This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2. Synopsis

MERCK RESEARCH LABORATORIES MK-0633 L-001330395, Tablet Chronic Asthma	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Double-Blind, Randomized, Placebo-Controlled, Multicenter, Parallel-Group, Dose-Ranging Study of MK-0633 in Adult Patients with Chronic Asthma #007

PROTECTION OF HUMAN SUBJECTS: This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research. For study audit information, see [16.1.8.1].

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter in the Asia Pacific (54), Europe, Middle East, Africa (EMEA) (4), Latin America (18), North America (78) [16.1.3; 16.1.4] [16.1.3.1; 16.1.4.1; 16.1.4.2].

PUBLICATION(S): None

PRIMARY THERAPY PERIOD: 13-Mar-2008 to 26-May-2009 | **CLINICAL PHASE:** IIb

DURATION OF TREATMENT: Period I—2-week placebo run-in; Period II—6-week, double-blind, dose-ranging efficacy period; Period III—18-week, double-blind, optional extension period

OBJECTIVE(S): [16.1.1] **Primary: (1)** To demonstrate that MK-0633, compared with placebo, results in dose-related improvement in forced expiratory volume in 1 second (FEV_1) over the last 4 weeks of the 6-week active treatment period in patients aged 18 to 70 years with chronic asthma. **(2)** To determine the dose-related safety and tolerability of MK-0633 over 6 weeks in patients aged 18 to 70 years with chronic asthma.

Secondary: To demonstrate that MK-0633, compared with placebo, results in dose-related improvement in asthma symptoms scores (both daytime and nighttime) over the last 4 weeks (diary data collected at Weeks 4, 5 and 6) of the 6-week active treatment period in patients aged 18 to 70 years with chronic asthma.

Tertiary: (1) To demonstrate that MK-0633, compared with placebo, results in dose-related improvements in the following other endpoints over the last 4 weeks of the 6-week active treatment period in patients aged 18 to 70 years with chronic asthma: "as-needed" β-agonist use, AM and PM peak expiratory flow rate (PEFR; patient measured), asthma exacerbations[1], asthma attacks[2], oral corticosteroid rescues for worsening asthma, asthma control days[3], asthma-specific quality of life questionnaire (AQLQ), Asthma Control Questionnaire (ACQ), post β-agonist FEV_1, and average total peripheral blood eosinophil counts. **(2)** To estimate the additive effect of MK-0633, compared with placebo, to inhaled corticosteroids (ICS) or combination therapy with ICS and long-acting β-agonists (LABA) on the primary, secondary and other endpoints.

---

[1] Asthma exacerbation is defined as a day with any of the following criteria: a decrease from baseline in AM PEFR of more than 20%, or AM PEFR less than 180 L/min, or an increase in β-agonist use of more than 70% and a minimum increase of at least 2 puffs, or an increase from baseline in daytime asthma symptom score of more than 50%, or overnight asthma symptom="Awake all night", or an asthma attack.

[2] Asthma attack is defined as asthma symptoms during the previous 24 hours requiring one of the following: corticosteroid use (systemic), or unscheduled visit to the doctor or urgent care clinic, or unscheduled visit to the emergency department, or hospitalization.

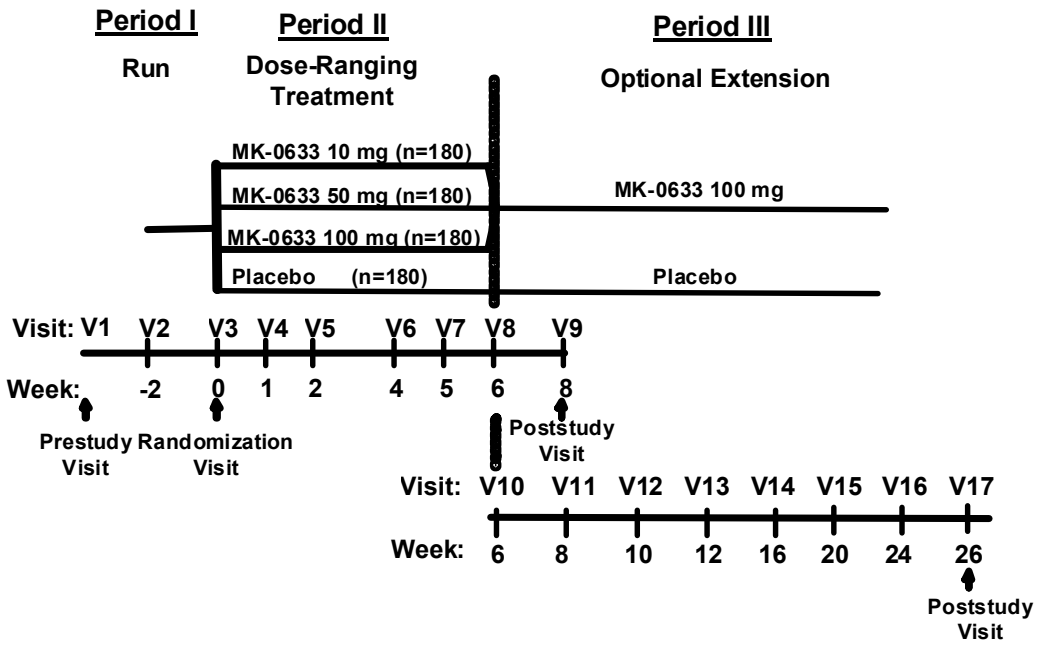
[3] Asthma control day is defined as a day with all of the following criteria: <2 puffs β-agonist use and no nighttime awakenings and no asthma attack

Exploratory: (1) To explore the treatment effect on the following endpoints: Pharmacokinetics (PK) measurements of MK-0633, change from baseline in urine for leukotriene E_4 (LTE_4) excretion, and plasma biomarkers (including Immunoglobulin E [IgE] and eosinophilic cationic protein [ECP]). **(2)** To explore the relationship between exploratory endpoints and change from baseline in FEV_1 and other efficacy endpoints. **(3)** To estimate the efficacy of MK-0633, compared with placebo, on the primary, secondary and other efficacy endpoints over a 12-week and over a 24-week treatment period. **(4)** To explore the safety profile of MK-0633 over a 12-week and over a 24-week treatment period.

STUDY DESIGN: Multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study (Figure 2-1). Period I: 2-week, single-blind, placebo run-in period. Period II: 6-week, double-blind, efficacy period with 4 treatment groups: (1) MK-0633 10 mg, (2) MK-0633 50 mg, (3) MK-0633 100 mg, and (4) placebo. Period III: 18-week, double-blind, optional extension period with 2 treatment groups: (1) MK-0633 100 mg and (2) placebo. A subset of patients in the study also participated in a sputum substudy.

Figure 2-1

Study Schematic



Data Source: [16.1.1.1]

Protocol 007-00 and 007-01 were finalized on October 2006 and November 2006, respectively. The study was initiated with Protocol 007-02 [16.1.1.1], finalized in August, 2007. Subsequent amendments 007-03, 007-04 and 007-05 were finalized in October, 2007, February 2008, and June 2008, respectively.

For additional study information, see [16.1.1; 16.1.2; 16.1.3; 16.1.7] [16.1.5.1] [16.1.5.2].

SUBJECT/PATIENT DISPOSITION:

	Placebo N (%)	MK-0633 10 mg N (%)	MK-0633 50 mg N (%)	MK-0633 100 mg N (%)	Total N (%)
SCREENING FAILURES:					1318
RANDOMIZED:	239	239	238	238	954
Male (age range)	84 (35.1)	85 (35.6)	101 (42.4)	99 (41.6)	369 (38.7)
Female (age range)	155 (64.9)	154 (64.4)	137 (57.6)	139 (58.4)	585 (61.3)
COMPLETED:	150 (62.8)	149 (62.3)	152 (63.9)	147 (61.8)	598 (62.7)
DISCONTINUED:	89 (37.2)	90 (37.7)	86 (36.1)	91 (38.2)	356 (37.3)
Clinical adverse experience	8§ (3.3)	4 (1.7)	7 (2.9)	7 (2.9)	26§ (2.7)
Laboratory adverse experience	3§ ↓ (1.3)	1 (0.4)	0 (0.0)	2 (0.8)	6§ ↓ (0.6)
Lost to follow-up	5 (2.1)	6 (2.5)	5 (2.1)	7 (2.9)	23 (2.4)
Protocol Violation	3 (1.3)	6 (2.5)	5 (2.1)	2 (0.8)	16 (1.7)
Study Terminated by Sponsor	55 (23.0)	50 (20.9)	49 (20.6)	57 (23.9)	211 (22.1)
Withdrawal by Subject	13 (5.4)	19 (7.9)	15 (6.3)	15 (6.3)	62 (6.5)
Other†	2 (0.8)	4 (1.7)	4‡ (1.7)	1 (0.4)	11‡ (1.1)

† Other refers to Lack of Efficacy (1), Physician Decision (5) and Pregnancy (5‡).

‡ [redacted] Since no corresponding AE was identified as causing the discontinuation, this patient is not counted as discontinued due to a clinical AE or a laboratory AE. This patient should have been counted in the discontinued due to Other category. Therefore, the total number of patients who discontinued due to Other should be 12, the number of patients who discontinued due to Other in the MK-0633 50mg group should be 5, and the number of patients who discontinued due to Pregnancy should be 6.

§ [redacted]

↓ [redacted] Subsequent to database lock, the site confirmed this patient was discontinued due to 2 laboratory AEs. Therefore, the actual number of patients who discontinued due to a laboratory AE should be 1 greater than that shown in the Placebo group and in the Total column.

Data Source: [16.2.7.1]

DOSAGE/FORMULATION NOS.: After randomization, patients in Period II received MK-0633 10 mg, MK-0633 50 mg, MK-0633 100 mg (2 tablets of MK-0633 50 mg were used), or matching-image placebo tablets once daily in the evening at bedtime with or without food. In Period III, patients who had received any dose of MK-0633 during Period II received MK-0633 100 mg (2 tablets of MK-0633 50 mg were used), and patients who had received placebo during Period II continued to receive placebo. In Period III, patients were again instructed to take study drug once daily in the evening at bedtime with or without food.

Formulation numbers for MK-0633 10 mg were [redacted] for MK-0633 50 mg were [redacted] the formulation number for the matching-image placebo for MK-0633 10 mg was [redacted] and for the matching-image placebo for MK-0633 50 mg, [redacted]

DIAGNOSIS/INCLUSION CRITERIA: Males and females, 18 to 70 years of age, with a history of chronic asthma across the range of asthma severities, evidence of reversibility of airway obstruction defined as an increase of FEV_1 of 12% or greater after β-agonist administration, and an FEV_1 of 45 to 85% of the predicted value [16.1.1.1].

EVALUATION CRITERIA:

EFFICACY MEASUREMENTS: Pre-β-agonist FEV_1 and forced vital capacity (FVC), post β-agonist FEV_1 and FVC, "as-needed" β-agonist use, daytime and nighttime symptoms, AM and PM PEFR, asthma exacerbation days, asthma attacks, systemic corticosteroid rescues for worsening asthma, asthma control days, AQLQ, ACQ, peripheral blood eosinophils, MK-0633 pharmacokinetic measurements, urine for LTE4 excretion, and plasma and sputum biomarkers [16.1.1.1].

SAFETY MEASUREMENTS: Clinical and Laboratory Adverse Experiences, physical examinations, vital signs, electrocardiograms (ECGs), laboratory safety studies -- blood hematology and chemistry measures, urinalysis, serum β-hCG, urine for N-Acetyl-β-Glucosaminidase (NAG) and microalbumin.

Sample case report forms are in [16.1.2.1] [16.1.2.2].

STATISTICAL PLANNING AND ANALYSIS: [16.1.9.1]

EFFICACY: Assuming 180 evaluable patients per treatment group for the Period II analysis, there was 92% power to detect (at α=0.05, two-sided t-test) a treatment difference of 0.12L between an active group and placebo in change from baseline in pre-β-agonist FEV_1 assuming a standard deviation of 0.34L.

Period II Analysis: The primary efficacy endpoint (FEV_1) was analyzed using changes from baseline assessed at Weeks 1, 2, 4, 5, and 6 in a Longitudinal Analysis Model (LDA) with the Tukey linear trend test for assessing dose-response. The LDA model included factors for treatment, week, concomitant corticosteroid/combination therapy stratum, baseline FEV_1 and a treatment-by-week interaction. The treatment effect averaged over the last 4 weeks (Weeks 2, 4, 5 and 6) of the 6-week treatment period was obtained by using the appropriate contrast in the analysis model. Other continuous efficacy variables were analyzed in a similar fashion, if appropriate. A similar ANCOVA model, without the week factor, was used if the efficacy endpoint was only assessed at one timepoint (Post β-agonist FEV_1, ACQ and AQLQ scores, PK measurements of MK-0633, urinary LTE_4 and plasma biomarkers). Binary efficacy variables were analyzed using a logistic model with the Tukey linear trend test for assessing dose-response. The model included factors for treatment, % predicted FEV_1 at baseline, and concomitant corticosteroid stratum.

The effect of MK-0633 on the change from baseline in sputum biomarkers (including leukotriene B4) was analyzed using an ANCOVA model with factors for treatment, concomitant corticosteroid/combination therapy stratum, study center, and baseline sputum biomarker as covariate. Estimates of the difference between MK-0633 and placebo were obtained by defining the appropriate contrast within the same model.

Period III Analysis: The efficacy analyses of the optional extension period focused on estimation rather than hypothesis testing. The same efficacy endpoints as in Period II (except PK measurements, plasma biomarkers and sputum biomarkers) were assessed over Period III/at the end of Period III using similar models as in Period II (LDA, logistic regression). The factor for treatment had 4 levels (taking into account the treatment assigned in Period II). The primary comparison for the Period III efficacy was MK-0633 100 mg versus placebo (irrespective of the dose in Period II).

SAFETY: Period II Analysis: Safety and tolerability were assessed by a clinical review of all relevant parameters, including adverse experiences (AEs), laboratory safety parameters, ECGs, and vital signs. A tiered approach was used for the clinical and laboratory AEs. Tier 1 AEs included the percentage of patients who discontinued because of worsening of asthma and the percentage of patients who met the N-Acetyl-β-Glucosaminidase (NAG) criterion for discontinuation. They were compared between the groups using the Cochran-Armitage trend test. Other Tier 1 AEs were the percentage of patients with percent change in urinary NAG and in urinary microalbumin in the following categories: <100%, 100% to <200%, and ≥200%. They were compared between groups using the Jonckhere-Terpstra test. All other specific AEs exhibited by at least 4 patients within one of the treatment groups were Tier 2 AEs for which within-group incidences, between-group differences with placebo, and the associated 95% CIs were displayed. Other Tier 2 AEs included broad AE categories of the percentage of patients with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, and who discontinued because of an AE. Other safety parameters were summarized by treatment group.

Period III Analysis: The same safety endpoints as in Period II were assessed over Period III using a similar approach as for Period II.

RESULTS:

EFFICACY: Period II efficacy: Primary Endpoint: There was a significant difference (p-value=0.004) from placebo through MK-0633 100 mg on the change from baseline in Pre β-agonist FEV_1(L) over the last 4 weeks of Period II, using a trend test. The difference was not significant (p-value=0.201) from placebo through MK-0633 50 mg. The estimated difference in change from baseline in Pre β-agonist FEV_1(L) over the last 4 weeks of Period II between MK-0633 100 mg and placebo was 0.07 L (95% confidence interval = [0.02,0.13]). The effect size was generally similar within the 2 stratum levels within a given dose. The treatment effect was stronger for the Japanese subpopulation (n=207), as the estimated difference between MK-0633 100 mg and placebo was 0.17 L (95% confidence interval = [0.06,0.28]), reflecting an increase in FEV_1 of 0.25L on MK-0633 and an increase in FEV_1 of 0.08L on placebo. This stronger treatment effect in Japanese patients was also observed in both strata.

Secondary Endpoints: The trend tests showed a non-significant difference between MK-0633 doses and placebo on the change from baseline in daytime and nighttime symptoms score over the last 4 weeks of Period II (p-value=0.369 and 0.072, respectively). The estimated difference between MK-0633 100 mg and placebo was -0.08 (95% CI = [-0.21,0.06]) for the daytime symptoms score and -0.07 (95% CI = [-0.15,0.02]) for the nighttime symptoms score. There was also no significant difference observed between MK-0633 doses and placebo in the Japanese subpopulation.

Results of analysis of the primary and secondary endpoints are summarized in Table 2-1.

Table 2-1

Analysis of Primary and Secondary Endpoints in Period II
(Full Analysis Set)

Treatment	N	Raw Mean	Adjusted mean†	Comparison to Placebo	Trend Test Through Placebo
Change From Baseline in Pre β-Agonist FEV_1(L) Over the Last 4 Weeks					
		Mean (SD)	LS Mean (95% CI) †	Difference in LS Means (95% CI)	p-Value
Placebo	234	0.13 (0.32)	0.13 (0.09, 0.16)		
MK-0633 10 mg	232	0.14 (0.26)	0.14 (0.10, 0.18)	0.01 (-0.04, 0.07)	0.586
MK-0633 50 mg	232	0.16 (0.27)	0.16 (0.12, 0.20)	0.03 (-0.02, 0.09)	0.201
MK-0633 100 mg	234	0.20 (0.28)	0.20 (0.16, 0.24)	0.07 (0.02, 0.13)	0.004
Change From Baseline in Daytime Asthma Symptom Score (0-6 scale) Over the Last 4 Weeks					
		Mean (SD)	LS Mean (95% CI) †	Difference in LS Means (95% CI)	p-Value
Placebo	233	-0.22 (0.71)	-0.25 (-0.34,-0.15)		
MK-0633 10 mg	231	-0.26 (0.70)	-0.30 (-0.40,-0.21)	-0.05 (-0.19,0.08)	0.404
MK-0633 50 mg	232	-0.25 (0.66)	-0.26 (-0.36,-0.17)	-0.01 (-0.15,0.12)	0.828
MK-0633 100 mg	232	-0.29 (0.62)	-0.32 (-0.42, -0.23)	-0.08 (-0.21,0.06)	0.369
Change From Baseline in Nighttime Asthma Symptom Score (0-3 scale) Over the Last 4 Weeks††					
		Mean (SD)	LS Mean (95% CI) †	Difference in LS Means (95% CI)	p-Value
Placebo	188	-0.17 (0.38)	-0.19 (-0.25,-0.14)		
MK-0633 10 mg	177	-0.20 (0.38)	-0.21 (-0.27,-0.16)	-0.02 (-0.10,0.06)	0.652
MK-0633 50 mg	168	-0.21 (0.39)	-0.25 (-0.31,-0.19)	-0.06 (-0.14,0.02)	0.130
MK-0633 100 mg	161	-0.25 (0.35)	-0.26 (-0.32,-0.20)	-0.07 (-0.15,0.02)	0.072

† Based on LDA model for change from baseline with factors for treatment; week (as categorical variable); concomitant corticosteroid stratum; baseline value as a covariate and a treatment-by-week interaction.
†† The FAS population is restricted to the subset of patients with nighttime symptoms at baseline.

Tertiary Endpoints: Significant differences from placebo through MK-0633 100 mg were observed with the trend tests on some of the tertiary endpoints in Period II: the change from baseline in total daily β-agonist use, the change from baseline in AM and PM PEFR, the percentage of patients with at least one systemic corticosteroid rescue, the change from baseline in overall AQLQ score and in AQLQ symptoms domain, the change from baseline in ACQ Score, and the change from baseline in post β-agonist FEV_1. Those results demonstrate that, in addition to pre β-agonist FEV_1 (L), MK-0633, compared to placebo, shows dose-related improvements in some aspects of asthma.

Table 2-2 summarizes the trend test p-values (Placebo through MK-0633 100 mg) and the estimated treatment differences on the tertiary endpoints between MK-0633 100 mg and Placebo.

Results of the sputum substudy are summarized in Appendix [16.1.9.2].

Table 2-2

Analysis of Tertiary Endpoints in Period II
(Full Analysis Set)

Tertiary Endpoints	MK-0633 100 mg vs Placebo	Trend Test p-Value
Change from baseline in total daily β-agonist use (puffs) over the last 4 weeks of Period II	-0.27 (-0.57, 0.03)†	0.022 *
Change from baseline in AM PEFR (L/sec) over the last 4 weeks of Period II	5.75 (-0.14, 11.65)†	0.015 *
Change from baseline in PM PEFR (L/sec) over the last 4 weeks of Period II	5.37 (-0.69, 11.42)†	0.038 *
Percentage of patients with an asthma attack in Period II	0.7 (0.3, 1.4)††	0.112
Percentage of patients with at least one systemic corticosteroids rescue during Period II	0.5 (0.2, 1.2)††	0.036 *
Percentage of days with asthma exacerbations over the last 4 weeks of Period II	-3.24 (-7.88, 1.41)†	0.066
Percentage of days with asthma control over the last 4 weeks of Period II	0.69 (-5.71, 7.10)†	0.361
Change from baseline in overall AQLQ score (1-7 scale) at the end of Period II	0.18 (0.02, 0.34)†††	0.030 *
Change from baseline in activity AQLQ score (1-7 scale) at the end of Period II	0.15 (-0.01, 0.32)†††	0.071
Change from baseline in emotion AQLQ score (1-7 scale) at the end of Period II	0.18 (-0.02, 0.38)†††	0.060
Change from baseline in environment AQLQ score (1-7 scale) at the end of Period II	0.14 (-0.06, 0.34)†††	0.200
Change from baseline in symptoms AQLQ score (1-7 scale) at the end of Period II	0.26 (0.09, 0.43)†††	0.003 **
Change from baseline in ACQ score (0-6 scale) assessed at the end of Period II	-0.24 (-0.37, -0.10)†††	<0.001 ***
Change from baseline in post β-agonist FEV_1 (L) at the end of Period II	0.06 (0.01, 0.11)†††	0.006 **
Change from baseline in total peripheral blood eosinophils ($10^3/\mu L$) at the end of Period II	-0.02 (-0.06, 0.02)†††	0.130

*, **, ***: p-Value of the trend test (Placebo through MK-0633 100 mg) significant at a level <0.05, <0.01 or <0.001 resp.
† Difference in LS Means (95% CI) based on LDA model with factors for treatment; week (as categorical variable); concomitant corticosteroid stratum; baseline value as a covariate and a treatment-by-week interaction.
†† Adjusted odds ratio (95% CI) based on logistic regression model with terms for treatment, % predicted FEV_1 at baseline and concomitant corticosteroid stratum.
††† Difference in LS Means (95% CI) based on ANCOVA model with factors for treatment, concomitant corticosteroid stratum and baseline value as a covariate.

Period III efficacy: There was a significant difference (p-value=0.034) between MK-0633 100 mg and placebo on the change from baseline in FEV_1(L) pre β-agonist over Period III. The estimated difference in change from baseline between MK-0633 100 mg and placebo was 0.06 L (95% confidence interval = [0.00,0.11]). The change from baseline for each of the 2 treatment groups remained stable over Period III.

The difference between MK-0633 100 mg and placebo on the change from baseline in daytime symptoms score over Period III was non-significant (p-value=0.322). The estimated difference between MK-0633 100 mg and placebo was -0.07 (95% CI = [-0.20,0.07]).

There was no significant difference between MK-0633 100 mg and placebo on the change from baseline in nighttime symptoms score over Period III (p-value=0.566). The estimated difference between MK-0633 100 mg and placebo was -0.02 (95% CI = [-0.10,0.05]). Results of the analyses on primary and secondary endpoints in Period II are presented in Table 2-3.

Results of analyses of tertiary endpoints (change from baseline in total daily β-agonist use over Period III, change from baseline in AM PEFR and PM PEFR over period III, percentage of patients with an asthma attack in Period III, percentage of patients with at least one systemic corticosteroids rescue in Period III, percentage of days with asthma control and asthma exacerbation over last 16 weeks of Period III, change from baseline in AQLQ and ACQ score over Period III, change from baseline in post β-agonist FEV_1 over Period III and change from baseline in eosinophil count over Period III) are presented in Sections 6.8.3 and 6.8.4 of statistical report [16.1.9.2].

Table 2-3

Analysis of Primary and Secondary Endpoints over Period III
(Extension Full Analysis Set)

Treatment	N	Raw Mean	Adjusted mean†	Comparison to Placebo	
Change From Baseline in Pre β-Agonist FEV_1(L)					
		Mean (SD)	LS Mean (95% CI) †	Difference in LS Means (95% CI)	p-Value
Placebo	167	0.16 (0.31)	0.16 (0.12, 0.21)		
MK-0633 100 mg	522	0.22 (0.30)	0.22 (0.19, 0.25)	0.06 (0.00, 0.11)	0.034
Change From Baseline in Daytime Asthma Symptom Score (0-6 scale)					
		Mean (SD)	LS Mean (95% CI) †	Difference in LS Means (95% CI)	p-Value
Placebo	168	-0.38 (0.82)	-0.35 (-0.47,- 0.24)		
MK-0633 100 mg	520	-0.42 (0.79)	-0.42 (-0.49, -0.35)	- 0.07 (-0.20, 0.07)	0.322
Change From Baseline in Nighttime Asthma Symptom Score (0-3 scale) ††					
		Mean (SD)	LS Mean (95% CI) †	Difference in LS Means (95% CI)	p-Value
Placebo	138	-0.29 (0.46)	-0.29 (-0.35, -0.22)		
MK-0633 100 mg	377	-0.31 (0.41)	-0.31 (-0.35, -0.27)	-0.02 (-0.10, 0.05)	0.566

† Based on LDA model for change from baseline with factors for treatment; week (as categorical variable); concomitant corticosteroid stratum; baseline value as a covariate and a treatment-by-week interaction.
†† Nighttime asthma symptom score analysis performed in subpopulation with nighttime asthma symptoms at baseline.

SAFETY: Period II safety: During Period II, a total of 9 serious adverse experiences (SAEs) (Table 2-4) were reported; there were no deaths. There were a total of 16 patients who discontinued due to an adverse experience (AE); five of these 16 patients discontinued due to a drug-related AE. There were 2 discontinuations due to a SAE, and no discontinuations due to a drug-related SAE.

The Tier 1 adverse experiences evaluated included the percentage of patients who discontinued because of worsening of asthma and the percentage of patients who met the NAG criterion for discontinuation, No significant differences between treatment groups were observed on either of these endpoints.

The overall percentage of patients with at least one AE was similar across treatment groups, as was the overall incidence of drug-related AEs (Table 2-4). The percentage of patients with at least one clinical AE and the percentage of patients with at least one laboratory AE were similar across treatment groups, as shown in Table 2-5 (Clinical) and Table 2-6 (Laboratory). The percentage of patients with drug-related clinical AEs was numerically higher in the MK-0633 100mg group than in the other treatment groups. The percentage of patients with a drug-related laboratory AE was similar across treatment groups. Full AE listings are found in [16.2.7.2] [16.2.7.3].

There was 1 serious and drug related AE of liver disorder, characterized by AST and ALT elevations of 20 to 30-fold the upper limit of normal. A thorough evaluation did not reveal an etiology for the abnormalities, and the patient's transaminases gradually returned to normal over several weeks after discontinuation of study drug (the patient received MK-0633 100 mg). A more detailed description of this patient's clinical course is found in [16.2.7] [16.2.7.4]. There was an increased incidence of elevations in liver transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) in patients receiving the 100 mg dose of MK-0633 compared with placebo (Table 2-7). Narratives for patients who experienced AST or ALT values greater than 3x the upper limit of normal are in [16.2.7] [16.2.7.4].

Table 2-4

Adverse Event Summary
Overall Adverse Experience Summary
(All-Patients-as-Treated Population)

	Placebo		MK-0633 10 mg		MK-0633 50 mg		MK-0633 100 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	238		237		237		238		950	
with one or more adverse events	93	(39.1)	96	(40.5)	84	(35.4)	100	(42.0)	373	(39.3)
with no adverse event	145	(60.9)	141	(59.5)	153	(64.6)	138	(58.0)	577	(60.7)
with DRUG-related[†] adverse events	18	(7.6)	17	(7.2)	15	(6.3)	21	(8.8)	71	(7.5)
with serious adverse events	2	(0.8)	1	(0.4)	2	(0.8)	4	(1.7)	9	(0.9)
with serious DRUG-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.1)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued[‡] due to an adverse event	3	(1.3)	4	(1.7)	3	(1.3)	6	(2.5)	16	(1.7)
discontinued due to a DRUG-related adverse event	1	(0.4)	1	(0.4)	0	(0.0)	3	(1.3)	5	(0.5)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)	2	(0.2)
discontinued due to a serious DRUG-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the DRUG.

[‡] Study medication withdrawn.

Table 2-5

Adverse Event Summary
Clinical Adverse Experience Summary
(All-Patients-as-Treated Population)

	Placebo		MK-0633 10 mg		MK-0633 50 mg		MK-0633 100 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	238		237		237		238		950	
with one or more adverse events	88	(37.0)	93	(39.2)	83	(35.0)	95	(39.9)	359	(37.8)
with no adverse event	150	(63.0)	144	(60.8)	154	(65.0)	143	(60.1)	591	(62.2)
with DRUG-related† adverse events	12	(5.0)	15	(6.3)	12	(5.1)	18	(7.6)	57	(6.0)
with serious adverse events	2	(0.8)	1	(0.4)	2	(0.8)	4	(1.7)	9	(0.9)
with serious DRUG-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.1)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	3	(1.3)	3	(1.3)	3	(1.3)	4	(1.7)	13	(1.4)
discontinued due to a DRUG-related adverse event	1	(0.4)	1	(0.4)	0	(0.0)	2	(0.8)	4	(0.4)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)	2	(0.2)
discontinued due to a serious DRUG-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the DRUG.

‡ Study medication withdrawn.

Table 2-6

Adverse Event Summary
Laboratory Adverse Experience Summary
(All-Patients-as-Treated Population)

	Placebo		MK-0633 10 mg		MK-0633 50 mg		MK-0633 100 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	238		237		237		238		950	
with one or more adverse events	12	(5.0)	9	(3.8)	8	(3.4)	15	(6.3)	44	(4.6)
with no adverse event	226	(95.0)	228	(96.2)	229	(96.6)	223	(93.7)	906	(95.4)
with DRUG-related[†] adverse events	7	(2.9)	3	(1.3)	4	(1.7)	5	(2.1)	19	(2.0)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
with serious DRUG-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued[‡] due to an adverse event	1	(0.4)	1	(0.4)	0	(0.0)	2	(0.8)	4	(0.4)
discontinued due to a DRUG-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.1)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious DRUG-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the DRUG.

[‡] Study medication withdrawn.

Table 2-7

Number(%) of Patients with LFT Elevation During the Treatment Period
(All-Patients-as-Treated Population)

Criterion	Placebo n/N	(%)	MK-0633 10 mg n/N	(%)	MK-0633 50 mg n/N	(%)	MK-0633 100 mg n/N	(%)
Alkaline Phosphatase (IU/L)								
Increase ≥ 100% and >ULN	0/236	(0.00)	0/234	(0.00)	1/232	(0.43)	2/234	(0.85)
Increase ≥ 50% and >1.5*ULN	0/236	(0.00)	1/234	(0.43)	0/232	(0.00)	2/234	(0.85)
Increase ≥ 50% and >2*ULN	0/236	(0.00)	0/234	(0.00)	0/232	(0.00)	1/234	(0.43)
>3*ULN	0/236	(0.00)	0/234	(0.00)	0/232	(0.00)	0/234	(0.00)
>5*ULN	0/236	(0.00)	0/234	(0.00)	0/232	(0.00)	0/234	(0.00)
Alanine Aminotransferase (IU/L)								
Increase ≥ 100% and >ULN	7/236	(2.97)	6/233	(2.58)	6/232	(2.59)	17/233	(7.30)
Increase ≥ 50% and >1.5*ULN	10/236	(4.24)	7/233	(3.00)	9/232	(3.88)	11/233	(4.72)
Increase ≥ 50% and >2*ULN	2/236	(0.85)	5/233	(2.15)	3/232	(1.29)	7/233	(3.00)
>3*ULN	2/236	(0.85)	2/233	(0.86)	0/232	(0.00)	5/233	(2.15)
>5*ULN	0/236	(0.00)	1/233	(0.43)	0/232	(0.00)	2/233	(0.86)
Aspartate Aminotransferase (IU/L)								
Increase ≥ 100% and >ULN	3/236	(1.27)	3/234	(1.28)	5/232	(2.16)	12/234	(5.13)
Increase ≥ 50% and >1.5*ULN	4/236	(1.69)	5/234	(2.14)	8/232	(3.45)	11/234	(4.70)
Increase ≥ 50% and >2*ULN	1/236	(0.42)	4/234	(1.71)	3/232	(1.29)	7/234	(2.99)
>3*ULN	0/236	(0.00)	2/234	(0.85)	0/232	(0.00)	6/234	(2.56)
>5*ULN	0/236	(0.00)	1/234	(0.43)	0/232	(0.00)	2/234	(0.85)
Bilirubin (mg/dL)								
Increase ≥ 100% and >ULN	3/236	(1.27)	3/234	(1.28)	3/232	(1.29)	1/234	(0.43)
Increase ≥ 50% and >1.5*ULN	2/236	(0.85)	0/234	(0.00)	2/232	(0.86)	0/234	(0.00)
Increase ≥ 50% and >2*ULN	0/236	(0.00)	0/234	(0.00)	1/232	(0.43)	0/234	(0.00)
>3*ULN	0/236	(0.00)	0/234	(0.00)	0/232	(0.00)	0/234	(0.00)
>5*ULN	0/236	(0.00)	0/234	(0.00)	0/232	(0.00)	0/234	(0.00)

ULN = Upper limit of normal range.

Period III safety: During Period III, there were a total of 4 SAEs (Table 2-8); there were no deaths. There were a total of 15 patients who discontinued due to an AE; five of these patients discontinued due to a drug related AE. There was 1 discontinuation due to a SAE, and no discontinuations due to a drug-related SAE.

The overall percentage of patients with at least one AE was similar across treatment groups, as was the overall incidence of drug-related AEs (Table 2-8). Similarly, the percentage of patients with at least one clinical AE (Table 2-9) and the percentage of patients with at least one laboratory AE (Table 2-10) were similar across treatment groups. The percentage of patients with a drug related clinical AE was similar across treatment groups, and the percentage of patients with a drug related laboratory AE was similar across treatment groups. Full AE listings are found in [16.2.7]. The incidence of elevations in liver transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) in patients receiving the 100 mg dose and patients receiving placebo were similar, as shown in Table 2-11.

Table 2-8

Adverse Event Summary
Overall Adverse Experience Summary During Period III
(All Patients as Treated in Extension)

	Placebo		MK-0633 100 mg		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	174		533		707	
with one or more adverse events	90	(51.7)	258	(48.4)	348	(49.2)
with no adverse event	84	(48.3)	275	(51.6)	359	(50.8)
with DRUG-related[†] adverse events	14	(8.0)	38	(7.1)	52	(7.4)
with serious adverse events	1	(0.6)	3	(0.6)	4	(0.6)
with serious DRUG-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
discontinued[‡] due to an adverse event	7	(4.0)	8	(1.5)	15	(2.1)
discontinued due to a DRUG-related adverse event	3	(1.7)	2	(0.4)	5	(0.7)
discontinued due to a serious adverse event	0	(0.0)	1	(0.2)	1	(0.1)
discontinued due to a serious DRUG-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the DRUG.
[‡] Study medication withdrawn.

Table 2-9

Adverse Event Summary
Clinical Adverse Experience Summary During Period III
(All Patients as Treated in Extension)

	Placebo		MK-0633 100 mg		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	174		533		707	
with one or more adverse events	85	(48.9)	253	(47.5)	338	(47.8)
with no adverse event	89	(51.1)	280	(52.5)	369	(52.2)
with DRUG-related[†] adverse events	11	(6.3)	28	(5.3)	39	(5.5)
with serious adverse events	1	(0.6)	3	(0.6)	4	(0.6)
with serious DRUG-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
discontinued[‡] due to an adverse event	5	(2.9)	8	(1.5)	13	(1.8)
discontinued due to a DRUG-related adverse event	2	(1.1)	2	(0.4)	4	(0.6)
discontinued due to a serious adverse event	0	(0.0)	1	(0.2)	1	(0.1)
discontinued due to a serious DRUG-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the DRUG.
[‡] Study medication withdrawn.

Table 2-10

Adverse Event Summary
Laboratory Adverse Experience Summary During Period III
(All Patients as Treated in Extension)

	Placebo		MK-0633 100 mg		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	174		533		707	
with one or more adverse events	8	(4.6)	21	(3.9)	29	(4.1)
with no adverse event	166	(95.4)	512	(96.1)	678	(95.9)
with DRUG-related[†] adverse events	3	(1.7)	10	(1.9)	13	(1.8)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with serious DRUG-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
discontinued[‡] due to an adverse event	2	(1.1)	0	(0.0)	2	(0.3)
discontinued due to a DRUG-related adverse event	1	(0.6)	0	(0.0)	1	(0.1)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious DRUG-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the DRUG.

[‡] Study medication withdrawn.

[redacted] The number of patients who discontinued due to an adverse event should be increased by 1 in the Placebo group and Total columns.

Table 2-11

Number(%) of Patients with LFT Elevation During Period III
(All Patients as Treated in Extension)

Criterion	Placebo n/N	Placebo (%)	MK-0633 100 mg n/N	MK-0633 100 mg (%)
Alkaline Phosphatase (IU/L)				
Increase ≥ 100% and >ULN	1/170	(0.59)	4/527	(0.76)
Increase ≥ 50% and >1.5*ULN	0/170	(0.00)	5/527	(0.95)
Increase ≥ 50% and >2*ULN	0/170	(0.00)	3/527	(0.57)
>3*ULN	0/170	(0.00)	1/527	(0.19)
>5*ULN	0/170	(0.00)	0/527	(0.00)
Alanine Aminotransferase (IU/L)				
Increase ≥ 100% and >ULN	15/170	(8.82)	37/525	(7.05)
Increase ≥ 50% and >1.5*ULN	12/170	(7.06)	29/525	(5.52)
Increase ≥ 50% and >2*ULN	8/170	(4.71)	15/525	(2.86)
>3*ULN	1/170	(0.59)	3/525	(0.57)
>5*ULN	0/170	(0.00)	1/525	(0.19)
Aspartate Aminotransferase (IU/L)				
Increase ≥ 100% and >ULN	11/170	(6.47)	23/527	(4.36)
Increase ≥ 50% and >1.5*ULN	12/170	(7.06)	24/527	(4.55)
Increase ≥ 50% and >2*ULN	8/170	(4.71)	14/527	(2.66)
>3*ULN	1/170	(0.59)	7/527	(1.33)
>5*ULN	1/170	(0.59)	2/527	(0.38)
Bilirubin (mg/dL)				
Increase ≥ 100% and >ULN	4/170	(2.35)	6/527	(1.14)
Increase ≥ 50% and >1.5*ULN	1/170	(0.59)	5/527	(0.95)
Increase ≥ 50% and >2*ULN	1/170	(0.59)	1/527	(0.19)
>3*ULN	1/170	(0.59)	0/527	(0.00)
>5*ULN	0/170	(0.00)	0/527	(0.00)

ULN = Upper limit of normal range.

STUDY DISCONTINUATION: While the study was ongoing, Merck Research Laboratories discontinued the Asthma Phase IIb Study (Protocol 007-05) of MK-0633 and its extension study (Protocol 007-10). This decision was based on the benefit-risk profile observed from the 6-week main analysis and 12-week interim analysis specified in Protocol 007-05.

CONCLUSIONS: In adult patients aged 18 to 70 years with chronic asthma: (1) MK-0633 through the 100 mg dose, compared with placebo, resulted in a statistically significant improvement in the primary endpoint of FEV_1, but not in the key secondary endpoint of daytime asthma symptoms score during the 6-week dose-ranging period of the study (Period II). (2) MK-0633 through the 100 mg dose, compared with placebo, resulted in a statistically significant improvement in several tertiary endpoints during the 6-week dose-ranging period of the study (Period II). (3) An increased incidence of elevations in liver transaminases (ALT, alanine aminotransferase and AST, aspartate aminotransferase) was observed in patients receiving the 100 mg dose of MK-0633 during the 6-week dose-ranging period of the study (Period II). In the 18-week optional extension period, MK-0633 100 mg continued to demonstrate a

statistically significant difference from placebo in change from baseline in FEV1 pre β-agonist. There were no significant differences in daytime or nighttime symptom scores during the extension period between MK-0633 and placebo. No increased incidence of elevations in liver transaminases on MK-0633 100 mg, compared to placebo, was observed during the optional extension period.

AUTHORS: [redacted]