



Published in final edited form as:

*Lancet*. 2011 February 19; 377(9766): 650–657. doi:10.1016/S0140-6736(10)62145-9.

## Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial

Fernando D Martinez, Vernon M Chinchilli, Wayne J Morgan, Susan J Boehmer, Robert F Lemanske Jr, David T Mauger, Robert C Strunk, Stanley J Szeffler, Robert S Zeiger, Leonard B Bacharier, Elizabeth Bade, Ronina A Covar, Noah J Friedman, Theresa W Guilbert, Hengameh Heidarian-Raissy, H William Kelly, Jonathan Malka-Rais, Michael H Mellon, Christine A Sorkness, and Lynn Taussig

Arizona Respiratory Center, College of Medicine, University of Arizona, Tucson, AZ, USA (Prof F D Martinez MD, Prof W J Morgan MD); Department of Public Health Sciences, Penn State Hershey College of Medicine, Hershey, PA, USA (Prof V M Chinchilli PhD, S J Boehmer MA, Prof D T Mauger PhD); University of Wisconsin School of Medicine and Public Health, Madison, WI, USA (Prof R F Lemanske Jr MD, T W Guilbert MD, Prof C A Sorkness PharmD); Department of Pediatrics, Washington University School of Medicine, St Louis, MO, USA (Prof R C Strunk MD, L B Bacharier MD); National Jewish Health, Denver, CO, USA (Prof S J Szeffler MD, R A Covar MD, J Malka-Rais MD); Department of Allergy, Kaiser Permanente and University of California, San Diego, La Jolla, San Diego, CA, USA (Prof R S Zeiger MD, N J Friedman MD, M H Mellon MD); University of Wisconsin, Aurora UW Medical Group, Milwaukee, WI, USA (E Bade MD); Pediatrics Pulmonary, University of New Mexico, Albuquerque, NM, USA (H Heidarian-Raissy PharmD, Prof H W Kelly PharmD); and Denver University, Denver, CO, USA (Prof L Taussig MD)

### Summary

**Background**—Daily inhaled corticosteroids are an effective treatment for mild persistent asthma, but some children have exacerbations even with good day-to-day control, and many discontinue treatment after becoming asymptomatic. We assessed the effectiveness of an inhaled corticosteroid (beclomethasone dipropionate) used as rescue treatment.

**Methods**—In this 44-week, randomised, double-blind, placebo-controlled trial we enrolled children and adolescents with mild persistent asthma aged 5–18 years from five clinical centres in the USA. A computer-generated randomisation sequence, stratified by clinical centre and age group, was used to randomly assign participants to one of four treatment groups: twice daily beclomethasone with beclomethasone plus albuterol as rescue (combined group); twice daily beclomethasone with placebo plus albuterol as rescue (daily beclomethasone group); twice daily

---

Correspondence to: Prof Fernando D Martinez, 1501 N Campbell, Room 2349, The University of Arizona, Tucson, AZ 85724, USA, fernando@arc.arizona.edu.

#### Contributors

All authors contributed to the design and running of the study. VMC and SJB did all data analyses. FDM, VCM, RFL, RCS, SJS, RSC, and LT wrote the draft of this paper. All authors have seen and approved the final version.

#### Conflicts of interest

All other authors declare that they have no conflicts of interest.

placebo with beclomethasone plus albuterol as rescue (rescue beclomethasone group); and twice daily placebo with placebo plus albuterol as rescue (placebo group). Twice daily beclomethasone treatment was one puff of beclomethasone (40 µg per puff) or placebo given in the morning and evening. Rescue beclomethasone treatment was two puffs of beclomethasone or placebo for each two puffs of albuterol (180 µg) needed for symptom relief. The primary outcome was time to first exacerbation that required oral corticosteroids. A secondary outcome measured linear growth. Analysis was by intention to treat. This study is registered with [clinicaltrials.gov](https://clinicaltrials.gov), number NCT00394329.

**Results**—843 children and adolescents were enrolled into this trial, of whom 288 were assigned to one of four treatment groups; combined (n=71), daily beclomethasone (n=72), rescue beclomethasone (n=71), and placebo (n=74)—555 individuals were excluded during the run-in, according to predefined criteria. Compared with the placebo group (49%, 95% CI 37–61), the frequency of exacerbations was lower in the daily (28%, 18–40, p=0.03), combined (31%, 21–43, p=0.07), and rescue (35%, 24–47, p=0.07) groups. Frequency of treatment failure was 23% (95% CI 14–43) in the placebo group, compared with 5.6% (1.6–14) in the combined (p=0.012), 2.8% (0–10) in the daily (p=0.009), and 8.5% (2–15) in the rescue (p=0.024) groups. Compared with the placebo group, linear growth was 1.1 cm (SD 0.3) less in the combined and daily arms (p<0.0001), but not the rescue group (p=0.26). Only two individuals had severe adverse events; one in the daily beclomethasone group had viral meningitis and one in the combined group had bronchitis.

**Interpretation**—Children with mild persistent asthma should not be treated with rescue albuterol alone and the most effective treatment to prevent exacerbations is daily inhaled corticosteroids. Inhaled corticosteroids as rescue medication with albuterol might be an effective step-down strategy for children with well controlled, mild asthma because it is more effective at reducing exacerbations than is use of rescue albuterol alone. Use of daily inhaled corticosteroid treatment and related side-effects such as growth impairment can therefore be avoided.

**Funding**—National Heart, Lung and Blood Institute.

## Introduction

In children with mild persistent asthma, guidelines recommend the daily use of inhaled corticosteroids in low doses as the preferred treatment for the control of symptoms and asthma exacerbations.<sup>1,2</sup> Often, parents or children have great difficulty adhering to twice daily treatment during long asymptomatic periods, and either use inhaled corticosteroids sparingly or interrupt treatment altogether.<sup>3</sup> Moreover, for children whose illness is well controlled with such treatment, no studies have established the optimum period for which treatment should be maintained, or at which point an individual should be weaned from treatment. Guidelines<sup>1</sup> suggest weaning or withdrawal (step-down) of treatment after asthma control is achieved and maintained, without any clear evidence to support these recommendations.

Even when good day-to-day control is achieved with inhaled corticosteroids, children with mild persistent asthma can have a high frequency of exacerbations.<sup>4,5</sup> Thus, two essential and related challenges exist in the treatment of childhood asthma. First, what is the best strategy for discontinuing treatment in children with well controlled, mild asthma, but who

are still at risk for exacerbations. Second, is there a treatment regimen that will decrease the risk of exacerbations in children with mild disease to a greater extent than is achieved with daily inhaled corticosteroids? Does this regimen need to be added to continued treatment with daily inhaled corticosteroids or can it be given on an as-needed basis?

Use of inhaled corticosteroids as rescue medication in combination with a bronchodilator can substantially decrease the frequency of asthma exacerbations that require prednisone.<sup>6-9</sup> Use of budesonide plus formoterol as rescue, when added to daily treatment with either budesonide or budesonide plus formoterol, substantially reduces the frequency of asthma exacerbations in both children and adults.<sup>6-8</sup> In adults with mild asthma who took placebo twice daily, the use of beclomethasone plus albuterol as rescue was associated with substantially fewer exacerbations than was treatment with rescue albuterol alone, and with a similar frequency of exacerbations as with beclomethasone twice daily.<sup>9</sup> These results suggest that inhaled corticosteroids used together with a bronchodilator as rescue could provide additional protection against exacerbations in children who are taking daily inhaled corticosteroids, and might also decrease the frequency of exacerbations in those who are not.

The goals of this TREXA study were to establish whether discontinuation of daily inhaled corticosteroids in children with well controlled, mild persistent asthma is associated with an increased risk of exacerbations, and whether or not the use of beclomethasone plus albuterol for relief, with or without concomitant use of daily beclomethasone, provides better protection against exacerbations than does a rescue strategy that uses albuterol alone.

## Methods

### Participants

Between January, 2007, and May, 2009, we recruited children and adolescents aged between 6 and 18 years from five clinical centres in the USA: Denver, CO; Madison, WI; Saint Louis, MO; San Diego, CA; and Tucson, AZ (satellite centres in Milwaukee, WI, and Albuquerque, NM, also recruited participants). All individuals recruited had a history of mild persistent asthma during the previous 2 years, and qualified for interruption or discontinuation of controller treatment because their illness was well controlled (as defined in US National Asthma Education and Prevention Program asthma care guidelines<sup>10</sup>). Participants were defined as having mild persistent asthma if they had, on average, more than 2 days per week with symptoms (eg, wheezing), more than 2 days a week on which they had to use albuterol to control symptoms, or more than two awakenings at night per month when not using controller medication, or if they had to use daily controller treatment to keep their disorder well controlled.<sup>1</sup>

Participants were eligible for inclusion if they were naive to controller treatment and had a history of one to two exacerbations in the previous year, if they were treated for the previous 8 weeks with a monotherapy other than inhaled corticosteroids, or if their illness was controlled for the previous 8 weeks on low-dose corticosteroids as monotherapy (  $160\text{ }\mu\text{g}$  daily with a beclomethasone equivalent). Participants were excluded from the study if they had a prebronchodilator forced expiratory volume in 1 s (FEV<sub>1</sub>) of less than 60% predicted at the first visit; were admitted to hospital for asthma in the previous year; had any asthma

exacerbation in the previous 3 months or more than two in the previous year; had a history of life-threatening asthma exacerbations that required intubation or mechanical ventilation, or that resulted in a hypoxic seizure (see webappendix p 1 for further details about eligibility criteria).

TREXA was approved by local Institutional Review Boards. Parents or guardians provided written informed consent and children provided verbal or written assent.

## Procedures

TREXA was a 44-week randomised, double-blind, four-treatment trial with a two by two factorial design. Participants entered a 4-week run-in period (described in detail in the webappendix p 1), during which they received twice daily treatment with one puff of beclomethasone dipropionate (hereafter called beclomethasone; 40 µg per puff) and rescue treatment with a placebo inhaler added to rescue albuterol every time they needed albuterol. Participants were included in the 44-week treatment phase only if their disease remained well controlled and they did not have any exacerbations during the run-in period.

After the run-in period, eligible participants were randomly assigned to one of four treatment groups: twice daily beclomethasone with beclomethasone plus albuterol as rescue (combined group); twice daily beclomethasone with placebo plus albuterol as rescue (daily beclomethasone group); twice daily placebo with beclomethasone plus albuterol as rescue (rescue beclomethasone group); and twice daily placebo with placebo plus albuterol as rescue (placebo group). Twice daily beclomethasone treatment was one puff of beclomethasone (hydrofluoroalkane formulation; 40 µg per puff) or placebo given in the morning and evening. Rescue beclomethasone treatment was two puffs of beclomethasone (hydrofluoroalkane formulation) or placebo for each two puffs of albuterol (180 µg) needed for symptom relief. Details about study treatment regimens and follow-up during the trial are provided in the webappendix (pp 1–2).

The primary outcome measure was the time to first exacerbation that required treatment with prednisone. Exacerbations were defined as the use of more than 12 puffs of albuterol in 24 h (excluding preventive use before exercise), a peak expiratory flow of less than 70% of reference value before each albuterol use, symptoms that led to inability to sleep or do daily activities for 2 or more consecutive days, a peak expiratory flow of less than 50% of reference value despite relief treatment, or an emergency room visit because of worsening of asthma symptoms. Excessive inhaled corticosteroid use because of controller plus rescue corticosteroids or rescue corticosteroid use alone was also defined before the trial started (webappendix p 3) and prompted a prednisone course, which counted as an exacerbation.

Details about the criteria for treatment failure are provided in the webappendix p 3. Secondary outcomes included spirometry FEV<sub>1</sub>, fractional exhaled nitric oxide (FENO), symptom diaries and control and quality of life questionnaires, and linear growth.

---

See [Online](#) for webappendix

## Randomisation and Masking

The Data Coordinating Center (DCC; Penn State Hershey College, PA, USA) generated the random allocation sequence. The DCC had no interaction with participants, but was responsible for management of data and statistical analyses. The randomisation sequence was stratified according to clinical centre and age group (6–11 years and 12–18 years), in blocks of four. A pharmaceutical vendor was selected to package, code, and ship the drug packets to each clinical centre. When a clinical centre deemed that a participant was eligible for randomisation, the clinical centre coordinator logged onto the secure CARE Network website, entered the relevant information to confirm participant eligibility, and received the appropriate drug packet code to be assigned to the participant. Drug groups were labelled as A, B, C, and D to mask statisticians to treatment group during the first complete run-through of data analyses.

## Statistical analysis

The target sample size of the TREXA study was 280 randomised participants (70 per treatment group), which provides 90% statistical power for a two-sided, 0.05 significance level test, allowing for 10% withdrawals, to detect a hazard ratio of 0.5 in the time to first exacerbation for each main effect in the two by two factorial design. In this design, the daily beclomethasone main effect was the effect of the combined group plus the daily beclomethasone group versus the rescue beclomethasone group plus the placebo group; the rescue beclomethasone main effect was the effect of the combined group plus the rescue beclomethasone group versus the daily beclomethasone group plus the placebo group. Kaplan-Meier curves were constructed for graphical displays of the time-to-event outcomes, and proportional hazards regression analyses were applied to test main effects. For factorial designs, main effect analyses underestimate the effects of individual drugs if subadditive interactions occur.<sup>11,12</sup> When subadditive interactions do occur, the recommended analysis is pairwise treatment effect comparisons of each drug group against the control group.<sup>11,13</sup> In our trial, there was an expected, clear evidence of a subadditive interaction between daily beclomethasone and rescue beclomethasone.<sup>11</sup> Therefore, we focused on the individual treatment effect comparisons, with Hochberg adjustment for multiple comparisons<sup>14</sup> (webappendix p 3), rather than the factorial design main effects on which the study was powered.

For secondary outcomes measured on a continuous scale, or constructed as between-visit averages from the diary cards, a linear mixed-effects model was applied. Poisson regression was used to assess differential risk between groups for exacerbation rates. All the statistical analyses included the stratification variables of clinical centre and age group as covariates. In January, 2008, the data and safety monitoring board approved changes in the TREXA eligibility criteria, by which neither FEV<sub>1</sub> reversibility of 12% or more or a participant's methacholine PC<sub>20</sub> of 12.5 mg/mL or less were needed for randomisation. This was justified by the fact that many screened children who fulfilled all other entry criteria (including mild persistent asthma and controlled symptoms) tested negative for both. An indicator variable of which eligibility criterion the participant satisfied was also included as a covariate in all statistical analyses. All analyses were by intention to treat. SAS version 9.2 was used for all

statistical analyses and to generate the randomisation sequence. This study is registered with [clinicaltrials.gov](https://clinicaltrials.gov), number NCT00394329.

### Role of the funding source

The study was funded by grants from the National Heart, Lung and Blood Institute, which also established and managed the independent data and safety monitoring board; TEVA Pharmaceutical Industries Ltd (Horsham, PA, USA) provided beclomethasone dipropionate-HFA and placebo. The corresponding author had full responsibility for the study design, data collection, statistical analysis, and interpretation of data, and for the writing of the report. The authors had complete independence over the conduct, integrity, and publication of the study.

### Results

843 children were enrolled into the trial, of whom 288 (34%) were assigned to one of the four treatment groups (figure 1). Sociodemographic and clinical characteristics were much the same between participants who were randomised and those who were enrolled but were not eligible for the treatment phase (n=555; webappendix p 4). Baseline characteristics were much the same between individuals in the four treatment groups (table 1).

Figure 2 shows the Kaplan-Meier plots for time to first exacerbation that required a prednisone course for each of the four treatment groups. Because of the subadditive interaction between daily beclomethasone and rescue beclomethasone, the effects of both treatments were underestimated by the factorial main effects analyses (table 2). Thus, analyses were focused on the effect of individual treatment groups compared with the placebo group, with Hochberg adjustment for multiple comparisons. Compared with the placebo group, the hazard ratios for asthma exacerbations were significantly lower in the daily beclomethasone group and the combined group, but the difference was not significant in the rescue beclomethasone group (table 2). The probability of a first exacerbation by the end of the trial were 31% (95% CI 21–43, n=22) in the combined group, 28% (18–40, n=20) in the daily beclomethasone group, 35% (24–47, n=25) in the rescue beclomethasone group, and 49% (37–61, n=36) in the placebo group (data not shown).

During the course of the trial there were 29 treatment failures, 17 (60%) of which occurred in the placebo group (figure 3). The frequency of treatment failures in the placebo group was 23% (95% CI 14–34, n=17), which was greater than it was in the other three treatment groups: 5.6% (1.6–14, n=4) in the combined group (p=0.012), 2.8% (0–10, n=2) in the daily beclomethasone group (p=0.009), and 8.5% (2–15, n=6) in the rescue beclomethasone group (p=0.024). The only criterion met by participants for treatment failure was the requirement for a second dose of prednisone within any 6-month period.

Individuals in the combined and daily beclomethasone groups used roughly 2.0–2.2 puffs per day during the trial, whereas individuals in the rescue beclomethasone group used an average of only 0.3–0.5 puffs per day (webappendix p 5). Albuterol use increased in all participants during the course of the trial, but there was no difference in increase between treatment groups (webappendix p 6).



The proportion of asthma control days was high (80–90%) during the trial and did not differ significantly between treatment groups (webappendix p 7). Use of rescue beclomethasone was not associated with changes in proportion of asthma control days (webappendix p 7), asthma control tests, impulse oscillometry, quality of life indices, and frequency of albuterol use (webappendix p 6). Prebronchodilator percentage predicted FEV<sub>1</sub> decreased in all treatment groups during the trial (webappendix p 8). Although the reduction was only significant in the placebo group (–6.6%, SD 1.7,  $p=0.0001$ ) and the rescue beclomethasone group (–4.1%, 1.8,  $p=0.024$ ), whereas differences between individual treatment groups were not significant (data not shown).

We recorded no difference in FENO between study groups at the randomisation visit (week 4; webappendix p 9). However, we noted increases in FENO, beginning at week 8, in individuals in the rescue beclomethasone and placebo groups; individuals in the combined and daily beclomethasone groups had low FENO during the trial ( $p<0.0001$ ) compared with the combined and daily beclomethasone groups). No differences were recorded in methacholine bronchial responsiveness between treatment groups at week 24 of the trial (data not shown). We noted no difference in either peak flow variability or measures of quality of life (webappendix pp 10–11) between treatment groups.

Compared with individuals in treatment groups that did not use daily beclomethasone (placebo and rescue beclomethasone), we noted less linear growth in the treatment groups that used daily beclomethasone (daily beclomethasone and combined; figure 4). During the course of the trial, children in the combined and daily beclomethasone groups grew 1.1 cm (SD 0.3) less than did children in the placebo group ( $p<0.0001$  for both comparisons; data not shown). We noted no significant growth effect in children in the rescue beclomethasone group (0.3 cm [SD 0.2] less than the placebo group,  $p=0.26$ ). No significant differences in weight gain were recorded between groups (data not shown).

Only two individuals had severe adverse events; one in the daily beclomethasone group had viral meningitis and one in the combined group had bronchitis.

## Discussion

In this trial, we noted that, compared with treatment with only albuterol as rescue, daily beclomethasone reduced the risk for a first exacerbation by half, whereas rescue beclomethasone decreased the risk by more than a third, but this effect was not significant. Treatment failures were also substantially decreased in both groups that used daily beclomethasone and in the rescue beclomethasone group. Our results therefore suggest that rescue beclomethasone can lower the risk of exacerbations and treatment failures, but to a lesser degree than does daily beclomethasone.

Treatment failure occurred in nearly a quarter of participants in the placebo group who received rescue albuterol as their only active treatment. This finding emphasises the fact that discontinuation of inhaled corticosteroid use in children with well controlled, mild persistent asthma substantially increases the risk of asthma exacerbations. However, continuation of maintenance inhaled corticosteroids in such children is often resisted and seldom followed

by the affected children or by their parents.<sup>3</sup> Moreover, several studies<sup>5,15–17</sup> of long-term inhaled corticosteroid use have shown that individuals who received such daily treatment, even in low doses, had less linear growth than did individuals who received placebo treatment. Such drawbacks of corticosteroid treatment necessitate the search for alternative treatments for mild persistent asthma. As far as we are aware, no other trial has examined the use of inhaled corticosteroids as rescue with albuterol in school children, an age at which exacerbations play a major part in asthma morbidity.<sup>18</sup> Several studies<sup>19–23</sup> have assessed the use of inhaled corticosteroids at high doses and for fixed periods during asthma exacerbations, with mixed and inconclusive results. These studies differ from ours in that the high dose of inhaled corticosteroids were given when signs and symptoms of an asthma exacerbation were already evident, not whenever albuterol was needed, as in our study.

Our study was designed to assess whether inhaled beclomethasone plus albuterol combination could be used as rescue to reduce the frequency of exacerbations irrespective of concomitant use of daily beclomethasone. Our assumption was that the risk of exacerbations would be reduced by half in the daily beclomethasone and rescue beclomethasone groups, and reduced additively by 75% in the combined group. Our results did not confirm our assumption; we noted a clinically significant subadditive interaction between treatments, with the combined group showing no further lessening in frequency of exacerbations compared with the daily beclomethasone and rescue beclomethasone groups. The frequency of exacerbations in all three groups that received inhaled corticosteroid (ie, combined, daily beclomethasone, and rescue beclomethasone) was lower than it was in the placebo group, and at frequencies that were much the same as has been previously reported with use of twice daily corticosteroid.<sup>4,5</sup> The studies<sup>6,7,8</sup> on which we based our assumptions showed an additive effect when an inhaled corticosteroid was used together with a bronchodilator in addition to daily inhaled corticosteroid use. Such an additive effect was not recorded in this trial, perhaps because of the different intrinsic properties of short-acting and long-acting bronchodilators or differences in asthma severity between study populations. Alternatively, corticosteroids as rescue treatment might have only a small effect on reduction of exacerbations when individuals also receive daily low-dose corticosteroid treatment.

In view of the unanticipated subadditive interaction between treatments, a major deviation from the planned analysis was necessary. Instead of a two by two factorial analysis, we compared the effects recorded in the individual active treatment groups with the effects recorded in the placebo group. Because our study was powered on the basis of a factorial design, such change in analysis decreased the study's power substantially. Moreover, the recorded effects of the two groups in which rescue beclomethasone was used were less than those assumed when the study was planned, which further decreased the study's power.

The substantial reduction in lung function that occurred during the trial in the rescue beclomethasone group is concerning, but reductions (albeit less pronounced) were also recorded in the two groups in which beclomethasone was used daily, and as a consequence, declines in FEV<sub>1</sub> did not differ between treatment groups. Such reduction in lung function in all groups might be explained by regression towards the mean, because to be eligible for the treatment phase children had to have normal lung function during the run-in period. An increase in FENO was shown in both the rescue beclomethasone group and the placebo



group. In other studies,<sup>24,25</sup> a rise in FENO after discontinuation of inhaled corticosteroid treatment has been associated with loss of asthma control and an increase in the frequency of exacerbations, but no evidence of such an effect was noted in this trial.

Children in the rescue beclomethasone group received 15–25% of the daily inhaled corticosteroid dose that children in the combined and daily beclomethasone groups received. No significant growth effect was recorded in the rescue beclomethasone group compared with the placebo group, but a significant effect was seen in both groups that used daily beclomethasone, which accords with several other studies<sup>5,10,15,16</sup> that recorded restricted linear growth with use of daily inhaled corticosteroid. The beclomethasone hydrofluoroalkane formulation therefore seemingly causes a similar adverse growth effect as previously recorded with the chlorofluoro carbon formulation.<sup>26</sup>

Assessed from a risk-benefit point of view, our data suggest that, in children with mild persistent asthma, use of rescue inhaled corticosteroid could be an effective step-down alternative to discontinuation of such treatment after asthma control is achieved. We speculate that rescue inhaled corticosteroids could also be an alternative, step 2 therapeutic approach for mild persistent asthma even in individuals who have not previously received a course of daily corticosteroid treatment, but our study was not designed to specifically address this issue.

Children with mild persistent asthma should not be treated with rescue albuterol alone and the most effective treatment to prevent exacerbations in this age group is daily inhaled corticosteroids. Our data suggest that inhaled corticosteroids used as rescue together with albuterol show benefits over rescue albuterol alone and avoids the growth effects associated with use of daily inhaled corticosteroids.

## Acknowledgments

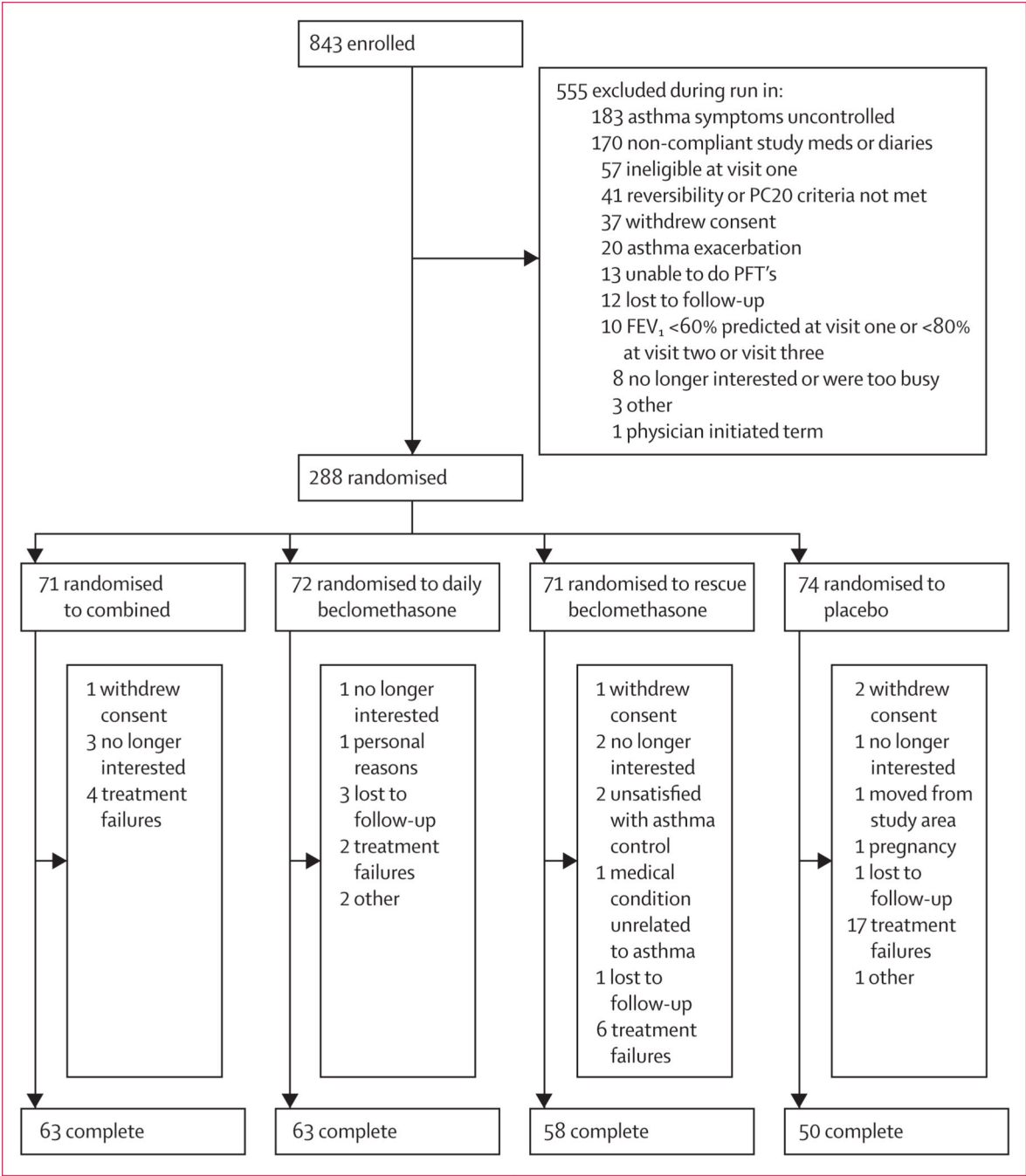
FDM is a board member at MedImmune and Merck, has received consulting fees from GlaxoSmithKline, and MedImmune, honoraria from Merck, and pending grant support from AstraZeneca. WJM has received consulting fees from Genentech, Novartis, and Cystic Fibrosis Foundation, honoraria from Vertex Pharmaceuticals and Phadia AB, and pending grant support from Novartis. RFL has received consulting fees from MAP Pharmaceuticals, Gray Consulting, Smith Research, Merck Childhood Asthma Network, Novartis, Quintiles/Innovax, RC Horowitz and Co, AstraZeneca, and Scienomics Group, and has pending grant support from Pharmaxis. RFL has also received honoraria from Merck; AstraZeneca; Doernbecher Children's Hospital; Washington University; Medicus Group; Park Nicolet Institute; American College of Allergy, Asthma and Immunology; LA Allergy Society; Michigan Allergy/Asthma Society; Medical College of Wisconsin; Toronto Allergy Society; Fund for Medical Research and Education (Detroit); Children's Hospital of Minnesota; Detroit Beaumont Hospital; University of Illinois; Canadian Society of Allergy and Clinical Immunology; New York Presbyterian Hospital; SRA; and Western Society of Allergy, Asthma and Immunology. DTM has received consulting fees from Biocryst, Watermark, and Parexel, and honoraria from Roche. SJS has received consulting fees from Merck, Genentech, Schering, Boehringer-Ingelheim, and Novartis; honoraria from Merck; and research grants from GlaxoSmithKline and Ross (Division of Abbott). RSZ has received consulting fees from Aerocrine AB, AstraZeneca, Genentech, GlaxoSmithKline, Merck, and Schering Plough, and has a pending grant support from Genentech, GlaxoSmithKline, and Merck. LBB has received consulting fees from Aerocrine, GlaxoSmithKline, Genentech, Novartis, Merck, and Schering Plough, and honoraria from Aerocrine, AstraZeneca, Genentech, GlaxoSmithKline, Merck, Novartis, and Schering Plough. TWG has received consulting fees from GlaxoSmithKline, AstraZeneca, Genentech/Novartis, Merck/Schering Plough, and MAP Pharmaceuticals; honoraria from GlaxoSmithKline, AstraZeneca, Merck, Peerpoint Medical Education Institute, Antidote CME programs, Schering-Plough, Novartis, and American Academy of Allergy, Asthma, and Immunology; and pending grant support from Altus Pharmaceuticals and Inspire Pharmaceuticals. HWK has received consulting fees from AstraZeneca, GlaxoSmithKline, MAP, Merck, and Novartis, and honoraria from AstraZeneca. MHM has received consulting fees from AstraZeneca, and honoraria

from AstraZeneca and Schering Plough. CAS has received consulting fees from GlaxoSmithKline, Schering Plough, and AstraZeneca, and has pending grant support from Schering Plough, Pharmaxis, and Sandoz.

## References

1. National Asthma Education Prevention Program Coordinating Committee Expert Panel. [accessed 17 Jan, 2011] Guidelines for the diagnosis and management of asthma. 2007. <http://www.nhlbi.nih.gov/guidelines/asthma/>
2. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. 2009 <http://www.ginasthma.com/Guidelineitem.aspx?l1=2&l2=1&intId=1561>.
3. Burgess SW, Sly PD, Morawska A, Devadason SG. Assessing adherence and factors associated with adherence in young children with asthma. *Respirology*. 2008; 13:559–563. [PubMed: 18422868]
4. Sorkness CA, Lemanske RF Jr, Mauger DT, et al. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial. *J Allergy Clin Immunol*. 2007; 119:64–72. [PubMed: 17140647]
5. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med*. 2000; 343:1054–1063. [PubMed: 11027739]
6. O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med*. 2005; 171:129–136. [PubMed: 15502112]
7. Rabe KF, Pizzichini E, Stallberg B, et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. *Chest*. 2006; 129:246–256. [PubMed: 16478838]
8. Bisgaard H, Le Roux P, Bjamer D, Dymek A, Vermeulen JH, Hultquist C. Budesonide/formoterol maintenance plus reliever therapy: a new strategy in pediatric asthma. *Chest*. 2006; 130:1733–1743. [PubMed: 17166990]
9. Papi A, Canonica GW, Maestrelli P, et al. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. *N Engl J Med*. 2007; 356:2040–2052. [PubMed: 17507703]
10. National Asthma Education Prevention Program Coordinating Committee. Guidelines for the diagnosis and management of asthma. National Institutes of Health; 1997. Expert Panel II.
11. McAlister FA, Straus SE, Sackett DL, Altman DG. Analysis and reporting of factorial trials: a systematic review. *JAMA*. 2003; 289:2545–2553. [PubMed: 12759326]
12. Lubsen J, Pocock SJ. Factorial trials in cardiology: pros and cons. *Eur Heart J*. 1994; 15:585–588. [PubMed: 8055995]
13. Plint AC, Johnson DW, Patel H, et al. Epinephrine and dexamethasone in children with bronchiolitis. *N Engl J Med*. 2009; 360:2079–2089. [PubMed: 19439742]
14. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika*. 1988; 75:800–802.
15. Verberne AA, Frost C, Duiverman EJ, Grol MH, Kerrebijn KF. Addition of salmeterol versus doubling the dose of beclomethasone in children with asthma—The Dutch Asthma Study Group. *Am J Respir Crit Care Med*. 1998; 158:213–219. [PubMed: 9655732]
16. Simons FE. A comparison of beclomethasone, meterol, and placebo in children with asthma. Canadian Beclomethasone Dipropionate-Salmeterol Xinafoate Study Group. *N Engl J Med*. 1997; 337:1659–1665. [PubMed: 9385125]
17. Guilbert TW, Morgan WJ, Zeiger RS, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med*. 2006; 354:1985–1997. [PubMed: 16687711]
18. Martinez FD. Managing childhood asthma: challenge of preventing exacerbations. *Pediatrics*. 2009; 123(suppl 3):S146–S150. [PubMed: 19221157]
19. Turpeinen M, Nikander K, Pelkonen AS, et al. Daily versus as-needed inhaled corticosteroid for mild persistent asthma (The Helsinki early intervention childhood asthma study). *Arch Dis Child*. 2008; 93:654–659. [PubMed: 17634183]
20. Ducharme FM, Lemire C, Noya FJ, et al. Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. *N Engl J Med*. 2009; 360:339–353. [PubMed: 19164187]

21. FitzGerald JM, Becker A, Sears MR, Mink S, Chung K, Lee J. Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. *Thorax*. 2004; 59:550–556. [PubMed: 15223858]
22. Bacharier LB, Phillips BR, Zeiger RS, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol*. 2008; 122:1127–1135. [PubMed: 18973936]
23. Boushey HA, Sorkness CA, King TS, et al. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med*. 2005; 352:1519–1528. [PubMed: 15829533]
24. Jones SL, Kittelson J, Cowan JO, et al. The predictive value of exhaled nitric oxide measurements in assessing changes in asthma control. *Am J Respir Crit Care Med*. 2001; 164:738–743. [PubMed: 11549525]
25. Pijnenburg MW, Hofhuis W, Hop WC, De Jongste JC. Exhaled nitric oxide predicts asthma relapse in children with clinical asthma remission. *Thorax*. 2005; 60:215–218. [PubMed: 15741438]
26. Pedersen S, Warner J, Wahn U, et al. Growth, systemic safety, and efficacy during 1 year of asthma treatment with different beclomethasone dipropionate formulations: an open-label, randomized comparison of extrafine and conventional aerosols in children. *Pediatrics*. 2002; 109:e92. [PubMed: 12042586]



**Figure 1. Trial profile**  
PC<sub>20</sub>=provocation concentration of inhaled methacholine needed to reduce FEV<sub>1</sub> by 20%.  
FEV<sub>1</sub>=forced expiratory volume in 1 s.

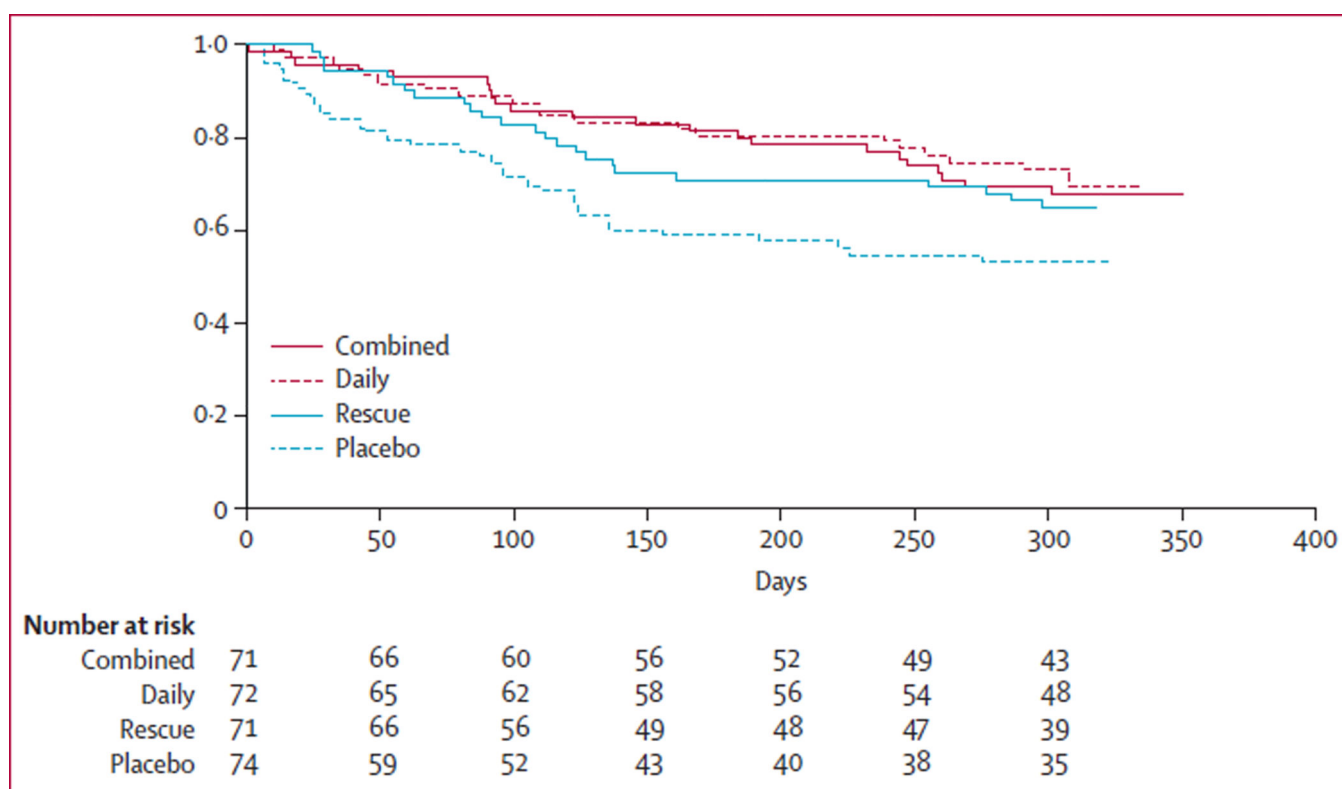
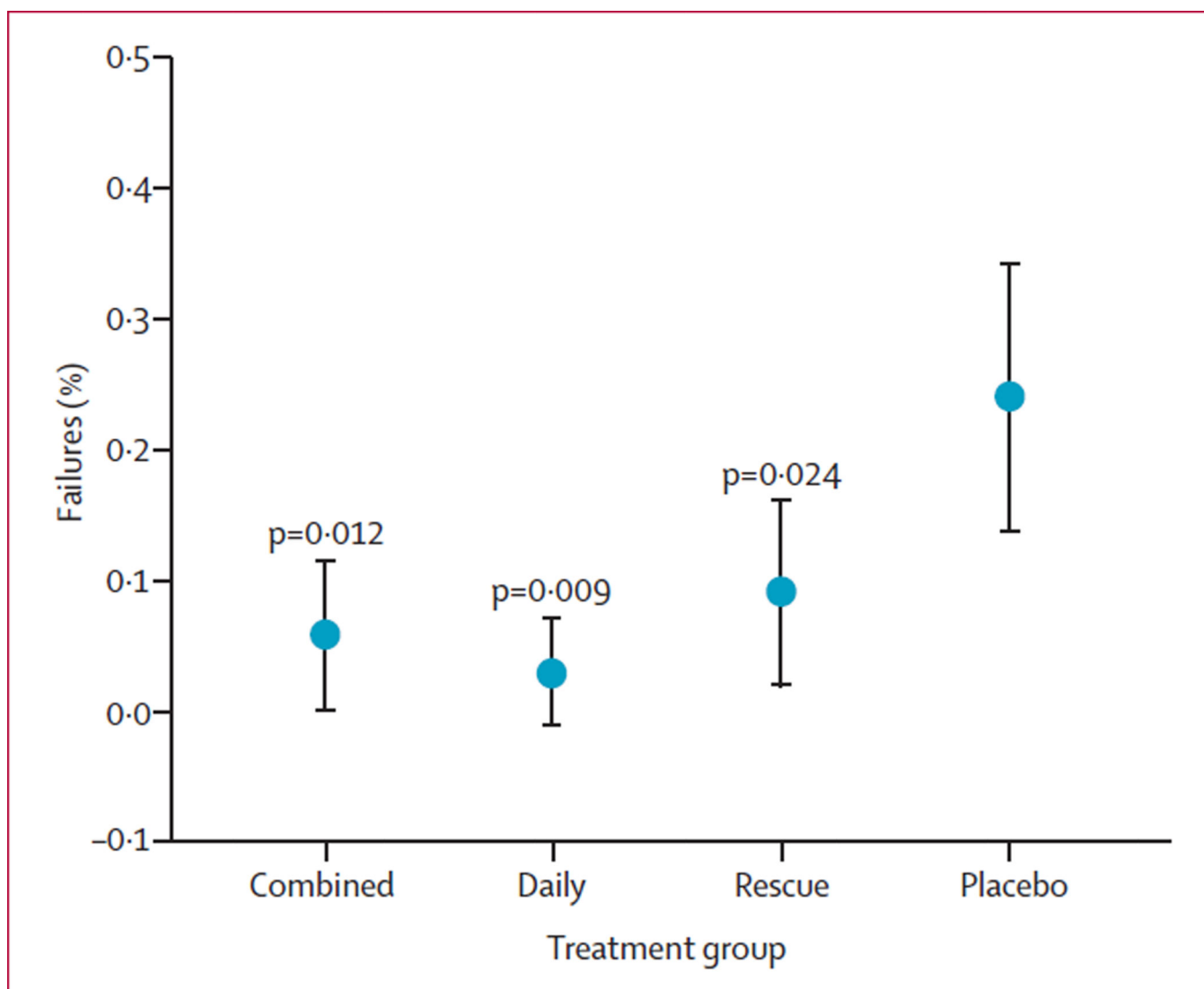


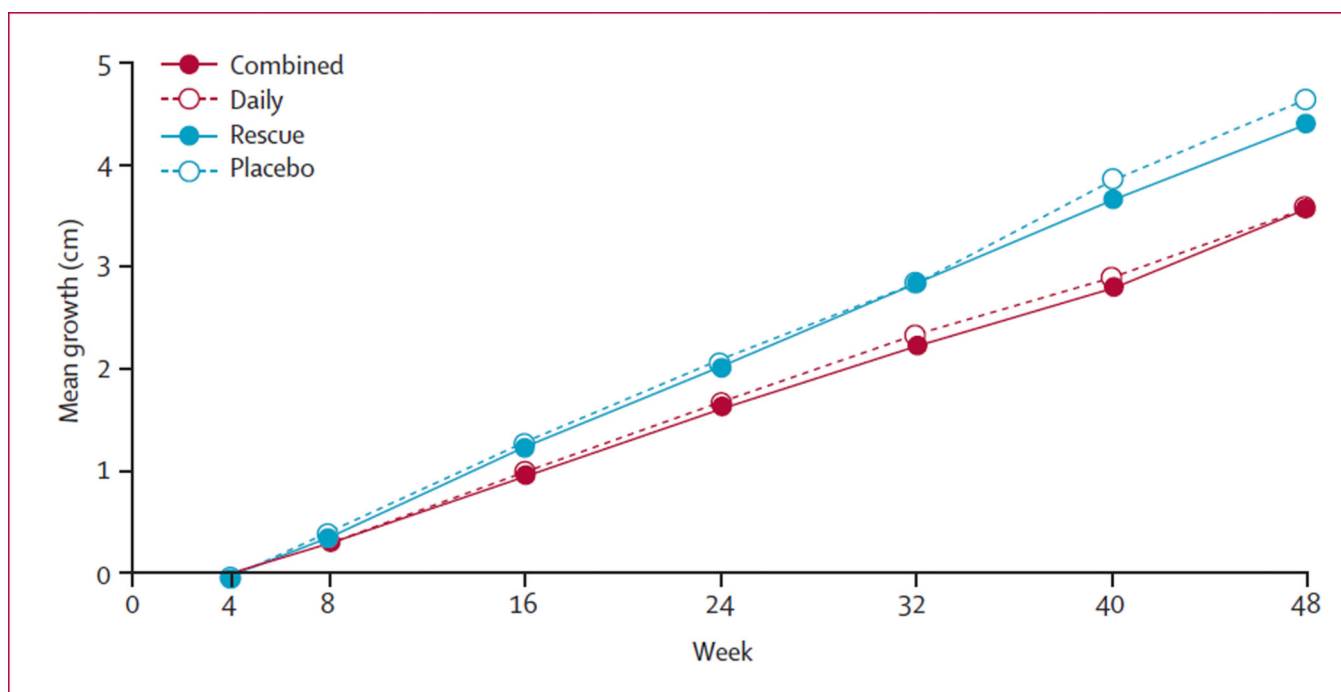
Figure 2. Kaplan-Meier curves showing the time to first exacerbation



**Figure 3. Treatment failures**

Vertical bars are 95% CIs. p values are based on the estimated relative risks from the proportional hazards regression analysis that compared each treatment group with the placebo group.





**Figure 4. Linear growth by treatment group**  
Randomisation took place at week 4.

**Table 1**

Baseline characteristics by treatment group

|  | Combined (n=71) | Daily (n=72)   | Rescue (n=71)  | Placebo (n=74) |
|--|-----------------|----------------|----------------|----------------|
| Age (years)  | 11.4 (3.1)      | 10.8 (3.5)     | 10.4 (2.8)     | 10.4 (3.2)     |
| Sex (male))  | 39 (55%)        | 42 (58%)       | 37 (52%)       | 41 (55%)       |
| White  | 50 (70%)        | 51 (71%)       | 57 (80%)       | 59 (78%)       |
| Height (cm)  | 146.6 (17.4)    | 141.9 (19.4)   | 143.6 (18.4)   | 140.6 (18.2)   |
| Weight (kg)  | 46.1 (22.9)     | 44.1 (19.9)    | 44.1 (19.1)    | 42.3 (19.2)    |
| Body-mass index (kg/m <sup>2</sup> )                                 | 20.3 (5.8)      | 20.9 (5.6)     | 20.4 (4.7)     | 20.4 (5.1)     |
| Age at asthma diagnosis (years)                                      | 4.5 (3.8)       | 3.7 (2.7)      | 4.1 (2.9)      | 4.1 (3.1)      |
| Age at onset of asthma symptoms (years)                              | 3.7 (3.4)       | 2.7 (2.5)      | 2.9 (2.6)      | 3.1 (2.9)      |
| Father asthma diagnosis  | 20 (28%)        | 15 (21%)       | 12 (16%)       | 16 (22%)       |
| Mother asthma diagnosis  | 16 (23%)        | 20 (28%)       | 21 (30%)       | 23 (31%)       |
| Atopic eczema  | 36 (51%)        | 34 (47%)       | 37 (52%)       | 36 (49%)       |
| Positive aeroallergen skin tests                                     | 2.3 (1.9)       | 2.1 (1.9)      | 2.3 (1.6)      | 2.1 (1.8)      |
| One or more aeroallergen skin test                                   | 57 (80%)        | 52 (74%)       | 57 (85%)       | 54 (73%)       |
| Positive perennial aeroallergen skin tests                           | 1.1 (1.2)       | 1.0 (1.2)      | 1.1 (0.9)      | 1.1 (1.1)      |
| One or more perennial aeroallergen-positive skin test                | 45 (63%)        | 38 (54%)       | 50 (75%)       | 48 (65%)       |
| Serum IgE (IU/mL [95% CI])   | 139.0 (38–334)  | 214.7 (55–528) | 214.7 (70–448) | 186.0 (59–329) |
| Blood eosinophils (%)  | 3.5 (2.3)       | 3.8 (2.9)      | 3.9 (2.5)      | 3.9 (2.7)      |
| Inhaled ICS use in previous year                                     | 54 (76%)        | 59 (82%)       | 51 (72%)       | 57 (77%)       |
| Leukotriene inhibitor or antagonist use in previous year             | 11 (16%)        | 7 (10%)        | 14 (20%)       | 13 (18%)       |
| Salmeterol xinafoate use in previous year                            | 0               | 1 (1%)         | 0              | 0              |
| Theophylline use in previous year                                    | 0               | 0              | 0              | 0              |
| Sodium cromoglicate or nedocromil sodium use in previous year        | 0               | 0              | 1 (1%)         | 0              |
| Fluticasone/salmeterol or budesonide/formoterol use in previous year | 4 (6%)          | 3 (4%)         | 5 (7%)         | 5 (7%)         |
| One or more prednisone course in previous year                       | 19 (27%)        | 19 (26%)       | 24 (34%)       | 21 (28%)       |
| Prebronchodilator FEV <sub>1</sub> (% predicted)                     | 101.5 (11.7)    | 100.1 (10.8)   | 101.4 (12.1)   | 100.4 (11.4)   |
| Prebronchodilator FEV <sub>1</sub> /FVC (%)                          | 81.5 (7.3)      | 83.5 (6.4)     | 82.4 (6.1)     | 82.4 (6.3)     |
| Bronchodilator response four puffs (%)                               | 7.4 (7.0)       | 6.7 (5.7)      | 7.9 (5.8)      | 7.2 (6.5)      |
| Average morning peak flow during run-in                              | 321.0 (113.1)   | 301.8 (125.9)  | 300.4 (94.7)   | 286.9 (100.3)  |
| Asthma-control days during run-in period (%)                         | 94.4 (10.9)     | 89.5 (16.5)    | 90.5 (18.5)    | 93.6 (12.7)    |
| ACT/C-ACT score  | 23.5 (2.7)      | 23.6 (2.5)     | 23.6 (2.3)     | 24.0 (2.2)     |
| Exhaled nitric oxide (parts per billion) [median (Q1, Q3)]           | 12.8 (8, 22)    | 14.2 (7, 21)   | 11.5 (8, 20)   | 11.2 (7, 20)   |
| Methacholine PC20 during run-in period (mg/ml) [median (Q1, Q3)]     | 4.6 (1, 18)     | 3.1 (1, 22)    | 3.6 (1, 10)    | 2.4 (1, 12)    |
| Hospital visit in previous year for asthma                           | 0.3 (0.6)       | 0.3 (0.8)      | 0.2 (0.4)      | 0.2 (0.5)      |

Data are mean (SD) or number (%) unless stated otherwise. Act/c-act=asthma control test/child -asthma control test. FEV<sub>1</sub>=forced expiratory volume in 1 s. FVC=forced vital capacity. ICS=inhaled corticosteroids. PC20=provocation concentration of inhaled methacholine needed to reduce FEV<sub>1</sub> by 20%. Q=quartile.

**Table 2**

## Treatment effects

|   | <b>Hazard ratio*<br/>(95% CI)</b> | <b>Unadjusted<br/>p value</b> | <b>Hochberg adjusted<br/>p value</b> |
|---|-----------------------------------|-------------------------------|--------------------------------------|
| Daily beclomethasone main effect        | 0.66 (0.44–0.99)                  | 0.033                         | ..                                   |
| Rescue beclomethasone main effect       | 0.84 (0.56–1.26)                  | 0.280                         | ..                                   |
| Combined <i>vs</i> placebo              | 0.56 (0.32–0.96)                  | 0.033                         | 0.066                                |
| Daily beclomethasone <i>vs</i> placebo  | 0.49 (0.28–0.85)                  | 0.011                         | 0.033                                |
| Rescue beclomethasone <i>vs</i> placebo | 0.62 (0.37–1.05)                  | 0.073                         | 0.073                                |

\* For pairwise comparisons, the hazard ratio is the group receiving beclomethasone compared with placebo. Hochberg adjusted p values are for comparison with the placebo group.