

A Randomized Trial of Montelukast in Respiratory Syncytial Virus Postbronchiolitis

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Infants often develop reactive airway disease after respiratory syncytial virus (RSV) bronchiolitis. Cysteinyl-leukotrienes (cys-LT) are released during RSV infection and may contribute to the inflammation. We hypothesized that a cys-LT receptor antagonist would ameliorate reactive airway disease subsequent to RSV bronchiolitis. One hundred and thirty infants who were 3 to 36 months old, hospitalized with acute RSV bronchiolitis, were randomized into a double-blind, parallel comparison of 5-mg montelukast chewable tablets or matching placebo given for 28 days starting within 7 days of symptom debut. Infants with a suspected history of asthma were excluded. One hundred sixteen infants provided diary card data for the treatment period. Median age was 9 months. Infants on montelukast were free of any symptoms on 22% of the days and nights compared with 4% of the days and nights in infants on placebo ($p = 0.015$). Daytime cough was significantly reduced on active treatment ($p = 0.04$). Exacerbations were significantly delayed from montelukast compared with placebo ($p < 0.05$). In conclusion, cys-LT antagonist treatment reduces lung symptoms subsequent to RSV bronchiolitis.

Keywords: respiratory syncytial virus; bronchiolitis; bronchial hyperresponsiveness; infant; leukotriene receptor antagonist

Respiratory syncytial virus (RSV) bronchiolitis is the most common cause of pneumonia and bronchiolitis in infants and a major health burden worldwide. The steep rise during winter months of hospital admissions for pneumonia and bronchiolitis in infants and young toddlers, mean age typically 3 months, is the signature of RSV, which is ubiquitous and highly contagious, with most infants affected by 2 years of age.

RSV bronchiolitis accounts for a significant burden in young infants due to hospital admission and postbronchiolitis reactive airway disease (RAD). The hospitalization rate for bronchiolitis in infants has more than doubled in recent decades and now constitutes one in six of all hospitalizations in infancy (1). Nearly 50% of all infants hospitalized with lower respiratory disease were associated with RSV bronchiolitis. In addition, RSV represents a major burden of outpatient visits for RSV airway infections presenting as upper respiratory tract infections and exacerbations of bronchitis and asthma.

RSV bronchiolitis is commonly followed by RAD with recurrent wheeze and other asthma-like symptoms (2–4). Recent prospective data suggest that the postinfectious course of even mild RSV bronchiolitis is characterized by an

increased risk of RAD but not atopic asthma, and may account for an important subgroup of the asthmatic syndrome in childhood and particularly in young children (5). RAD mainly occurs after the more severe cases of RSV postbronchiolitis (2). Because RSV bronchiolitis requiring hospitalization has been increasing in recent decades, this may account for some of the increase in the incidence of early childhood wheeze.

There is no evidence-based therapy against RSV bronchiolitis or the subsequent recurrent wheeze. The usefulness of bronchodilators is controversial (6), and steroids are ineffective on the acute and long-term clinical outcome whether administered systemically (7–9) or topically (10–12).

The inflammatory response to viral-induced bronchiolitis includes bronchial obstruction, increased airway secretion, mucosal edema, and infiltration of inflammatory cells including eosinophil granulocytes (13). Cysteinyl-leukotrienes (cys-LTs) are released during RSV airway infection in infants (14–16). Cys-LTs are known to cause bronchial obstruction, mucosal edema, and infiltration of eosinophilic granulocytes and increase bronchial responsiveness (17). Cys-LT does therefore represent a potential target for treating RSV bronchiolitis and the subsequent hyperresponsiveness. Recently specific cys-LT receptor antagonists (LTRA) have become available. We therefore performed a randomized study to assess the effect of LTRA on the postinfectious course of RSV bronchiolitis.

METHODS

This study was approved by the local Ethics Committee (KF 02-081/99) and the National Health Authorities (2612-1132). A parent or guardian of every infant provided written informed consent.

The study was designed as a randomized, placebo-controlled, double-blind, parallel-group study in a multicenter, secondary care setting.

Patients were recruited among infants 3 to 36 months of age hospitalized with RSV bronchiolitis. RSV was verified in nasal secretions by an enzyme-linked immunosorbent assay (in-house). Bronchiolitis was documented from coryza, cough, wheeze, and respiratory distress but independent of chest X-ray. Patients were required to have moderate to severe symptoms requiring hospital admission. All the 11 Danish pediatric centers recruiting for this study were secondary referral centers enrolling infants from their local region. Patients were included over two winter seasons from December 1999 until March 2001.

Patients were excluded if they had a history of asthma symptoms and had ever used antiasthma medication except for occasional use of oral β_2 -agonist syrups. Birth before Week 36 and known chronic diseases were also reasons for exclusion.

Acute treatment during the hospital admission was at the discretion of the investigator.

Study treatment was given as 5-mg montelukast chewable tablets or matching placebos in the evening for 28 days. Inactive, identical, flavored, chewable look-alike tablets (normally used as “taste-tablets” for demonstration purpose) were obtained from the Danish branch of Merck Sharp and Dohme and used as placebo. Blinding of active and placebo tablets were provided by the University Pharmacy, Glostrup, Copenhagen, in numbered containers with 32 tablets in each. This pharmacy also provided the computer-generated randomization sequence in blocks of four.

(Received in original form July 25, 2002; accepted in final form October 2, 2002)

Funding for this study was provided by the University Hospital of Copenhagen.

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Am J Respir Crit Care Med Vol 167, pp 379–383, 2003

Originally Published in Press as DOI: 10.1164/rccm.200207-7470C on October 3, 2002

Internet address: www.atsjournals.org

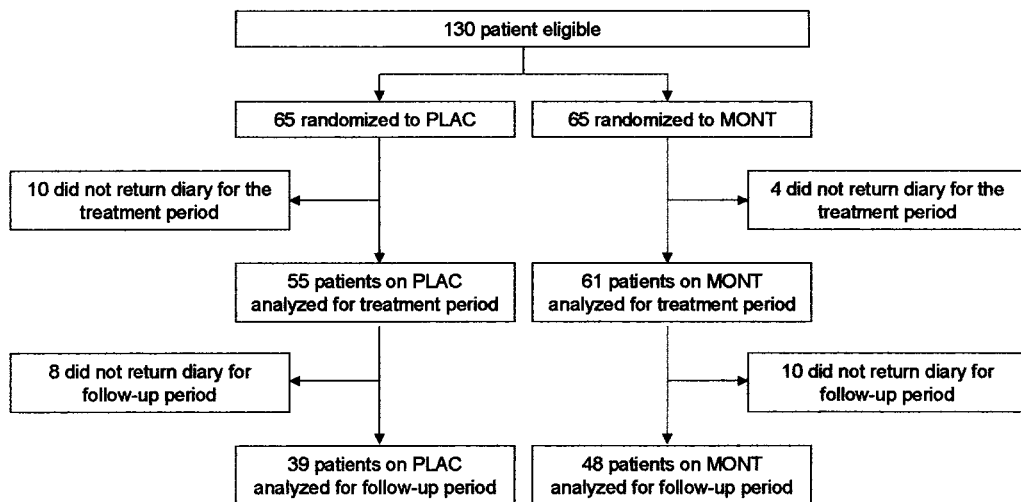


Figure 1. Participant flow.

Patients were consecutively assigned to their randomization number at each center by the local investigator. Allocation was concealed in sealed envelopes by the principal investigator.

Adherence was enforced by telephone contact to the family from a study nurse twice during the treatment period and was finally estimated from pill counts.

Withdrawal from the study was at the discretion of the investigator if wheezing and coughing were judged to be too troublesome for continuation in this placebo-controlled trial.

All clinical assessments in the study were done by the investigators, who are all trained pediatricians.

Symptoms were recorded on diary cards during the 4-week treatment period and for further 4 weeks starting 2 months after enrollment, i.e., 4 weeks after end of the treatments. The diary card was previously validated for use in young children with recurrent wheeze (18). The caretaker rated the symptoms of nighttime cough, daytime cough, wheeze, dyspnea, and limitation of activity on a five-point scale from 0 = "no symptoms" to 4 = "very severe symptoms." The number of β_2 -rescue treatments day and night and attendance to an emergency ward or a hospital for lung symptoms was noted.

Nasal lavage samples were collected at randomization and at the end of the treatment period by instilling sterile saline into each nostril and then aspirating the lavage fluid. Interferon- γ , interleukin-13 and total cys-LT were determined. Lower limits of detection for the assays for interferon- γ and interleukin-13 (Endogen, Rockford, IL) were 2 and 7 pg/ml, respectively, and 13 pg/ml for cys-LT (Cayman Chemical Co., Ann Arbor, MI). Mediator levels were normalized as a ratio to urea nitrogen concentration (colorimetric assays from Sigma Diagnostics, St. Louis, MO; lower limit of detection of 1 mg/dl). The inter- and intra-assay variability of all assays was less than 10%. All assays were performed in duplicate by a single operator blinded to patient status.

Statistical Analyses

Complete blinding of patients, investigators, and statisticians was maintained until all data had been locked after double data entry. Thereafter data were grouped according to treatment code without revealing their identity. The data were unblinded after completion of the statistical analyses.

Data were analyzed based on the intention-to-treat principle. The STATISTICA (www.statsoftinc.com) software package was used.

The primary outcome was 24-hour symptom-free days and nights during the 4-week treatment period, defined as no symptoms in all five symptom variables.

Days with missing values were excluded from analysis.

The secondary outcome was individual symptom scores, exacerbations (withdrawal, attendance of emergency room or hospitalization due to wheezy symptoms), and use of rescue treatment during the treatment period. In addition, 24-hour symptom-free days and nights during the third month follow-up period was a secondary outcome.

Mediators in nasal lavage samples were considered exploratory end-points.

Power was approximated from previous studies in toddlers with asthma treated with inhaled corticosteroids and montelukast using similar diary cards (19, 20).

The data distribution was skewed. Descriptive statistics are therefore given as median and (quartiles), and test statistics applied nonparametric methods. Comparison of medians (ranks) employed the Mann-Whitney test using z-approximations whenever n is more than 25; otherwise the U-statistic was used. Comparison of time to first event was analyzed by survival analysis using the Kaplan-Meier method and the log-rank test. Comparison of frequency data (i.e., proportions) was done by the Fishers exact test. Two-tailed statistical tests and a significance level of 5% were applied.

RESULTS

One hundred and thirty infants were randomized. The flow of the participants is depicted in Figure 1. Fourteen infants were excluded as no diary card was returned. One hundred and sixteen infants provided diary cards from the 4-week treatment period (61 on active and 55 on placebo treatment), of whom 100/116 (86%) provided diary cards for more than 23 of the intended 28 days. Eighty-seven infants provided diary cards from the follow-up period starting 56 days (median) after randomization.

The treatment groups did not differ with respect to age, sex, atopic heredity, day care attendance, or exposure to pets or tobacco (Table 1). Nor did the groups differ in disease severity as assessed by the symptom score during the first day of symptom monitoring, length of hospital admission, need for O₂ or continuous positive airway pressure (CPAP), or use of inhaled β_2 -agonist (Table 1).

Symptoms of acute bronchiolitis were moderate to severe (Table 1) with an overall length of hospital admission of 4 days [3–6]. Study treatment was delayed by a median of 3 days [2–4] from admission.

Symptoms of the postbronchiolitis RAD during the 4-week trial period were mild with an overall median composite symptom score of 0.9 (0.5–1.2) on the five-point scale. Symptom score during the follow-up period during the third month was significantly lower, 0.3 (0.1–0.7).

Adherence, as estimated from tablets returned compared with the diary card period, showed that the median number of days without treatment was 0 (0–1) with no significant difference between treatment groups.

TABLE 1. DEMOGRAPHICS (MEDIAN AND QUARTILES)

	Montelukast	Placebo
Demographics		
n	61	55
Age, mo	9.1	9.9
Male	24	32
Atopic heredity	28	21
Day care	32	25
Pets at home	30	26
Tobacco exposure	29	25
Hospital admission		
Days	5 (3–7)	4 (2–6)
Treatment		
O ₂ , N	17	17
CPAP, N	8	10
β ₂ -agonist, N	51	43
Symptom score, 0–4 Day 1		
Night cough	2.5	3
Day cough	4	4
Wheeze	2	3
Dyspnea	2	3
Activity	2	3

Definition of abbreviation: CPAP = continuous positive airway pressure. None of the comparisons showed any significant differences.

The primary outcome was in favor of active treatment, as infants on montelukast were free of daytime and nighttime symptoms on 6 of 28 days (22% of the treatment period) as compared with 1 of 28 days (4% of the treatment period) in infants on placebo (Mann–Whitney test, $p = 0.015$) (Figure 2). Significantly, more infants reported at least one symptom-free day and night on active treatment (Fisher’s Exact test, $p = 0.045$). The separation of the treatment effect from the control treatment became apparent during the last 2 weeks of the treatment period (Figure 2).

Daytime cough was significantly reduced on active treatment (Mann–Whitney test, $p = 0.04$) (Table 2). All other individual symptoms and the composite symptom score were numerically in favor of active treatment but did not reach statistical significance. Similarly, use of β₂-agonist rescue day and night was numerically but not statistically significantly in favor of active treatment.

Three infants on montelukast were withdrawn from the study due to symptom severity versus 8 infants on placebo (Fisher, $p = 0.11$). Inhaled steroid treatment was subsequently instituted in these patients. Median time to withdrawal was 10 days on placebo and 27 days on active treatment ($p = 0.067$).

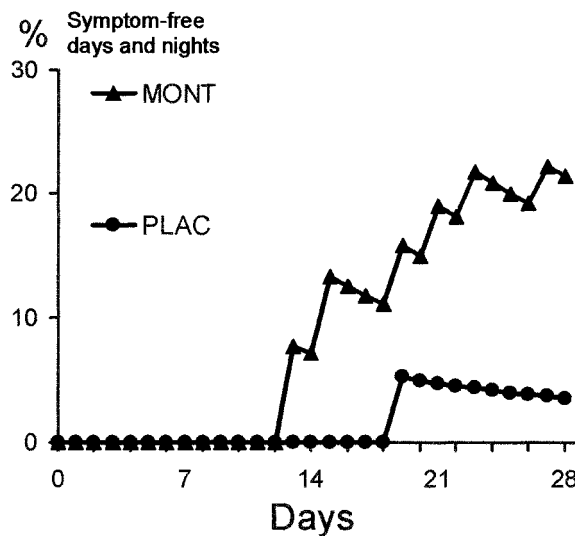


Figure 2. Daily medians of the percentage of days and nights without any symptoms. Missing data were considered to be symptomatic days. Difference between treatments was significant ($p = 0.015$).

Exacerbations (withdrawal due to symptom severity or attending emergency room or hospitalization due to lung symptoms) occurred in 4 infants on montelukast and 10 on placebo (Fischer, $p = 0.08$). Time to exacerbation was 8 days in the placebo group and 23 days in the montelukast-treated group ($p = 0.044$) (Table 2).

During follow-up starting 2 months after enrollment there were no significant differences between treatment groups in any of the outcomes, and the trends seemed randomly directed.

There were no adverse events reported.

Cys-LT:urea nitrogen levels in nasal secretions did not differ significantly between placebo- and LTRA-treated groups at baseline (206 [n = 49] and 203 [n = 43], respectively) nor at the end of the treatment periods (176 [n = 42] and 154 [n = 50], respectively). The numeric fall in standardized levels of cys-LT were not statistically significant ($p > 0.1$).

The ratio of interferon-γ to interleukin-13 were 0.6 and 0.4 at baseline (n = 38) in the placebo and LTRA groups, respectively ($p = 0.08$). There were no significant changes after treatment (ratios 0.5 and 0.3, respectively; $p > 0.1$).

TABLE 2. CLINICAL OUTCOMES DURING THE 4-WEEK TREATMENT PERIOD

	Placebo (n = 55)	Montelukast (n = 61)	p Level
Percentage of symptom free days and nights	4% (0–29)	22% (4–39)	0.015
Night cough symptom score (0–4)	0.9 (0.5–1.3)	0.8 (0.5–1.1)	0.563
Day cough symptom score (0–4)	1.4 (1.0–1.9)	1.3 (0.8–1.6)	0.043
Wheeze symptom score (0–4)	0.5 (0.2–0.9)	0.4 (0.2–1.0)	0.786
Dyspnea symptom score (0–4)	0.7 (0.4–1.0)	0.5 (0.2–0.9)	0.164
Activity symptom score (0–4)	0.6 (0.2–1.0)	0.5 (0.2–0.8)	0.386
Mean composite symptom score (0–4)	0.9 (0.5–1.0)	0.7 (0.5–1.1)	0.168
Percentage of days without rescue β ₂ -agonist	64% (25–96)	75% (37–93)	0.538
Percentage of nights without rescue β ₂ -agonist	89% (76–100)	96% (79–100)	0.701
Patients receiving rescue steroid	15%	5%	0.113
Time to rescue steroid	9 days (7–24)	27 days (2–34)	0.067
Patients with exacerbations	18%	7%	0.085
Time to exacerbations	8 days (6–22)	23 days (2–27)	0.044

Symptoms score on a five-point scale from 0 = “no symptoms” to 4 = “very severe symptoms.” Data are given as median (quartiles).

DISCUSSION

RSV postbronchiolitis symptoms improved during treatment with an LTRA in this randomized, double-blind trial. Symptom-free days and nights were increased, daytime cough was reduced, and exacerbations were delayed significantly from LTRA. The numerical differences were consistently in favor of active treatment in every clinical outcome, which supports the general conclusion of a beneficial effect from LTRA. The treatment effect became apparent 2 weeks into the treatment period (Figure 2). This suggests that the treatment affects the RAD secondary to the bronchiolitis rather than the acute inflammatory changes of the bronchiolitis.

The treatment effect seen in this study seems clinically relevant. The number of symptom-free days and nights was increased from 4% on placebo to 22% on montelukast. The magnitude of this effect is somewhat larger than the effect seen in toddlers with asthma treated with inhaled corticosteroids or leukotriene receptor antagonists where similar diary cards were used. In our recent studies using 200 mcg fluticasone propionate daily in 1- to 3-year-old toddlers with moderately severe asthma (19), as well as our study on the effect of montelukast in 2- to 5-year-old children with moderately severe asthma (20), we found approximately 10% improvement of symptom-free days and nights and halving of exacerbation rate from active treatment compared with placebo.

The median overall composite symptom level during the post-bronchiolitis trial period of the present trial was 0.9, i.e., between the two mildest categories (no symptoms and very mild symptoms) on a five-point scale. A floor effect can therefore be expected with little room for improvement. Only daytime cough scored higher (between 1 and 2) and was accordingly the only individual symptom showing statistical difference between treatment groups. Such low symptom levels conform to the previous observations of a strong bias toward low level scoring. Even lower levels were found in the aforementioned two studies in asthmatic toddlers, where similar diary cards were applied, and reflect the low sensitivity of symptom scoring for detecting lung disease in infants and young children. The experience from these previous studies also supports the present observation that the composite measure of symptom-free days and nights is the more sensitive measure.

These caregiver-reported symptoms suggest that RAD after RSV bronchiolitis initially manifests as a persistence of low-grade lower respiratory symptoms.

The study was sufficiently powered to see an effect on the primary outcome, symptom-free days and nights. If withdrawal due to symptoms severity is used for study powering and the observed proportion of patients is assumed to reflect the real incidence, a study of over 300 infants would be required to achieve a power of 80% at a Type I error level of 5% for this outcome.

There is a sound rationale for the observed effect of a cys-LT modifier on RSV bronchiolitis. The airway's immune response to viral infections in many ways resembles that after exposure to allergens including the release of an array of proinflammatory cytokines, influx of macrophages, lymphocytes and eosinophils (13, 21), and the release of mediators such as cys-LT, which are found in excessive amounts in airway secretion during RSV infection in infants (14–16). Cys-LTs are potent proinflammatory mediators, which cause increased mucosal blood flow and mucosal edema through increased vascular permeability and interstitial transport of macromolecules. Such escape of plasma proteins into the tissue provides the source of potent plasma protein-derived inflammatory mediators. Cys-LTs are potent bronchoconstrictors and enhance bronchial responsiveness. *In vitro*, they

reduce the ciliary efficiency, and are potent airway mucus secretagogues. Finally, they are chemoattractants for eosinophilic granulocytes (17). Cys-LTs are therefore rational targets for the treatment of RSV bronchiolitis and its sequelae. The present finding of a clinical improvement from targeted treatment of cys-LT provides evidence for the role of cys-LT in RSV postbronchiolitis symptoms.

In an exploratory extension of the study we measured cys-LT, interleukin-13, and interferon- γ in nasal secretions at randomization and at the end of the 4-week treatment period. Cys-LT exhibited a numerical reduction in both treatment groups. The ratio between interleukin-13 and interferon- γ was measured attempting to gauge the Th1/Th2 cytokine activity. This ratio did not change over the observation period.

The infants included had documented RSV airway infection and bronchiolitis characterized by coryza, cough, wheeze, and respiratory distress. Patients with a suspected history of asthma-like symptoms were excluded. Still, perhaps some of the infants included may have had undiagnosed asthma, which may account for part of the effect observed (20).

The investigation was a conceptual pilot study of LTRA treatment in RSV postbronchiolitis. The investigation was initiated, designed, and conducted by the primary investigator without access to pharmacokinetic data on the optimal drug dose. Recent dose-titration studies have shown that 4 mg is the appropriate dose for infants from 6 months of age, if it is the aim to bridge similar pharmacokinetic profiles from adults with asthma to infants (B. Knorr, personal communication). However, it was considered safe to use the commercially available 5 mg tablets in view of the beneficial pediatric safety profile of montelukast in young children (20) and the short treatment period of 4 weeks. Active and placebo tablets were only accessible to the investigator as chewable tablets. The need to use tablets necessitated the lower age limit of inclusion of 3 months as the age when an infant can normally be spoon feed. The median age was therefore 9 months, whereas the median age of infants typically suffering from RSV bronchiolitis is 3 months. A definitive study applying appropriate drug dosing and formulation for this age group would be needed.

The study design aimed to evaluate the treatment effect on RSV postbronchiolitis symptoms, i.e., airway symptoms during the 4 weeks after the acute infection rather than the acute bronchiolitis itself. Treatment was delayed by a median of 3 days from admission and up to 7 days from the first symptoms. It is possible that the treatment effect is better if started earlier during the course of inflammation. Subsequent studies may address the effect of cys-LT antagonists when started at an earlier stage of the RSV infection. Particularly, a separate study would be needed to evaluate a possible effect on the acute symptoms of RSV bronchiolitis.

The treatment effect of LTRA in RSV postbronchiolitis symptoms may benefit the very large group of infants with RSV bronchiolitis who often suffer RAD for months or years thereafter. Many observational studies have reported reduced airway function, increased bronchial hyperresponsiveness, and RAD in infants subsequent to severe RSV bronchiolitis, and a link between RSV bronchiolitis and asthma has been proposed (2–4). However, it is unknown whether this is a causative relationship or an association with predisposing airway abnormalities. Stein and coworkers showed that even mild RSV bronchiolitis was associated with RAD through the first decade of life, though not with atopy. Postbronchiolitis RAD may constitute part of the heterogeneous spectrum of asthma-like symptoms in young children, who often respond poorly to steroid treatment. It is tempting to speculate that such postbronchiolitis wheeze would respond to regular LTRA treatment. We were unable to see

a delayed treatment effect on symptoms 2 months after RSV bronchiolitis, i.e., 1 month after the end of LTRA treatment, but chronic treatment for persistent wheeze after RSV-bronchiolitis should be tested. More sensitive outcomes such as lung function measurements and tests of bronchial hyperresponsiveness will be needed to see if modifying cys-LT may modify the course of postbronchiolitis hyperresponsive airways.

It has been proposed that RSV infections may stimulate an immune response to influence and modify the risk of subsequent asthma (2–4). There are no valid control groups for studies of such a potential link, as the infection is universal. Instead randomized, controlled trials using specific therapeutic agents such as LTRA will provide a powerful test of the relationship between RSV infection and long-term respiratory sequelae (22). Therefore the present finding suggests that future studies address the potential effect on the natural course of asthma from protection against the early triggering events from severe RSV infection.

The implications of these findings may not be restricted to RSV bronchiolitis but may reflect a general effect on postviral hyperresponsive airway symptoms. Such treatment may have important implications for the treatment of viral-induced exacerbations of asthma and perhaps other chronic obstructive airway diseases in children and adults.

In conclusion, this study suggests that regular LTRA provides clinical improvement of RSV postbronchiolitis RAD in infants.

Acknowledgment: Mogens Bildsøe, KLIFO, www.klifo.dk performed the statistical analyses. The Danish branch of Merck Sharp and Dohme provided the inactive, flavored chewable tablets identical to montelukast tablets.

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APPENDIX

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