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, Capsule Chronic Obstructive Pulmonary Disease (COPD)	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study, Conducted Under In-House Blinding Conditions of MK-0633 in Patients With COPD — #009

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter study (36): Canada (3), Chile (2), Colombia (3), Israel, (2), Japan (5), Lithuania (2), (1) Puerto Rico, and United States (18).

PRIMARY THERAPY PERIOD: 15-Jan-2008 to 10-Mar-2009 | **CLINICAL PHASE:** IIa

DURATION OF TREATMENT: Period I was a 2-week, single-blind, placebo run-in period. Period II was a 12-week, double-blind, active treatment period immediately following Period I. Eligible patients were randomized to 1 of 2 treatments, which they received daily: MK-0633 100 mg or placebo.

OBJECTIVE(S):

Main Study: (1) To investigate the treatment effect of MK-0633, compared with placebo, on the predose (trough) forced expiratory volume in 1 second (FEV_1), measured over a 12-week treatment period in patients with Chronic Obstructive Pulmonary Disease (COPD); (2) To evaluate the safety and tolerability of MK-0633 in patients with COPD; (3) To investigate the treatment effect of MK-0633, compared with placebo, on the secondary endpoints of overall daytime symptoms score, postdose FEV_1, total daily β-agonist use, dyspnea, and Chronic Respiratory Questionnaire (CRQ) score, measured over a 12-week treatment period in patients with COPD; (4) To investigate the treatment effect of MK-0633, compared with placebo, on the other endpoints including AM and PM peak expiratory flow rate (PEFR), individual daytime COPD symptoms and nocturnal awakenings, COPD exacerbations, patient global COPD evaluation, predose forced vital capacity (FVC), and post-bronchodilator FEV_1 and FVC measured over a 12-week treatment period in patients with COPD.

Lung Volume Substudy: (1) To explore the efficacy of MK-0633 on lung volume measurements in patients with COPD; (2) To correlate lung volume measurements with other key COPD endpoints collected in the base study, such as FEV_1 and overall symptom score.

STUDY DESIGN:

Main Study: This was a randomized, double-blind, placebo-controlled, parallel-group, 2-arm, multicenter study in patients 40 to 75 years of age with COPD. Period I was a 2-week, single-blind, placebo run-in period. Period II was a 12-week, double-blind treatment period.

Lung Volume Substudy: A lung volume substudy was conducted in a subset of patients enrolled in the main study. Details of the lung volume substudy are in Appendix 6.10. of the protocol.

SUBJECT/PATIENT DISPOSITION:

	Placebo	MK-0633	Total
SCREENING FAILURES:			165
RANDOMIZED:	133	133[†]	266
Male (age range)	100 (40 to 75)	88 (45 to (75)	188 (40 to 75)
Female (age range)	33 (45 to 73)	45 (45 to 75)	78 (45 to 75)
COMPLETED:	121	118	239
DISCONTINUED:	12	13	25
Clinical adverse experience	5	5[‡]	10
Laboratory adverse experience	0	0	0
Other[§]	7	10	17

[†] [redacted] A total of 132 patients received MK-0633.

[‡] [redacted] Therefore, a total of 3 patients discontinued from the MK-0633 group due to a post-randomization clinical adverse experience.

[§] Includes lost to follow-up (3), progressive disease (1), protocol violation (4), study terminated by sponsor (1), and withdrawal by subject (8).

DOSAGE/FORMULATION NOS.: Period I: 2 placebo capsules once daily in the morning with food. Period II: MK-0633 100 mg (two 50-mg capsules) or matching-image placebo once daily in the morning with food. Supplies were packaged in desiccated high-density polyethylene (HDPE) bottles, with 34 capsules in each bottle. Formulation numbers for MK-0633 were [redacted] and [redacted] those for the matching-image placebo were [redacted]

DIAGNOSIS/INCLUSION CRITERIA:

Main study: Male and postmenopausal female outpatients 40 to 75 years of age, inclusive, with at least 1-year consistent clinical history of intermittent or persistent COPD symptoms including, but not limited to dyspnea, wheezing, chest tightness, cough, sputum production, or nocturnal awakening, smoking history of ≥10 pack-years, post-β-agonist FEV_1/FVC ratio ≤70%, FEV_1 25% to 75% predicted (inclusive), and minimum predefined level of daytime COPD symptoms and β-agonist use.

Lung Volume Substudy: Patients able to perform the necessary panting maneuvers required for whole body plethysmography (WBP) measurements.

EVALUATION CRITERIA:

Main Study:

EFFICACY MEASUREMENTS: Primary endpoint: predose (trough) FEV_1. Secondary endpoints: overall daytime symptoms score, postdose FEV_1, total daily β-agonist use, dyspnea, and CRQ score. Other endpoints: AM and PM PEFR, individual daytime COPD symptoms and nocturnal awakenings, COPD exacerbations[1], patient global COPD evaluation, predose FVC, and post-bronchodilator FEV_1 and FVC.

SAFETY MEASUREMENTS: Clinical evaluations (physical examinations, vital signs, electrocardiograms [ECGs]), clinical and laboratory adverse experience monitoring, and proportions of patients outside predefined limits of change for prespecified laboratory safety tests.

Lung Volume Substudy:

EFFICACY MEASUREMENTS: Primary endpoint: thoracic gas volume (TGV) at functional residual capacity (FRC). Other endpoints: slow vital capacity (SVC), inspiratory capacity (IC), expiratory reserve volume (ERV), total lung capacity (TLC = TGV + IC), residual volume (RV = TLC – SVC), and airway resistance (R_{aw}).

[1] COPD exacerbation is defined as any change in symptoms or functional status that leads to administration (at the investigator's discretion) of systemic corticosteroids and/or antibiotics, or an unscheduled, COPD-related hospitalization, emergency room visit, or doctor visit.

STATISTICAL PLANNING AND ANALYSIS:

Main Study:

EFFICACY: The primary objective was assessed using a longitudinal linear model. Change from baseline in FEV_1 at each visit was the dependent variable; the independent variables included treatment, region, concomitant long-acting bronchodilator use, smoking status, baseline FEV_1 reversibility, baseline FEV_1, and treatment-by-visit interaction. The covariance across visits within each subject was modeled using a general unstructured covariance matrix. The primary timepoint was the average across the last 2 weeks of the treatment period (Weeks 10 and 12). The comparison was performed using the appropriate contrast from the model.

The secondary and exploratory endpoints that are continuous or ordinal in nature were analyzed in the same fashion as the primary endpoint.

The Fisher Exact Test was used to evaluate between-treatment comparisons in the proportion of patients with at least one COPD exacerbation. The Kaplan-Meier procedure and the log-rank test were used to compare the time-to-the-first COPD exacerbation curves. Change from baseline in the percentage of the COPD symptom-free days over the last 2 weeks of the treatment period was analyzed using the analysis of covariance (ANCOVA) model with factors for treatment, region, concomitant long-acting bronchodilators use, smoking status, and baseline percentage of COPD symptom-free days as a covariate. The proportion of patients in each collapsed category for patient COPD global evaluation by treatment groups was summarized and tested using the Cochran-Mantel-Haenszel test.

The Full Analysis Set (FAS) was the primary population for the efficacy analyses, which includes all patients who had a baseline and at least one posttreatment measurement. Patients were analyzed according to the treatment group to which they were randomized.

SAFETY: Safety and tolerability were assessed by a statistical and clinical review of all safety parameters, including adverse experiences (AEs), laboratory values, ECGs, and vital signs. Statistical tests were performed and the 95% confidence intervals (CIs) and p-values were displayed on the Tier 1 AEs and/or tolerability parameters (prespecified safety parameters of interest). For Tier 2 events (that included, among other categories of AEs, individual AEs that occurred in at least 4 patients in one or more of the groups), 95% CIs of the between treatment group difference of incidence rates were provided. For all other clinical and laboratory AEs, events were listed and summarized by frequency of occurrence; only the counts and percentages were tabulated by treatment group. For the Tier 2 AEs, 95% CIs for the between-group differences were derived using the Miettinen and Nurminen method. Vital signs and selected laboratory tests were also summarized.

All-Patients-As-Treated (APaT) approach was used for the safety analyses. The APaT population uses all randomized patients who received at least 1 dose of double-blind study therapy. Patients were analyzed according to the treatment group they received.

Lung Volume Substudy:

EFFICACY: Lung volume measurements (TGV, SVC, IC, ERV, and R_{aw}) were measured at Visit 3 (baseline) and Visit 8 (Week 12). For each lung volume measurement, change from baseline to Week 12 was analyzed.

RESULTS:

Main Study:

EFFICACY: For the primary efficacy endpoint of predose (trough) FEV_1, MK-0633 100 mg demonstrated a small numerical improvement, compared with placebo, over the 12-week treatment period; the treatment effect was not significantly different from placebo (p=0.556). For the secondary and other efficacy endpoints, MK-0633 demonstrated general trends of numerical improvement, compared with placebo, over the 12-week treatment period. The treatment effect was significantly different from placebo for patient COPD global evaluation (p<0.001) and approached significance in AM PEFR (p=0.074), patient-reported amount of mucus (p=0.054), and patient-reported amount of time coughed (p=0.087). For the rest of the endpoints, the treatment effects were not statistically significant.

Subgroup analyses of patients who were on concomitant long-acting bronchodilators showed larger treatment effects compared with the overall effect on most of the efficacy endpoints (e.g., for predose (trough) FEV_1, the difference in LS means versus placebo was 0.04 L versus 0.01 L in patients receiving long-acting bronchodilators and patients not receiving long-acting bronchodilators, respectively).

A summary of treatment effect expressed in LS means for the primary and some other key efficacy endpoints are provided in the following table.

Summary of Key Efficacy Analyses Results
Full-Analysis-Set (Excluding the Two Outliers[†])

Treatment	N	Raw Value		Change from Baseline[‡]	Difference in LS Means[╪] (95% CI)	p-Value
		Baseline Mean (SD)	Treatment[‡] Mean (SD)	LS Mean (95% CI)		
Predose (Trough) FEV_1 (*Primary Endpoint*)						
MK-0633 100 mg	127	1.30 (0.45)	1.32 (0.46)	0.015 (-0.017, 0.048)	0.013 (-0.030, 0.056)	0.556
Placebo	131	1.37 (0.53)	1.37 (0.53)	0.002 (-0.030, 0.034)		
Overall Daytime Symptoms Score						
MK-0633 100 mg	117	2.10 (0.66)	1.96 (0.88)	-0.17 (-0.28, -0.06)	-0.04 (-0.19, 0.11)	0.592
Placebo	122	2.05 (0.57)	1.94 (0.68)	-0.13 (-0.24, -0.02)		
CRQ Total Score						
MK-0633 100 mg	118	4.77 (0.98)	4.97 (1.04)	0.19 (0.04, 0.35)	0.05 (-0.16, 0.25)	0.653
Placebo	118	4.80 (0.98)	4.96 (0.94)	0.15 (-0.01, 0.30)		
AM PEFR						
MK-0633 100 mg	117	220.96 (73.02)	231.14 (80.27)	8.73 (3.03, 14.43)	7.09 (-0.68, 14.86)	0.074
Placebo	122	237.37 (86.04)	239.01 (85.90)	1.64 (-3.94, 7.21)		
Patient-Reported Amount of Time Coughed						
MK-0633 100 mg	117	1.84 (0.74)	1.65 (0.79)	-0.21 (-0.32, -0.09)	-0.13 (-0.29, 0.02)	0.087
Placebo	122	1.79 (0.67)	1.73 (0.72)	-0.07 (-0.18, 0.04)		
Patient-Reported Amount of Mucus						
MK-0633 100 mg	117	1.84 (0.96)	1.56 (0.99)	-0.25 (-0.38, -0.13)	-0.17 (-0.34, 0.00)	0.054
Placebo	122	1.72 (0.89)	1.64 (0.93)	-0.08 (-0.21, 0.04)		
Patient COPD Global Evaluation[#]						
MK-0633 100 mg	114	----	1.40 (1.19)	1.46 (1.22, 1.69)	0.51 (0.21, 0.81)	0.001
Placebo	122	----	0.90 (1.27)	0.95 (0.72, 1.17)		

[†] Examination of the spirometry data revealed the presence of two outliers, whose improvement in FEV_1 greatly exceeded that of all the other randomized patients. Both patients had been randomized to receive MK-0633. Upon review of spirometry data, it was concluded that these two patients were suffering from an acute exacerbation of their COPD at baseline. Because of this, it was concluded that the apparent clinical improvement in these patients was due to their exacerbation resolving after baseline. Therefore, for the purposes of data presentation, data from these two patients are excluded for all the efficacy analyses included in the Synopsis and Section 11; the efficacy results on the complete data set are provided in Section 14.1.
[‡] Average of the last two weeks of the 12-week treatment period.
[╪] Based on a longitudinal linear model for all the endpoints except global evaluation.
[#] For global evaluation, values at Week 12 were analyzed using an ANCOVA model.
ANCOVA = analysis of covariance; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CRQ = Chronic Respiratory Questionnaire; FAS = full analysis set; FEV_1 = forced expiratory volume in 1 second; LS = least squares; PEFR = peak expiratory flow rate; SD = standard deviation.

SAFETY: The safety profile of MK-0633 was generally comparable to that of placebo. No patients in either treatment group met the N-acetyl-betaglucosaminadase criterion for discontinuation.

Adverse Event Summary
Clinical and Laboratory Adverse Experience Summary
All-Patients-as-Treated Population

	Placebo		MK-0633		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	133		132		265	
with one or more adverse events	63	(47.4)	56	(42.4)	119	(44.9)
with no adverse event	70	(52.6)	76	(57.6)	146	(55.1)
with drug-related[†] adverse events	14	(10.5)	12	(9.1)	26	(9.8)
with serious adverse events	4	(3.0)	6	(4.5)	10	(3.8)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	1	(0.8)	1	(0.4)
discontinued[‡] due to an adverse event	5	(3.8)	3	(2.3)	8	(3.0)
discontinued due to a drug-related adverse event	1	(0.8)	1	(0.8)	2	(0.8)
discontinued due to a serious adverse event	2	(1.5)	1	(0.8)	3	(1.1)
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.

Lung Volume Substudy:

EFFICACY: There were no significant differences in change from baseline in total lung capacity, thoracic gas volume at functional residual capacity, expiratory reserve volume, inspiratory capacity, residual volume, slow vital capacity, and airway resistance.

CONCLUSIONS: In adult patients with COPD: (1) MK-0633, compared with placebo, does not result in significant improvement in the primary endpoint of predose (trough) FEV_1 over the 12-week treatment period. (2) MK-0633 is generally well tolerated, with no significant differences in clinical and laboratory adverse experiences or other safety parameters. There is, however, a small numerical increase in urinary N-acetyl-betaglucosaminadase (NAG) with MK-0633 treatment, compared with placebo. (3) MK-0633, compared with placebo, does not result in significant improvements in any of the secondary endpoints over the 12-week treatment period. (4) MK-0633, compared with placebo, does not result in significant improvements in most exploratory endpoints over the 12-week treatment period. MK-0633, however, does result in significant improvement in patient COPD global evaluation. (5) MK-0633, compared with placebo, does not improve lung volume measurements. (6) In general, in the subgroup of patients who received MK-0633 and concurrent long-acting bronchodilators, trends in several endpoints (e.g., cough, mucus production) are greater than those observed for the overall patient population.

AUTHORS: [redacted]