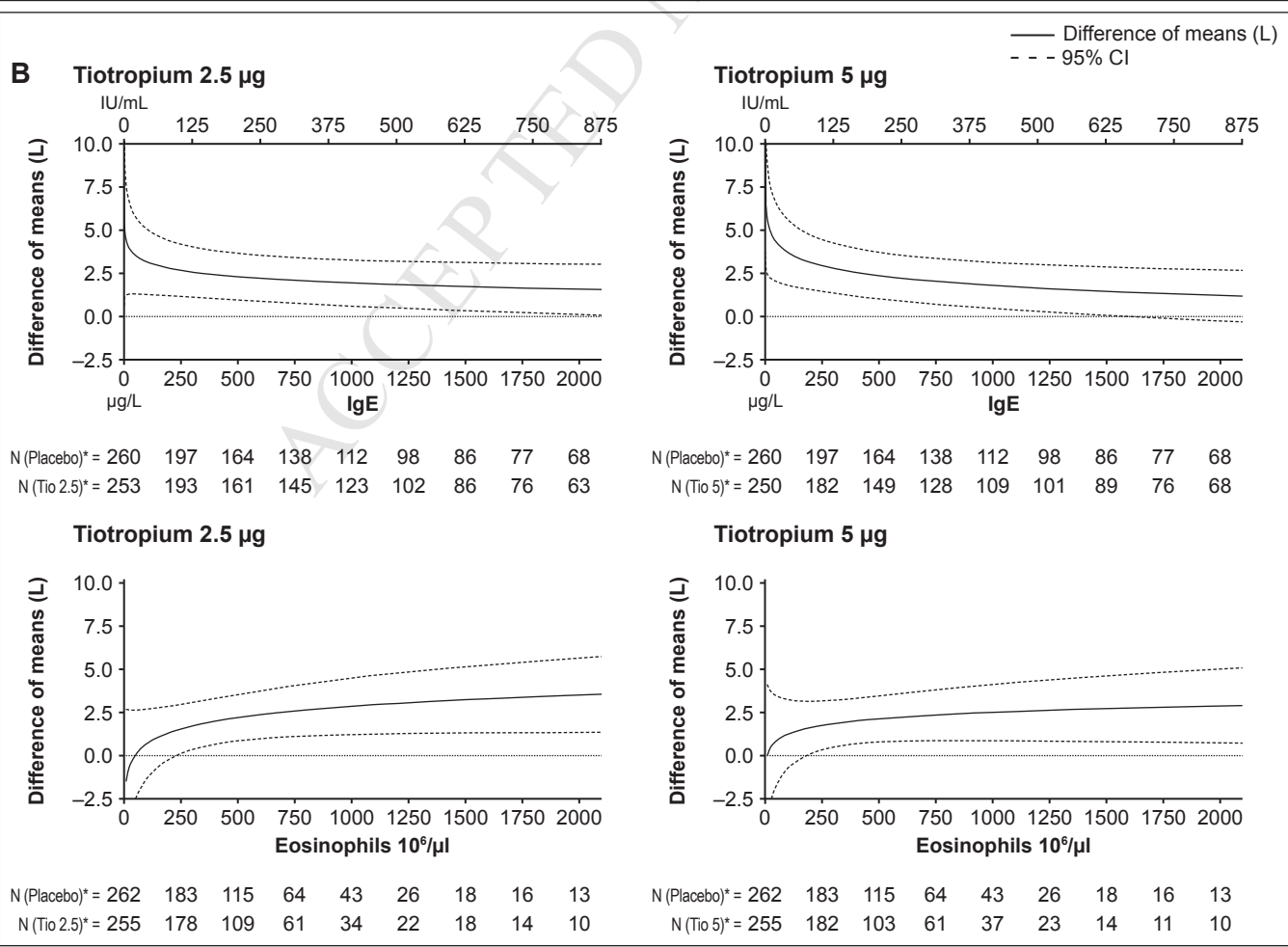
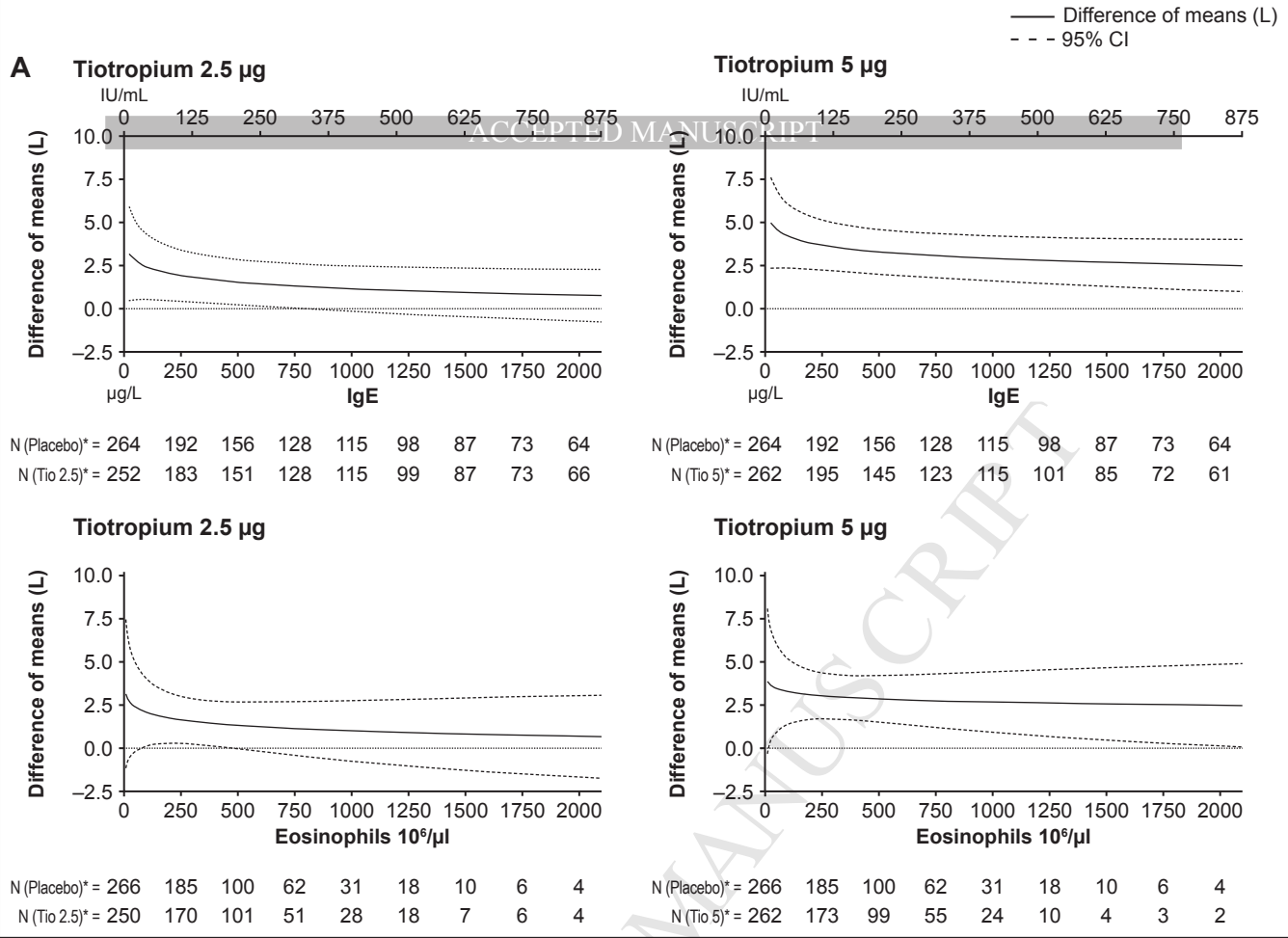


— Difference of means (L)
- - - 95% CI

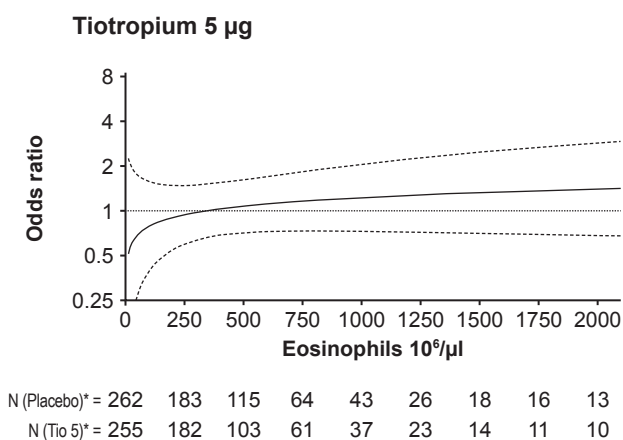
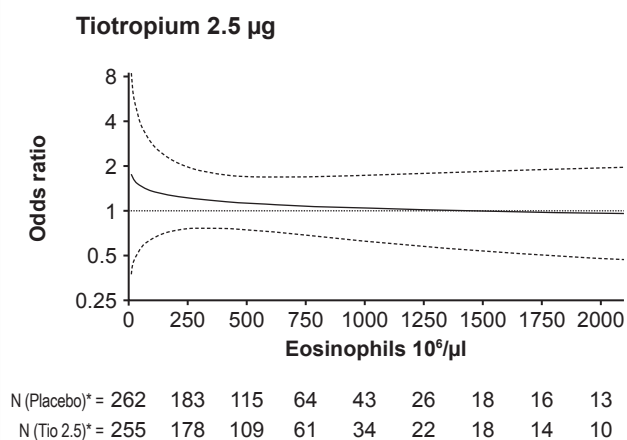
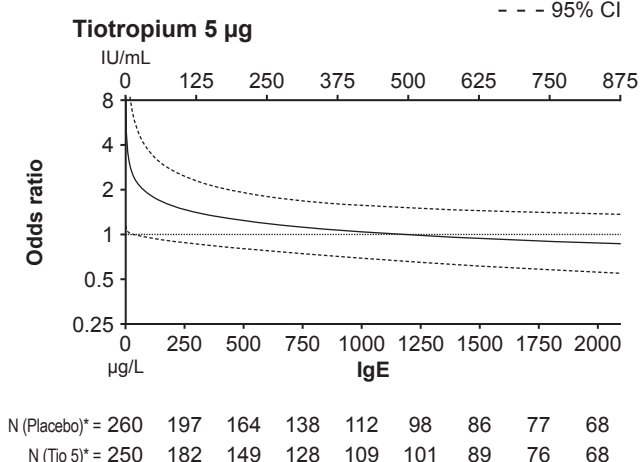
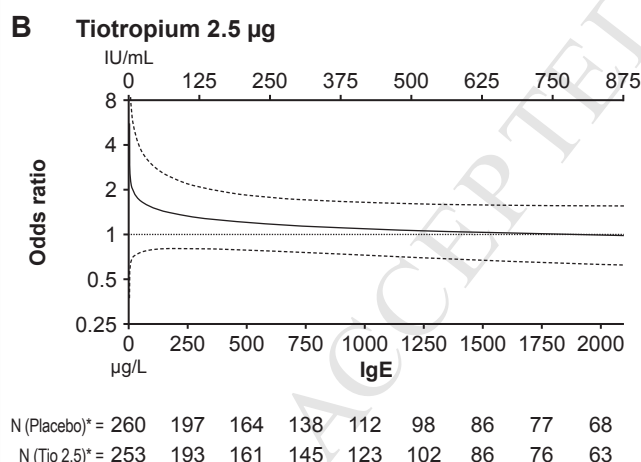
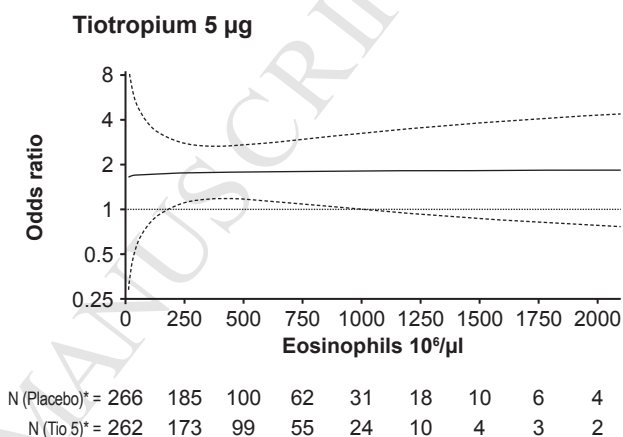
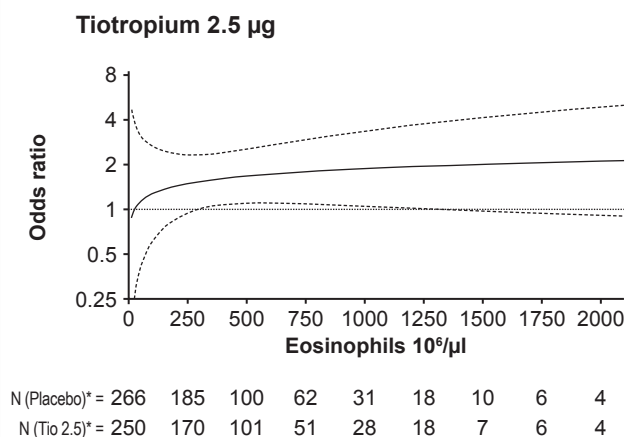
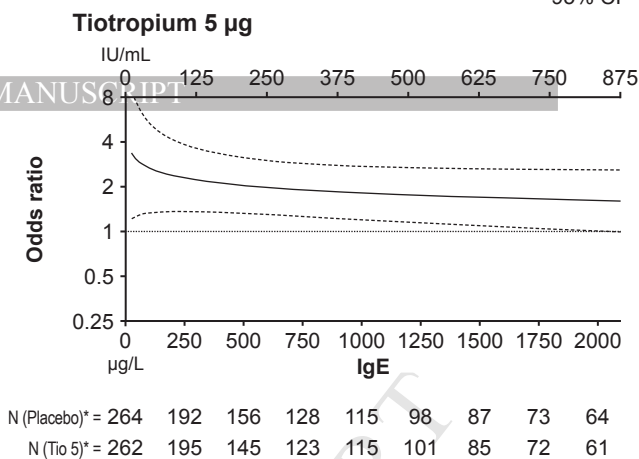
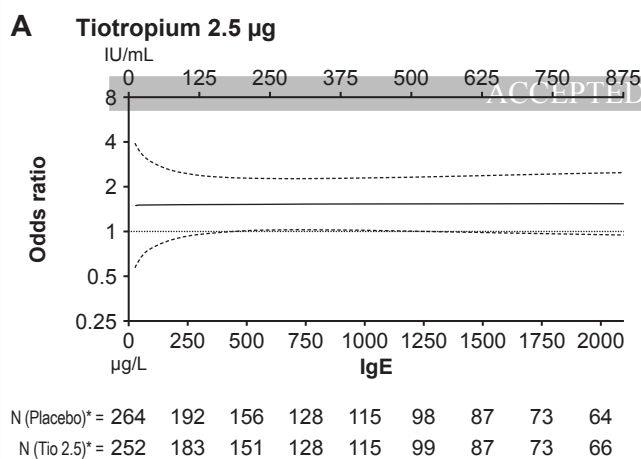


— Difference of means (L)
- - - 95% CI

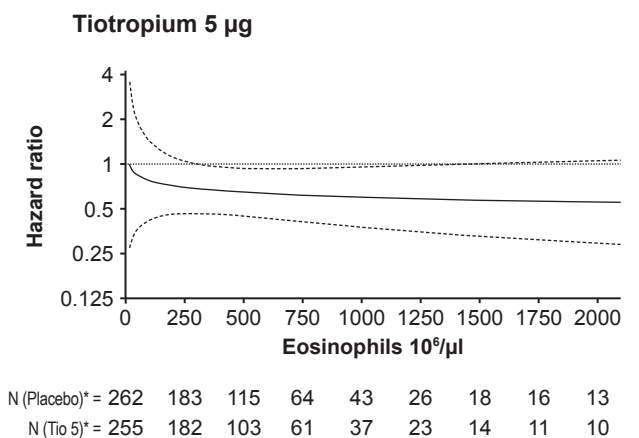
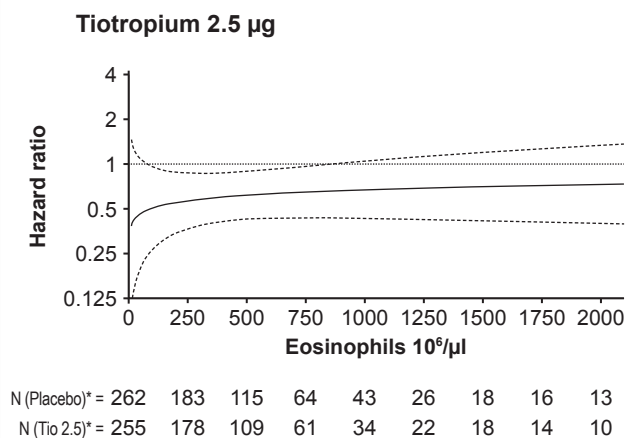
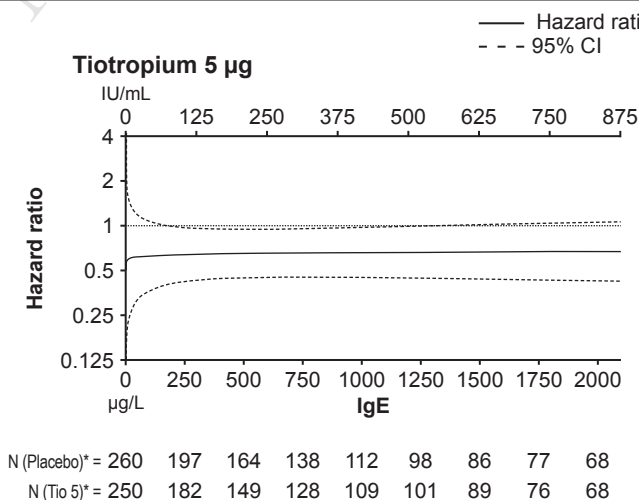
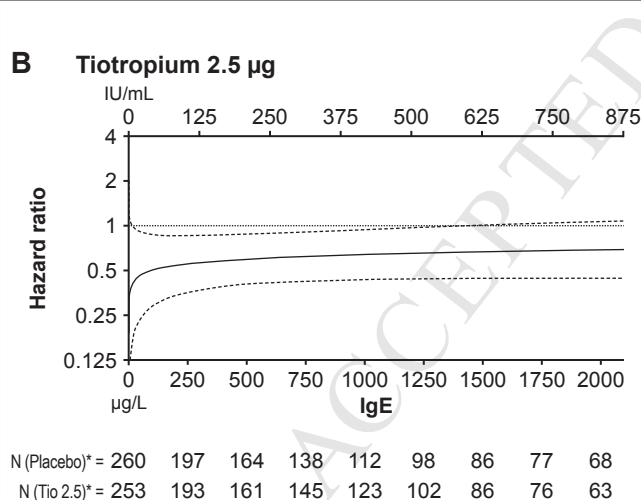
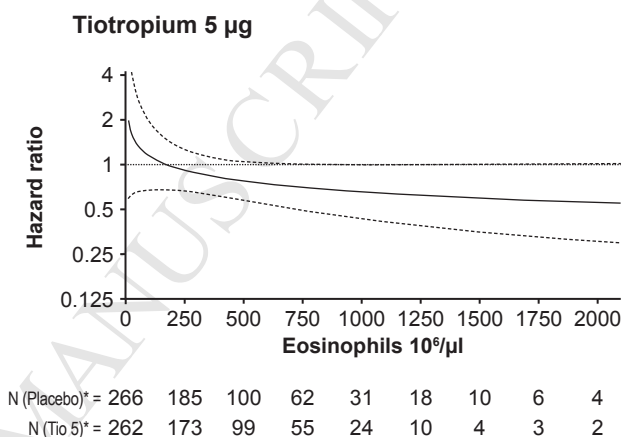
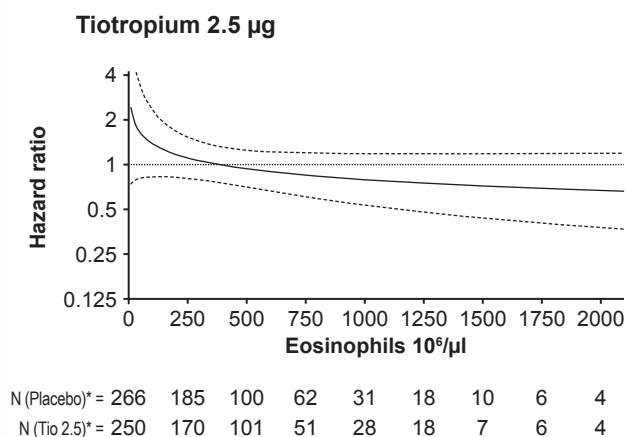
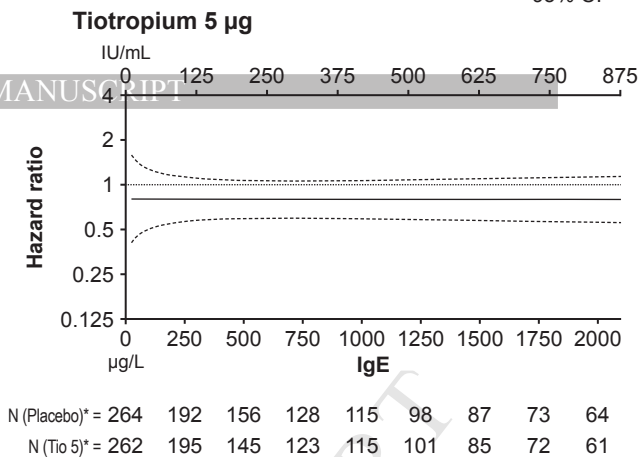
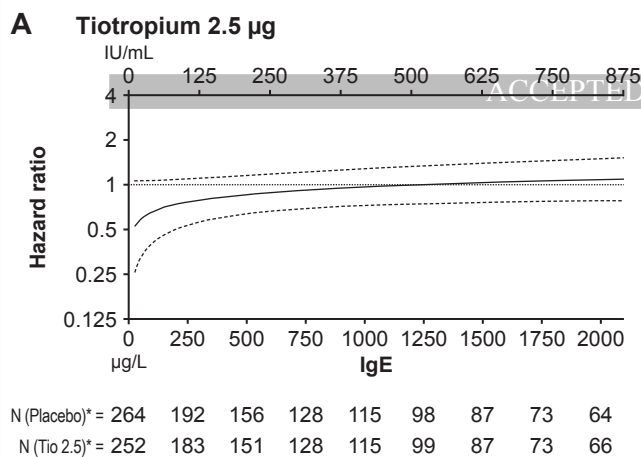




— Odds ratio
- - - 95% CI



— Hazard ratio
- - - 95% CI



1 Supplementary material

2 Table E1. Overview of study designs and key inclusion criteria

	CanoTinA-asthma®	RubaTinA-asthma®	VivaTinA-asthma®	PensieTinA-asthma®
Phase and design	Phase III, randomized, double-blind, placebo-controlled, parallel-group			
Patient population	6–11 years old; symptomatic moderate asthma	12–17 years old; symptomatic moderate asthma	6–11 years old; symptomatic severe asthma	12–17 years old; symptomatic severe asthma
History of asthma	≥6 months	≥3 months	≥6 months	≥3 months
Symptomatic asthma	ACQ-IA ≥1.5	ACQ ≥1.5	ACQ-IA ≥1.5	ACQ ≥1.5
Pre-bronchodilator FEV₁ % predicted normal at screening	60–90%			
FEV₁ reversibility at screening	≥12%, 15–30 minutes after 200 µg salbutamol	≥12% and ≥200 mL, 15–30 minutes after 400 µg salbutamol (age >14 years) or ≥12% only (age 12–14 years)	≥12%, 15–30 minutes after 200 µg salbutamol	≥12% and ≥200 mL, 15–30 minutes after 400 µg salbutamol (age >14 years) or ≥12% only (age 12–14 years)
Treatment	Tiotropium 5 µg, 2.5 µg or placebo, as two puffs once daily			
Background treatment	200–400 µg budesonide/ equivalent ± LTRA (no LABA)	200–800 µg budesonide/equivalent ± LTRA (no LABA)	High-dose ICS: >400 µg budesonide or equivalent + one or more controller medications (e.g. LABA and/or LTRA) OR medium-dose ICS: 200–400 µg budesonide or equivalent + two or more controller medications (e.g. LABA and/or LTRA and/or sustained- release theophylline)	High-dose ICS: >400 µg budesonide or equivalent in patients aged 12–14 years and 800–1600 µg budesonide or equivalent in patients aged 15–17 years, + one or more controller medications (e.g. LABA and/or LTRA) OR medium-dose ICS: 200–400 µg budesonide or equivalent in patients aged 12–14 years and 400–800 µg budesonide or equivalent in patients aged 15–17 years, + two or more controller medications (e.g. LABA and/or LTRA and/or sustained-release theophylline)
Treatment duration	48 weeks	48 weeks	12 weeks	12 weeks
Number of patients treated	401	397	400	392

- 3 ACQ, Asthma Control Questionnaire; ACQ-IA, interviewer-administered Asthma Control Questionnaire;
4 FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist;
5 LTRA, leukotriene receptor antagonist.

Supplementary Figure legends

Figure E1. FEV₁/FVC responses in (A) patients with moderate asthma (RubaTinA-

asthma®/CanoTinA-asthma®) and in (B) patients with severe asthma (VivaTinA-

asthma®/PensieTinA-asthma®) according to baseline serum IgE levels and blood eosinophil counts

*Number of patients above threshold. Full analysis set. Difference of means, percentage (solid line) and 95% CIs (dotted line) are presented.

CI, confidence interval; Eos, eosinophils; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E.

Figure E2. ACQ responder rate in (A) patients with moderate asthma (RubaTinA-

asthma®/CanoTinA-asthma®) and in (B) patients with severe asthma (VivaTinA-

asthma®/PensieTinA-asthma®) according to baseline serum IgE levels and blood eosinophil counts

*Number of patients above threshold. Full analysis set. OR (solid line) and 95% CIs (dotted line) are presented.

ACQ, Asthma Control Questionnaire (ACQ-IA in children aged 6–11 years); CI, confidence interval; IgE, immunoglobulin E; OR, odds ratio.

Figure E3. Risk of exacerbation in (A) patients with moderate asthma (RubaTinA-

asthma®/CanoTinA-asthma®) and in (B) patients with severe asthma (VivaTinA-

asthma®/PensieTinA-asthma®) according to baseline serum IgE levels and blood eosinophil counts

*Number of patients above threshold. Full analysis set. HRs (solid line) and 95% CIs (dotted line) are presented.

CI, confidence interval; IgE, immunoglobulin E; HR, hazard ratio.