

Reports of suicidality in clinical trials of montelukast

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Background: In recent years, a number of drugs and drug classes have come under scrutiny by the US Food and Drug Administration regarding suicidality (including suicidal behavior and ideation).

Objective: We sought to perform 2 reviews (requested by the US Food and Drug Administration) of the number of events possibly related to suicidality reported in Merck clinical trials of montelukast.

Methods: Method 1 was a descriptive review of clinical adverse experiences (AEs) from 116 studies (double-blind and open-label, adult and pediatric, and single- and multiple-dose studies) completed as of March 2008. Summaries were constructed from investigator-reported AE terms possibly related to suicidality (completed suicide, suicide attempt, and suicidal ideation) or self-injurious behavior. Method 2 used a retrospective adjudication of investigator-reported AEs and other events listed in the study database described as possibly suicidality-related adverse events (PSRAEs) in a prespecified set of 41 double-blind, placebo-controlled trials completed as of April 2008.

Results: No completed suicides were reported in any study. For the descriptive review, 20,131 adults and children received montelukast, 9,287 received placebo, and 8,346 received active control; AEs possibly related to suicidality were rare and were similar between the montelukast and placebo or active-control groups. For the adjudicated review across 22,433 patients, there were 730 adjudicated events. In 9,929 patients taking montelukast, 1 PSRAE was identified (classified as suicidal ideation); none were identified in 7,780 and 4,724 patients taking placebo and active control, respectively.

Conclusions: Assessed by using 2 complementary methods, there were no reports of completed suicide, and reports of PSRAEs were rare in patients receiving montelukast and similar to those seen in control subjects. (*J Allergy Clin Immunol* 2009;124:691-6.)

Key words: Montelukast, placebo, clinical trial, suicide, suicidality, adverse experiences, asthma, allergic rhinitis

Montelukast sodium (SINGULAIR; Merck & Co, Inc, Rahway, NJ), a potent and selective cysteinyl leukotriene type

Abbreviations used

AE: Adverse experience
C-CASA: Columbia Classification Algorithm of Suicide Assessment
FDA: US Food and Drug Administration
MRL: Merck Research Laboratories
PSRAE: Possibly suicidality-related adverse event
SCC: Suicide Classification Center

1 receptor antagonist, has been available in the United States for more than 11 years and has been widely prescribed for the treatment of asthma and allergic rhinitis in the United States and around the world. Based on a limited number of postmarketing suicide-related adverse experience (AE) reports, the US prescribing information for SINGULAIR was voluntarily updated to include “suicidal thinking and behavior,” and similar changes were submitted to regulatory agencies around the world in October 2007. As part of their continued attention to this issue, the US Food and Drug Administration (FDA) posted an Early Communication about an Ongoing Safety Review of Montelukast (SINGULAIR) on their Web site on March 27, 2008,¹ and posted follow-up communications on January 13, 2009,² and June 12, 2009.³ In response to (and guided by) ongoing dialogue with the FDA, the authors performed a scientific review of the available clinical trial database on montelukast regarding suicidality.

There are a number of drugs and drug classes that have come under scrutiny by the FDA regarding suicidality, prompting specifically directed analyses in adolescent patients taking antidepressants,^{4,5} patients taking the cannabinoid receptor 1 antagonist rimonabant for treatment of obesity,⁶ and, most recently, patients taking antiepileptic drugs.⁷ In response to requests for information received from the FDA in 2008 related to montelukast, data were reviewed from the clinical trials of montelukast conducted by Merck, and these data were provided to the agency. Two separate and complementary methods were used to assess suicidality in clinical trials of montelukast. The first method was a broad descriptive review across a very large dataset of montelukast clinical trials (including placebo-controlled and non-placebo-controlled trials) that examined AEs as reported by study investigators during the trials. The second method was a specific analysis using a published method⁴ of adjudication of events based on information in the study database limited to placebo-controlled clinical trials selected based on prespecified criteria, as requested by the FDA. This dual approach allows 2 alternate views of the available clinical trial data to provide insights into the frequency of events that were possibly related to suicidality in clinical trials of montelukast sodium.

METHODS

The **Methods** section of the Online Repository (available at www.jacionline.org) provides detailed descriptions of the methods used and the studies reviewed in this article.

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TABLE I. Codes of the C-CASA for PSRAEs

Code	Event
1	Completed suicide
2	Suicide attempt
3	Preparatory acts toward imminent suicidal behavior
4	Suicidal ideation
5	Self-injurious behavior, intent unknown
6	Not enough information (fatal)
7	Self-injurious behavior, no suicidal intent
8	Other: accident; psychiatric; medical
9	Not enough information (nonfatal)

Method 1: Descriptive review

A review was performed of AEs reported by investigators in 116 studies completed as of March 11, 2008, that were conducted by Merck headquarters personnel. Studies were included across all age ranges of patients and regardless of approval status for any particular indication; a listing and description of the studies is provided in [Table E1](#) (available in this article's Online Repository at www.jacionline.org). Studies included early (phase I and phase IIa) trials and late (phase IIb and phase III) trials categorized as (1) double-blind, placebo-controlled studies with or without active control; (2) double-blind, active-controlled studies without placebo control; and (3) open-label studies with or without active control. Data were reviewed to identify investigator-reported AE terms suggestive of suicidality (including terms of completed suicide, suicide attempt, and suicidal ideation) or self-injurious behavior. Data were consolidated to generate summary counts; no statistical testing was planned or performed.

Method 2: Focused analysis using adjudication methodology

This analysis used a retrospective adjudication of possibly suicidality-related adverse events (PSRAEs), as defined by the FDA, that occurred during clinical trials of montelukast. Adjudication of PSRAEs with the Columbia Classification Algorithm of Suicide Assessment (C-CASA)⁴ was performed by an independent Suicide Classification Center (SCC; Columbia University, New York, NY) blinded to treatment assignment.

The primary objective of this focused analysis was to compare the incidence of adjudicated PSRAEs in patients receiving montelukast versus placebo in randomized, double-blind, placebo-controlled clinical trials. The clinical trials for analysis were all selected according to prespecified requirements; similarly, primary, secondary, and exploratory end points were all prespecified. The primary end point was a composite of the initial 4 C-CASA classifications rated as suicidal ideation or worse (codes 1, 2, 3, or 4; [Table I](#)) corresponding to "suicidal behavior or ideation" (also termed "suicidality"). The 2 secondary end points were components of the primary end point corresponding to "suicidal behavior" (codes 1, 2, or 3) and "suicidal ideation" (code 4). An exploratory end point corresponded to the broad range of classifications denoting "possible or definite suicidality" (codes 1, 2, 3, 4, 5, 6, or 9).

Surveillance to identify PSRAEs was performed by means of review of the electronic dataset for all randomized patients in each study, regardless of treatment allocation, to identify the following:

- all deaths, regardless of cause;
- all serious AEs (defined using regulatory criteria), regardless of cause;
- all AEs of "accidental injury"; and
- all nonserious AEs, as well as any comment fields in the study database that contained at least one of a series of prespecified text strings (listed in the [Methods](#) section of this article's Online Repository) that could be related to suicidality. After electronically searching for all patients with information containing the specified text strings, Merck personnel reviewed this information to identify "false-positive hits" that were unambiguously not related to suicide (eg, the text string "hang" within the word "change"). These were reviewed by the independent SCC;

those it agreed were false positive were excluded from further analysis, which is consistent with the published methodology.³

Data for adjudication were identified and collated by using prespecified parameters per the FDA's request (detailed parameters are described in the [Methods](#) section of this article's Online Repository). Narrative summaries were then written by Merck personnel for all events that were not deemed false positive. These narratives were edited to remove treatment assignment and other information related to patient identification and then sent to the SCC for adjudication. Each PSRAE narrative was classified by the SCC into one of 9 C-CASA classifications¹ ([Table I](#)) for further analysis.

Per the FDA's request, studies conducted by Merck with a completion date on or before April 25, 2008, that met all of the following prespecified criteria were included in the review: randomized, double-blind, placebo-controlled studies; multiple-dose administration; parallel-group or crossover study designs; and at least 20 patients aged 6 years and older per treatment arm. Studies were included regardless of approval status for any particular indication under study. The selection criteria yielded 41 studies for analysis; a listing and description of these studies is provided in [Table E2](#) (available in this article's Online Repository at www.jacionline.org).

The primary analysis was prespecified as the odds ratio estimate for suicidality based on adjudicated events and analyzed as a binary variable for subjects in the montelukast arm versus subjects in the placebo arm (see the [Methods](#) section of this article's Online Repository). The odds ratio analysis was stratified by the individual trials; a stratified analysis incorporates the different event rates from the individual trials. Because of the low incidence rate of suicidality (see the Results section), the full, planned, prespecified analysis could not be conducted, and no sensitivity analyses or subgroup analyses were performed.

RESULTS

Descriptive review

Placebo-controlled studies. The cumulative review of randomized, double-blind, placebo-controlled clinical trials included 12,218 adults and children who received montelukast and 8,883 adults and children who received placebo. The total follow-up times were 1,764.3 patient-years for the montelukast group and 1,291.5 patient-years for the placebo group, which are proportionate to the patient numbers. Because the times exposed to montelukast versus placebo were comparable, the crude incidence rates reported will approximate the true incidence rates. There were no investigator-reported AEs of suicidality (including terms of completed suicide, suicide attempt, and suicidal ideation) in the patients who received montelukast ([Table II](#)). One patient in a pediatric placebo-controlled trial (see footnote "a" in [Table II](#)) had an investigator-reported AE of intentional self-injury. This was reported as "bite in mouth" (verbatim term) in a 4-year-old patient receiving placebo; the bite was considered nonserious and rated as not drug related by the investigator.

Active-controlled studies. The cumulative review of randomized, double-blind clinical trials that compared montelukast with other active agents included 3,953 adults and children who were treated with montelukast and 3,493 who were treated with other asthma therapies. The total follow-up times were 2,174.3 patient-years for the montelukast group and 2,053.7 patient-years for the active-control group, which again are approximately proportionate to patient numbers.

There was 1 patient who received montelukast who had 2 investigator-reported AEs (self-harm behavior and suicide attempt). This patient (see footnote "b" in [Table II](#)) in one of the adult studies was an 18-year-old woman who was given a diagnosis of depression during the study and experienced 3

aborted suicide attempts that were each rated as nonserious, mild, and not drug related by the investigator. The patient continued on the study drug and completed the study. Two weeks after completing the study, the depression continued, and the patient was to be followed by her family doctor.

Three patients in the active-control group in the adult studies (see footnote “c” in Table II) were reported to have suicide-related AEs. These AEs were rated as serious and not drug related by the investigator in all 3 patients.

A 20-year-old woman allocated to beclomethasone took an overdose of 59 placebo tablets (for montelukast) in a suicide attempt and was hospitalized for depression for approximately 10 days. The patient fully recovered and discontinued from the study.

A 30-year-old woman allocated to salmeterol plus fluticasone attempted suicide and was hospitalized for approximately 2 weeks. Discharge diagnoses were moderate depression disorder, suicidal tendencies, and immature personality traits. The patient fully recovered and withdrew consent after the suicide attempt.

A 16-year-old girl allocated to fluticasone took an overdose of phenobarbital (380 mg), propranolol (150 mg), and amobarbital (250 mg) in a suicide attempt after arguments with her parents and was hospitalized for approximately 3 days. The patient fully recovered and discontinued from the study.

Open-label studies. The cumulative review of open-label trials that compared montelukast with other active agents included 3,077 adults and children who were treated with montelukast and 1,464 patients who were treated with other therapies. There was 1 patient who received montelukast who had an investigator-reported AE of suicidal ideation. As reported by Bisgaard et al,⁸ this patient in an open-label pediatric trial (see footnote “d” in Table II) was a 12-year-old boy with a prior history of attention deficit disorder and depression. While receiving open-label montelukast (on treatment for >1 year), the patient was hospitalized for depression and suicidal ideation, neither of which was considered drug related by the investigator; montelukast was temporarily stopped. The patient recovered, and after hospital discharge, montelukast therapy was resumed, and depression was not reported to recur.

Focused analysis with adjudication methodology

For the retrospective adjudication of PSRAEs, there were 22,433 patients (9,929 in the montelukast group, 7,780 in the placebo group, and 4,724 in the active-control group). Of the 41 trials, 6 were conducted in a pediatric population aged 6 to 14 years (including 2,826 pediatric patients, comprising 1,432 in the montelukast group, 1,275 in the placebo group, and 119 in the active-control group). Patients were mainly enrolled in seasonal allergic rhinitis (42%) and asthma (42%) trials. The majority of patients in the active-control group were enrolled in seasonal allergic rhinitis studies.

Surveillance to identify PSRAEs across the patients assigned to montelukast or placebo (or active control) yielded 730 events that were adjudicated. From these, 1 patient, an adult treated with montelukast, had a PSRAE that was classified as code 4 (suicidal ideation). The event, which the investigator reported as an AE diagnosis of schizoaffective disorder, was identified in the search of comment fields in the study database for prespecified text strings (specifically, “suic-”). Because no PSRAEs were observed in the placebo group, the odds ratios for the comparison of the montelukast and placebo groups cannot be calculated.

TABLE II. Patients with AEs* possibly related to suicidality from the descriptive review

Investigator-reported AEs* by study category	Montelukast (n = 20,131)		Placebo (n = 9,287)		Other drugs (n = 8,346)	
	n/N	%	n/N	%	n/N	%
Phase I and IIa studies	0		0		0	
Adult studies	0/753	0.0	0/360	0.0	0/73	0.0
Pediatric studies	0/130	0.0	0/44	0.0	0/0	0.0
Phase IIb and III studies: double-blind, placebo-controlled (with or without active control)	0		1 ^a		0	
Adult studies	0/8,974	0.0	0/6,456	0.0	0/3,164	0.0
Pediatric studies	0/3,244	0.0	1/2,427	<0.1	0/152	0.0
Phase IIb and III studies: double-blind, active-controlled (without placebo)	1 ^b		NA		3 ^c	
Adult studies	1/3,458	<0.1	NA		3/2,994	<0.1
Pediatric studies	0/495	0.0	NA		0/499	0.0
Phase IIb and III studies: open-label (with or without active control)	1 ^d		NA		0	
Adult studies	0/1,590	0.0	NA		0/564	0.0
Pediatric studies	1/1,487	<0.1	NA		0/900	0.0

n/N, number of patients with ≥1 AE/number of patients in treatment group; NA, not applicable.

*Data were reviewed to identify investigator-reported AE terms: completed suicide, suicide attempt, suicidal ideation, and other terms suggesting self-injurious behavior.

^aAE term = Intentional self-injury (nonserious and rated not drug related by the investigator); reported as “bite in mouth” (verbatim term) in a 4-year-old patient.

^bAE terms = Self-harm behavior and suicide attempt (each nonserious and rated not drug related by the investigator) reported in an 18-year-old patient.

^cSerious and rated not drug related by the investigator in all 3 patients.

^dSerious and rated not drug related by the investigator.

This patient in the adjudicated dataset classified as having suicidal ideation was a 32-year-old man with a medical history of narcissistic personality disorder (diagnosed approximately 15 years before study entry) who was randomized to receive montelukast, 10 mg once daily. The patient reported complaints of anxiety and increased stress starting on day 17 after randomization and stopping on day 22. The patient was given a diagnosis of schizoaffective disorder on day 22, and study medication was discontinued. The patient was hospitalized on day 24 after randomization with an initial diagnosis of acute schizophrenia; the patient was judged to be paranoid-psychotic and suicidal. After recovery and hospital discharge on day 44 after randomization, the patient quit his job and moved without leaving a forwarding address. On day 63, the patient was seen at the investigator’s site and discontinued from the study because of the clinical AE diagnosis of schizoaffective disorder, which was determined by the investigator to be probably not related to study therapy.

DISCUSSION

In this report, events that could be considered possibly related to suicidality were assessed in controlled clinical trials of montelukast performed by Merck using 2 separate and complementary methods. First, a broad descriptive review examined AEs

as reported by study investigators during the trials. Second, a focused analysis used a published independent adjudication method⁴ (also used previously by the FDA)⁵⁻⁷ to examine investigator-reported AEs, as well as other events captured in the study databases of a prespecified set of clinical trials, as requested by the FDA. No completed suicides were reported in any study. Based on the descriptive review across 116 controlled clinical trials, events possibly related to suicidality were rare in more than 20,000 adults and children who received montelukast, and numbers of events were similar between montelukast and placebo or active-control treatment groups. The focused analysis of 41 studies to identify and adjudicate PSRAEs identified only 1 patient with a PSRAE in the montelukast group (rated as suicidal ideation) and none in the placebo group, which obviated the prespecified odds ratio analysis. Thus, as assessed by using each of these 2 methods, reports of events that were possibly related to suicidality were very rare in clinical trials of montelukast. Others who have completed analyses of adverse event data from clinical trials have likewise reported no completed suicides or increased suicidality with montelukast.⁹ A recent report of a population-based cohort study using the United Kingdom General Practice Research Database similarly found no suicides in 23,500 patients exposed to montelukast using cumulative data from February 1998 through March 2007.¹⁰

Relevant to exploring a potential role for a drug in the presentation of a particular event or behavior (eg, suicidality) is the prevalence of that event or behavior in the general and targeted populations. The annual incidence rate of suicidal ideation in the general US population using data from 2001–2003 was reported to be 3.3%, with suicide attempt rates reported as 0.6%.¹¹ In a recent systematic review of suicide and suicidal behavior, Nock et al¹² reported that estimates of the annual prevalence of suicidal ideation in US adults ranged from 2.1% to 10.0%, and the prevalence for suicide attempts in the previous year ranged from 0.2% to 2.0%, with higher rates (for both ideation and attempts) in younger adults and adolescents. The annual incidence of completed suicide in the United States was 11.1 per 100,000 in the general population,¹³ and suicide was reported to be the third-leading cause of death among youths and young adults (10–24 years of age) in the United States in 2004.¹⁴ In a World Health Organization cross-national survey of suicide prevalence and risk factors, 9.2% overall reported ever having suicidal ideation, with 3.1% having a plan and 2.7% making an attempt.¹⁵ The prevalence of ideation varied substantially among countries, but the probability of a plan or an attempt conditional on ideation was relatively consistent in the general population across geographies.

Rates of suicidal ideation and attempts in patients with asthma and allergy are reported to be higher than in the general population. Druss and Pincus¹⁶ found that the presence of a general medical condition predicted an increased odds of suicidal ideation (adjusted odds ratio, 1.32; $P = .03$) and suicide attempt (adjusted odds ratio, 1.56; $P = .03$), with even higher odds if the illness were asthma (suicidal ideation: adjusted odds ratio, 1.69; $P = .01$; suicide attempt: adjusted odds ratio, 4.34; $P = .001$). Goodwin and Eaton¹⁷ performed a community-based survey of the Baltimore, Maryland area and found that the annual incidence of suicidal ideation in the general adult population was 7.6%, but that in the asthmatic population was 11.3%. Lifetime rates of suicidal ideation were 9.2% for the general population and 13.9% for the asthmatic population. A similar study in youth aged 9 to 17 years in the United States also found an increased

likelihood of suicidal ideation with asthma (adjusted odds ratio, 3.25; $P < .05$).¹⁸ Suicide attempt rates in the Baltimore study were 3.2% (current year) and 4.0% (lifetime) in the general population and 5.3% (current year) and 6.6% (lifetime) in the asthmatic population.¹⁷ Several recent studies have suggested associations between mood disorders or suicidality and a seasonal presentation associated with pollen counts.¹⁹⁻²² A recent review discusses the evidence for a link between allergy and depression and notes the available reports on possible relationships between allergy, montelukast, and suicidality.²³

Acknowledging these background rates of suicidality in the general population and the apparently higher rates of suicidality in the asthmatic and allergic populations, it could be anticipated that some patients being treated for asthma or allergic rhinitis with montelukast could report suicidal ideation or behavior. It could also be expected that such reports would come to light through surveillance of postmarketing experience with montelukast.

Broadly speaking, after a medication is approved for marketing by regulatory agencies, drug safety can be evaluated through various mechanisms, including postmarketing surveillance, in which information is voluntarily provided by physicians, patients, or any others who state they have knowledge of an adverse event, even through casual observation. Thus postmarketing adverse event reports usually are in the nature of spontaneous anecdotal reports. Furthermore, the information in these reports can be incomplete; for example, whether a patient might have had undiagnosed symptoms before or while being treated with a product is not always available in the spontaneous anecdotal information that is generally received in postmarketing experience. Therefore it is generally not possible to establish or exclude a causal relationship to drug exposure. A limited number of postmarketing suicide-related AEs in patients taking SINGULAIR have been reported. Although the fact that a postmarketing AE has been reported does not reflect a conclusion that the postmarketing experience is caused by the drug, receipt and review of these postmarketing reports prompted Merck to make a voluntary label change in October 2007 to include the terms “suicidal thinking and behavior” in the US prescribing information for SINGULAIR²⁴ because a causal relationship to montelukast cannot be excluded based on these postmarketing data. As reported here with clinical trial data, both when reviewed across a broad dataset of studies and when analyzed by using a focused analysis of adjudicated reports, reports of suicidality were rare in patients receiving montelukast and similar in control groups. Nevertheless, given the postmarketing experience, it is prudent for prescribers to be alert for events consistent with suicidality and to carefully evaluate the risks and benefits of continuing treatment if such events occur, which is consistent with the FDA’s recent updated information on leukotriene modifiers.³

If a drug were suspected of causing an event, one would also examine the biology of the drug or the pathway affected by the drug to try to explain why the event might have occurred. In the preclinical and clinical literature there is no apparent biologic mechanism to explain why a leukotriene receptor antagonist might cause suicidal ideation because there are few data describing central nervous system effects on behavior mediated by the cysteinyl leukotriene type 1 receptor. Most drugs that have been implicated with concerns of suicidality are known to have therapeutic mechanisms that are centrally acting (eg, antidepressants, antiepileptic drugs, cannabinoid receptor 1 antagonists for

obesity, and varenicline for smoking cessation²⁵). In contrast, montelukast treats asthmatic and allergic inflammation primarily in the airway. Studies in rats indicate minimal distribution of radiolabeled montelukast across the blood-brain barrier;²⁴ similar studies have not been performed in human subjects. Recent studies in rodents suggest cysteinyl leukotrienes could be part of an inflammatory response to ischemic central nervous system injury and that inhibition of this pathway might play a protective role.^{26,27} The only preclinical evidence relating behavioral changes to involvement of the leukotriene pathway is associated with the 5-lipoxygenase enzyme, which is required to synthesize leukotriene B₄ and the cysteinyl leukotrienes.²⁸ This enzyme was reported to be upregulated in postmortem studies of brains obtained after suicide.²⁹ In rodents, reduced leukotriene biosynthesis (including in 5-lipoxygenase knockout mice) appeared to decrease anxiety-related behavior in mice.^{30,31}

A limitation of the analyses presented here is that these studies were generally designed as clinical trials of asthma and allergic rhinitis and were generally of short duration (with <2 months of follow-up per patient on average); therefore conclusions related to long-term use are limited. Importantly, the studies included in these analyses had not been specifically designed to determine the incidence of suicidality with montelukast treatment because the available preclinical data (and emerging clinical trial data) did not suggest that a risk of suicidality with montelukast treatment had supportive biologic plausibility. Similarly, these studies were not designed to compare the rate of suicidality in patients taking montelukast with the rate in patients taking other antiasthma agents (although we have noted those rates using the data available in this review of clinical trial data). Without systematic assessments for suicidality during the conduct of these trials,³² some suicidality events might not have been reported; however, one advantage of the adjudication method used in this article is that other available information in the study records could be used to deduce suicidality, even if an AE were not explicitly labeled as “suicidal” by the study investigator during the clinical trial.

Finally, in these clinical trials patients were generally excluded who had clinically significant psychiatric disorders (other than mild depression that does not interfere with work or social activities). This approach optimized study performance by allowing exclusion of patients who might have been at higher risk for noncompliance with study procedures. However, excluding patients possibly at higher risk for suicidality because of psychiatric comorbidities might have reduced the number of reports of suicidality in these studies (compared with background populations); hence these clinical trial data do not address questions about montelukast specifically in such high-risk populations.

In conclusion, reports of suicidality were rare in clinical trials of montelukast, and there were no completed suicides in any clinical trial. Assessed by using 2 complementary methods across large datasets of clinical trials of montelukast, reports of PSRAEs were rare in patients receiving montelukast and similar in control groups. Although these clinical trials were not specifically designed to examine suicidality, these clinical trial results do not provide evidence to support a causal association for montelukast with regard to suicidality.

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Clinical implications: Although these studies were not designed specifically to examine suicidality, available data from clinical trials do not provide evidence to support a causal association between montelukast use and suicidal behavior or ideation.

REFERENCES

1. US Food and Drug Administration. Early communication about an ongoing safety review of montelukast (SINGULAIR) Available at: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm095019.htm>. Accessed August 10, 2009.
2. US Food and Drug Administration. Update of safety review: follow-up to the March 27, 2008, communication about the ongoing safety review of montelukast (Singulair), January 13, 2009. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm079523.htm>. Accessed August 10, 2009.
3. US Food and Drug Administration. Updated information on leukotriene inhibitors: montelukast (marketed as Singulair), zafirlukast (marketed as Accolate), and zileuton (marketed as Zylflo and Zylflo CR), June 12, 2009. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm165489.htm>. Accessed August 10, 2009.
4. Posner K, Oquendo M, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry* 2007;164:1035-43.
5. Psychopharmacologic Drugs Advisory Committee. Available at: <http://www.fda.gov/ohrms/dockets/ac/cder04.html#PsychopharmacologicDrugs>. Accessed August 10, 2009.
6. US Food and Drug Administration. FDA briefing document: ZimultiTM (rimonabant) tablets, 20 mg. Available at: <http://www.fda.gov/OHRMS/DOCKETS/AC/07/briefing/2007-4306b1-00-index.htm>. Accessed August 10, 2008.
7. Suicidal behavior and ideation and antiepileptic drugs. Available at: <http://www.fda.gov/cder/drug/infopage/antiepileptics/default.htm>. Accessed August 10, 2009.
8. Bisgaard H, Skoner D, Boza ML, Tozzi CA, Newcomb K, Reiss TF, et al. Safety and tolerability of montelukast in placebo-controlled pediatric studies and their open-label extensions. *Pediatr Pulmonol* 2009;44:568-79.
9. Holbrook JT, Harik-Khan R. Montelukast and emotional well-being as a marker for depression: results from 3 randomized, double-masked clinical trials. *J Allergy Clin Immunol* 2008;122:828-9.
10. Jick H, Hagberg KW, Egger P. Rate of suicide in patients taking montelukast. *Pharmacotherapy* 2009;29:165-6.
11. Kessler RC, Berglund P, Borges G, Nock M, Wang PS. Trends in suicide ideation, plans, gestures, and attempts in the United States, 1990-1992 to 2001-2003. *JAMA* 2005;293:2487-95.
12. Nock MK, Borges G, Bromet EJ, Cha CB, Kessler RC, Lee S. Suicide and suicidal behavior. *Epidemiol Rev* 2008;30:133-54.
13. Centers for Disease Control and Prevention (CDC). Web-based Injury Statistics Query and Reporting System (WISQARS [online]) 2005. National Center for Injury Prevention and Control, CDC (producer). Available at: <http://www.cdc.gov/ViolencePrevention/suicide/index.html>. Accessed August 10, 2009.
14. Centers for Disease Control and Prevention (CDC). Suicide trend among youths and young adults aged 10-24 years—United States, 1990-2004. *MMWR Morb Mortal Wkly Rep* 2007;56:905-8.
15. Nock MK, Borges G, Bromet EJ, Alonso J, Angermeyer M, Beautrais A, et al. Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. *Br J Psychiatry* 2008;192:98-105.
16. Druss B, Pincus H. Suicidal ideation and suicide attempts in general medical illnesses. *Arch Intern Med* 2000;160:1522-6.
17. Goodwin RD, Eaton WW. Asthma, suicidal ideation, and suicide attempts: findings from the Baltimore Epidemiologic Catchment Area follow-up. *Am J Public Health* 2005;95:717-22.
18. Goodwin RD, Marusic A. Asthma and suicide ideation among youth in the community. *Crisis* 2004;25:99-102.
19. Postolache TT, Stiller JW, Herrell R, Goldstein MA, Shreeram SS, Zebrak R, et al. Tree pollen peaks are associated with increased nonviolent suicide in women. *Mol Psychiatry* 2005;10:232-8.

20. Guzman A, Tonelli LH, Roberts D, Stiller JW, Jackson MA, Sorian JJ, et al. Mood-worsening with high-pollen-counts and seasonality: a preliminary report. *J Affective Disorders* 2007;101:269-74.
21. Yip PSF, Yang KCT, Qin P. Seasonality of suicides with and without psychiatric illness in Denmark. *J Affect Disord* 2006;96:117-21.
22. Postolache TT, Komarow H, Tonelli LH. Allergy: a risk factor for suicide? *Curr Treat Options Neurol* 2008;10:363-76.
23. Manalai P, Woo J-M, Postolache TT. Suicidality and montelukast. *Expert Opin Drug Saf* 2009;8:273-82.
24. SINGULAIR® (montelukast sodium) prescribing information. Whitehouse Station (NJ): Merck & Co, Inc; 2009.
25. The smoking cessation aids varenicline (marketed as Chantix) and bupropion (marketed as Zyban and generics): suicidal ideation and behavior. US Food and Drug Administration Drug Safety Newsletter. Available at: www.fda.gov/downloads/Drugs/DrugSafety/DrugSafetyNewsletter/ucm107318.pdf. Accessed August 10, 2009.
26. Fang SH, Wei EQ, Zhou Y, Wang ML, Zhang WP, Yu GL, et al. Increased expression of cysteinyl leukotriene receptor-1 in the brain mediates neuronal damage and astrogliosis after focal cerebral ischemia in rats. *Neuroscience* 2006;140: 969-79.
27. Ciana P, Fumagalli M, Trincavelli ML, Verderio C, Rosa P, Lecca D, et al. The orphan receptor GPR17 identified as a new dual uracil nucleotides/cysteinyl-leukotrienes receptor. *EMBO J* 2006;25:4615-27.
28. Peters-Golden M, Henderson WR Jr. Leukotrienes. *N Engl J Med* 2007;357: 1841-54.
29. Uz T, Dwivedi Y, Pandey GN, Roberts RC, Conley RR, Manev R, et al. 5-Lipoxygenase in the prefrontal cortex of suicide victims. *Open Neuropsychopharmacol J* 2008;1:1-5.
30. Uz T, Dimitrijevic N, Tueting P, Manev H. 5-lipoxygenase (5LOX)-deficient mice express reduced anxiety-like behavior. *Restor Neurol Neurosci* 2002;20: 15-20.
31. Uz T, Dimitrijevic N, Imbesi M, Manev H, Manev R. Effects of MK-866, a 5-lipoxygenase activating protein (FLAP) inhibitor, and 5-lipoxygenase deficiency on the forced swimming behavior of mice. *Neurosci Lett* 2008;436: 269-72.
32. Brent DA, Emslie GJ, Clarke GN, Asarnow J, Spirito A, Ritz L, et al. Predictors of spontaneous and systematically assessed suicidal adverse events in the treatment of SSRI-resistant depression in adolescents (TORDIA) study. *Am J Psychiatry* 2009; 166:418-26.

METHODS

Two separate review methods were used to describe the number of events possibly related to suicidality reported in clinical trials of montelukast conducted by Merck. Method 1 included both placebo-controlled and non-placebo-controlled trials and was therefore broadly inclusive of available clinical trial experience with montelukast. In contrast, Method 2 included only trials that were placebo controlled and thus supported more rigorous analysis according to a published method using independent adjudication.

Method 1: Descriptive review

A review was performed of AEs reported by investigators from 116 studies completed as of March 11, 2008, that were conducted by Merck (Table E1). Studies were included regardless of design (eg, parallel group or crossover) or number of patients or subjects per treatment arm. Single- and multiple-dose studies of adults and children as young as age 1 month were included, regardless of indication or approval status for any particular indication. Studies included early trials (phase I and Phase IIa) and later trials (phase IIb and Phase III) that were further categorized as (1) randomized, double-blind, placebo-controlled clinical trials with or without an active control; (2) randomized, double-blind, active-controlled clinical trials without a placebo control; and (3) open-label clinical trials with or without an active control.

Studies not included in this descriptive review were generally in 3 categories: (1) studies conducted by Merck headquarters personnel that were considered ongoing and/or for which database lock had not been achieved by March 11, 2008; (2) investigator-initiated studies (studies for which Merck is not the sponsor; although these studies do receive financial and/or material support from Merck, the study data belong to the investigator and not to Merck); (3) subsidiary studies (ex-US studies performed by local/country subsidiaries of Merck around the world and, generally, data reside in the country in which the study was performed). Additionally, a study in the laropiprant clinical development program that also included montelukast treatment was not included in the descriptive review. In this study^{E1} montelukast was used as a single-blind active control, which was added to both the placebo group and the laropiprant group during part of a crossover period to look for additive effects for the treatment of asthma. No reports of AE terms suggestive of suicidality or self-injurious behavior were identified in this study.

Data were reviewed to identify investigator-reported AE terms suggestive of suicidality (including terms of completed suicide, suicide attempt, and suicidal ideation) or self-injurious behavior. An AE was defined as any unfavorable and unintended change in structure, function, or chemistry of the body temporally associated with any use of active study drug or placebo, irrespective of whether it was considered related to the use of the active study drug or placebo. Any worsening of a preexisting condition temporally associated with the use of active study drug or placebo was also an AE. AEs included in the descriptive review were reported in the clinical trial database and occurred after randomization.

Data conventions used in the descriptive review:

- AEs were included even if they occurred after discontinuing randomized treatment or if they occurred during a period of tapering treatment. In studies that included a protocol-specified placebo washout after the double-blind treatment period, AEs that occurred during the washout were attributed to randomized therapy (eg, AEs occurring during the placebo washout period in patients who received montelukast before the placebo washout were attributed to montelukast).
- Subjects randomized to montelukast alone or montelukast plus another protocol-specified medication (either concomitantly or in combination) were counted in the montelukast group.
- All postrandomization crossover treatment periods were included, and subjects were counted as having been exposed to each treatment actually received. If an AE continued as a subject switched from one treatment to another (ie, crossed over), the AE was assigned only to the treatment the patient received when the AE began. If an AE occurred during a protocol-specified off-drug period (eg, washout), the AE was assigned to the previous treatment received.

Method 2: Focused analysis with adjudication methodology

This analysis used a retrospective adjudication of PSRAEs, as defined by the FDA, that occurred during completed clinical trials of montelukast. Adjudication of PSRAEs was performed according to the C-CASA and blinded to treatment assignment. Data management responsibilities in support of this analysis were split between 2 committees: one consisting of personnel from Merck Research Laboratories (MRL), who constituted an MRL Coordinating Center that was responsible for identifying and collating data to be adjudicated, and an independent SCC at Columbia University (New York, NY) that was responsible for the adjudication for PSRAEs. No member of the SCC was an employee of Merck nor had any member been involved in the conduct of the clinical trials in any capacity. The SCC principal investigator was responsible strictly for the determination of suicidality and did not attempt to determine the causal relation of study drug to an event. Personnel in the MRL Coordinating Center were considered unblinded to patients' treatment group assignments because the studies in this analysis had already been completed and the databases unblinded; however, personnel in the independent SCC remained blinded to treatment for all adjudications.

A listing and description of the clinical studies included in this focused analysis is in Table E2. Per the FDA request, adult and pediatric studies conducted by Merck with a completion date on or before April 25, 2008, that met all of the following prespecified criteria were included in the review: randomized, double-blind, placebo-controlled, and multiple-dose study designs; parallel-group or crossover study designs; and at least 20 patients or subjects aged 6 years and older per treatment arm. Because suicidality was considered unlikely in very young children, it was deemed appropriate (and therefore prespecified) to include studies with adult and pediatric patients only as young as age 6 years. Studies were included in the analysis regardless of indication or approval status for any particular indication. Studies not included in this focused analysis were (1) studies that were considered ongoing and/or for which database lock had not been achieved by April 25, 2008, and (2) investigator-initiated studies, which are studies for which Merck is not the sponsor. Based on these prespecified criteria, 41 studies were selected for analysis: 26 studies were on asthma, 12 were on seasonal allergic rhinitis, 2 were on perennial allergic rhinitis, and 1 was on migraine headache.

Data for adjudication were identified and collated by the MRL Coordinating Center by using the following parameters prespecified by the FDA. Surveillance for PSRAEs was limited to the data collected (1) in parallel-group studies during the double-blind, placebo-controlled phase of treatment or within 1 day of stopping treatment and (2) in crossover studies during the first double-blind, placebo-controlled active-treatment period or within 1 day of stopping double-blind treatment. Events were not included if they occurred before randomization or more than 1 day after discontinuing from randomized treatment. If a trial had a period of tapering treatment, the end of the treatment period for analysis was set at the beginning of the tapering period. Events were excluded if they occurred more than 1 day after discontinuing randomized treatment, even if discontinuation occurred before the expected end point of the trial. Events that occurred at some prior time or were preexisting at baseline were counted as treatment emergent if they recurred during the course of a trial. The population of interest included all randomized patients who had been documented to receive at least 1 dose of active treatment in the period of interest.

Subjects randomized to montelukast alone were counted in the montelukast group, whereas subjects randomized to montelukast plus the active control were counted in the active-control group, unless all randomized patients in a study received the same additional protocol-specified active control. For example, if patients were randomized to either montelukast or salmeterol but all patients also received fluticasone throughout the study (eg, montelukast plus fluticasone or salmeterol plus fluticasone), patients receiving montelukast plus fluticasone were counted in the montelukast group and patients receiving salmeterol plus fluticasone were counted in the active-control group.

By using the above-mentioned parameters, surveillance for PSRAEs was performed by means of review of the electronic dataset for all randomized patients in each included study, regardless of treatment allocation, to identify the following:

- All deaths, regardless of cause.
- All serious AEs (defined using regulatory criteria), regardless of cause. A serious AE is any AE that results in death, is life-threatening (places the patient, in the view of the investigator, at immediate risk of death from the experience as it occurred), results in a persistent or significant disability/incapacity, results in or prolongs an existing inpatient hospitalization, is a congenital anomaly/birth defect (in offspring of patient taking the product regardless of time to diagnosis), is a cancer, or is an overdose (whether accidental or intentional). Other important medical events that might not result in death, not be life-threatening, or not require hospitalization might be considered a serious AE when, based on appropriate medical judgment, the event might jeopardize the patient and might require medical or surgical intervention to prevent one of the outcomes listed previously.
- All AEs of "accidental injury."
- All nonserious AEs, as well as any comments in the study database, that contained at least 1 of the following text strings: "accident," "attempt," "burn," "cut," "drown," "gas," "gun," "hang," "hung," "immolates," "injury," "jump," "monoxide," "mutilates," "overdose," "self damage," "self harm," "self inflict," "self injury," "shoot," "slash," "suicide," "poison," "asphyxiation," "suffocation," and "firearm." After identifying all subjects/patients with information that contained the specified text strings (as "hits"), the MRL Coordinating Center then reviewed this information to identify "hits" that were unambiguously not related to suicide (and therefore considered "false-positive hits"). For instance, any terms identified by the search because the text string was a substring of an unrelated word (eg, the text string "hang" within the word "change") were considered false positive. A list of all events identified as false-positive hits was provided to the SCC principal investigator for evaluation. If the SCC principal investigator determined that an event on the false-positive list was possibly suicidality related, the event was considered a PSRAE and removed from the false-positive list. The final list of events considered false-positive hits were excluded from further analysis.

Narrative summaries, based on patient information reported for the event in the respective clinical study database or from other sources, were written by the MRL Coordinating Center for all events identified by the surveillance for PSRAEs that were not deemed false positive. These narratives were edited to remove treatment assignment and other patient-identifying information. After 2 separate MRL Coordinating Center reviewers ensured that the documentation requirements for adjudication were met, the narratives were sent to the SCC for adjudication. Each PSRAE narrative was classified by the SCC principal investigator, in a blinded manner, into one of 9 C-CASA classification codes¹ (Table I), which then was used for further analysis.

Because of the low incidence rate of suicidality (only 1 event classified as possible or definite suicidality of 730 adjudicated events), the full, planned, prespecified analysis could not be conducted. The primary analysis consisted of estimating the odds ratio of suicidality (analyzed as a binary variable) for patients in the montelukast group compared with patients in the placebo group based on adjudicated events. An exact analysis was performed, as stratified by the individual trials; a stratified analysis incorporates the different event rates from the individual trials. The analysis was also performed without stratifying. No sensitivity analyses or subgroup analyses were performed.

Of the 41 studies that met the prespecified criteria for Method 2, 35 studies were performed under headquarters data management; these 35 studies are among the 116 studies in Method 1. In contrast, 6 subsidiary studies were included in Method 2 that had not been included in Method 1. Although these 6 studies were not specified for inclusion in Method 1, subsequent review of these results identified no reports of AE terms that were suggestive of suicidality or self-injurious behavior in these studies.

REFERENCE

- E1. Philip G, van Adelsberg J, Loeys T, Liu N, Wong P, Lai E, et al. Clinical studies of the DP1 antagonist laropiprant in asthma and allergic rhinitis. *J Allergy Clin Immunol*. In press 2009.

TABLE E1. Listing of montelukast clinical studies included in the descriptive review

Protocol no.	Study design	Citation
Phase I and IIa: Adult studies		
002	Double-blind, placebo-controlled, 3-period, alternating, 2-panel, single-rising-dose in healthy volunteers	Schoors DF, et al. Br J Clin Pharmacol 1995;40:277-80
003	Double-blind, placebo-controlled, serial-panel, time-lagged, multiple-dose to determine preliminary pharmacokinetics of montelukast (capsule formulation) in healthy volunteers	Data on file
004	Double-blind, 2-period, placebo-controlled, incrementally increasing dose, crossover to evaluate safety and tolerability of single doses of montelukast (capsule formulation) in patients with mild asthma	Data on file
005	Double-blind, 2-part, 2-panel, placebo-controlled, crossover	De Lepeleire I, et al. Clin Pharmacol Ther 1997;61:83-92
006	Double-blind, placebo-controlled, 3 period, crossover	Reiss TF, et al. Thorax 1997;52:45-8
007	Double-blind, 2-period, placebo-controlled, multiple-dose, crossover	Reiss TF, et al. J Allergy Clin Immunol 1996;98:528-34
008	Double-blind, multiple-dose, 2-period crossover in healthy volunteers	Malmstrom K, et al. Am J Ther 1998;5:189-95
010	Open-label, single-dose, 3-period, crossover to determine relative bioavailability of tablet versus capsule formulations of montelukast in healthy volunteers	Data on file
011	Double-blind, placebo-controlled, 3-period crossover	De Lepeleire I, et al. Clin Pharmacol Ther 1997;61:83-92
012	Double-blind, placebo-controlled, parallel group in healthy volunteers	Malmstrom K, et al. Am J Ther 1998;5:189-95
013	Double-blind, placebo-controlled, 3-period crossover	Reiss TF, et al. Thorax 1997;52:1030-5
014	Open-label, single-oral-dose, 3-part to determine the relative bioavailability of tablet versus capsule formulations of montelukast in healthy volunteers	Data on file
017	Double-blind, placebo- and active-controlled, parallel-group pilot to determine safety and tolerability of montelukast (capsule formulation) in patients with allergic rhinitis	Data on file
018	Double-blind, placebo-controlled, 2-period crossover in healthy volunteers	Knorr B, et al. Clin Exp Allergy Rev 2001;1:254-60
021	Open-label, 2-period, single-dose	Knorr B, et al. Clin Exp Allergy Rev 2001;1:254-60
023	Open-label, single oral dose in healthy volunteers	Balani SK, et al. Drug Metab Dispos 1997;25:1282-7.
026	Open-label, single-dose, 7-period, crossover to determine oral dose proportionality, effect of food and dosing time on kinetics, and relative bioavailability of several tablet formulations of montelukast in healthy volunteers	Data on file
028	Double-blind, 4-period, incomplete block, crossover	Bronsky EA, et al. Clin Pharmacol Ther 1997;62:556-61
033	Double-blind, placebo-controlled, 2-part, 8-period, single-rising-dose in healthy volunteers	Cheng H, et al. Pharmacol Res 1996;13:445-8
034	Open-label, 4-period, crossover in healthy volunteers	Knorr B, et al. J Clin Pharmacol 1999;39:786-93
035	Double-blind, placebo-controlled, parallel-group	Kundu S, et al. Am Rev Respir Dis 1997;155(suppl):A352
038	Double-blind, placebo-controlled, 2-period, crossover	Ramakrishnan R, et al. Pharmacol Res 2005;22:532-40
045	Open-label, 2-panel, single- and multiple-dose (healthy young adult subjects); open-label, 2-period crossover (healthy elderly subjects)	Zhao JJ, et al. Biopharm Drug Dispos 1997;18:769-77
047	Double-blind, placebo-controlled, 2-period, crossover in healthy volunteers	Malmstrom K, et al. Am J Ther 1998;5:189-95
048	Double-blind, 2-period, crossover in healthy volunteers	Knorr B, et al. Clin Exp Allergy Rev 2001;1:254-60
050	Double-blind, placebo-controlled, 2-period, crossover	Diamant Z, et al. Clin Exp Allergy 1999;29:42-51
051	Open-label, single oral dose in healthy volunteers	Balani SK, et al. Drug Metab Dispos 1997;25:1282-7
053	Double-blind, placebo-controlled, 2-period crossover in healthy volunteers	Depre M, et al. J Clin Pharmacol 1999;39:941-4
055	Double-blind, placebo-controlled, 2-period crossover in healthy volunteers	Van Hecken A, et al. J Clin Pharmacol 1999;39:495-500
057	Open-label, 2-period, crossover in subjects with hepatic insufficiency	Knorr B, et al. Clin Exp Allergy Rev 2001;1:254-60
058	Double-blind, fixed-sequence, 2-period in healthy volunteers	Knorr B, et al. Clin Exp Allergy Rev 2001;1:254-60
060	Open-label, 5-period, crossover in healthy volunteers	Knorr B, et al. Clin Exp Allergy Rev 2001;1:254-60
090	Open-label, 3-period, crossover to evaluate the bioequivalence of the chewable tablet and oral granules formulations of montelukast in healthy volunteers	Data on file

(Continued)

TABLE E1. (Continued)

Protocol no.	Study design	Citation
086	Open-label, 4-period crossover pilot to investigate the pharmacokinetics of montelukast and loratadine administered as a combination tablet in healthy volunteers	Data on file
127	Open-label, 3-period, crossover to determine dose proportionality of montelukast oral granules in healthy volunteers	Data on file
129	Open-label, partially fixed sequence, 3-period, crossover to determine the relative bioavailability of montelukast and loratadine administered concomitantly and as a combination tablet in healthy volunteers	Data on file
175	Open-label, 2-period, crossover to determine the relative bioavailability of montelukast chewable tablets and loratadine syrup administered concomitantly and as a combination chewable tablet in healthy volunteers	Data on file
183	Open-label, balanced, 3-period, crossover to evaluate the bioequivalence of the chewable tablet and oral granules formulations of montelukast in healthy volunteers	Data on file
310	Open-label, 2-period, crossover in healthy volunteers	Kim K-A, et al. Br J Clin Pharmacol 2007;63:339-45
Phase I and IIa: Pediatric studies		
036	Open-label, 1-period, single oral dose	Knorr B, et al. J Clin Pharmacol 1999;39:786-93
039	Double-blind, parallel-group	Knorr B, et al. J Clin Pharmacol 1999;39:786-93
040	Double-blind, placebo-controlled, 2-period, crossover	Kemp JP, et al. J Pediatr 1998;133:424-8
066	Open-label, single-dose	Knorr B, et al. J Clin Pharmacol 2001;41:612-9
136/138	Open-label, single-dose	Migoya E, et al. J Clin Pharmacol 2004;44:487-94
268	Period I: open-label single-dose; periods II and III: double-blind, placebo-controlled	Knorr B, et al. J Clin Pharmacol 2006;46:620-7
297	Period I: open-label single-dose; periods II and III: double-blind, placebo-controlled	Kearns GL, et al. J Clin Pharmacol 2008;48:502-11
Phase IIb and III: Placebo-controlled with or without active control—adult studies		
009 base	Double-blind, placebo-controlled, parallel-group	Altman LC, et al. J Allergy Clin Immunol 1998;102:50-6
015 base	Double-blind, placebo-controlled, parallel-group	Dahlen SE, et al. Am J Respir Crit Care Med 2002;165:9-14
020 base	Double-blind, placebo- and active-controlled, parallel-group	Malmstrom K, et al. Ann Intern Med 1999;130:487-95
025	Double-blind, placebo-controlled, parallel-group	Noonan MJ, et al. Eur Respir J 1998;11:1232-9
029	Double-blind, parallel-group, placebo-controlled (in United States only), active-controlled, additivity removal	Laviolette M, et al. Am J Respir Crit Care Med 1999;160:1862-8
031 base	Double-blind, placebo-controlled, parallel-group	Reiss TF, et al. Arch Intern Med 1998;158:1213-20
042	Double-blind, placebo-controlled, parallel-group	Leff JA, et al. N Engl J Med 1998;339:147-52
044	Double-blind, placebo-controlled, 3-period crossover	Dockhorn RJ, et al. Thorax 2000;55:260-5
046	Double-blind, placebo-controlled, parallel-group	Löfdahl CG, et al. BMJ 1999;19:87-90
056	Double-blind, placebo-controlled, parallel-group	Pizzichini E, et al. Eur Respir J 1999;14:12-8
059	Double-blind, placebo-controlled, parallel-group	Ramsay CF, et al. Respir Med 2009;103:995-1003
068	Double blind, placebo- and active-controlled, parallel-group	Meltzer EO, et al. J Allergy Clin Immunol 2000;105:917-22
069	Double-blind, placebo- and active-controlled, parallel-group	Baumgartner RA, et al. Eur Respir J 2003;21:123-8
070	Double-blind, placebo- and active-controlled, parallel-group	Israel E, et al. J Allergy Clin Immunol 2002;110:847-54
077	Double-blind, placebo- and active-controlled, parallel-group	Philip G, et al. Eur Respir J 2004;24(suppl 48):P888
102	Double-blind, active- and placebo-controlled, parallel-group	Philip G, et al. Eur Respir J 2004;24(suppl 48):P888
113	Double-blind, active- and placebo-controlled, parallel-group	Storms W, et al. Respir Med 2004;98:1051-62
116	Double-blind, placebo-controlled, parallel-group	Camargo CA Jr, et al. Am J Respir Crit Care Med 2003;167:528-33
117	Double-blind, placebo- and active-controlled, parallel-group	Nayak AS, et al. Ann Allergy Asthma Immunol 2002;88:592-600
162	Double-blind, placebo- and active-controlled, parallel-group	Philip G, et al. Clin Exp Allergy 2002;32:1020-8
192	Double-blind, active- and placebo-controlled, parallel-group	Chervinsky P, et al. Ann Allergy Asthma Immunol 2004;92:367-73
235	Double-blind, active- and placebo-controlled, parallel-group	van Adelsberg J, et al. Ann Allergy Asthma Immunol 2003;90:214-22
240	Double-blind, active- and placebo-controlled, parallel-group	van Adelsberg J, et al. Allergy 2003;58:1268-76
246	Double-blind, active- and placebo-controlled, parallel-group	Alon A, et al. Proc Am Thorac Soc 2005;2:A341
256	Double-blind, placebo-controlled, crossover	Perry TT, et al. Ann Allergy Asthma Immunol 2004;93:431-8
265	Double-blind, placebo-controlled, parallel-group	Patel P, et al. Ann Allergy Asthma Immunol 2005;95:551-7
269	Double-blind, placebo-controlled, parallel-group	Philip G, et al. Curr Med Res Opin 2004;20:1549-58

(Continued)

TABLE E1. (Continued)

Protocol no.	Study design	Citation
270	Double-blind, placebo-controlled, 2-period, crossover	Pearlman DS, et al. Ann Allergy Asthma Immunol 2006;97:98-104
275	Double-blind, placebo-controlled, 2-period, crossover	Philip G, et al. Asthma 2007;44:213-7
288	Double-blind, placebo-controlled, parallel-group	Smithline H, et al. Acad Emerg Med 2008;15(suppl 1):S14
289	Double-blind, placebo-controlled, parallel-group	Busse WW, et al. Ann Allergy Asthma Immunol 2006;96:60-8
316	Double-blind, 3-period, placebo- and active-controlled, crossover	Philip G, et al. Chest 2007;132:875-83
Rofecoxib PN 125	Double-blind, placebo- and active-controlled, parallel-group	Brandes JL, et al. Headache 2004;44:581-6
Phase IIb and III: Placebo-controlled with or without active control—pediatric studies		
049 base	Double-blind, placebo-controlled, parallel-group	Knorr B, et al. JAMA 1998;279:1181-6
072 base	Double-blind, placebo-controlled, parallel-group	Knorr B, et al. Pediatrics 2001;108:e48 (1-10)
097	Double-blind, active- and placebo-controlled, parallel-group	Becker AB, et al. Ann Allergy Asthma Immunol 2006;96:800-7
176	Double-blind, placebo-controlled, parallel-group	van Adelsberg J, et al. Curr Med Res Opin 2005;21:971-9
219	Double-blind, placebo-controlled, parallel-group	Bisgaard H, et al. Pediatr Pulmonol 2009;44:568-79
254	Double-blind, placebo-controlled, 2 active-treatment periods, 2-arm, 2×2 crossover	Pedersen S, et al. Pediatr Pulmonol 2007;42:838-43
272	Double-blind, placebo-controlled, parallel-group	Bisgaard H, et al. Am J Respir Crit Care Med 2008;178:854-60
336	Double-blind, placebo-controlled, parallel-group	Papadopoulos N, et al. J Asthma 2009;46:413-20
340	Double-blind, placebo-controlled, parallel-group	Weiss KB, et al. Presented at the European Academy of Allergology and Clinical Immunology and European Respiratory Society Pediatrics Joint meeting, Lisbon, Portugal, October 20-23, 2007
906	Double-blind, 2-period, crossover	Simons FER, et al. J Pediatr 2001;138:694-8
907	Double blind, placebo-controlled, parallel-group	Bisgaard H, et al. Am J Respir Crit Care Med 2005;171:315-22
Phase IIb and III: Active-controlled without placebo control—adult studies		
020 extension	Double-blind, active-controlled, parallel-group, extension	Williams B, et al. Clin Exp Allergy 2001;31:845-54
062	Double-blind, placebo-controlled, 2 active-treatment period crossover	Reicin A, et al. Arch Intern Med 2000;160:2481-8
064	Double-blind, active-controlled, parallel-group	Edelman JM, et al. Ann Intern Med 2000;132:97-104
074 base	Double-blind, 3-part, 2×2 crossover	Lu S, et al. J Asthma 2009;46:465-9
120	Double-blind, active-controlled, parallel-group	Ilowite J, et al. Ann Allergy Asthma Immunol 2004;92:641-8
163 base	Double-blind, active-controlled, parallel-group	Zeiger RS, et al. Am J Med 2005;118:649-57
902	Double-blind, active-controlled, parallel-group	Villaran C, et al. J Allergy Clin Immunol 1999;104:547-53
905 base	Double-blind, active-controlled, parallel-group	Bousquet J, et al. J Appl Res 2005;5:402-14
908	Double-blind, active-controlled, parallel-group	Bjerner L, et al. BMJ 2003;327:891-5
909	Double-blind, active-controlled, parallel-group	Price DB, et al. Thorax 2003;58:211-6
Phase IIb and III: Active-controlled without placebo control—pediatric studies		
910	Double-blind, active-controlled, parallel-group	Garcia Garcia ML, et al. Pediatrics 2005;116:360-9
Phase IIb and III: Open-label with or without active control—adult studies		
009 extension	Open-label, uncontrolled, extension	Williams B, et al. Clin Exp Allergy 2001;31:845-54
015 extension	Two-period extension: first period: double-blind, placebo-controlled; second period: open, uncontrolled	Storms W, et al. Clin Exp Allergy 2001;3:77-87
031 extension	Open-label, active-controlled, extension	Williams B, et al. Clin Exp Allergy 2001;31:845-54
074 extension	Open-label, active-controlled	Lu S, et al. J Asthma 2009;46:465-9
076	Open-label, active-controlled, parallel-group	Hughes, et al. Am J Respir Crit Care Med 1999;159:A641
163 extension	Open-label, active-controlled, parallel group	Zeiger RS, et al. Am J Med 2005;118:649-57
904	Open-label, uncontrolled	Price DB, et al. Curr Ther Res 2001;62:743-75
905 extension	Open-label, active-controlled, parallel-group extension	Bousquet J, et al. J Appl Res 2005;5:402-14
Phase IIb and III: Open-label with or without active control—pediatric studies		
049 extension	Open-label, active-controlled	Williams B, et al Clin Exp Allergy 2001;31:845-54
065 base	Open-label, 2-period, crossover	Bisgaard H, et al. Pediatr Pulmonol 2009;44:568-79
065 extension	Open-label, parallel-group extension to the study of parent/guardian preference between montelukast and cromolyn; patients in the extension received either montelukast or beclomethasone	Bukstein D, et al. J Asthma 2003;40:475-85 Data on file
072 extension	Open-label, active-controlled	Davies GM, et al. Clin Ther 2004;26:1895-904 Bisgaard H, et al. Pediatr Pulmonol 2009;44:568-79
232	Open-label, active-controlled	Bisgaard H, et al. Pediatr Pulmonol 2009;44:568-79
903 base	Open-label, 2-period, crossover	Volovitz B, et al. Curr Ther Res 2000;61:490-506.
903 extension	Open-label, parallel-group	Maspero JF, et al. Curr Med Res Opin 2001;17:96-104

TABLE E2. Listing of montelukast clinical studies included in the focused analysis

Protocol no.	Study design	Citation
Double-blind, placebo-controlled (with or without active control)—adult studies		
009	Placebo-controlled, parallel-group	Altman LC, et al. J Allergy Clin Immunol 1998;102:50-6
012	Placebo-controlled, parallel-group	Malmstrom K, et al. Am J Ther 1998;5:189-95
015*	Placebo-controlled, parallel-group	Dahlen SE, et al. Am J Respir Crit Care Med 2002;165:9-14 (main) Storms W, et al. Clin Exp Allergy 2001;3:77-87 (extension study)
017	Placebo- and active-controlled, parallel-group pilot to determine safety and tolerability of montelukast (capsule formulation) in patients with allergic rhinitis	Data on file
020	Placebo- and active-controlled, parallel-group	Malmstrom K, et al. Ann Intern Med 1999;130:487-95
025	Placebo-controlled, parallel-group	Noonan MJ, et al. Eur Respir J 1998;11:1232-9
029	Placebo- and active-controlled, parallel-group	Laviolette M, et al. Am J Respir Crit Care Med 1999;160:1862-8
031	Placebo-controlled, parallel-group	Reiss TF, et al. Arch Intern Med 1998;158:1213-20
042	Placebo-controlled, parallel-group	Leff JA, et al. N Engl J Med 1998;339:147-52
046	Placebo-controlled, parallel-group	Löfdahl CG, et al. BMJ 1999;19:87-90
059	Placebo-controlled, parallel-group	Ramsay CF, et al. Respir Med 2009;103:995-1003
068	Placebo- and active-controlled, parallel-group	Meltzer EO, et al. J Allergy Clin Immunol 2000;105:917-22
069	Placebo- and active-controlled, parallel-group	Baumgartner RA, et al. Eur Respir J 2003;21:123-8
070	Placebo- and active-controlled, parallel-group	Israel E, et al. J Allergy Clin Immunol 2002;110:847-54
073	Placebo-controlled, parallel-group safety study in patients with chronic asthma (needed for a single country-specific registration)	Data on file
075	Placebo-controlled, parallel-group	Vaquero MJ, et al. Thorax 2003;58:204-10
077	Placebo- and active-controlled, parallel-group	Philip G, et al. Eur Respir J 2004;24(suppl 48):P888
087	Placebo-controlled, parallel-group	Montelukast Net. J Tuberc Respir Dis 2002;25:180-1
102	Placebo- and active-controlled, parallel-group	Philip G, et al. Eur Respir J 2004;24(suppl 48):P888
113	Placebo- and active-controlled, parallel-group	Storms W, et al. Respir Med 2004;98:1051-62
116*	Placebo-controlled, parallel-group	Camargo CA Jr, et al. Am J Respir Crit Care Med 2003;167:528-33
117	Placebo- and active-controlled, parallel-group	Nayak AS, et al. Ann Allergy Asthma Immunol 2002;88:592-600
162	Placebo- and active-controlled, parallel-group	Philip G, et al. Clin Exp Allergy 2002;32:1020-8
192	Placebo- and active-controlled, parallel-group	Chervinsky P, et al. Ann Allergy Asthma Immunol 2004;92:367-73
A202	Placebo-controlled, parallel-group	Miyamoto T, et al. J Clin Therap Med 2001;17:493-517
235	Placebo- and active-controlled, parallel-group	van Adelsberg J, et al. Ann Allergy Asthma Immunol 2003;90:214-22
240	Placebo- and active-controlled, parallel-group	van Adelsberg J, et al. Allergy 2003;58:1268-76
246	Placebo- and active-controlled, parallel-group	Philip G, et al. Allergy Asthma Proc 2007;28:296-304
256	Placebo-controlled, crossover	Perry TT, et al. Ann Allergy Asthma Immunol 2004;93:431-8
265	Placebo-controlled, parallel-group	Patel P, et al. Ann Allergy Asthma Immunol 2005;95:551-7
269	Placebo-controlled, parallel-group	Philip G, et al. Curr Med Res Opin 2004;20:1549-58
289	Placebo-controlled, parallel-group	Busse WW, et al. Ann Allergy Asthma Immunol 2006;96:60-8
378	Placebo-controlled, parallel-group	Okubo K, et al. Allergol Int 2008;57:247-55
A402	Placebo-controlled, parallel-group	Tohda Y, et al. Clin Exp Allergy 2002;32:1180-6
Rofecoxib PN 125†	Placebo- and active-controlled, parallel-group	Brandes JL, et al. Headache 2004;44:581-6
Double-blind, placebo-controlled (with or without active control)—pediatric studies		
049	Placebo-controlled, parallel-group	Knorr B, et al. JAMA 1998;279:1181-6
097	Placebo- and active-controlled, parallel-group	Becker AB, et al. Ann Allergy Asthma Immunol 2006;96:800-7
219‡	Placebo-controlled, parallel-group	Bisgaard H, et al. Pediatr Pulmonol 2009;44:568-79
336	Placebo-controlled, parallel-group	Papadopoulos N, et al. J Asthma 2009;46:413-20
340	Placebo-controlled, parallel-group	Weiss KB, et al. Presented at the European Academy of Allergology and Clinical Immunology and European Respiratory Society Pediatrics Joint meeting, Lisbon, Portugal, October 20-23, 2007
906	Placebo-controlled, crossover	Simons FER, et al. J Pediatr 2001;138:694-8

*Includes the main and extension studies.

†This study was not part of the montelukast clinical program for respiratory disease but was part of the rofecoxib clinical program for migraine.

‡Protocol 219 included patients aged 2 to 14 years, but only patients aged 6 years and older at randomization were included in the adjudication process.