Original Investigation

Early Administration of Azithromycin and Prevention of Severe Lower Respiratory Tract Illnesses in Preschool Children With a History of Such Illnesses
A Randomized Clinical Trial

Leonard B. Bacharier, MD; Theresa W. Guilbert, MD; David T. Mauger, PhD; Susan Boehmer, MA; Avraham Beigelman, MD; Anne M. Fitzpatrick, PhD; Daniel J. Jackson, MD; Sachin N. Baxi, MD; Mindy Benson, MSN, PN; Carey-Ann D. Burnham, PhD; Michael Cabana, MD; Mario Castro, MD, MPH; James F. Chmiel, MD, MPH; Ronina Covar, MD; Michael Daines, MD; Jonathan M. Gaffin, MD, MMSc; Deborah Ann Gentile, MD; Fernando Holguin, MD; Elliot Israel, MD; H. William Kelly, PharmD; Stephen C. Lazarus, MD; Robert F. Lemanske Jr, MD; Ngoc Ly, MD; Kelley Meade, MD; Wayne Morgan, MD; James Moy, MD; Tod Olin, MD; Stephen P. Peters, MD; Wanda Phipatanakul, MD, MS; Jacqueline A. Pongracic, MD; Hengameh H. Raissy, PharmD; Kristie Ross, MD; William J. Sheehan, MD; Christine Sorkness, PharmD; Stanley J. Szefler, MD; W. Gerald Teague, MD; Shannon Thyne, MD; Fernando D. Martinez, MD; for the National Heart, Lung, and Blood Institute's AsthmaNet

IMPORTANCE Many preschool children develop recurrent, severe episodes of lower respiratory tract illness (LRTI). Although viral infections are often present, bacteria may also contribute to illness pathogenesis. Strategies that effectively attenuate such episodes are needed.

OBJECTIVE To evaluate if early administration of azithromycin, started prior to the onset of severe LRTI symptoms, in preschool children with recurrent severe LRTIs can prevent the progression of these episodes.

DESIGN, SETTING, AND PARTICIPANTS A randomized, double-blind, placebo-controlled, parallel-group trial conducted across 9 academic US medical centers in the National Heart, Lung, and Blood Institute's AsthmaNet network, with enrollment starting in April 2011 and follow-up complete by December 2014. Participants were 607 children aged 12 through 71 months with histories of recurrent, severe LRTIs and minimal day-to-day impairment.

INTERVENTION Participants were randomly assigned to receive azithromycin (12 mg/kg/d for 5 days; n = 307) or matching placebo (n = 300), started early during each predefined RTI (child's signs or symptoms prior to development of LRTI), based on individualized action plans, over a 12- through 18-month period.

MAIN OUTCOMES AND MEASURES The primary outcome measure was the number of RTIs not progressing to a severe LRTI, measured at the level of the RTI, that would in clinical practice trigger the prescription of oral corticosteroids. Presence of azithromycin-resistant organisms in oropharyngeal samples, along with adverse events, were among the secondary outcome measures.

RESULTS A total of 937 treated RTIs (azithromycin group, 473; placebo group, 464) were experienced by 443 children (azithromycin group, 223; placebo group, 220), including 92 severe LRTIs (azithromycin group, 35; placebo group, 57). Azithromycin significantly reduced the risk of progressing to severe LRTI relative to placebo (hazard ratio, 0.64 [95% CI, 0.41-0.98], P = .04; absolute risk for first RTI: 0.05 for azithromycin, 0.08 for placebo; risk difference, 0.03 [95% CI, 0.00-0.06]). Induction of azithromycin-resistant organisms and adverse events were infrequently observed.

CONCLUSIONS AND RELEVANCE Among young children with histories of recurrent severe LRTIs, the use of azithromycin early during an apparent RTI compared with placebo reduced the likelihood of severe LRTI. More information is needed on the development of antibiotic-resistant pathogens with this strategy.

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: Members of the National Heart, Lung, and Blood Institute's AsthmaNet are listed in Supplement 2.

Corresponding Author: Leonard B. Bacharier, MD, Washington University in St Louis School of Medicine, Department of Pediatrics, Campus Box 8116, 660 S Euclid Ave, St Louis, MO 63110 (bacharier_l@kids.wustl.edu).

Acute episodes of severe lower respiratory tract illness (LRTI) are common among preschoolers, and up to 14% to 26% of preschoolers present with recurrent wheezing during the first 6 years of life.[1,2] These severe episodes are often associated with substantial morbidity, resulting in unscheduled visits to physician offices, urgent care, and emergency departments. Many of these young children are diagnosed with asthma, and among them, 20.9% seek emergency department care and 6.5% are hospitalized each year.[3] Thus, identification of novel treatment approaches that attenuate the severity of these recurrent episodes would provide substantial benefit to preschool children with recurrent severe LRTI.

The etiology of these acute episodes has not been completely elucidated. Although initial reports showed frequent detection of respiratory viruses in nasopharyngeal secretions obtained during episodes of wheezing in preschoolers,[4,5] bacteria are also often present during such episodes.[6] In children with asthma aged 4 through 12 years, isolation of *Streptococcus pneumoniae* or *Moraxella catarrhalis* from nasal samples also containing rhinovirus was associated with increased likelihood of having an asthma exacerbation.[7] The ketolide antibiotic telithromycin, when started within the first 24 hours of acute asthma episodes, significantly improved symptom scores and lung function relative to placebo and unrelated to bacteriologic status,[8] suggesting a mechanism unrelated to direct antimicrobial action. These findings are compatible with the decrease in neutrophilic inflammation observed in patients with severe asthma treated with the macrolide clarithromycin[9] and higher neutrophil counts and rates of isolation of pathogenic bacteria in bronchoalveolar lavage fluid in recurrently wheezing preschool children.[10] The primary chemoattractant for neutrophils is interleukin 8 (IL-8), and it has been shown that a polymorphism in the *IL-8* gene, rs4073, modulates IL-8 production.[11]

Based upon these findings, we conducted a randomized clinical trial of early administration of the macrolide azithromycin, started early in the course of an RTI and prior to the onset of severe LRTI symptoms, in preschool children with recurrent severe LRTIs to determine if this intervention can safely prevent the progression of such episodes.

Methods

Participants

The full protocol and statistical analysis plan are available in Supplement 1. The institutional review board at each center approved and monitored the study. Parents or guardians provided written informed consent. Participants received compensation for time and travel expenses. Details about inclusion and exclusion criteria are provided in Supplement 2. Briefly, eligible participants were children aged 12 through 71 months with recurrent severe wheezing in the context of clinically significant LRTIs that required systemic corticosteroids, an unscheduled physician office visit, an urgent or emergency department visit, or hospitalization. Exclusion criteria included more than 4 courses of systemic corticosteroids or more than 1 hospitalization in the past 12 months, or use of long-term controllers for asthma for more than 8 months in the past 12 months. These criteria excluded children with more severe disease who require daily controller medication. Children receiving monotherapy with asthma controllers (either low-dose inhaled corticosteroids or montelukast) at enrollment were eligible but had their controller discontinued upon study entry, consistent with recommendations for step-down therapy. Children with significant symptomatic asthma and those with inadequate adherence to diary card completion (<80% of days) during the 2 to 4 week run-in period (defined in Supplement 2) were also excluded. Race was assessed by parent/guardian report, using National Institutes of Health race/ethnicity reporting standards and categories.

A participant was classified as having a positive modified asthma predictive index (API) if the participant had experienced at least 4 wheezing episodes in the past year and had 1 major criterion (physician-diagnosed atopic dermatitis, parental history of asthma, or allergic sensitization to ≥1 aeroallergen) or 2 minor criteria (wheezing unrelated to colds, blood eosinophils ≥4%, or allergic sensitization to milk, eggs, or peanuts).[12]

Study Design and Treatment

The study was a double-blind, parallel-group trial (eFigure 1 in Supplement 2), in which participants were randomized in a 1:1 ratio to receive either oral azithromycin (12 mg/kg once daily for 5 days) or matching placebo. Parents or guardians were provided with an individualized care plan, developed with the study team, that instructed starting study therapy as soon as participants developed the symptoms or signs that parents or guardians defined as the child's usual starting point before the development of a severe LRTI.[13-15] During RTIs, all participants received albuterol inhalation treatments 4 times daily while awake for the first 48 hours as well as whenever needed at any time during the RTI.[13-15]

Computer-generated randomization was implemented via a secure web-based randomization module at the Data Coordinating Center and stratified by clinical center and age (12-41 months or 42-71 months), with treatment assignments made in random permuted blocks of size 4.

The trial began in April 2011 with a follow-up period of 52 weeks, and with study treatment used during a maximum of 3 treated RTIs not progressing to severe LRTI. In June 2012, based upon a prespecified interval assessment that demonstrated a lower than expected RTI rate, the follow-up period was extended to 78 weeks for those participating in the study at that time (n = 164) or enrolled thereafter (n = 292) and allowed for use of study treatment during a maximum of 4 treated RTIs.

Antibiotic Resistance, Viral Detection, and *IL-8* rs4073 Genotyping

To assess the effect of azithromycin therapy on colonization with antimicrobial-resistant bacteria, screening cultures were performed on deep oropharyngeal swab samples

(see eMethods in Supplement 2) from participants at a single site (St Louis) at randomization (n = 86) and at study completion at least 14 days after the final dose of study medication (n = 81). Samples were inoculated onto sheep's blood agar containing 2 μg/mL of azithromycin (Remel) incubated at 35°C in 5% carbon dioxide, and evaluated after 18 to 24 hours. The absence or presence of normal upper respiratory tract flora was assessed, and pathogenic organisms were isolated and identified. Susceptibility testing was performed on pathogenic bacteria using disk diffusion for azithromycin, erythromycin, clindamycin, clarithromycin, and cefoxitin (to assess for *Staphylococcus aureus)*.

Nasal secretions were collected by direct "nasal blow technique" or nasal swab at scheduled visits at randomization and during each treated RTI at home by a trained parent or guardian. Samples were frozen for later analysis for respiratory virus detection by polymerase chain reaction-based diagnostic assays.[16] This assay detects the following viruses: rhinovirus or enteroviruses (not distinguishable by this assay); coronaviruses; adenoviruses B, C, and E; influenza A and B; parainfluenza viruses I-IV; respiratory syncytial virus A and B; metapneumovirus; and bocavirus.

Participants were genotyped for the *IL-8* rs4073 single-nucleotide polymorphism by polymerase chain reaction amplification of the region containing the polymorphism and selective restriction endonuclease digestion (restriction fragment-length polymorphism). Further details are provided in Supplement 2.

Outcome Measures

The primary outcome measure was the number of treated RTIs not progressing to severe LRTI among participants experiencing at least 1 treated RTI, which was based on a predefined level of parent/guardian-reported symptom severity that triggered the prescription of an additional rescue intervention. Parents or guardians were instructed to call the clinical center if any of the following levels of symptoms that represented a severe LRTI occurred: (1) having symptoms that were more than mild after 3 albuterol administrations over 1 hour, (2) requiring albuterol administrations more often than once every 4 hours, (3) requiring more than 6 albuterol treatments over a 24-hour period, or (4) having moderate to severe cough or wheeze for 5 or more days since study medication was initiated. If the study physician concurred that the patient was experiencing this degree of symptomatology, the primary end point was reached. Early termination status was assigned if the child developed any of the following prior to, or on the same day as, initiating study medication according to the individualized care plan: (1) presence of predefined severe respiratory symptoms requiring emergent care, (2) need for open-label systemic corticosteroids, (3) symptoms consistent with uncontrolled persistent asthma, or (4) withdrawal from the study by physician discretion for respiratory-related problems (see Supplement 2 for further details). Episodes culminating in early termination were not considered to have met the primary outcome. Study participation was completed after the first severe LRTI or after assignment of early termination status, in which case the primary end point was not reached. An RTI was deemed not to have progressed to severe LRTI if a severe RTI did not occur within 14 days of initiating study medication. Dropout status was assigned if the participant withdrew consent, was withdrawn from the study by physician discretion for nonrespiratory-related reasons or was lost to follow-up. Secondary prespecified outcome measures included numbers of urgent care visits, emergency department visits, and hospitalizations. Measures of disease impairment reflected by symptom severity and albuterol use during treated RTI were assessed through parental completion of the validated Preschool Asthma Diary[17] daily during treated RTIs, beginning on the first day of each illness and continuing until all symptoms had resolved for 2 consecutive days. We also prespecified comparisons of parent-reported, drug-related adverse effects and development of azithromycin-resistant pathogens.

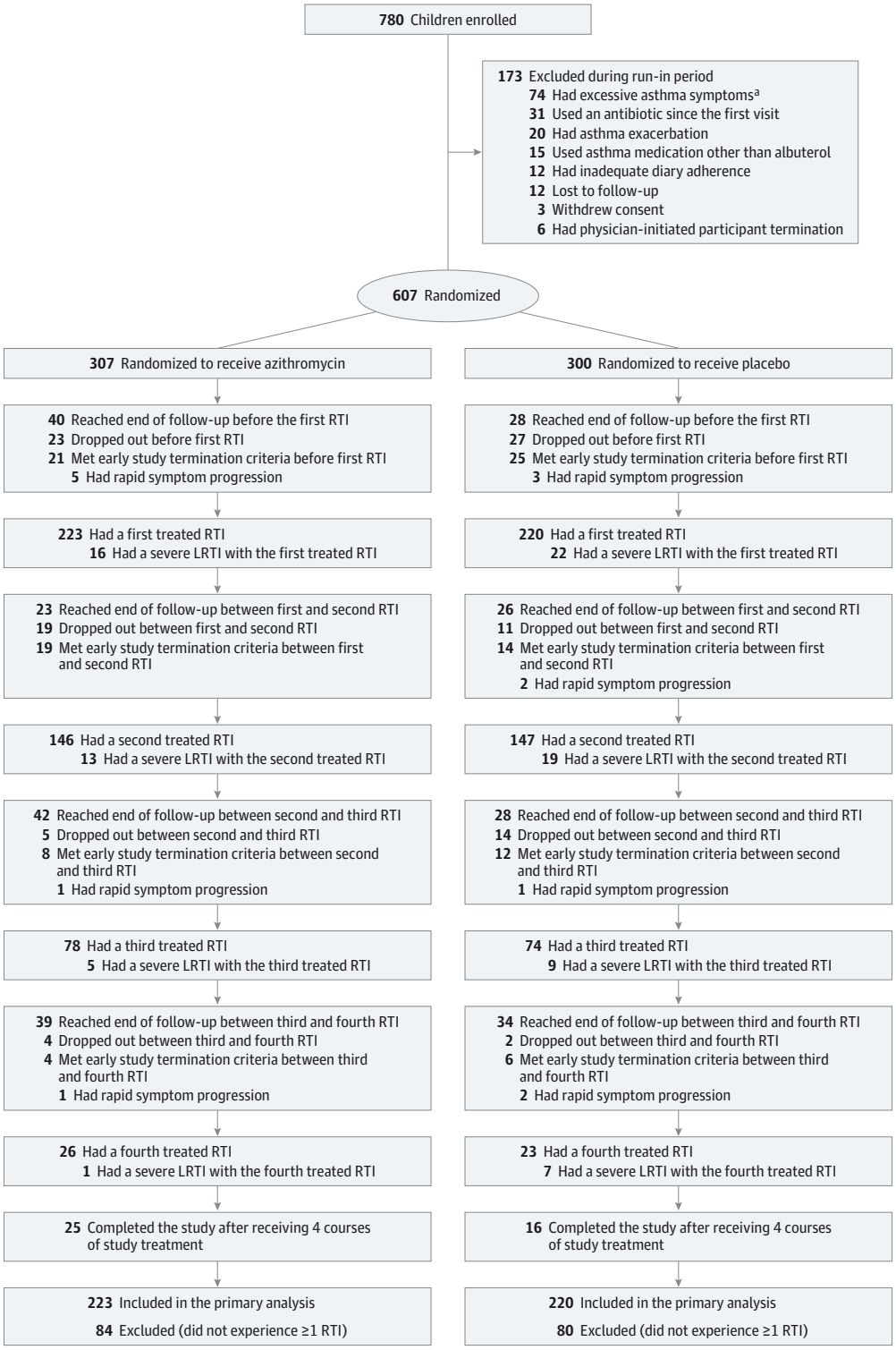
Statistical Analysis

The primary outcome, number of treated RTIs not progressing to severe LRTI, is similar to familiar "time to event" outcomes except that time is measured discretely by the occurrence of RTIs rather than by the passage of time. The primary analysis tested the null hypothesis that azithromycin and placebo do not differ using a discrete-time proportional hazards regression model including the following covariates: study site, age at randomization (12-42 months vs 43-71 months), modified API[18] status, season during which the RTI occurred (a time-dependent covariate), and whether the child enrolled before or after the study was extended to 78 weeks. The primary outcome was considered to be right-censored if the participant dropped out or reached the end of follow-up prior to experiencing a fourth treated RTI. The proportional hazards assumption was assessed by comparing the goodness-of-fit of the proportional hazards model with the goodness-of-fit of the nonproportional hazards model using the Akaike information criterion.[19]

Secondary outcomes of health care utilization and respiratory-related symptoms during RTIs were explored using repeated measures analysis of variance with compound symmetry to account for multiple treated RTIs in the same individual. RTIs during which symptom data were missing (9% of RTIs) were not included in the analysis. Treatment-effect modification was explored in prespecified subgroups of participants, defined by age at randomization, sex, modified API status, presence of viral infection during RTI, season during which the RTI occurred, and *IL-8* rs4073 genotype.[11] The statistical significance of possible differences between subgroups in the treatment effect was tested with interaction terms. No adjustments for multiple tests were made. To assess if azithromycin decreased the frequency of subsequent RTIs, time to second RTI was compared between study groups using Kaplan-Meier curves and the log-rank test. All tests were 2-sided and based on a significance criterion of a *P* value less than .05. All analyses were performed with the use of SAS (SAS Institute), version 9.3.

The target sample size of 600 children (300 per treatment group) was chosen so that the study would have

Figure 1. Flow Diagram of the Study Enrollment and Outcomes for Preschool Children With a History of Respiratory Tract Illness



LRTI indicates lower respiratory tract illness. No information was recorded on potential participants screened but not enrolled.

[a] Presence of excessive asthma symptoms was defined as, on average, more than 4 days per week or more than 1 nighttime awakening requiring albuterol during the 2-week run-in period (for controller naïve children) or during the latter 2 weeks of a 4 week run–in period (for children receiving low-dose inhaled corticosteroids or montelukast monotherapy at enrollment).

Table 1. Demographic Characteristics of Study Participants

	All Randomized Participants (N = 607)	Participants With at Least 1 Treated RTI (n = 443)	Participants With No RTI (n = 164)	Participants With at Least 1 Treated RTI	
				Azithromycin (n = 223)	Placebo (n = 220)
Demographics, No. (%)					
Age at enrollment, mean (SD), mo	41.5 (16.5)	41.4 (16.5)	41.81 (16.27)	42.5 (16.4)	40.2 (16.6)
12-42	327 (53.9)	241 (54.4)	86 (52.4)	115 (51.6)	126 (57.3)
43-71	280 (46.1)	202 (45.6)	78 (47.6)	108 (48.4)	94 (42.7)
Boys	365 (60.1)	274 (61.9)	91 (55.)5	139 (62.3)	135 (61.4)
Entered study on controller medication	48 (7.9)	41 (9.3)	7 (4.3)	25 (11.2)	16 (7.3)
Race					
American Indian or Alaskan Native	8 (1.3)	7 (1.6)	1 (0.6)	3 (1.3)	4 (1.8)
Asian	10 (1.6)	7 (1.6)	3 (1.8)	4 (1.8)	3 (1.4)
Black or African American	157 (25.9)	89 (20.1)	68 (41.5)	47 (21.1)	42 (19.1)
White	362 (59.6)	290 (65.5)	72 (43.9)	141 (62.3)	149 (67.7)
More than 1 race specified	70 (11.5)	50 (11.3)	20 (12.2)	28 (12.6)	22 (10.0)
Ethnicity					
Hispanic or Latino	183 (30.1)	130 (29.3)	53 (32.3)	63 (28.3)	67 (30.5)
Not Hispanic or Latino	424 (69.9)	313 (70.7)	111 (67.7)	160 (71.7)	153 (69.5)
Height, mean (SD), cm	98.5 (11.7)	98.3 (11.7)	98.87 (11.67)	99.2 (11.4)	97.4 (12.1)
Weight, mean (SD), kg	16.8 (4.6)	16.8 (4.6)	17.0 (4.6)	17.1 (4.5)	16.4 (4.6)

Abbreviation: RTI, respiratory tract illness.

power of at least 0.9 with 2-sided α of .05 if the hazard ratio (HR) for progressing to severe LRTI with azithromycin compared with placebo was 0.65 or smaller. These calculations assumed an average of 2.75 RTI per child-year with overall dropout rate of 33%. A prespecified interim feasibility analysis conducted when 50% of the children had completed 6 months of follow-up revealed that the average RTI rate per child-year was close to 2.0 and that the power for a hazard rate of 0.65 would be approximately 0.80. The data and safety monitoring board and AsthmaNet Steering Committee approved continuation of the trial.

Results

Participants

Of 780 participants enrolled, 607 underwent randomization: 307 participants to the azithromycin group and 300 participants to the placebo group (**Figure 1**). Baseline demographic and clinical characteristics for all 607 randomized participants and for the subgroup that experienced at least 1 treated RTI are shown in **Table 1** and **Table 2**. Among participants who experienced at least 1 treated RTI and were included in the primary analysis, treatment groups were comparable except for a greater proportion with day-care attendance in the azithromycin group. Atopy was common, with 39.1% demonstrating allergic sensitization to at least 1 allergen and 46.8% meeting criteria for being at high risk for asthma by virtue of a positive modified API.[18] At baseline, any nasal virus was detected among 261 of 588 randomized participants (44.4%), 188 of 432 participants with at least 1 treated RTI (43.5%), 73 of 156 participants with no RTI (46.8%), 99 of 220 participants receiving azithromycin with at least 1 treated RTI (45.0%), and 89 of 212 participants receiving placebo with at least 1 treated RTI (42.0%).

Participant enrollment and disposition are shown in Figure 1. During the study, 164 participants did not experience a treated RTI (azithromycin group, 84; placebo group, 80). Compared with participants who experienced no treated RTI, participants who experienced at least 1 treated RTI were significantly more likely to be white, have lower rates of exposure to smoke or pet exposure, and higher rates of asthma controller (inhaled corticosteroids or montelukast) or oral corticosteroid use in the year prior to enrollment (Table 1). A total of 937 trial-defined RTIs occurred (azithromycin group, 473; placebo group, 464). During a first RTI, 443 participants were treated; during a second RTI, 293; during a 3rd RTI, 152; during a fourth RTI, 49, with comparable distributions of numbers of treated RTIs between treatment groups. Of the 937 RTIs included in the primary analysis, therapy was initiated 2 or more days after the start of the RTI in 21% of cases; 3 or more days after, 12% of cases; 4 or more days after, 7% of cases. Early termination criteria was met by 109 participants (azithromycin group, 52 ; placebo group, 57). There were 105 participants (azithromycin group, 51; placebo group, 54) who withdrew for other reasons or were lost to follow-up. The overall percentage of early termination and dropout was 35%.

Primary Outcome

The azithromycin group experienced significantly lower risk of progressing to severe LRTI than the placebo group (HR, 0.64 [95% CI, 0.41-0.98], P = .04; absolute risk for first RTI: 0.05 for azithromycin, 0.08 for placebo; risk difference, 0.03 [95% CI, 0.00-0.06]), after adjustment for study site, age, modified API

Table 2. Characteristics of Study Participants

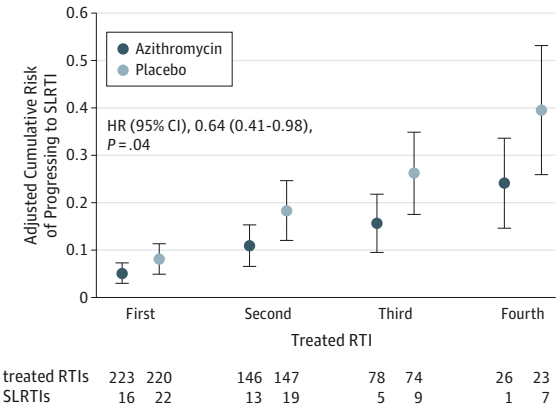
	All Randomized Participants (N = 607)	Participants With at Least 1 Treated RTI (n = 443)	Participants With No RTI (n = 164)	Participants With at Least 1 Treated RTI	
				Azithromycin (n = 223)	Placebo (n = 220)
Exposures, No. (%)					
Day-care attendance	307 (50.6)	220 (49.7)	87 (53.1)	123 (55.2)	97 (44.1)
Tobacco smoke exposure, No./total (%)	240/601 (39.9)	164/439 (37.4)	76/162 (46.9)	89/221 (40.3)	75/218 (34.4)
Pet in home	280 (46.1)	228 (51.5)	52 (31.7)	117 (52.5)	111 (50.5)
Feature of Previous Wheezing					
No. of wheezing episodes in the past year, mean (SD)	4.45 (3.15)	4.45 (3.14)	4.45 (3.19)	4.49 (3.41)	4.41 (2.86)
No. of urgent and/or ED visits in the past year, mean (SD)	2.48 (1.64)	2.53 (1.71)	2.34 (1.41)	2.52 (1.72)	2.54 (1.71)
Hospitalized in the past year, No. (%)	87 (14.3)	58 (13.1)	29 (17.7)	34 (15.2)	24 (10.9)
No. of hospitalizations in the past year, median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
At least 1 course of OCS in past year, No. (%)	361 (59.5)	276 (62.3)	85 (51.8)	143 (64.1)	133 (60.5)
No. of OCS courses in the past year, median (range)	1 (0-4)	1 (0-4)	1 (0-4)	1 (0-4)	1 (0-4)
ICS use in past year, No./total (%)	150/605 (24.8)	126/441 (28.6)	24/164 (14.6)	70/223 (31.3)	56/218 (25.7)
Montelukast use in the past year, No. (%)	54 (8.9)	48 (10.8)	6 (3.7)	25 (11.2)	23 (10.5)
Symptom Burden During 14-d Run-in Period					
No. of days in run-in period, median (IQR)	15 (14-19)	15 (14-19)	15 (14-19)	15 (14-19)	14 (14-19)
Percentage of asthma control days, mean (SD)[a]	77.4 (24.1)	76.6 (23.6)	79.6 (25.3)	76.3 (24.5)	77.0 (22.6)
No. of asthma control days per week, mean (SD)[a]	5.4 (1.7)	5.4 (1.7)	5.6 (1.8)	5.3 (1.7)	5.4 (1.6)
Percentage of nights with albuterol use, median (range)	0 (0-43)	0 (0-43)	0 (0-36)	0 (0-24)	0 (0-43)
Percentage of days with albuterol use, median (range)	0 (0-57)	0 (0-57)	0 (0-59)	0 (0-57)	0 (0-54)
Atopic Features					
Eczema, No./total (%)	328/592 (55.4)	242/430 (56.3)	86/162 (53.1)	112/215 (52.1)	130/215 (60.5)
Allergic rhinitis, No./total (%)	128/581 (22.0)	100/420 (23.8)	28/161 (17.4)	52/211 (24.6)	48/209 (23.0)
Parental asthma, No./total (%)	314/587 (53.5)	222/428 (51.9)	92/159 (57.9)	114/213 (53.5)	108/215 (50.2)
Physician-diagnosed asthma, No. (%)	345 (56.8)	248 (56.0)	97 (59.2)	127 (57.0)	121 (55.0)
Positive modified API, No. (%)[b]	284 (46.8)	208 (47.0)	76 (46.3)	104 (46.6)	104 (47.3)
Allergy					
Sensitivity to any allergen, No./total (%)	314/596 (52.7)	230/436 (52.8)	84/160 (52.2)	112/219 (51.1)	118/217 (54.4)
No. of allergens (of 16), median (IQR)	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)
Sensitivity to ≥1 aeroallergen, No./total (%)	233/596 (39.1)	169/436 (38.8)	64/160 (40.0)	85/219 (38.8)	84/217 (38.7)
No. of aeroallergens (of 13), median (IQR)	0 (0-2)	0 (0-2)	0 (0-2)	0 (0-2)	0 (0-2)
Sensitivity to ≥1 food allergen, No./total (%)	241/596 (40.4)	179/436 (41.1)	62/160 (38.8)	82/219 (37.4)	97/217 (44.7)
Immunoglobulin E, μg/L, median (IQR)	122.6 (35-408.7) n = 550	117.1 (34.8-421.1) n = 400	130 (43.7-382.8) n = 150	132 (34.8-430.1) n = 201	102.5 (31-403) n = 199
Peripheral blood eosinophils, median (IQR), %	3 (2-5.6) n = 568	3 (2-5.3) n = 411	3 (2-5.8) n = 157	3 (2- 6) n = 205	3 (2-5) n = 206
Eosinophils ≥4%, No./total (%)	234/568 (41.2)	166/411 (40.4)	68/157 (43.3)	85/205 (41.5)	81/206 (39.3)
Study Duration When Enrolled, No. (%)					
52 wk	315 (51.9)	238 (53.7)	77 (46.9)	117 (52.5)	121 (55.0)
78 wk	292 (48.1)	205 (46.3)	87 (53.1)	105 (47.5)	99 (45.0)

Abbreviations: API, asthma predictive index; ED, emergency department; ICS, inhaled corticosteroids; IQR, interquartile range; OCS, oral corticosteroids; RTI, respiratory tract illness.

[a] An asthma control day was a day without asthma-related symptoms, medication use, or health care utilization.

[b] A participant was classified as having a positive modified API if the individual had experienced at least 4 wheezing episodes in the past year and had 1 major criterion (physician-diagnosed atopic dermatitis, parental history of asthma, or allergic sensitization to ≥1 aeroallergen) or 2 minor criteria (wheezing unrelated to colds, blood eosinophils ≥4%, or allergic sensitization to milk, eggs, or peanuts).[12]

Figure 2. Cumulative Risk of Experiencing an Episode of Severe LRTI Across Treated RTIs for Preschool Children With a History of Severe LRTI



No. of treated RTIs	223	220	146	147	78	74	26	23
No. of SLRTIs	16	22	13	19	5	9	1	7

RTI indicates respiratory tract illness; SLRTI, severe lower RTI. Shown are risks and 95% CIs based on the discrete-time proportional hazards model of treatment effect adjusted for clinical site, age, modified Asthma Predictive Index status, season during which the treated RTI occurred, and whether the child enrolled before or after the study was extended to 78 weeks.

status,[18] season during which the RTI occurred, and whether the child enrolled before or after the study was extended to 78 weeks (**Figure 2**). The cumulative risk for a severe LRTI over a maximum of 4 RTIs was 0.40 in the placebo group and 0.24 in the azithromycin group. The number needed to treat (NNT) to prevent 1 severe LRTI varied by the number of treated RTIs each child experienced, with the NNT decreasing with each subsequent treated RTI (NNT: for 1 RTI, 33; for 2 RTIs, 14; for 3 RTIs, 10; for 4 RTIs, 7). We examined if a delay in initiation of therapy was a potential treatment effect modifier in our model and found no significant results.

Viral Detection

Viral pathogens were detected at randomization in 47% of children in the azithromycin group and 43% in the placebo group from whom nasal samples were collected (eTable 1A in Supplement 2). Nasal wash samples were obtained during 94% of all treated RTIs during the trial. Viral pathogens were detected during 83% of RTIs in the azithromycin group and 80% in the placebo group. Rhinovirus was the most commonly detected virus at randomization, during RTIs, and during severe LRTIs (eTable 1B in Supplement 2).

Subgroup Analyses

In prespecified subgroup analyses, we tested for the presence of an interaction between treatment group and age group (12-42 months vs 43-71 months at randomization), sex (boys vs girls), modified API status (positive vs negative), presence of virus detected during treated RTI (no virus detected vs rhinovirus or rhinovirus/enterovirus vs other virus), season during which the RTI occurred (September-November, June-August, March-May, and December-February), and *IL-8* rs4073 genotype (TT vs AA/AT). No statistically significant interactions were demonstrated for any of these factors, indicating no significant differences in the HRs between subgroups (**Figure 3**).

Secondary Outcomes

Symptom Scores and Albuterol Use During Treated RTIs

Azithromycin therapy decreased the overall severity of symptoms during severe LRTIs compared with placebo, as reflected by lower mean total symptom scores over the duration of RTI, but not during episodes not progressing to severe LRTI (**Figure 4**). Total albuterol use during treated RTIs did not differ to a statistically significant extent between treatment groups (eFigure 2 in Supplement 2).

Health Care Utilization

Urgent care and emergency department visits were infrequent, occurring in 3.6% of participants receiving azithromycin and 5.4% of participants receiving placebo . There were 28 participants hospitalized for respiratory illnesses (azithromycin group, 13; placebo group, 15) over the duration of the trial, 11 of whom (azithromycin group, 5; placebo group, 6) were hospitalized within 14 days of study medication use.

Time to Second Treated RTI

Comparable numbers of RTIs occurred in the azithromycin and placebo groups (azithromycin group, 473; placebo group, 464). Furthermore, there was no statistically significant difference in the time from the first treated RTI to the start of a second treated RTI between treatment groups (eFigure 3 in Supplement 2), suggesting azithromycin treatment did not prevent subsequent RTIs.

Development of Azithromycin-Resistant Organisms

An azithromycin-resistant organism was isolated from 5 of 41 participants treated with azithromycin (12.2%) and 4 of 45 participants not treated with azithromycin (8.9%) at randomization, and from 8 of 40 participants treated with azithromycin (20.0%) and 7 of 41 participants not treated with azithromycin (17.0%) at study completion. Over the duration of the study, 6 of 36 participants treated with azithromycin (16.7%) and 4 of 37 participants not treated with azithromycin (10.8%) acquired azithromycin-resistant organisms. *S aureus* was the most common azithromycin-resistant organism isolated.

Adverse Events

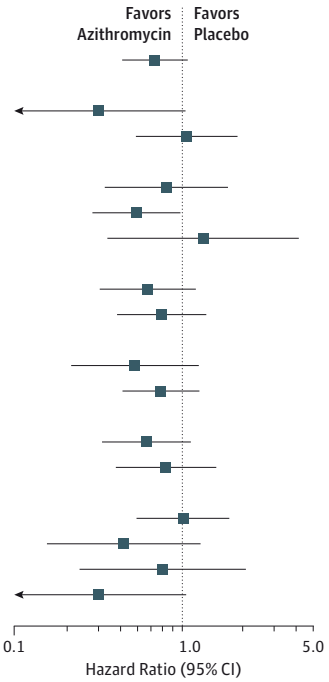
Gastrointestinal symptoms during treated RTIs, reported by 4 participants (azithromycin group, 3; placebo group, 1), were mild and did not lead to study discontinuation.

Discussion

This randomized clinical trial enrolled preschool children with severe intermittent wheezing in the context of RTIs, representing an early life wheezing phenotype typically cared for in primary care settings. Azithromycin started at the earliest signs of an RTI was effective in significantly reducing the risk of experiencing progression to severe LRTI along with reducing symptom severity during episodes of severe LRTI. Positive effects were detectable irrespective of modified API status, identifying a treatment option for children at both high and low risk for subsequent persistent asthma. Furthermore,

Figure 3. Potential Treatment-Effect Differences in Prespecified Subgroups for Risk of an Episode of Severe LRTI Among Preschool Children With a History of Severe LRTI

	Azithromycin			Placebo		
	No. of Patients	No. of RTIs	No. of Severe LRTIs	No. of Patients	No. of RTIs	No. of Severe LRTIs
Overall	223	473	35	220	464	57
IL-8 genotype (rs4073)[a]						
TT	41	80	4	46	91	16
AA/AT	82	178	17	81	186	20
Nasal virus						
Other virus[b]	46	119	11	55	113	14
Rhinovirus or enterovirus	123	247	18	105	237	37
No virus	39	77	5	51	87	5
Age group, mo						
43- 71	108	213	16	94	200	28
12-42	115	260	19	126	264	29
Sex						
Girls	84	172	8	85	185	20
Boys	139	301	27	135	279	37
mAPI status						
Positive[c]	104	221	19	104	219	33
Negative	119	252	16	116	245	24
Season						
Sept-Nov	77	163	20	75	164	24
Dec-Feb	62	145	6	53	114	11
Mar-May	31	81	5	43	101	10
June-Aug	53	84	4	49	85	12



IL-8 indicates interleukin-8 gene; LRTI, lower respiratory tract illness; mAPI, modified Asthma Predictive Index. Estimates and CIs were obtained from separate discrete-time proportional hazards models, each incorporating an interaction between treatment and the factor indicated on the y-axis. All models included adjustments for clinical site, age, modified API status, season during which the treated respiratory tract illness occurred, and whether the child enrolled before or after the study was extended to 78 weeks. No significant differences between treatment effects (blue circles) are noted between subgroups.

[a] *IL-8* rs4073 genotype results shown include only Hispanic and non-Hispanic white participants with an adjustment for ethnicity.

[b] Other virus indicates coronaviruses; adenoviruses B, C, and E; influenza A and B; parainfluenza viruses I-IV; respiratory syncytial virus A and B; metapneumovirus; and bocavirus.

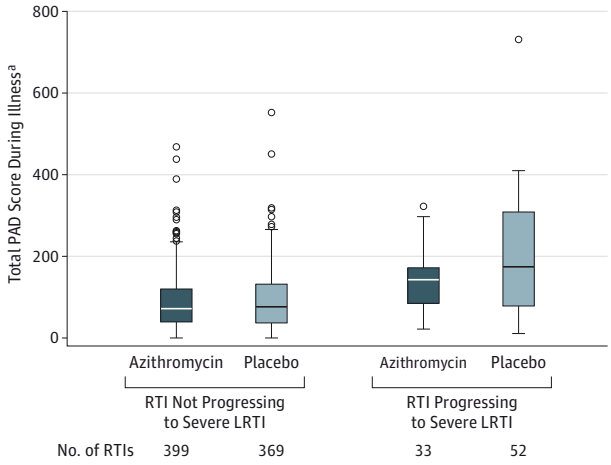
[c] A participant was classified as having a positive mAPI if the individual had experienced at least 4 wheezing episodes in the past year and had 1 major criterion (physician-diagnosed atopic dermatitis, parental history of asthma, or allergic sensitization to ≥1 aeroallergen) or 2 minor criteria (wheezing unrelated to colds, blood eosinophils ≥4%, or allergic sensitization to milk, eggs, or peanuts).[12]

azithromycin therapy was well tolerated, with low rates of treatment-related adverse effects. Prevention of severe LRTIs is a highly desirable outcome given recent evidence that oral corticosteroids, the typical rescue strategy for such episodes, may not be effective in reducing symptom burden in the preschool age group,[20,21] in contrast to their efficacy in older children with established asthma.

The mechanisms by which azithromycin reduced the risk of progressing to severe LRTI remain uncertain. Azithromycin may have reduced the risk of severe LRTI via its established antibacterial effects, a concept supported by recent evidence of the importance of bacterial pathogens in acute wheezing illnesses. Children with rhinovirus infections along with detectable *Streptococcus pneumoniae* or *Moraxella catarrhalis* were at heightened risk of an asthma exacerbation.[7] Although in vitro studies have demonstrated that azithromycin reduces rhinovirus replication and increases interferon gene expression,[22] we did not detect an interaction between rhinovirus presence and treatment response. Viral infections are associated with neutrophilic airway inflammation and increased expression of the dominant neutrophil chemoattractant IL-8,[23,24] and azithromycin has recently been demonstrated to reduce IL-8 levels in nasal secretions during respiratory syncytial virus bronchiolitis.[25] However, although polymorphisms in the *IL-8* gene also have been shown to modulate IL-8 production,[11] we did not observe a significant interaction between reduced risk of progressing to severe LRTI and the *IL-8* rs4073 polymorphism.

The use of antibiotics in young children with wheezing illnesses has been a matter of controversy.[26] Although not recommended by national asthma guidelines,[27] antibiotics (frequently macrolides) are widely used in clinical practice during RTIs and asthma episodes.[26,28-30] A major, justified concern in general pediatrics is the overuse of antibiotics for viral illnesses leading to the potential development of antibiotic-resistant pathogens.[31,32] Such concern needs to be balanced, however, with the potential for macrolides to improve the quality of life of children with recurrent, severe LRTI. The rate of exposure to study medicine in this study was 1.87 courses per participant-year. Although limited to 86 participants at a single

Figure 4. Symptom Scores Over the Duration of Treated RTIs Among Preschool Children With a History of Severe LRTI



LRTI indicates lower respiratory tract illness; PAD, Preschool Asthma Diary. *P* values are based on repeated measures analysis of variance with compound symmetry (RTIs not progressing to severe LRTI) or 2-sample *t* test (RTIs progressing to severe LRTI). The bottom and top edges of the box indicate the first and third quartiles, respectively. The line inside the box indicates the median. The error bars that extend from each end of the box indicate the range of values that are outside of the interquartile range, but not more than 1.5 times the interquartile range above the third quartile. Circles indicate values that are more than 1.5 times the interquartile range above the third quartile.

[a] The PAD was completed daily starting on the first day an illness kit was used and continued until the participant was symptom-free for 2 days. It contains questions of frequency of respiratory symptoms, each scored on a scale of 1 through 7, with higher scores representing increasingly frequent symptoms, with daily scores ranging from 0 (asymptomatic) to a maximum of 102. The total PAD score is the sum of the daily individual symptom scores over the duration of the illness, with higher scores representing more frequent symptoms.

study site, we found numerically higher rates of acquisition of azithromycin-resistant organisms in oropharyngeal samples in participants receiving azithromycin and those who did not, along with evidence of acquisition of azithromycin-resistant organisms even in participants not treated with azithromycin. Real-world rates of development of azithromycin-resistant organisms may be greater, potentially due to failure to complete the full duration of therapy often seen in clinical practice. Given the small sample size, further studies are needed to assess the potential increased risk of antibiotic resistance vs the comparative effectiveness of azithromycin with respect to other asthma medications to prevent severe LRTI.

This study has limitations that need to be considered when interpreting our results. The randomized portion of the trial was extended from 52 to 78 weeks and up to 4 (instead of 3) courses of study medication were allowed. These modifications were decided by the AsthmaNet Steering Committee while blinded to outcome and were approved by the data and safety monitoring board. The extension was justified by the mild nature of the initial viral respiratory seasons during the trial, which threatened to decrease the power of the study. Although results were independent of study duration, it is possible that the protective effect of azithromycin could have been stronger had all participants been followed for 78 weeks. Many participants had received study therapy during a prior RTI without progressing to severe LRTI, but subsequently experienced a severe LRTI or early termination. Once participants experienced a severe LRTI, their study participation was complete. Therefore, the potential efficacy of azithromycin during future RTIs among patients who experience a severe LTRI while receiving azithromycin is uncertain. The decreasing NNT for multiple episodes may represent selection of responders who continued in the trial. This study examined the proactive administration of azithromycin at the early signs of RTIs, and these findings should not be extrapolated to azithromycin's potential role as a rescue therapy for patients already experiencing severe LRTI symptoms. We enrolled children with intermittent, yet severe, disease, who did not require daily controller therapy—thus, our findings are applicable to such populations, whereas the role of azithromycin in children receiving daily controller therapy requires future investigation. Due to logistical and ethical concerns, lower airway sampling for bacterial infection was not performed. Parental report may have underestimated or overestimated the severity of their child's respiratory symptoms; however, this strategy has been used in several previous studies.[13,14,33] Comparable proportions of participants in both treatment groups experienced rapid symptom progression early during RTIs that did not allow for initiation of study intervention; these rapidly progressing episodes do not appear to be appropriate for early intervention with azithromycin. Acute care emergency department visits and hospitalizations for respiratory illnesses were infrequent, both in the year preceding the study and during the study, potentially reflecting enrollment of a population at low risk for hospitalization. Alternatively, the extensive disease-related education and round-the-clock availability of study personnel for telephone consultation and as-needed study visits may have further reduced hospitalization risks and improved overall outcomes relative to routine care.

In children with the phenotype of wheezing studied herein, clinicians may consider a therapeutic trial of azithromycin early in the course of RTIs based on a parent-initiated individualized plan. Children who demonstrate an azithromycin response, as reflected by less-severe episodes of RTI, may benefit from repeating such therapy with subsequent illnesses. Attention should be paid to the frequency of RTIs prompting azithromycin use and response to the intervention given the concern of antimicrobial resistance. Studies replicating the findings reported herein would provide further support to this conclusion, and future studies comparing the relative benefits of early azithromycin therapy with either daily or intermittent high-dose inhaled corticosteroids may help determine the relative efficacies of these treatment strategies.

Conclusions

Among young children with histories of recurrent severe LRTIs, the use of azithromycin early during an apparent RTI compared with placebo reduced the likelihood of severe LRTI. More information is needed on the development of antibiotic-resistant pathogens with this strategy.

ARTICLE INFORMATION

Author Affiliations: Department of Pediatrics, Washington University in St Louis School of Medicine, St Louis, Missouri (Bacharier, Beigelman, Castro); Cincinnati Children's Hospital and Medical Center, Cincinnati, Ohio (Guilbert); Department of Public Health Sciences, Pennsylvania State University, Hershey (Mauger, Boehmer); Department of Pediatrics, Emory University, Atlanta, Georgia (Fitzpatrick); Pediatrics Section of Allergy, Immunology, and Rheumatology, University of Wisconsin School of Medicine and Public Health, Madison (Jackson); Division of Allergy/Immunology, Boston Children's Hospital, Boston, Massachusetts (Baxi, Phipatanakul, Sheehan); Benioff Children's Hospital, Oakland, California (Benson, Meade); Department of Pathology and Immunology, Washington University in St Louis School of Medicine, St Louis, Missouri (Burnham); University of California, San Francisco, Medicine, San Francisco (Cabana, Lazarus); Rainbow Babies and Children's Hospital, Cleveland, Ohio (Chmiel, Ross); Department of Pediatrics, National Jewish Health, Denver, Colorado (Covar, Olin); University of Arizona, Arizona Respiratory Center, Tucson (Daines, Morgan); Division of Respiratory Diseases, Boston Children's Hospital, Boston, Massachusetts (Gaffin); Department of Pediatrics, Allegheny General Hospital, Pittsburgh, Pennsylvania (Gentile); The University of Pittsburgh Asthma Institute, Pittsburgh, Pennsylvania (Holguin); Brigham and Women's Hospital, Boston, Massachusetts (Israel); Department of Pediatrics, University of New Mexico School of Medicine, Albuquerque, New Mexico (Kelly); Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison (Lemanske); Airway Clinical Research Center, University of California, San Francisco, San Francisco, California (Ly); Stroger Hospital of Cook County Pediatric Services, Chicago, Illinois (Moy); Wake Forest University School of Medicine, Winston-Salem, North Carolina (Peters); Ann and Robert H Lurie Children's Hospital of Chicago, Chicago, Illinois (Pongracic); Department of Pediatrics/Pulmonary, University of New Mexico, Albuquerque (Raissy); University of Wisconsin-Madison, Madison (Sorkness); The Breathing Institute, Children's Hospital Colorado, Denver (Szefler); University of Virginia School of Medicine, Charlottesville (Teague); Department of Pediatrics, San Francisco General Hospital, San Francisco, California (Thyne); Arizona Respiratory Center, University of Arizona, Tucson, Arizona (Martinez).

Author Contributions: Drs Bacharier and Guilbert had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Bacharier and Guilbert contributed equally to this article.
Study concept and design: Bacharier, Guilbert, Mauger, Beigelman, Fitzpatrick, Jackson, Burnham, Chmiel, Covar, Holguin, Israel, Kelly, Lazarus, Lemanske, Meade, Peters, Phipatanakul, Pongracic, Raissy, Teague, Thyne, Szefler, Martinez.
Acquisition, analysis, or interpretation of data: Bacharier, Guilbert, Mauger, Boehmer, Beigelman, Fitzpatrick, Jackson, Baxi, Benson, Burnham, Cabana, Castro, Chmiel, Covar, Daines, Gaffin, Gentile, Israel, Lazarus, Lemanske, Ly, Meade, Morgan, Moy, Olin, Peters, Phipatanakul, Raissy, Ross, Sheehan, Sorkness, Teague, Thyne, Martinez.
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Study supervision: Bacharier, Guilbert, Mauger, Beigelman, Fitzpatrick, Jackson, Baxi, Castro, Chmiel, Covar, Daines, Gentile, Lazarus, Moy, Olin, Phipatanakul, Pongracic, Raissy, Ross, Sorkness, Szefler.

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