Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Zeiger RS, Mauger D, Bacharier LB, et al. Daily or intermittent budesonide in preschool children with recurrent wheezing. N Engl J Med 2011;365:1990-2001.

Daily or Intermittent Budesonide in Preschool Children with Recurrent Wheezing

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SELECTED METHODS

PATIENTS

The following criteria determines modified asthma predictive index (mAPI) status as operationally used in the CARE Prevention of Early Asthma in Kids (PEAK) trial[1] and modified for MIST. Patients needed to have a history of 4 or more wheezing episodes in the prior year with at least one physician diagnosed or 3 or more wheezing episodes in the prior year with at least one physician diagnosed and at least 3 months of asthma controller therapy in the prior year. We added the latter option [1 less wheezing episode with the preconditioned at least 3 month use of inhaled glucocorticosteroid (ICS)] to not lose from enrollment appropriate patients in order to account for the more frequent use of ICS in m-API children than were used almost a decade before during PEAK enrollment owing to recent guideline recommendations. In addition, the patient must have met at least one of the following major criteria (parental history of asthma, physician diagnosed atopic dermatitis or aeroallergen sensitization) or $\geq$2 minor criteria (food sensitization, blood eosinophil count $\geq$4%, or wheezing unrelated to colds).

Other exclusions at enrollment were a history of a life threatening wheezing episode, systemic glucocorticosteroids within 2 weeks of enrollment, presence of other significant lung or other medical conditions, uncontrolled gastroesophageal reflux, current antibiotic use for sinusitis, birth before 34 weeks gestational age or significant developmental delay or failure to thrive. During the 2-week run-in, parents administered placebo inhalation suspension nightly and albuterol as needed for symptoms, and also completed diary cards twice daily. Children were randomized if none of the following occurred during run-in: (1) albuterol use on average three or more days per week or 2 or more night time asthma awakenings; (2) less than 75% of days with diary card completion or placebo inhalation use; or (3) use of any asthma medication except albuterol.

PROCEDURES

The protocol was reviewed and approved by the National Health Lung Blood Institute (NHLBI)-appointed Protocol Review Committee and Data and Safety Monitoring Board (also monitored the trial).

Clinic visits were scheduled four weeks following randomization, and then every eight weeks, while telephone calls were scheduled two weeks following randomization, followed by calls four weeks after each scheduled clinic visit (Figure S1).

Study medications were administered using a Pari Ultra II compressor with LC Sprint reusable nebulizer and a mask (Bubbles The Fish™ II or Pari Baby mask), if needed, or a mouth-piece depending upon the age of the child. Rescue albuterol was administered at a dose of 180 mcg/treatment by metered-dose inhalation (Ventolin HFA®, GlaxoSmithKline, Research Triangle Park, NC) via AeroChamber Z-STAT Plus™ with FlowSIGnal Whistle with ComfortSeal® Mask (Monhagan Medical Corp, Plattsburgh, NY) or albuterol solution 2.5 mg per treatment by nebulization by protocol during a respiratory-tract illness (four times daily while awake for the first 48 hours) and on an as needed basis.

Total serum IgE level by Pharmacia CAP system[2], skin-prick testing or CAP FEIA testing (if skin testing was contraindicated), with a core battery of food and aeroallergens (mite mix, cockroach mix, cat, dog, mold mix, grass mix, tree mix, weed mix, milk, egg, and peanut)[1] and blood eosinophil count[1] were done prior to randomization. Quality of life by the Infant Toddler Quality of Life (http://www.healthact.com/itq.html) validated questionnaire was performed at specified visits during the trial.[3]

The off-line, tidal breathing, face mask based technique was used at specified visits to determine fractional exhaled nitric oxide ($FE_{NO)}$ modeled from Baraldi, et al,[4] measured as recommended by both the European Respiratory Society/ American Thoracic Society (ERS/ATS)[5], using the NIOX Flex system (Aerocrine, New Providence,

NJ).[6] This technique was used successfully in the CARE Acute Intermittent Asthma Management (AIMS) trial.[6] Seated on the laps of their parents/guardian, children breathed through a special face mask (Hand Rudolph, inc. as the above picture) designed to collect only orally exhaled air. The exhaled air was collected during quiet and regular tidal breathing since $F_{E_{NO}}$ is highly flow dependent. The mask was connected to a two-way non-re-breathing valve (Hand Rudolph, Inc) which allowed inspiration of low NO air (<5ppb) from an inspiratory (NO) gas filter (Ionics Instrument Business Group) to ensure no contamination by ambient NO and expiration into a NO-inert (polyethylene) collection bag. A 5 cm H2O resister was connected to an expiratory port of the valve to maintain an expiratory resistance more than 2 cm H2O at the mouth which provided an effective closure of the soft palate and minimized contamination of NO from nasal passages. To assure the resistance as required, a pressure gauge was used to monitor the resistance at the mouth. The collection bag was attached to a stopcock of the expiratory port. The stopcock directed orally exhaled air into the collection bag once the breathing pattern stabilized and after ten breaths to permit a wash-out of NO in the dead space and lungs. Five breaths of exhaled air were collected for a sample in duplicate from each participant during quiet and regular tidal breathing. The samples were then analyzed by NIOX OFFLINE Kit and the NIOX system for $F_{E_{NO}}$ levels within 3 hours of collection. Measurements of $F_{E_{NO}}$ were obtained from subjects at 4 times during the course of the study. The overall success rate for obtaining $F_{E_{NO}}$ measurements was 70.9% across the entire study and 65% at baseline. There was an unmistakable trend for better performance in older children. In terms of reproducibility, when patients were able to provide $F_{E_{NO}}$ measurements at all, they achieved at least two measurements within 10% or 5ppb of each other 95% of the time.

Nasal secretions were collected by direct “nasal blow technique” or nasal swab at scheduled visits at randomization and at visit 5 and during each respiratory-tract illness

at home by a trained parent/guardian and then frozen for later analysis for respiratory virus enumeration by PCR-based diagnostic assays.[7] Parents were given the option of using a "nasal blow technique" or nasal swab to collect samples at home during respiratory-tract illnesses. The nasal blow technique has previously been employed for home collection by parents with reliable results.[8] The nasal swab technique has previously been published by a group in Finland.[9] Viral infections are the major trigger of wheezing in children 1-5 years of life and we wished to determine the quantity and type of viruses associated with respiratory tract illnesses. Furthermore, we also sought to determine whether specific viruses were associated with a response or lack of response to study treatments. In particular, rhinovirus is the most frequent virus associated with early life wheezing illnesses and it also interacts with atopy both of which are associated with development of persistent asthma.[10] Moreover, treatment of an initial rhinovirus wheezing infection with oral glucocorticosteroids has been associated with reduced risk of recurrent wheezing compared to children that did not receive oral glucocorticosteroid treatment.[11] Reduction in length of hospitalization during a wheezing illness after treatment with oral glucocorticosteroids was observed in children with a median age 1.6 years with the following characteristics: rhinovirus infection, a positive modified asthma predictive index/asthma, or ICS treatment. Oral glucocorticosteroid treatment also significantly decreased relapses in children with rhinovirus infection, eczema and nasal eosinophilia.[12] Thus, these findings support the importance of determining respiratory viruses in clinical trials of recurrent wheezing young children.

Height and weight were measured at every visit with an upright stadiometer (Harpenden, Holtain, UK) and by standard scale by established procedures.[1, 13] Length was measured using an infant stadiometer for children 1-2 years of age. Head circumference was determined at randomization and at the final visit using the SECA non-flexible head circumference tape specific for infants and one specific for older

children by standard procedures (cdc.gov/nchs/data/nhanes/nhanes_05_06/BM.pdf).

Oral glucocorticosteroids (prednisolone) were available for all children at home and were started after physician consultation (telephone or in-person) based upon a specific published protocol[14] at a dose of 2mg/kg (maximum 60 mg) for 2 days and 1 mg/kg (maximum 30 mg) for 2 days. Oral glucocorticosteroids were started with physician direction for **any** of the following situations: (1) symptoms not improved after 3 albuterol treatments every 15 minutes, (2) >6 albuterol nebulization treatments or more than 12 puffs per day for >24 hours, (3) moderate-severe cough or wheeze for 5 or more days in the past week, and (4) physician discretion with stated rationale. Other asthma medications were not permitted during the study, but use of non-asthma medications was not restricted.

The methods used to instruct parents on the appropriate use of intermittent treatments is detailed in Figure S2. These efforts were instituted to minimize the use of intermittent ICS treatment during mild upper respiratory illnesses that by history did not lead to wheezing episodes.

OUTCOME MEASURES

Treatment failure was defined as the occurrence of four oral glucocorticosteroid courses, or any hospitalization or intubations for wheezing, hypoxic seizure, serious adverse event related to a study medication, and physician discretion. Severity of respiratory-tract Illnesses was calculated as the area under the curve for symptoms (cough, wheeze, trouble breathing score, or interference with activity) from days 1 to 14 during respiratory-tract Illnesses adjusted for baseline symptom levels from days -7 to -13 as was used during the CARE AIMS trial.[14]

Total ICS exposure was calculated under the intent-to-treat paradigm. Specifically, the total ICS exposure was calculated as 14 mg multiplied by the number of

respiratory-tract illness treatments for the intermittent ICS group, and as 0.5 mg multiplied by the number of days on study for the daily ICS group.

Exploratory outcomes included determining whether specific respiratory viruses were associated with a differential response to budesonide treatments or exacerbations requiring systemic glucocorticosteroids.

STATISTICAL ANALYSES

The run-in period was considered the baseline evaluation period. The initial statistical analysis focused on summarizing the baseline characteristics of the study participants. Descriptive statistics (means and standard deviations, or medians and inter-quartile ranges) were calculated for continuous baseline measures such as current age, age at first asthma diagnosis, asthma/wheezing history, FE_{NO}, and current asthma symptom severity. Frequency tables were generated for categorical baseline measures such as gender, prior medication history, parental asthma, and skin test results. Statistics were calculated for the entire study population and by treatment group in order to confirm similarity. Partial censoring of the primary outcome variable was done if a patient dropped out of the study early or reached treatment failure status as defined above. In such cases, the observed number of exacerbations requiring systemic glucocorticosteroids was used in the primary analysis. Because of this, the average number of observed exacerbations was a downward biased estimate of the true annual rate of exacerbations.

Although the primary analysis consists of a nonparametric test, the primary hypothesis of MIST is framed in terms of the annual rate of exacerbations. Therefore, unbiased estimates of the rates were important to obtain. The primary parametric analysis utilized maximum likelihood estimation based on the log-linear regression model for outcomes following the negative binomial distribution. This analysis incorporates the follow-up time so that rates can be estimated as appropriate when the

observed number of exacerbations for a given subject follows a Poisson distribution, with variability across subjects in the expected number exacerbations, also described as over-dispersion. In addition to treatment effect, these models also incorporated covariates including age, clinical center, parental asthma, skin test sensitivity, gender, the mAPI and its individual components, serum IgE level, and blood eosinophil count Additional secondary analyses examined the effect of treatment on other outcomes. For outcome variables that are also measured as counts, such as number of unscheduled visits for acute wheezing episodes and number of days missed from daycare or parental work, a similar log-linear model maximum likelihood analysis was applied. Standard ANCOVA was applied for outcomes measured on a roughly continuous scale, such as FE_{NO}, average symptom scores, and linear growth. For outcomes that are not approximately normally distributed, appropriate transformations were applied prior to ACNOVA. Proportional hazards regression was applied for time-to-event outcomes such as time to first exacerbation.

The target sample size for MIST was 250 randomized children. The expected exacerbation rates (oral glucocorticosteroid use) utilized for the sample size calculations were estimated using the results of the PEAK and AIMS studies. The relative rate of exacerbations for daily ICS versus placebo in the subset of children with positive mAPI and prior year asthma emergency department or hospitalization in the PEAK trial was 0.45. The relative rate of exacerbations for intermittent ICS versus placebo in the subset of children with positive mAPI and prior year oral glucocorticosteroid, emergency department, or hospitalization in the AIMS trial was 0.75. However, the PEAK and AIMS trials are not directly comparable, even within the positive API and previous ED history exacerbation subgroups, because the study participants were selected differently. This is demonstrated by the fact that the placebo exacerbations rates for PEAK and AIMS were very different; 1.54 and 0.96 respectively in the relevant subgroups. In order to use the

PEAK and AIMS data for designing MIST, we developed the concept of a “hypothetical placebo” treatment group.

This concept represents the expected exacerbation rate in the MIST target population hypothetically treated with placebo. For the MIST study, the rate of exacerbations for hypothetical placebo was assumed to be 1.25 per year which is the midpoint of the range defined by PEAK and AIMS. If, in the MIST population, the relative rate of exacerbations for daily ICS versus hypothetical placebo is 0.45, as was observed in PEAK, then the expected rate of exacerbations for daily ICS is 0.56 per year (0.45 x 1.25). Similarly, if the relative rate of exacerbations for intermittent ICS versus hypothetical placebo is 0.75, then the expected rate of exacerbations for intermittent ICS is 0.93 per year (0.75 x 1.25). Power calculations based on the proposed nonparametric test indicate that a sample size of 250 will yield between 80% and 90% power at the 0.05 significance level if the exacerbations rates in the two treatment arms are 0.56 and 0.93 per year. This accounts for a 10% drop-out. There are no closed-form power calculation methods available for this test so these estimates were calculated via Monte Carlo simulation based on over-dispersed Poisson distributions for the number of exacerbations. The power depends upon the extent of over-dispersion. With minor over-dispersion (3% variance inflation) the estimated power is 88% and with moderate over-dispersion (40% variance inflation) the estimated power is 79%. Closed-form approximate power calculations based on the z-statistic agree with these estimates; 90% power with minor over-dispersion and 81% power with moderate overdispersion.

The choice of 1.25 as the hypothetical placebo exacerbation rate was not inconsequential. Assuming that the relative exacerbation rates between the daily or intermittent ICS treatment and the hypothetical placebo are 0.45 and 0.75 respectively, the sample size required to achieve 90% power ranged between 200 and 325 as the hypothetical placebo rate ranged between 0.9 and 1.6. Although the conservative

sample size choice of 325 would yield at least 90% power even if the hypothetical placebo rate was as low as 0.9, the power would be greater than 98% if the hypothetical placebo rate was similar to what was observed in PEAK. Study designs with power that high are not cost-effective. On the other hand, the intermediate choice of 250 behaves reasonably well across the entire range of hypothetical placebo exacerbation rates yielding power between 80% and 95%.

SELECTED RESULTS

PATIENTS

Of the 278 study patients, 192 (69.1%) were male, 173 (62.2%) were Caucasian, and 127 (45.7%) ages 12-32 months. Respiratory illness burden was considerable in the year prior to enrollment with high rates/patient/year of urgent/emergency department visits (4.8±4.2), wheezing episodes (6.7±5.4), days of child absences (5.2±8.4) and frequent asthma controller use (69.8% of patients). Atopic features were frequent with histories of eczema in 52.5%, allergic rhinitis in 37.8%, and allergen sensitization in 67.5% of the cohort.

Diaries were completed on about 85% of study days. 95% of days with diary card completion noted daily study drug use. This equates to at least 80% of study days with daily study treatment which was greater than the 75% adherence threshold required for eligibility as determined on nightly placebo respules used during run-in.

Respiratory symptom scores during run-in were low and characteristic of a more intermittent illness phenotype. Only 23/288 (8%) of patients qualified for enrollment based on 3 wheezing episodes and controller use for at least 3 months in the prior year.

Quality of life was comparable to a normal population[15] except for lower scores for general health perceptions and parental impact emotional, for which the standardized effect sizes (Cohen's d)[16] were 1.0 and 0.5 respectively. With respect to a population with at least 4 wheezing episodes in the prior year[15], the present cohort scored significantly higher for physical abilities, growth and development, bodily pain, and temperament and moods. Quality of life changes from baseline were generally not significantly different between treatment groups (Table S4).

Nasal viruses were identified in about half the children at baseline. There were no differences in any of the above parameters by treatment group.

NON-COMPLETION

The rate of non-completion was higher than planned, but we recruited 10% more patients to account for this loss and maintained the planned 90% power for the primary analysis, since we had 235 years of patient data instead of the planned 225, which included both the completers and data to the time of non-completion. The rate and characteristics of non-completers was comparable between groups. Non-completion rate was 23.3%, with non-completers being comprised of more females ($P<0.05$) and homes with smokers ($P<0.01$) (Table S1). Non-completion, though numerically less frequent in the intermittent group (N=26) than in the daily group (N=39) (Table S2) ($P=0.09$), time to final study contact among non-completers was longer in the daily group (145 days vs 139 days, $P=0.6$) and importantly, participant characteristics did not differ by non-completers between budesonide treatment groups ($P>0.2$ for all) (Table S2). The principal reasons for non-completion involved family issues and very infrequently dissatisfaction with asthma control.

PARENT AND COORDINATOR ASSESSMENTS

The respiratory-illness questionnaires given to parents that assessed the constellation of signs and symptoms that they felt fairly confident preceded wheezing episodes were practical and modestly predictive.[17] The combination respiratory symptom complex of either cough, noisy chest, breathing problems or noisy breathing were the predominant first symptoms that led caregivers to start respiratory-tract illness treatments in the intermittent (68.5%) and daily (73.1%) budesonide groups ($P=0.6$) (Table S3).

About 85% of caregivers reported fair to very good control of wheezing during the study with both treatments ($P=0.9$). Only 14/107 (13.1%) in the daily group and 17/117 (14.5%) in the intermittent budesonide groups reported difficulty with the inhalational treatments ($P=0.81$). Caregivers in both the daily (71.7%) and intermittent (57.8%)

budesonide groups assessed their children as being on daily treatment (P=0.04). Coordinators were unable to distinguish treatment groups (P=0.23 for group difference).

RESPIRATORY-TRACT ILLNESSES

Symptom severity for both treatment groups were not significantly different (Table S4). The severity of symptoms during respiratory-tract illnesses was greater during exacerbations than without exacerbations for both treatment groups with no treatment group differences observed (Figure S3). No treatment group differences were seen for symptom severity when the AUC was examined from days 1-14 or either days 1-7 (data not presented).

NASAL VIRUSES

Rhinovirus was the virus most frequently identified both during scheduled clinic visits and respiratory-tract illnesses and were similarly identified during respiratory-tract illnesses in the intermittent [(181/394 (45.9%)] and daily [(165/348 (47.4%)] treatment groups (P=0.14 for difference in distribution)] (Table S5). Most viral associated respiratory-tract illnesses did not lead to an exacerbation in both budesonide treatment groups, and exacerbations were no more frequent when viruses were or were not present in either group (Table S5).

GROWTH

Changes in height and weight are shown by absolute value in Figure S4 and are not significantly different between groups..

ADVERSE EVENTS

A 4^{th} exacerbation or an asthma hospitalization occurred in 12 patients in the intermittent and 7 patients in the daily groups (P=0.3). One patient in the intermittent budesonide group had 2 additional asthma hospitalizations after treatment failure, off study treatment, and on physician discretion. The frequencies of patients with adverse

events were not significantly different between treatments (Table S6). Thrush was noted in only 2 patients, both in the daily budesonide group.

DISCUSSION

Our study found no significant evidence against the null hypothesis that the two ICS treatments are different with regards to prevention of asthma exacerbations, but they do not prove that the two treatments are equally efficacious. Indeed, our data can not prove that either treatment is efficacious, which would require the presence of a true placebo treatment arm. In the absence of a placebo arm, the efficacy of the two treatments may be considered in light of a putative or hypothetical placebo.[18, 19] That is, if the study had included a placebo arm, then we would have been able to directly estimate the efficacy of both ICS treatments individually as well as comparing them to each other. Any specific assumptions about what would have happened in a placebo arm in this study would be difficult to support objectively, but by considering a broad range of possible placebo arm results, we can speculate about the clinical implications of our results in a way that is transparent and free from possible investigator bias. The graph in the upper panel in Figure S5 reveals how the exacerbation rates observed in our study could be interpreted over a range of possibilities from highly pessimistic, the ICS treatment was no better than placebo, to optimistic, the ICS treatment reduced exacerbations by 50%. Examination of the confidence limits reflected in the graph reveals the magnitude of statistical uncertainty associated with our results. Similarly, the confidence limits for the relative rate of the two treatments compared to each other can be used to investigate what conclusions these data support in regards to the degree of superiority either treatment might have over the other (lower panel). The appropriate interpretation of this figure is that although our best estimate is that daily and intermittent ICS have comparable efficacy, our data do not rule out the possibility that either treatment could be up to 35% more efficacious than the other.

The MIST cohort was selected for high-risk and low-impairment and as such, it was not expected that episode-free days would be markedly increased with either ICS regimens when patients already exhibited only 33% episode days during run-in. Excluding respiratory tract illnesses, the MIST cohort exhibited only 15% episode days during the study, evidencing the intermittent nature of the illness of the children.

In the MIST study, a virus was detected during more than 80% of respiratory-tract illnesses (Table 2), clearly demonstrating the robustness of the collection methods used in this study. With regard to the question of infection vs. colonization, samples obtained during the Childhood Origins of Asthma (COAST) study consistently demonstrated increased rates of virus detection during illnesses compared to asymptomatic periods using the multiplex method employed in this trial.[20] Furthermore, when prolonged illnesses or repeated detection of rhinoviruses occurred in the COAST study, 95% of the time these were caused by an infection with an additional strain of rhinovirus, not persistence of the initial infection, arguing against colonization.[21] Finally, in MIST, the type of virus detected was not associated with response to therapy.

The MIST primary analysis was based on frequency of exacerbation and the unit of analysis was child. For the secondary analysis regarding virus, the unit of analysis was respiratory-tract Illness so that we could investigate whether the presence of a specific virus might modify treatment response. This was accomplished by way of the interaction between virus type and treatment. No differences in symptom burden or exacerbations were seen between treatment groups during rhinovirus infections. The literature has demonstrated reduction in length of hospitalization or wheezing episodes in children with rhinovirus infection treated with oral glucocorticosteroids compared to those who were not treated with oral glucocorticosteroids. In MIST, both study groups received treatment with either daily or high dose intermittent inhaled glucocorticosteroids which may have reduced our ability to detect a difference between groups.

Although not reported here, but being analyzed in a separate cost-effectiveness study, the reduced ICS exposure with the high-dose intermittent regimen should lower medication costs, given that outcomes were not significantly different between daily and intermittent treatments. In addition, the convenience of intermittent administration should improve acceptance by parents and improve adherence, but this requires further study.

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Figure S1. MIST study schedule for various tests and procedures.

Procedures	**Enrollment**	**Randomization**	**Treatment Phase: 52 Weeks**						
Week	-2	0	4	12	20	28	36	44	52
Physical exam and stadiometry	+	+	+	+	+	+	+	+	+
Safety monitoring	+	+	+	+	+	+	+	+	+
Allergen skin testing	**Either visit**								
Eosinophil count and serum IgE levels	**Either visit**								
Exhaled nitric oxide measurement	+	+			+				+
Diary Card assessment		+	+	+	+	+	+	+	+
Quality of life questionnaire		+	+			+			+
Nasal virus sampling		+			+				
Parental survey									+
Telephone contact			Every 4 weeks after each visit starting at week4						

Figure S2: Parental Respiratory-Tract Illness Questionnaire and instructions on when to start intermittent respiratory-tract Illness medications (CARE Network original form).

Parental Respiratory Illness Questionnaire and Starting Respiratory Illness Medications

Questionnaire

Please answer the following questions about your child's typical respiratory illness:

1. **What is usually the very first symptom you notice that leads you to believe that your child was starting a respiratory illness?**
Please choose one of the general categories in blue text from the list provided. Then choose the symptom in red text from the specific list within that category. (If the very first symptom is not on the list, please indicate the very first symptom in the 'Other' space.)

General: _____
Specific: _____
Other: _____

2. **Is there usually a symptom you notice that makes you very certain that the illness will lead to significant breathing problems?** ___ Yes ____ No

➡ **If NO, no further symptoms collected.**

2a. **What is usually the most important symptom you notice that makes you certain the illness will lead to significant breathing problems?**
Please choose one of the general categories in blue text from the list provided. Then choose the symptom in red text from the specific list within that category. (If the very first symptom is not on the list, please indicate the very first symptom in the 'Other' space.)

General: _____
Specific: _____
Other: _____

2b. **Is there usually a second symptom you notice that makes you very certain that the illness will lead to significant breathing problems?** ___ Yes ____ No

➡ **If NO, no further symptoms collected.**

3b. **What is usually the second symptom you notice that makes you feel certain the illness will lead to significant breathing problems?**
Please choose one of the general categories in blue text from the list provided. Then choose the symptom in red text from the specific list within that category. (If the very first symptom is not on the list, please indicate the very first symptom in the 'Other' space.)

General: _____
Specific: _____
Other: _____

MIST List of Symptoms of Respiratory Illness

General categories appear in bolded blue text.
Specific symptoms appear in red text.

Appearance Changes (100)
- dark circles under eyes (101)
- glassy eyes (102)
- watery eyes (103)
- other _____ (099)

Appetite Changes (200)
- eating less/won't eat (201)
- spitting-up/vomiting (202)
- other _____ (099)

Behavior Changes (300)
- bedwetting (301)
- fussy/cranky/irritable (302)
- hyperactive (303)
- less active (won't play) (304)
- emotional/crying at everything/quick to emotional outburst (305)
- short tempered/mean/angry (306)
- nervousness/anxiety (307)
- other _____ (099)

Breathing Problems (400)
- breathing worse (401)
- "can't breathe" (402)
- flaring of the nose (403)
- not breathing well/trouble breathing (404)
- pulling in of ribs/neck (405)
- rapid breathing (406)
- short of breath (407)
- breathing problems leading to color change (408)
- turning blue (409)
- other _____ (099)

Changes in Sleep Patterns (500)
- awakening during sleep (501)
- sleepy during the day/lethargic (502)
- sleep upright (503)
- sleepwalking (504)
- other _____ (099)

Cough A (600)
- infrequent (601)
- mild (602)
- not concerning (603)
- other _____ (099)

Cough B (700)
- concerning (701)
- constant (702)
- interrupts activities (703)
- interrupts sleep (704)
- repetitive (705)
- "THE asthma cough" (706)
- other _____ (099)

Fever (800)
- any fever (801)
- high fever (802)
- skin feels warm/hot to touch (803)
- other _____ (099)

Noisy Breathing (900)
- hoarse voice (901)
- snoring (902)
- other _____ (099)

Noisy Chest (1000)
- gurgling (1001)
- rattling (1002)
- wheezing (1003)
- other _____ (099)

Nose Symptoms (1100)
- congested/stuffy (1101)
- runny (1102)
- sneezing (1103)
- other _____ (099)

Activity Changes (1110)
- decreased activity/tired/sleepiness/lethargy (1111)
- lack of interest in regular activities (1112)
- other _____ (099)

Instructions to Start Respiratory Illness Medicines

- At the first 2 study visits you were asked questions to find out what **symptoms** your child has at the start of a breathing illness such as a cold that you think usually leads to a wheezing illness.
- These symptoms will be used to develop a plan just for YOUR CHILD to start the 7 day respiratory illness medicine.
- When your child develops these **symptoms** (listed on the MIST Action Plan), you will begin to give your child the respiratory illness medicine and do the following:
  - Obtain the nasal mucus collection from your child at the start of each respiratory illness in which the respiratory illness medicine is started.
  - Once you start the respiratory illness medicine, please continue it for the full 7 days, even if your child gets much better.
  - If you forget to give a dose of respiratory illness medicine, use the following guide to taking the next dose:
    - If a morning dose is missed, it should be given later in the day, and if not given then, give two doses at night.
    - If a night time dose is missed, give two doses the next morning and continue to give the usual dose twice a day until you are finished with all 7 days of respiratory illness medicine.
- When you are using the 7-day respiratory illness medicine **STOP** the daily study medicine and **RESTART** the daily study medicine after finishing the 7-day respiratory illness medicine treatment.
- If you feel that the kind of **symptoms** your child has with breathing illnesses change during the study, please inform your child's coordinator in order to modify the PLAN for use with future respiratory illnesses.

Figure S3. Symptom severity profiles for cough (Panel A), wheeze (Panel B), interference in activities (Panel C), and trouble breathing (Panel D) during respiratory-tract illnesses are not significantly different in intermittent and daily budesonide groups, both when prednisolone was given and when it was not. Day zero corresponds to the start of respiratory-tract illness treatment. Severity of respiratory-tract Illnesses was calculated as the area under the curve for symptoms (cough, wheeze, trouble breathing score, or interference with activity) from days 1 to 14 during respiratory-tract Illnesses adjusted for baseline symptom levels from days -7 to -13. Plotted values are the treatment group average on that day, stratified by use of prednisolone. P-values reflect treatment group comparison for total symptom burden over the time period shown.

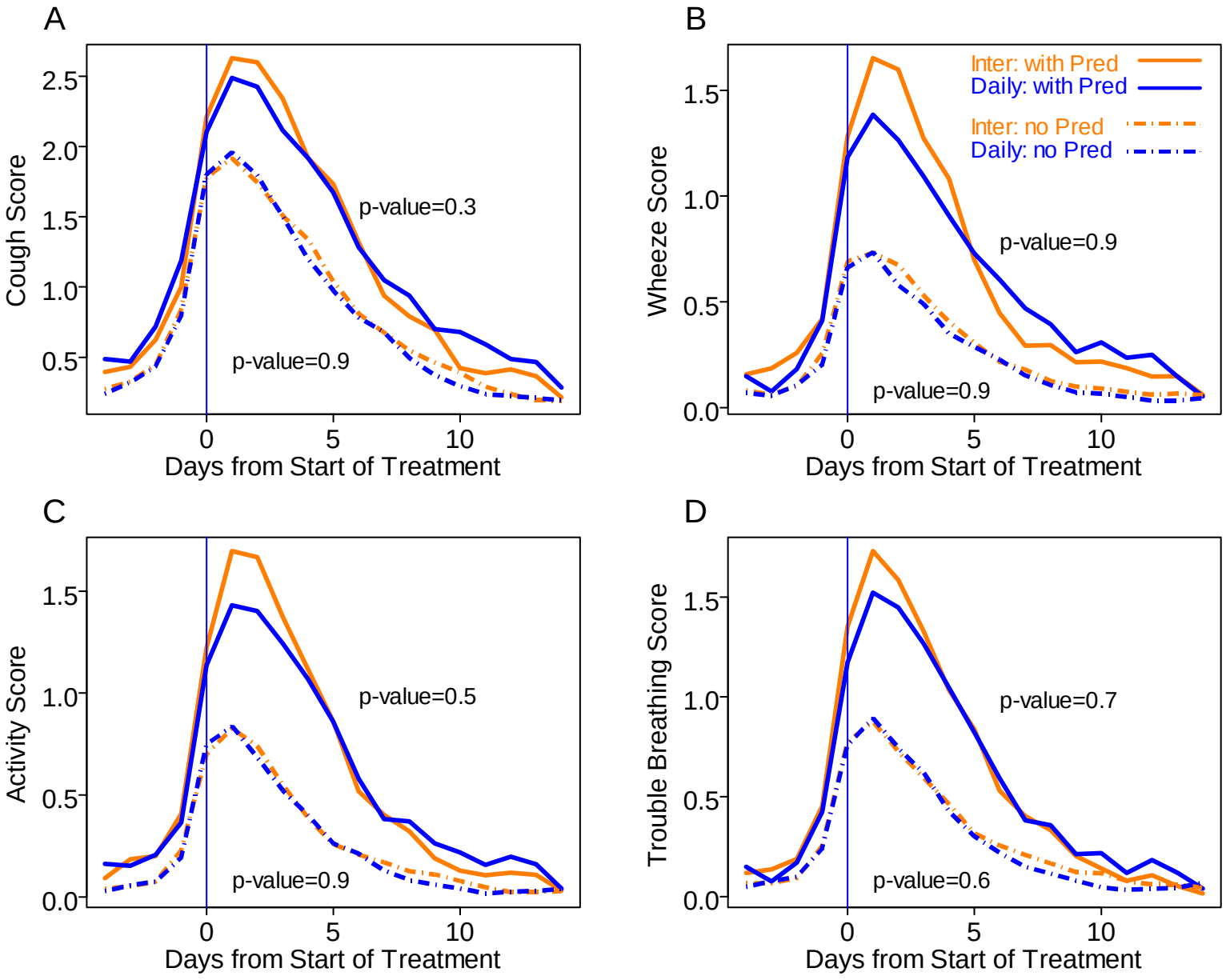


Figure S4. Growth outcomes: change in linear height (Panel A) and weight (Panel B). Error bars correspond to 95% confidence intervals based on mixed effects models adjusted for clinical center and age.

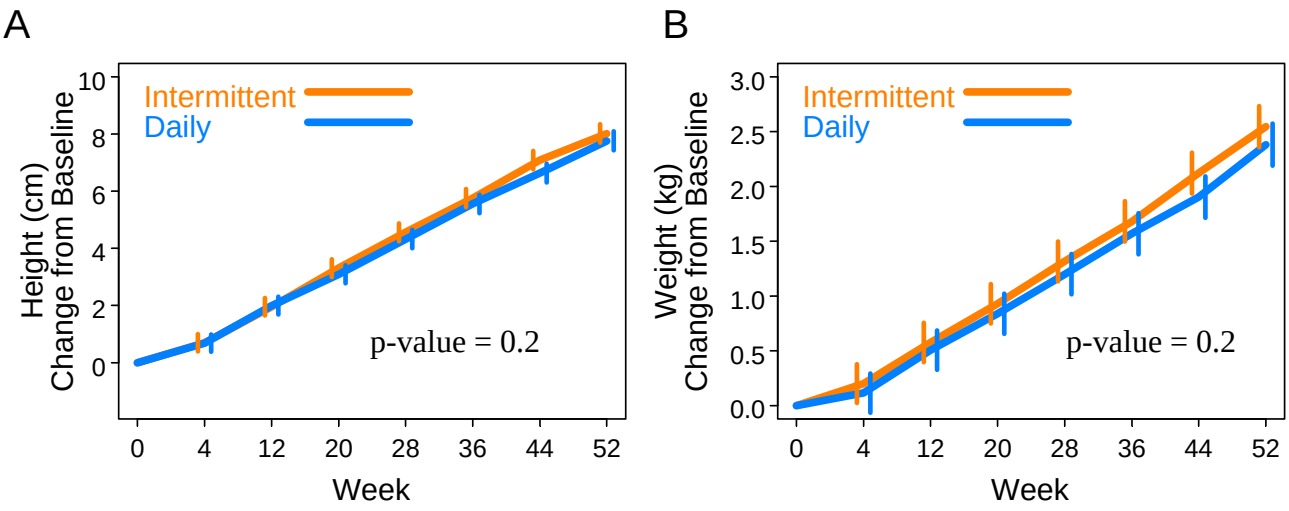
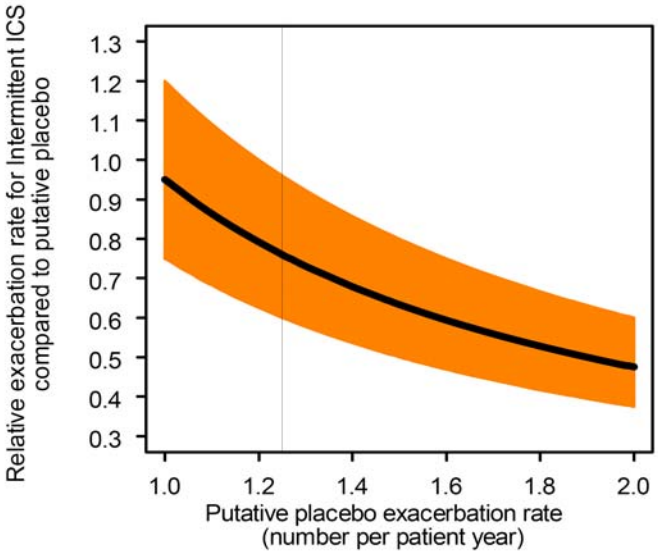


Figure S5. Panel A shows the relative exacerbation rate estimates for Intermittent ICS treatment compared to putative placebo treatment over a range of possible placebo exacerbation rates. The height of the shaded area indicates the uncertainty reflected in the 95% confidence intervals. The vertical line denotes the putative placebo exacerbation rate upon which the sample size was determined. Panel B compares the efficacy of the two active ICS treatments over a range of possible putative placebo exacerbation rates. The blue shaded area represents superiority of daily over intermittent ICS while the orange shaded area represents superiority of intermittent over daily ICS. The diagonal line denotes the presumed effect size (ie, the degree of superiority of daily over intermittent ICS) upon which the sample size was determined.



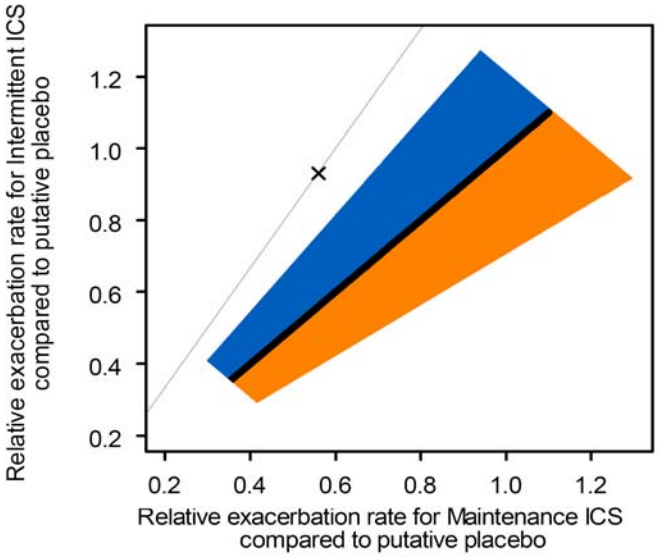


Table S1. Patient demographic and asthma characteristics in study completers and non-completers.

	Total (N=278)		Completers (N=213)	Non- completers (N =65)
Demographics				
Age (months) 12 – 32 months (%)	127 (45.7)		97(45.5)	30 (46.2)
Male (%)	192 (69.0)		155 (72.8)	37 (56.9)
Caucasian (%)	173 (62.2)		134 (62.9)	39 (60.0)
Asthma history				
Physician diagnosis of asthma (%)	198 (71.2)		155 (72.8)	43 (66.2)
Age at asthma diagnosis (yrs)*	1.5 ± 0.9		1.4 ± 0.9	1.6 ± 0.8
Age of onset of asthma (yrs)*	0.9 ± 0.7		0.9 ± 0.7	1.0 ± 0.8
Wheezing episodes past year	6.7 ± 5.4		6.7 ± 5.7	6.5 ± 4.0
Urgent/ED visits				
Rate	4.8 ± 4.2		4.6 ± 3.7	5.5 ± 5.5
Any (%)	269 (96.8)		205 (96.2)	64 (98.5)
Hospitalizations				
Rate	0.2 ± 0.5		0.3 ± 0.6	0.2 ± 0.5
Any (%)	53 (19.1)		42 (19.7)	11 (16.9)
Child absences past year (if day-cared or schooled)				
Rate	5.2 ± 8.4		5.4 ± 8.9	4.5 ± 6.7
Any (%)	105 (60.3)		83 (61.5)	22 (56.4)
	114 (41.0)		77 (36.2)	37 (56.9)
Tobacco smoke exposure since birth (%)	114 (41.0)		77 (36.2)	37 (56.9)
Asthma drugs in past year				
Any controller (%)	194 (69.8)		155 (72.8)	39 (60.0)
Inhaled glucocorticosteroid (%)	189 (68.0)		150 (70.4)	39 (60.0)
Leukotriene modifier (%)	49 (17.6)		37 (17.4)	12 (18.5)
Long-acting β-agonist (%)	1 (0.4)		1 (0.5)	0 (0.0)
Oral glucocorticosteroid courses (past year)				
Rate	1.7 ± 1.5		1.7 ± 1.4	1.8 ± 1.6
Any (%)	210 (75.5)		162 (76.1)	43 (73.9)
Atopic characteristics				
Any allergen sensitivity (%)	187 (67.5)		137 (64.3)	50 (78.1)
Any food sensitivity (%)	95 (34.8)		74 (34.9)	21 (34.4)
Any aeroallergen sensitivity (%)	161 (58.3)		119 (56.1)	42 (65.6)
IgE (IU/mL) [median (Q1, Q3)]	58 (21, 186)		58.9 (19.8, 186.5)	54.5 (27.3, 181.3)
Eosinophils $\geq$ 4% (%)	123 (47.3)		96 (47.8)	27 (45.8)
Eczema (%)	146 (52.5)		117 (54.9)	29 (44.6)
Allergic rhinitis (%)	105 (37.8)		82 (38.5)	23 (35.4)
Parental asthma (%)	171 (64.3)		134 (57.8)	37 (66.3)
Exhaled nitric oxide				
Able to perform procedure (%)	178 (64.0)		133 (62.4)	45 (69.2)
Exhaled nitric oxide $\geq$ 10 ppb (%)	78 (43.8)		63 (47.4)	15 (33.3)
Run-in Symptoms				
Percent episode-free days	67 ± 30		68 ± 29	64 ± 31
Average cough score†	0.4 ± 0.4		0.4 ± 0.4	0.5 ± 0.5
Average wheeze score†	0.1 ± 0.3		0.1 ± 0.3	0.2 ± 0.3
Average trouble breathing score†	0.1 ± 0.3		0.1 ± 0.3	0.1 ± 0.2

Average interference with activities score†	0.1 ± 0.2		0.1 ± 0.2	0.1 ± 0.3
Quality of Life (ITQOL ‡)				
Physical abilities	95.3 ± 11.1		96.0 ± 9.3	93.3 ± 15.7
Growth and development	91.8 ± 12.9		91.8 ± 13.6	91.5 ± 10.0
Bodily pain/discomfort	83.3 ± 17.7		83.1 ± 16.8	84.3 ± 20.4
Temperament and moods	81.9 ± 10.7		82.1 ± 10.9	81.3 ± 10.1
General behavior overall	70.8 ± 16.1		71.4 ± 15.9	69.0 ± 17.0
Behavior: getting along	73.9 ± 10.2		74.4 ± 10.4	72.3 ± 9.6
General health perceptions	59.2 ± 14.1		59.7 ± 14.2	57.4 ± 13.9
Parental impact-emotional	81.1 ± 18.0		81.7 ± 18.2	79.3 ± 17.4
Parental impact-time	89.3 ± 15.0		90.3 ± 14.5	86.2 ± 16.2
Family cohesion	77.3 ± 21.6		78.0 ± 21.4	75.2 ± 22.2
Physical characteristics				
Height (cm)	94.1 ± 9.1		94.3 ± 8.7	93.7 ± 10.1
Height (percentile)	53.8 ± 28.5		54.3 ± 28.5	52.2 ± 28.5
Height (z-score)	0.1 ± 1		0.1 ± 1	0.1 ± 1
Weight (kg)	15.2 ± 3.1		15.3 ± 3.1	15.1 ± 2.9
Weight (percentile)	63.2 ± 28		63 ± 27.9	63.9 ± 28.5
Weight (z-score)	0.5 ± 1.1		0.5 ± 1.1	0.5 ± 1
Head circumference (cm)	50 ± 1.9		50 ± 2	49.8 ± 1.8
Head circumference (percentile)	71.8 ± 25.9		71.6 ± 26.2	72.4 ± 25.2
Head circumference (z-score)	0.9 ± 1.1		0.9 ± 1.1	0.8 ± 1
Nasal viruses				
Any nasal virus identified (%)	148 (53.2)		111 (52.1)	37 (56.9)

Data are expressed as mean ± SD or frequency (%)
There were no statistically significant subgroup differences
*Among those participants with an asthma diagnosis
†Scored from 0 to 5
‡Infant Toddler Quality of Life: Highest possible score = 100

Table S2. Patient demographic and asthma characteristics in non-completers and by intermittent and daily budesonide groups.

	Total Not Completed (N=65)		Intermittent (N=26)	Daily (N =39)
Demographics				
Age (months) 12 – 32 months (%)	30 (46.2)		13 (50.0)	17 (43.6)
Male (%)	37 (56.9)		14 (53.9)	23 (59.0)
Caucasian (%)	39 (60.0)		18 (69.2)	21 (53.9)
Asthma history				
Physician diagnosis of asthma (%)	43 (66.2)		17 (65.4)	26 (66.7)
Age at asthma diagnosis (yrs)*	1.6 ± 0.8		1.6 ± 0.9	1.6 ± 0.7
Age of onset of asthma (yrs)*	1.0 ± 0.8		0.9 ± 0.8	1.0 ± 0.8
Wheezing episodes past year	6.5 ± 4.0		6.9 ± 5.2	6.2 ± 3.0
Urgent/ED visits				
Rate	5.5 ± 5.5		6.6 ± 7.7	4.7 ± 3.1
Any (%)	64 (98.5)		25 (96.2)	39 (100)
Hospitalizations				
Rate	0.2 ± 0.5		0.2 ± 0.5	0.2 ± 0.5
Any (%)	11 (16.9)		4 (15.4)	7 (18.0)
Child absences past year (if day-cared or schooled)				
Rate	4.5 ± 6.7		6.6 ± 8.7	2.5 ± 3.1
Any (%)	22 (56.4)		11 (57.9)	11 (55)
	37 (56.9)		15 (57.7)	22 (56.4)
Tobacco smoke exposure since birth (%)	37 (56.9)		15 (57.7)	22 (56.4)
Asthma drugs in past year				
Any controller (%)	39 (60.0)		16 (61.5)	23 (59.0)
Inhaled glucocorticosteroid (%)	39 (60.0)		16 (61.5)	23 (59.0)
Leukotriene modifier (%)	12 (18.5)		3 (11.5)	9 (23.1)
Oral glucocorticosteroid courses (past year)				
Rate	1.8 ± 1.6		1.7 ± 1.5	1.9 ± 1.7
Any (%)	48 (73.9)		20 (76.9)	28 (71.8)
Atopic characteristics				
Any allergen sensitivity (%)	50 (78.1)		21 (84.0)	29 (74.4)
Any food sensitivity (%)	21 (34.4)		8 (34.8)	13 (34.2)
Any aeroallergen sensitivity (%)	42 (65.6)		16 (64.0)	26 (66.7)
IgE (IU/mL) [median (Q1, Q3)]	55 (27, 181)		40 (22, 90)	85 (32, 194)
Eosinophils $\geq$ 4% (%)	27 (45.8)		9 (39.1)	18 (50.0)
Eczema (%)	29 (44.6)		9 (34.6)	20 (51.3)
Allergic rhinitis (%)	23 (35.4)		7 (26.9)	16 (41.0)
Parental asthma (%)	37 (57.8)		15 (57.7)	22 (57.9)
Exhaled nitric oxide				
Able to perform procedure (%)	45 (69.2)		15 (57.7)	30 (76.9)
Exhaled nitric oxide $\geq$ 10 ppb (%)	15 (33.3)		4 (26.7)	11 (36.7)
Run-in Symptoms				
Percent episode-free days	64 ± 31		65 ± 33	63 ± 31
Average cough score†	0.5 ± 0.5		0.5 ± 0.5	0.5 ± 0.5
Average wheeze score†	0.2 ± 0.3		0.1 ± 0.2	0.2 ± 0.3

Average trouble breathing score†	0.1 ± 0.2		0.1 ± 0.1	0.2 ± 0.2
Average interference with activities score†	0.1 ± 0.3		0.1 ± 0.3	0.2 ± 0.2
Quality of Life (ITQOL‡)				
Physical abilities	93.3 ± 15.7		91.5 ± 23.5	94.4 ± 7.4
Growth and development	91.5 ± 10.0		91.6 ± 9.7	91.4 ± 10.4
Bodily pain/discomfort	84.3 ± 20.4		84.7 ± 18.4	84.0 ± 21.8
Temperament and moods	81.3 ± 10.1		80.2 ± 8.5	82.0 ± 11.1
General behavior overall	69.0 ± 17.0		69.4 ± 15.1	68.7 ± 18.4
Behavior: getting along	72.3 ± 9.6		73.5 ± 7.7	71.6 ± 10.7
General health perceptions	57.4 ± 13.9		55.0 ± 14.6	58.9 ± 13.4
Parental impact-emotional	79.3 ± 17.4		79.0 ± 17.3	79.4 ± 17.7
Parental impact-time	86.2 ± 16.2		88.6 ± 17.6	84.7 ± 15.4
Family cohesion	75.2 ± 22.2		75.8 ± 18.4	74.9 ± 24.6
Physical characteristics				
Height (cm)	93.7 ± 10.1		92.2 ± 11.6	94.7 ± 8.9
Height (percentile)	52.2 ± 28.5		50.4 ± 30.2	53.5 ± 27.5
Height (z-score)	0.1 ± 1.0		0 ± 1.2	0.2 ± 0.9
Weight (kg)	15.1 ± 2.9		14.7 ± 3.0	15.4 ± 2.9
Weight (percentile)	63.9 ± 28.5		63.7 ± 27.5	64 ± 29.5
Weight (z-score)	0.5 ± 1.0		0.5 ± 0.9	0.5 ± 1.0
Head circumference (cm)	49.8 ± 1.8		49.7 ± 1.9	49.8 ± 1.8
Head circumference (percentile)	72.4 ± 25.2		75.8 ± 25.1	70.1 ± 25.3
Head circumference (z-score)	0.8 ± 1.0		1.0 ± 0.9	0.8 ± 1.0
Nasal viruses				
Any nasal virus identified (%)	37 (56.9)		13 (50.0)	24 (61.5)

Data are expressed as mean ± SD or frequency (%)
There were no statistically significant subgroup differences
*Among those participants with an asthma diagnosis
†Scored from 0 to 5
‡Infant Toddler Quality of Life: Highest possible score = 100

Table S3. Distribution of first most important symptom that led to start respiratory-tract illness treatments was comparable between intermittent and daily budesonide groups*.

First most important symptom	Intermittent	Daily
Cough	219 (53.4)	203 (58.0)
Noisy chest	31 (7.6)	34 (9.7)
Breathing problems	25 (6.1)	16 (4.6)
Noisy breathing	6 (1.5)	3 (0.9)
Change in appearance, appetite, behavior, activity, or sleep patterns	25 (6.1)	17 (4.9)
Nasal symptoms	88 (21.5)	67 (19.1)
Fever	16 (3.9)	10 (2.9)
Total respiratory-tract illness treatments	410	350

Data are expressed as frequency (%)
*P=0.6 for group difference

Table S4. Changes in symptom score during respiratory illness treatments and changes in quality of life in intermittent and daily budesonide groups.

	Intermittent	Daily	Treatment Effect
	Treatment Group Averages		Average Difference
Symptoms during respiratory-tract Illness treatments (change from pre-illness score)	(N=139)	(N=139)	
Cough	1.2 (0.9, 1.5)	1.4 (1.1, 1.7)	-0.2 (-0.6, 0.2)
Wheeze	0.5 (0.3, 0.7)	0.5 (0.2, 0.7)	0.0 (-0.3, 0.4)
Interference in activities	0.6 (0.3, 0.8)	0.7 (0.4, 1.0)	-0.2 (-0.5, 0.2)
Trouble breathing	0.6 (0.4, 0.8)	0.6 (0.4, 0.9)	-0.0 (-0.4, 0.3)
Infant Toddler Quality of Life Domains* (change from baseline)	(N=113)	(N=110)	
Physical abilities	1.6 (-2.1, 5.2)	1.7 (-1.1, 4.5)	-0.1 (-4.7, 4.4)
Growth and development	3.7 (0.9, 6.5)	2.0 (-0.1, 4.2)	1.7 (-1.8, 5.2)
Bodily pain and discomfort	7.5 (3.8, 11.2)	1.6 (-2.2, 5.5)	5.9 (0.6, 11.2)
Temperament and moods	1.4 (-0.8, 3.6)	1.1 (-1.0, 3.2)	0.3 (-2.7, 3.3)
General behavior overall	-1.9 (-4.3, 0.6)	1.7 (-1.7, 5.0)	-3.5 (-7.7, 0.7)
Behavior: getting along	1.0 (-0.8, 2.8)	2.0 (0.3, 3.6)	-1.0 (-3.4, 1.4)
General health perceptions	0.9 (-1.3, 3.2)	4.3 (1.7, 6.9)	-3.3 (-6.7, 0.1)
Parental impact – emotional	1.6 (-2.9, 6.1)	2.8 (-0.9, 6.4)	-1.1 (-6.9, 4.6)
Parental impact – time	0.6 (-2.6, 3.7)	1.2 (-1.9, 4.2)	-0.6 (-4.9, 3.8)
Family cohesion	0.3 (-4.2, 4.8)	0.6 (-3.3, 4.5)	-0.4 (-6.3, 5.6)

Results are expressed as estimate (95% Confidence Interval) and adjusted for age and clinical center with daily treatment in the denominator.
*Highest possible score = 100

Table S5. Distribution of type of nasal viruses identified in intermittent and daily budesonide groups at clinic visits (randomization and visit 5), during respiratory-tract illnesses, and during respiratory-tract illness exacerbations (prednisolone use)*.

Nasal virus	In-Clinic		Respiratory-tract illnesses		Respiratory-tract illnesses with exacerbations	
	Intermittent	Daily	Intermittent	Daily	Intermittent	Daily
Rhinovirus	68 (27.3)	68 (27.2)	181 (45.9)	165 (47.4)	31 (41.3)	27 (36.5)
Multiple viruses	28 (11.2)	28 (11.2)	59 (15.0)	56 (16.1)	12 (16.0)	9 (12.2)
Parainfluenza	2 (0.8)	4 (1.6)	18 (4.6)	13 (3.7)	3 (4.0)	4 (5.4)
RSV	1 (0.4)	0 (0.0)	7 (1.8)	13 (3.7)	1 (1.3)	8 (10.8)
Influenza	0 (0.0)	1 (0.4)	6 (1.5)	5 (1.4)	1 (1.3)	2 (2.7)
H1N1	1 (0.4)	2 (0.8)	8 (2.0)	11 (3.2)	1 (1.3)	3 (4.1)
Metapneumovirus	2 (0.8)	0 (0.0)	8 (2.0)	8 (2.3)	4 (5.3)	2 (2.7)
Enterovirus	3 (1.2)	3 (1.2)	14 (3.6)	7 (2.0)	4 (5.3)	3 (4.1)
Coronavirus	6 (2.4)	11 (4.4)	21 (5.3)	6 (1.7)	2 (2.7)	0 (0.0)
Adenovirus	1 (0.4)	3 (1.2)	2 (0.5)	1 (0.3)	0 (0.0)	0 (0.0)
Bocavirus	6 (2.4)	2 (0.8)	1 (0.3)	2 (0.6)	0 (0.0)	0 (0.0)
Negative viruses	131 (52.6)	128 (51.2)	69 (17.5)	61 (17.5)	16 (21.3)	16 (21.6)
Total samples (N)	249	250	394	348	75	74

Data are presented as frequency (%) or number (N)

*P value between treatments in-clinic (P=0.6), during respiratory-tract illnesses (P=0.3) and respiratory-tract illnesses with exacerbations (P=0.3).

Table S6: Frequency (%) of patients with serious and non-serious adverse events.

Adverse Event	Intermittent (N=139) Frequency (%)	Daily (N=139) Frequency (%)
Serious adverse events - hospitalizations		
Asthma exacerbation†	5 (4)†	4 (3)
Concussion	1 (1)	0 (0)
Gastroenteritis‡	1 (1)‡	1 (1)
Diarrhea	0 (0)	1 (1)
Flu	1 (0)	0 (0)
Pneumonia	0 (0)	1 (0)
Tonsillectomy	1 (1)	0 (0)
Car accident	1 (1)	0 (0)
Non-serious adverse events§		
URI/allergic rhinitis	98 (71%)	86 (62%)
Asthma	49 (35%)	47 (34%)
Otitis media	28 (20%)	23 (17%)
Fever	23 (17%)	24 (17%)
Dermatitis / nonspecific skin eruption	25 (18%)	19 (14%)
Influenza	24(17%)	21 (15%)
Pharyngitis/sore throat	13 (9%)	9 (6%)
Cough	11 (8%)	11 (8%)
Nausea and vomiting	11 (8%)	9 (6%)
Sinusitis	10 (7%)	7 (5%)
Diarrhea	6 (4%)	10 (7%)
Croup	7 (5%)	7 (5%)
Urticaria	7 (5%)	6 (4%)
Pneumonia	3 (2%)	7 (5%)
Epistaxis	4 (3%)	6 (4%)
Conjunctivitis	7 (5%)	2 (1%)

* P > 0.05 for all comparisons

† 1 patient with 2 additional asthma hospitalizations after treatment failure and in intention-to-treat phase off study treatments.

‡ 1 patient with 2 episodes

§Adverse events with at least 5% frequency