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Efficacy of Nasal Mometasone for the Treatment of Chronic Sinonasal Disease in Inadequately Controlled Asthma

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Abstract

Background—Chronic sinonasal disease is common in asthma and associated with poor asthma control; however there are no long term trials addressing whether chronic treatment of sinonasal disease improves asthma control.

Objective—To determine if treatment of chronic sinonasal disease with nasal corticosteroids improves asthma control as measured by the Childhood Asthma Control Test (cACT) and Asthma Control Test (ACT) in children and adults respectively.

Methods—A 24 week multi-center randomized placebo controlled double-blinded trial of placebo versus nasal mometasone in adults and children with inadequately controlled asthma. Treatments were randomly assigned with concealment of allocation.

Results—237 adults and 151 children were randomized to nasal mometasone versus placebo, 319 participants completed the study. There was no difference in the cACT (difference in change with mometasone – change with placebo [ΔM - ΔP]: -0.38, CI: -2.19 to 1.44, p = 0.68 ages 6 to 11) or the ACT (ΔM - ΔP: 0.51, CI: -0.46 to 1.48, p = 0.30, ages 12 and older) in those assigned to mometasone versus placebo. In children and adolescents, ages 6 to 17, there was no difference in asthma or sinus symptoms, but a decrease in episodes of poorly controlled asthma defined by a drop in peak flow. In adults there was a small difference in asthma symptoms measured by the

Asthma Symptom Utility Index (ΔM - ΔP: 0.06, CI: 0.01 to 0.11, p <0.01) and in nasal symptoms (sinus symptom score ΔM - ΔP: -3.82, CI: -7.19 to- 0.45, p =0.03), but no difference in asthma quality of life, lung function or episodes of poorly controlled asthma in adults assigned to mometasone versus placebo.

Conclusions—Treatment of chronic sinonasal disease with nasal corticosteroids for 24 weeks does not improve asthma control. Treatment of sinonasal disease in asthma should be determined by the need to treat sinonasal disease rather than to improve asthma control.

Keywords

Asthma; rhinitis; sinusitis; sinonasal; asthma control; lung function; asthma exacerbation

Introduction

Poor asthma control is a significant cause of morbidity. One important factor thought to affect asthma control is disease of the upper airway, rhinitis and sinusitis. [1-5] Therefore, chronic sinonasal disease is often treated in patients with asthma in an effort to improve asthma control. However, while acute and severe sinonasal disease clearly warrant treatment directed towards disease in the upper airway, it is not clear if treating chronic sinonasal disease improves asthma control.

Rhinitis, sinusitis and asthma are closely linked. At least 70% of asthmatics have rhinitis,[6,7] and 30 – 40 % report sinusitis.[6] A number of mechanisms link sinonasal disease and asthma, which may represent a common immune disorder affecting the whole respiratory system. Allergen challenge in one region produces inflammation in the other,[8,9] post-nasal drip of inflammatory mediators may occur,[10] and a nasobronchial reflex may produce bronchoconstriction.[11] Chronic sinonasal disease is very common in asthma, and may be part of a common disease process.

Despite sinonasal disease and asthma being closely related disease processes, it is not clear whether treatment of sinonasal disease affects the course of asthma. Treatment of severe and acute sinonasal disease is clearly warranted and may improve asthma control,[12,13] but most studies have been observational as such sinonasal disease requires treatment regardless of the effect on asthma. [12] Some small studies suggest that treatment of acute rhinitis improves airway reactivity[14,15] whereas others do not,[16,17] and some observational studies report that long term treatment for sinonasal disease improves asthma outcomes.[18] However, there are no controlled studies suggesting that long-term treatment of chronic sinonasal disease improves asthma control, although this is often done in clinical practice.[19]

One barrier to understanding the interaction between sinonasal disease and asthma is the lack of simple tests to diagnose rhinitis and sinusitis in asthma. We previously developed a clinical tool to identify chronic rhinitis and sinusitis in patients with inadequately controlled asthma. This questionnaire, which specifically asks about symptoms experienced over the last 3 months, identifies patients with chronic rhinitis and sinusitis with a sensitivity of 0.90 and specificity of 0.94.[20] This questionnaire accurately diagnoses chronic sinonasal disease

in asthma, is inexpensive and simple to use, and so facilitates the study of the relationship between chronic sinonasal disease and asthma.

Chronic sinonasal disease is common in asthma and may be associated with severe disease, but the effect of long-term treatment of sinonasal disease on asthma control is not known. The purpose of this study was to determine the efficacy of treating chronic sinonasal disease in children and adults with inadequately controlled asthma, as is common medical practice. There is supportive but inconclusive evidence that such treatment reduces asthma morbidity, and so this clinical trial addresses an important, practical issue that has extensive implications for public health and health care costs.

The trial was registered at ClinicalTrials.gov as NCT01118312 under the acronym Study of Asthma and Nasal steroids (STAN).

Methods

Study Design

This was a multicenter, randomized, placebo-controlled, double-masked, parallel (allocation ratio 1:1) design trial conducted at 19 clinical centers from June 2010 through February 2013. Randomization was stratified by center and age, 6 to 17 years or 18 or older, using permuted blocks of varying sizes. Participants aged 12 years and older received 2 sprays of mometasone or placebo per nostril daily (50 mcg mometasone per spray, versus vehicle control supplied by Merck), those age 6 to 11 years received 1 spray per nostril daily. After a two-week run-in, participants were randomized and followed for 24 weeks while on treatment. Allocation concealment was enforced as follows: clinical center personnel keyed eligibility data into a centralized, web-based randomization system to receive a study kit number that corresponded to the assigned treatment. Unique drug assignment numbers were used to distribute and track study drug. Personnel at the data coordinating center involved in randomization and drug distribution to the centers had access to the treatment information; no personnel at the clinical sites had access to the treatment codes. Analysts looked at treatment identity after data collection was completed and were aware of treatment assignment when performing the analyses of the completed dataset.

Participants

Participants were aged 6 years and older with a history of physician diagnosed asthma and either a positive methacholine challenge (20% fall in FEV_1 at less than 16mg/mL of methacholine) in the previous 2 years, or documentation of at least 12% and 200 cc increase in FEV_1 with bronchodilator in the previous 2 years. Subjects were required to meet the following inclusion criteria: poor asthma control defined as a score of 19 or less on the Childhood Asthma Control Test (c-ACT) (6-11 years)[21] or Asthma Control Test (ACT) (12 years or older)[22] (the ACT and cACT of ≤ 19 identifies “not well controlled asthma”, defined as an asthma specialist's rating of not controlled at all/poorly controlled/somewhat controlled) [21,23] and chronic symptoms of rhinitis and sinusitis as measured by a mean score of 1 or greater on the Sino-Nasal Questionnaire. [20] Participants were excluded if they had co-morbidities predisposing to complicated rhinosinusitis; chronic illnesses which in the

judgment of the physician would interfere with study participation; history of upper airway symptoms for less than 8 weeks at the time of randomization; fever >38.3°C within the prior 10 days; sinus surgery within the prior 6 months; use of systemic or nasal corticosteroids within the prior 4 weeks or anti-leukotriene medication within the prior 2 weeks; FEV_1 less than 50% predicted pre-bronchodilator; greater than 10 pack year smoking history or active smoking within the last 6 months; cataracts, history of glaucoma or other conditions resulting in increased intraocular pressure. Other exclusion criteria were non-adherence (<80% completion of daily diaries during run-in); inability to take study medications, perform baseline measurements or be contacted by telephone; or pregnancy.

Participants underwent allergen skin testing at baseline: Percutaneous allergen scratch skin testing was performed using a Multi-Test II device(Lincoln Diagnostics, Decatur, IL) and 16 allergens (Mite mix, Cockroach mix, Mouse, Rat, Penicillium, Alternaria, Aspergillus, Cladosporium, Cat, and Dog, 4 local center-specific allergens, and positive and negative controls) (Greer, Lenoir, NC). A positive test was defined as a wheal 3 mm greater than the negative control.

Participants were asked to refrain from taking non-study medications (other than topical decongestants or saline) for their nasal symptoms. They were trained to exhale all orally inhaled corticosteroids through the mouth, to avoid any potential benefit of orally inhaled corticosteroids on the nasal mucosa. Participants continued on their usual asthma medications during the trial. After randomization, participants kept daily diaries to record morning peak expiratory flow (PEF), medication use and asthma symptoms and returned for assessments at 4, 12 and 24 weeks. Procedures performed at each visit included: an interval medical history interview, asthma and sinus symptoms questionnaires, and spirometry (Koko Spirometer, Ferris Respiratory, Louisville, CO) according to ATS standards.[24] At baseline and the 24 week follow-up visits, exhaled nitric oxide (FeNO) was measured using the Insight eNO System (Apieron, Menlo Park, California) and methacholine challenge testing was performed. Allergen skin testing and the sinonasal questionnaire were administered at baseline.

Outcomes

The primary outcome measure was the change in childhood asthma control test (c-ACT for children under 12 years of age) [21]or asthma control test (ACT for those ages 12 and older[22]) at 24 weeks from baseline. Secondary outcomes included changes in methacholine reactivity, asthma symptoms (Asthma Symptom Utility Index [ASUI]),[25] asthma-related quality of life questionnaires (Childhood Health Survey for Asthma [CHSA][26] or Marks Asthma Quality of Life Questionnaire [Marks AQLQ][27]), sinusitis and rhinitis symptoms including a sinus symptom questionnaire[28] and sinusitis related quality of life questionnaires (SinoNasal survey-5 [SN5][29] for 6-17 years, and SinoNasal Outcome Test 22 [SNOT22][30] for 18 years and older), spirometry and exhaled nitric oxide. Secondary outcomes also included the rate of acute episodes of poor asthma control defined as a decrease of greater than 30% in morning peak flow rate from personal best (assessed during run-in) for 2 consecutive days, addition of an oral corticosteroid to treat asthma symptoms, unscheduled contact with a health care provider for asthma symptoms or increased use of short acting β-

agonists (≥ 4 additional puffs of rescue medication or ≥2 additional nebulizer treatments in 1 day). Participants were also questioned about potential adverse effects of treatment at each visit and rhinitis/sinusitis exacerbations.

Study Oversight

The Steering Committee of the ALA-ACRC designed, approved, and oversaw the study implementation. Active drug and placebo were supplied by Merck, who had no role in designing, conducting, or approving the study or analyzing the results. The study was approved by the Institutional Review Board at each center. The participant or their legal guardians signed informed consent statements. Participants under 18 years of age signed assents according to local regulatory policies. The ALA-ACRC is not bound by any confidentiality agreement in respect to the study results.

Statistical Approach

All analyses were stratified by age (pediatric [6-17] and adult [ages 18 and older]). The pediatric age category was further divided into younger children (ages 6-11) and adolescents (ages 12-17). The ACT score analysis was stratified by age groups of 6 to 11 years and 12 years and older, the age ranges validated for the pediatric cACT and adult ACT instruments, respectively. For all other outcomes, the two age groups were defined as 6 to 17 years and age 18 years and older. The randomization was stratified according to the age 18 cut-point.

The planned sample size of 190 adult participants (95 on active and 95 on placebo therapy) had 90% power to detect a difference of 2.8 in the change in ACT score from baseline to 24 weeks for the mometasone versus the placebo group with a type 1 error rate of 2.5% and a standard deviation of 5 (this standard deviation was based on prior data from studies by this research network, and previous publications).[31,32] Assuming equal recruitment, the same calculation was applied for pediatric patients for a total sample size of 380 and a total type 1 error rate of 5%. However, of the 151 participants less than 18 years of age enrolled in the study, only 86 were between the ages of 6 and 11, the age range for the cACT questionnaire, so the actual detectable difference was larger for that subgroup (approximately 4.1). The sample size calculations include an increase of 11% to account for missing data and lost-to-follow-up.

The analysis of the primary outcome, change in ACT score, incorporated the repeated measures through the use of linear mixed effects models, which are robust to data that is missing at random (MAR). Treatment, visit, and the interaction between treatment and visit were included as fixed effects and an unstructured variance-covariance matrix was used. Contrasts were used to produce the estimates for the change over 24 weeks.

Analyses of continuous secondary outcomes followed the same analytic strategy used for the primary outcome. PC_{20} (measured at baseline and 24 weeks) was analyzed on the log scale and results were translated into % change. Rates of exacerbations were evaluated using Negative Binomial models. All randomized individuals were included in the analysis according to their assigned treatment group. Robust variance estimates were used for all analytic models. The primary analyses were performed independently by two analysts to confirm the accuracy of data filters and analytic routines. Analyses were performed using

SAS (SAS/STAT User's Guide, Version 9.1, SAS, Inc, Cary NC), STATA (StataCorp. 2013, Stata Statistical Software, Release 13, College Station, TX) and, R (The R Project for Statistical Computing, Version 2.11.1, available at: http://www.r-project.org/).

Results

A total of 1567 participants were screened for eligibility (Figure 1). Three-hundred eighty-eight were randomized; 199 to placebo and 189 to mometasone. A similar number of adults (ages 18 and older) and children (ages 6-17) were randomized to both groups (120 adults and 79 children to placebo and 117 adults and 72 children to mometasone group). The lost to follow-up rate was similar in each group; 82% of participants completed the primary outcome questionnaire at week 24 and 90% of all follow-up visits were completed. Baseline characteristics of participants completing the study (n=319) were similar to those who did not complete the final visit (n=69) except for the fact that controller use was significantly higher in those who completed the study as compared to those who did not (74% vs 61%, p = 0.04) (Supplemental Table 1). Self-reported adherence to study treatments was high (> 90% of follow-up days) in both groups according to diary cards and interviews at study visits. Use of new sinus and new/increasing asthma medications was similar in placebo and mometasone groups (Supplemental Table 2).

Characteristics of study participants

Demographics, medication use, and measures of asthma and sinus disease were similar in both groups, though participants assigned to mometasone tended to have lower bronchial reactivity, indicated by a higher PC_{20}, at baseline (Table I). By design, participants had poor asthma control with an ACT score of less than 19 required at enrollment, although some improved beyond that threshold by randomization. Many participants (28%) were not taking controller medication for their asthma, this was not a requirement for study participation.

Effect of treatment on asthma control

After 24 weeks of study treatment, there was no significant difference in the change in childhood asthma control score (children ages 6-11) between those assigned to mometasone and those assigned to placebo (difference in change in mometasone – change in placebo [ΔM - ΔP]: -0.38, CI: -2.19 to 1.44, p = 0.68) (Table II). Asthma control scores tended to improve over the course of the trial in both treatment groups (range: 1.81 to 4.53, $p < 0.0001$ at all time points) (Supplemental Figure E1a). Similarly, there was no difference in the asthma control test for adults and adolescents (ages 12 and older) for those assigned to mometasone versus those assigned to placebo (Table II), and asthma control tended to improve in both treatment groups (range: 1.75 to 2.95, $p < 0.0001$ at all time points) (Supplemental Figure E1b).

Effect of treatment in children (ages 6-17) with poorly controlled asthma

There was no significant difference in the change in asthma symptoms, asthma quality of life, sinus symptom scores, or exhaled nitric oxide at 24 weeks compared to baseline in children assigned to placebo versus those assigned to mometasone (Table III). There was a small difference in improvement in lung function measured by FEV_1 (ΔM - ΔP: 3.45, 95%

CI: -0.52 to 7.42), and some evidence of larger improvement in forced vital capacity in children assigned to mometasone (ΔM - ΔP: 2.44, 95% CI: -0.60 to 5.48), although neither was statistically significant (p = 0.09 and 0.12, respectively). The percent improvement in PC_{20} was similar for both treatments (test of interaction: p = 0.52) at 89% (95% CI: 37% to 159%). There was a lower rate of episodes of poor asthma control (rate ratio 0.64, p=0.04) in children assigned to mometasone versus placebo. The effect was primarily driven by lower rates of episodes of decreased peak flow, defined as a 30% decrease in peak flow for two consecutive days (rate ratio 0.44, p = 0.03). No differences in the other components of episodes of poor asthma control, i.e., urgent care visits, use of systemic steroids, or use of rescue medications were noted (Table IV). In post-hoc analyses, we did not find any suggestion of a sub-group, as defined by gender, controller medication use or atopic status, that benefited from nasal steroids in this 24 week treatment trial.

Effect of treatment in adults (ages 18 and older) with poorly controlled asthma

There was a statistically significant improvement in the change in Asthma Symptom Utility Index at 24 weeks compared to baseline in adults assigned to mometasone versus placebo (ΔM - ΔP: 0.06, 95% CI: 0.01 to 0.11, p = 0.0095, Table V). There was no difference in the change in asthma quality of life, lung function or exhaled nitric oxide in those assigned to mometasone versus placebo. There was a significant greater decrease in the sinus symptom score in those assigned to mometasone (ΔM - ΔP: -3.82, 95% CI: -7.19 to -0.45, p = 0.026) as well as the change in SNOT-22 score (ΔM - ΔP: -4.83, 95% CI: -9.86 to 0.21), though the latter did not reach statistical significance (p = 0.06). Although the PC_{20} was higher at baseline for those treated with mometasone versus those treated with placebo (geometric mean: 1.64 vs. 0.77 (a difference that was statistically significant (p = 0.004)), there was not a significant difference in the percent change from baseline for the two groups (p = 0.42) with an overall improvement of 58% (95% CI: 19% to 111%, p = 0.002). There was no difference in the rate of episodes of poor asthma control in those assigned to mometasone versus placebo overall (p = 0.92, Table VI). In post-hoc analyses, we did not find any suggestion of a sub-group, as defined by gender, controller medication use or atopic status, that benefited from nasal steroids in this 24 week treatment trial.

Discussion

This study demonstrated that treatment of chronic sinonasal disease for 24 weeks does not improve asthma control in children or adults with inadequately controlled asthma. This study is unique in that it included a diverse patient population of adults and children with inadequately controlled asthma, and we studied the effect of nasal corticosteroids over a 24-week time period. The results of this study have important implications for the treatment of patients with asthma.

Sinonasal disease has been associated with severe asthma, and treatment of sinonasal disease is frequently advocated to improve asthma control. However, our current study provides important new insights into our understanding of the relationship between sinonasal disease and asthma, significantly expanding on previous studies. There have been many observational and small single center studies published on the effectiveness of treatment of

sinonasal disease for the control of asthma in patients with sinonasal disease and asthma. Some small studies suggest that short term treatment of seasonal and perennial allergic rhinitis improves airway reactivity in patients with asthma,[15,33] while others do not.[34] Recently there have been a few multi-center trials investigating the short-term effects of treating sinonasal disease in asthma. Dahl *et al* found no effect of 6 weeks of nasal corticosteroids on airway reactivity or induced sputum eosinophilia;[16] Katial *et al* and Nathan *et al* found that 4 weeks of intranasal corticosteroids improved nasal symptoms, but had no effect on asthma control.[35,36] These prior trials have studied the short-term efficacy of nasal corticosteroids in asthma, and suggest that the short-term treatment of sinonasal disease with nasal corticosteroids does not improve asthma outcomes. There have been very few prospective, controlled studies of longer term treatment of sinonasal disease in asthma. In one longer-term (16 week) single center study, Stelmach *et al* found that patients with allergic rhinitis and asthma had decreased pulmonary symptoms over the course of the study when treated with nasal corticosteroids; however there was no placebo group and all patient groups improved over the course of the study, as occurred in our own study.[37] Our trial is unique in that we measured the effects of nasal steroid compared with placebo over a longer time period (24 week) in both adults and children with chronic disease and poor asthma control. Our study shows that chronic nasal corticosteroids do not have a significant effect on asthma control.

We did find a small improvement in lung function in children assigned to nasal mometasone. This improvement was not simply in children not using controller medication. It may be that the added dose of nasal steroid was beneficial for lung function either through systemic effects or perhaps post nasal drip of corticosteroids. However, the clinical significance of this small improvement in lung function is uncertain.

We did see fewer episodes of two consecutive days with decrease in peak flow of ≥ 30 % in children. The reason for this is not known, though we speculate this may be related to some effect of post-nasal drip in the large airways. However, the clinical significance of this is uncertain given that it did not translate into improved asthma control, and was not associated with other more clinically significant markers of asthma exacerbations.

As anticipated, we did find that nasal corticosteroids improved sinus symptoms, and tended to improve quality of life related to sinus disease in adults. We did not see any improvement in sinus disease symptoms in children. The questionnaire we used to screen for sinonasal disease was developed in adults, but other measures of sinonasal disease gave scores similar to those previously reported for children with chronic rhinosinutis and perennial rhinitis, suggesting the study group had significant disease that could respond to intervention.[29,38-42] This lack of improvement was unexpected given that previous studies show nasal mometasone in the dose used in this study is effective for the treatment of rhinitis in children,[43] and nasal corticosteroids are considered first line therapy for the treatment of sinonasal disease in children.[44] Although we do not know the reason for the lack of improvement, it is possible that adherence or drug delivery was more challenging in children than adults. Adherence in this study was monitored from diary cards and appeared to be the same in adults and children (greater than 90%), but this was by self-report and so may be subject to reporter bias. The fact that we did see some improvement in lung function in

children assigned to nasal mometasone would also suggest that the children were using this medication, though it is possible that the drug was not being correctly delivered in children compared with adults.

We included both rhinitis and sinusitis in this trial, rather than trying to separate out the two. Asthma, rhinitis and sinusitis share a common pathophysiology with common inflammatory mediators and histopathological changes apparent in the upper and lower airways.[45] Rhinitis and sinusitis in asthma represent a disease continuum of the upper airway, which may be difficult to separate out without invasive testing, and so we did not attempt to distinguish the two.

The strengths of this study are that it was a large multi-center trial that enrolled a diverse patient population. It was of longer duration than prior studies, and so adds significantly to the previous literature. This study used a pragmatic design with regard to pre-existing asthma medications, which will enhance its applicability to a broad patient population. We assessed various sub-groups in post-hoc analyses (including atopic versus non-atopic participants, and participants on controller therapy versus those not on controller therapy), and did not find a sub-group that benefited from nasal steroids in terms of asthma control. We did not address whether treating acute and/or severe disease would improve asthma outcomes, but as these require treatment anyway, this is more compelling as a scientific than as a clinical question

In conclusion, this investigation shows that long term treatment with nasal corticosteroids does not improve asthma control in adults or children with inadequately controlled asthma. Sinonasal disease may be associated with severe asthma,[46,47] but the efficacy of treating sinonasal disease as a treatment modality for asthma alone is not supported by the current literature. Disease in the upper and lower airway may parallel one another in terms of severity, but treating one and to improve the other is of limited effectiveness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ASUI	Asthma Symptom Utility Index
ACT	Asthma Control Test
cACT	Childhood Asthma Control Test
CHSA	childhood health survey for asthma
FeNO	exhaled nitric oxide
PEF	peak expiratory flow rate
PC_{20}	mg/ml methacholine which causes a 20% fall in FEV_1
SNOT 22	Sino Nasal Outcomes Test 22
SN5	Sino Nasal survey 5

Clinical Implications

Treatment of chronic sinonasal disease with nasal corticosteroids does not improve asthma control.

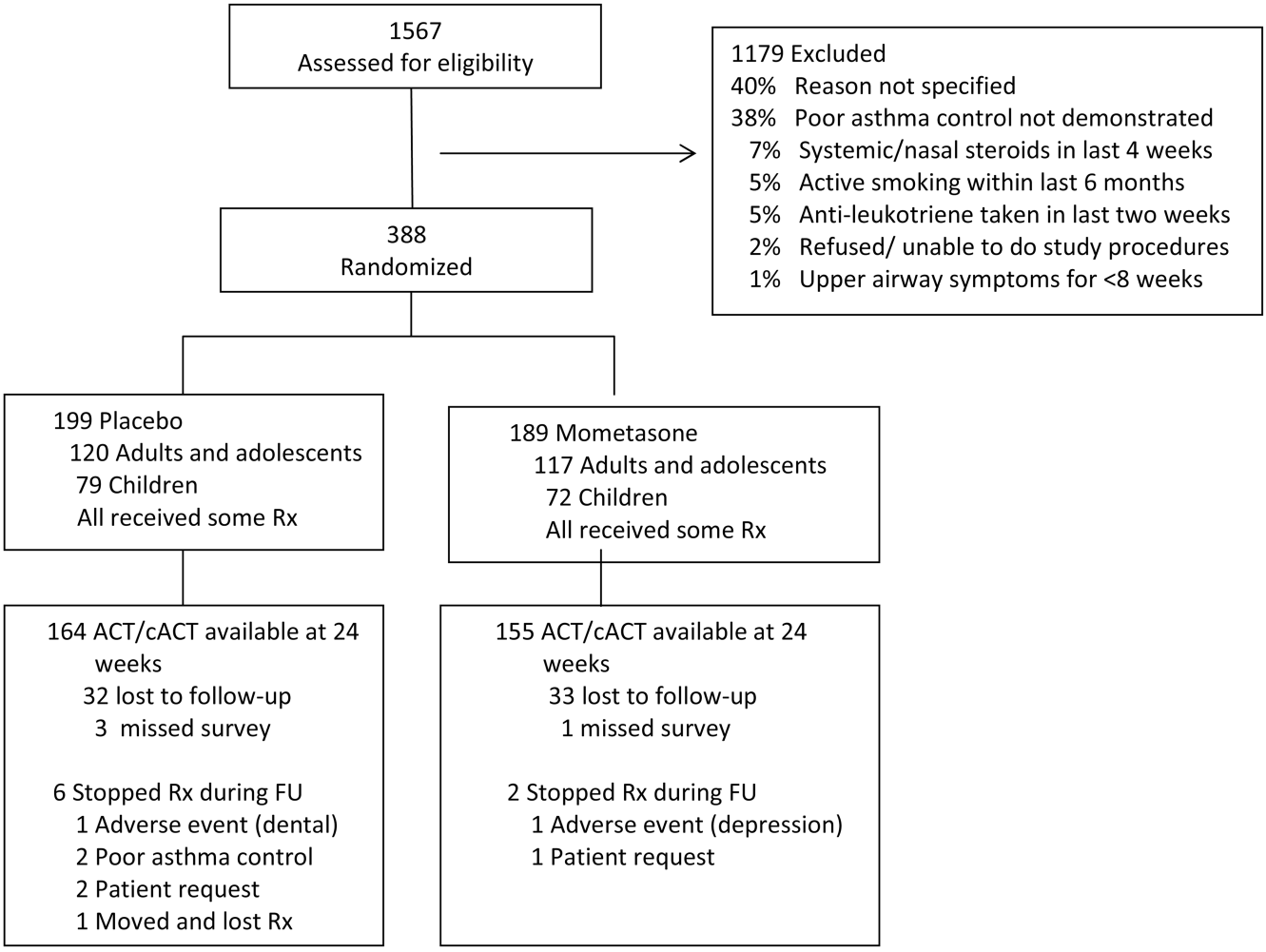

Figure 1.

Eligibility screening, randomization and follow up of study participants. All patients were included in the analysis based upon the assigned treatment.

Rx = therapy; FU = follow-up.

Table I
Characteristics of the study population at randomization

	Mometasone (N = 189)	Placebo (N = 199)
Demographics		
Age in years, Median (IQR)	27 (12, 46)	26 (12, 43)
Age categories, N (%)		
Pediatric (6-11 years old)	40 (21%)	46 (23%)
Adolescent (12-17 years old)	32 (17%)	33 (17%)
Adult (18 and older)	117 (62%)	120 (60%)
Race/ethnicity, N (%)		
White	71 (38%)	76 (38%)
Black	74 (39%)	73 (37%)
Hispanic	35 (19%)	46 (23%)
Other	9 (5%)	4 (2%)
Male, N (%)	84 (44%)	93 (47%)
Second-hand smoke exposure, N (%)	50 (26%)	42 (21%)
Atopy, N(%)	137 (82%)††	149 (84%)††
Asthma characteristics		
Age of asthma onset, Median (IQR)	5 (1, 13)	4 (1, 12)
Emergency visits in the past 12 months, N (%)	123 (65%)	125 (63%)
Steroid bursts in the past 12 months, N (%)	88 (47%)	102 (51%)
Using controller medication, N (%)*	134 (71%)	144 (72%)
ICS in combination with LABA	81 (43%)	85 (43%)
ICS without LABA	52 (28%)	59 (30%)
Lung function, Median (IQR)		
Pre-bronchodilator FEV_1 (% predicted)	85 (76, 96)	85 (73, 95)
Pre-bronchodilator FVC (% predicted)	96 (86, 106)	95 (86, 105)
Pre-bronchodilator FEV_1/FVC	0.75 (0.70, 0.80)	0.75 (0.68, 0.81)
Peak expiratory flow (L/min)	340 (280, 420)	350 (280, 430)
PC20 (mg/mL)	2.29 (0.53, 6.11)	0.67 (0.20, 3.01)
Questionnaires, Median (IQR)		
ACT score (range: 5-25) ↑†	16 (14, 19)	17 (14, 18)
cACT score (range: 0-27)↑†	17 (15, 19)	17 (14, 18)
Asthma symptom utility index (range: 0-1) ↑‡	0.77 (0.69, 0.88)	0.79 (0.69, 0.88)
Marks asthma quality of life questionnaire (range: 1-80)↓ §	17 (10, 30)	21 (11,31)
Children's health survey for asthma (range: 0-100)↑**		
Physical health (child)	77 (68, 87)	77 (68, 87)
Activities (child)	85 (65, 95)	85 (65, 100)
Activities (family)	96 (83, 100)	92 (83, 100)
Emotional health (child)	80 (65, 95)	80 (55, 95)

	Mometasone (N = 189)	Placebo (N = 199)
Emotional health (family)	79 (69, 90)	78 (71, 90)
Sinus symptom score (range: 1-60) ↓‡	25 (17, 32)	25 (16, 34)
SNOT-22 (range: 0-120)↓ §	37 (23, 54)	36 (21, 53)
SN-5 (range: 1-7)↓ **	3.3 (2.8, 4.0)	3.8 (3.0, 4.6)

* One individual was using LABA without ICS in mometasone arm.

† The ACT was administered to participants 12 years of age and older and the cACT was administered to participants aged 6 to 11 years.

‡ The ASUI and SSS were administered to all participants.

§ The Marks asthma quality of life questionnaire and the SNOT-22 were administered to participants aged 18 and older.

** The Children's health survey for asthma and the SN-5 were administered to participants ages 6 to 17 years.

†† A total of 168 participants in the mometasone and 178 participants in the placebo arm had valid skin testing data available. Thirty did not perform the test, 3 were missing data, and 9 did not have a valid test (i.e. the positive control was negative).

IQR = interquartile range; N = number; % = percent; ↑ = high scores indicate better health; ↓ = low scores indicate better health

Table II

Comparison of the change in asthma control for participants treated with mometasone versus placebo at 4, 12, and 24 weeks. Asthma control was measured by ACT for adolescent and adult participants (ages 12 and older) and by cACT for pediatric participants (ages 6-11).

	N*	Change from randomization (SE)		Difference in change from randomization (95% CI)	P-value
		Mometasone	Placebo	Mometasone – Placebo	
cACT: Pediatric (ages 6-11) ↑					
Week 4	82	1.81 (0.58)	2.69 (0.54)	-0.88 (-2.47 ,0.71)	0.27
Week 12	75	3.40 (0.61)	3.05 (0.71)	0.34 (-1.52 ,2.21)	0.71
Week 24	71	4.15 (0.64)	4.53 (0.65)	-0.38 (-2.19 ,1.44)	0.68
ACT: Adolescent and adult (ages 12 and over) ↑					
Week 4	277	1.89 (0.26)	1.75 (0.31)	0.14 (-0.66 ,0.94)	0.72
Week 12	262	2.69 (0.30)	2.25 (0.32)	0.44 (-0.43 ,1.31)	0.32
Week 24	248	2.95 (0.31)	2.44 (0.38)	0.51 (-0.46 ,1.48)	0.30

* N is the number of participants with follow-up at each time point (4, 12, and 24 weeks).

SE = standard error; CI = confidence interval; ↑ = an increase indicates improved control.

Table III

Twenty-four week change in asthma symptoms, lung function, and sinus symptoms in children (ages 6-17) treated with mometasone versus placebo.

	N	Change from randomization (SE)		Difference in change from randomization (95% CI)	P-value
		Mometasone	Placebo	Mometasone - Placebo	
Asthma Symptom Utility Index	126	0.04 (0.02)	0.1 (0.02)	-0.06 (-0.13 ,0.01)	0.07
Childhood health survey for asthma					
Physical health	123	6.37 (1.63)	7.33 (1.59)	-0.95 (-5.45 ,3.55)	0.68
Activities (child)	125	7.41 (2.03)	5.95 (2.38)	1.45 (-4.74 ,7.65)	0.64
Activities (family)	125	2.09 (1.74)	5.35 (1.43)	-3.26 (-7.72 ,1.20)	0.15
Emotional health (child)	125	3.87 (2.83)	7.35 (2.46)	-3.48 (-10.91 ,3.94)	0.36
Emotional health (family)	123	4.01 (1.61)	3.26 (1.55)	0.76 (-3.66 ,5.18)	0.74
Lung function					
Pre-bronchodilator FEV_1 (% predicted)	127	2.62 (1.68)	-0.83 (1.1)	3.45 (-0.52 ,7.42)	0.09
Pre-bronchodilator FVC (% predicted)	127	2.1 (1.24)	-0.34 (0.92)	2.44 (-0.60 ,5.48)	0.12
FEV_1/FVC	127	0.007 (0.009)	-0.007 (0.006)	0.013 (-0.009 ,0.035)	0.23
FeNO (ppb)*	123	10.92 (5.34)	5.65 (2.89)	5.28 (-6.72, 17.28)	0.39
Sinus symptoms					
Sinus Symptom Score	127	-7.38 (1.38)	-7.38 (1.43)	-0.004 (-3.94 ,3.93)	> 0.99
SN-5	126	-0.76 (0.12)	-0.98 (0.14)	0.22 (-0.14, 0.59)	0.22

*FeNO was measured at baseline and at 24 weeks.

N = number of participants evaluable at 24 weeks; CI = confidence interval; Δ = change. I

Table IV

Episodes of Poor Asthma control in children (ages 6-17) treated with mometasone versus placebo.

Episodes of poor asthma control	Treatment Assignment		Rate Ratio (95% CI)* Mometasome / Placebo	P-value*
	Mometasone (N = 66)	Placebo (N =75)		
Overall				
Patients with ≥ 1 event, N (%)	36 (55%)	42 (56%)		
Number of events	73	128		
Annual per-person event rate (95% CI)	2.7 (2.1, 3.6)	4.2 (3.1, 5.8)	0.64 (0.42, 0.97)	0.04
Individual components				
Drop in peak flow of ≥ 30 % for 2 consecutive days				
Patients with ≥ 1 event, N (%)	14 (21%)	20 (27%)		
Number of events	30	73		
Annual per-person event rate (95% CI)	1.1 (0.7, 1.9)	2.5 (1.5, 4.2)	0.44 (0.22, 0.90)	0.03
Urgent asthma care				
Patients with ≥ 1 event, N (%)	15 (22%)	10 (13%)		
Number of events	18	12		
Annual per-person event rate (95% CI)	0.7 (0.4, 1.1)	0.4 (0.2, 0.7)	1.75 (0.81, 3.80)	0.15
Systemic steroids				
Patients with ≥ 1 event, N (%)	13 (20%)	13 (17%)		
Number of events	13	13		
Annual per-person event rate (95% CI)	0.5 (0.3, 0.8)	0.4 (0.3, 0.7)	1.17 (0.57, 2.36)	0.67
Increased Rescue Medications				
Patients with ≥ 1 event, N (%)	27 (44%)	27 (38%)		
Number of events	47	67		
Annual per-person event rate (95% CI)	1.8 (1.3, 2.6)	2.3 (1.5, 3.4)	0.82 (0.49, 1.39)	0.44

* Rate Ratios, 95% Confidence Intervals (CI) and P-values are based on negative binomial regression.

Table V

Twenty-four week change in asthma symptoms, lung function, and sinus symptoms in adults (ages 18 and older) treated with mometasone versus placebo.

	N	Change from randomization (SE)		Difference in change from randomization (95% CI)	P-value
		Mometasone	Placebo	Mometasone - Placebo	
Asthma Symptom Utility Index	193	0.09 (0.01)	0.03 (0.02)	0.06 (0.01 ,0.11)	< 0.01
Marks asthma quality of life questionnaire	192	-5.26 (1.11)	-5.48 (1.06)	0.22 (-2.82 ,3.26)	0.89
Lung function					
Pre-bronchodilator FEV_1 (% predicted)	193	-1.40 (1.07)	0.51 (0.97)	-1.91 (-4.76 ,0.94)	0.18
Pre-bronchodilator FVC (% predicted)	193	-1.27 (0.95)	0.06 (0.85)	-1.33 (-3.85 ,1.19)	0.30
FEV_1/FVC	193	-0.001 (0.004)	0.004 (0.004)	-0.005 (-0.017 ,0.008)	0.43
FeNO (ppb)*	183	-0.08 (1.98)	-0.02 (2.96)	-0.06 (-7.08, 6.96)	0.99
Sinus symptoms					
Sinus Symptom Score	194	-9.46 (1.18)	-5.64 (1.24)	-3.82 (-7.19 ,-0.45)	0.03
SN-22	193	-11.2 (1.86)	-6.37 (1.75)	-4.83 (-9.86 ,0.21)	0.06

* FeNO was measured at baseline and at 24 weeks.

N = number of participants evaluable at 24 weeks; CI = confidence interval.

Table VI

Asthma symptoms, lung function and sinus symptoms in adults (ages 18 and older) treated with mometasone versus placebo.

	Treatment Assignment		Rate Ratio (95% CI)* Mometasome / Placebo	P-value*
	Mometasone (N = 111)	Placebo (N = 111)		
Episodes of poor asthma control, overall				
Patients with ≥ 1 event, N (%)	45 (41%)	48 (43%)		
Number of events	104	114		
Annual per-person event rate (95% CI)	2.5 (1.9, 3.5)	2.6 (1.9, 3.5)	0.98 (0.64, 1.51)	0.92
Episodes of poor asthma control, components				
Drop in peak flow of ≥ 30 % for 2 consecutive days				
Patients with ≥ 1 event, N (%)	14 (21%)	20 (27%)		
Number of events	38	68		
Annual per-person event rate (95% CI)	0.9 (0.5, 1.5)	1.7 (1.1, 2.6)	0.55 (0.27, 1.10)	0.09
Urgent asthma care				
Patients with ≥ 1 event, N (%)	6 (5%)	11 (9%)		
Number of events	6	14		
Annual per-person event rate (95% CI)	0.1 (0.1, 0.3)	0.3 (0.2, 0.6)	0.45 (0.16, 1.27)	0.13
Systemic steroids				
Patients with ≥ 1 event, N (%)	15 (14%)	17 (15%)		
Number of events	20	15		
Annual per-person event rate (95% CI)	0.3 (0.2, 0.5)	0.4 (0.3, 0.7)	0.78 (0.40, 1.52)	0.47
Increased Rescue Medications				
Patients with ≥ 1 event, N (%)	29 (28%)	27 (26%)		
Number of events	62	49		
Annual per-person event rate (95% CI)	1.7 (1.1, 2.5)	1.2 (0.8, 1.9)	1.42 (0.78, 2.59)	0.25

*Rate Ratios, 95% Confidence Intervals (CIs) and p-values are based on negative binomial regression.