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-0533 L-000444344, Tablet Type II Diabetes Mellitus	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: An Efficacy and Tolerability Study of MK-0533 in Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control #005

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 Appendix [16.1.8.1]. For protocol-specific informed consent forms, see Appendices [16.1.3.2; 16.1.3.3; 16.1.3.4]. All authors reviewed this CSR for accuracy and scientific content (see Principal Authors' Signatures in Appendix [16.1.5.2]). The Coordinating Investigator's signature is in Appendix [16.1.5.1].

INVESTIGATOR(S)/STUDY CENTER(S): Seventy-five sites received IRB/IEC approval and were shipped clinical supplies: 34 sites in the United States, nine sites in the Russian Federation, eight sites in Canada, five sites in Germany, five sites in Italy, and 14 sites in six countries in the rest of the world [16.1.3.1]. Curriculum vitae of these investigators are in Appendix [16.1.4].

PRIMARY THERAPY PERIOD: 26-Jun-2006 to 15-Aug-2007 | **CLINICAL PHASE:** IIa/IIb

DURATION OF TREATMENT: 12 weeks

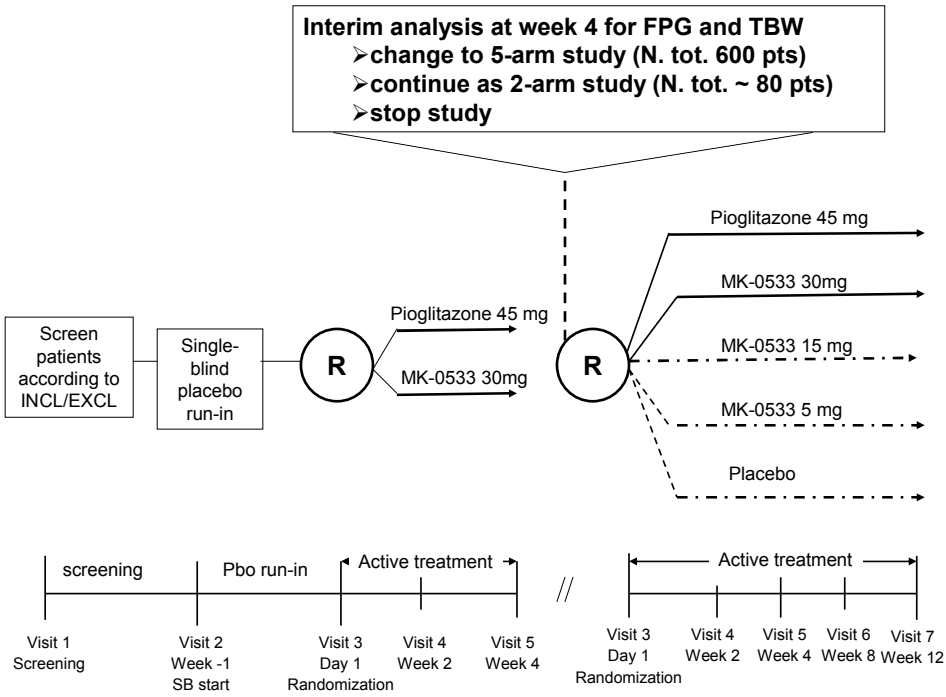
OBJECTIVE(S): In patients with type 2 diabetes mellitus with inadequate glycemic control on diet and exercise: Primary: (1) After 12 weeks, to assess the effect of treatment with MK-0533 compared with placebo on fasting plasma glucose (FPG); (2) To assess the safety and tolerability of MK-0533 after 12 weeks of double-blind treatment; Secondary: (1) After 12 weeks, to assess the effect of treatment with MK-0533 compared with placebo on hemoglobin A1c (A1C); (2) After 12 weeks, to assess the effect of treatment with MK-0533 compared with pioglitazone 45 mg on FPG; (3) After 12 weeks, to assess the effect of treatment with MK-0533 compared with pioglitazone 45 mg on total body water (TBW); Exploratory: After 12 weeks, to assess the effect of treatment with MK-0533 compared with pioglitazone 45 mg on extracellular water (ECW) and body weight; (2) After 12 weeks, to assess the effect of treatment with MK-0533 compared with pioglitazone 45 mg and placebo on A1C, triglycerides (TG), HDL-C, LDL-C, total cholesterol, non-HDL-C and ankle circumference; (3) After 12 weeks of treatment, to explore the characteristics of effectiveness, side effects and overall treatment satisfaction based on the Treatment Satisfaction Questionnaire for Medication (TSQM) for all treatment groups.

HYPOTHESES: In patients with type 2 diabetes mellitus with inadequate glycemic control on diet and exercise: Primary: (1) After 12 weeks, a dose-response will be seen across doses of MK-0533 and placebo in lowering FPG; (2) MK-0533 will be well-tolerated; Secondary: After 12 weeks, a dose-response will be seen across doses of MK-0533 and placebo in lowering A1C.

STUDY DESIGN: MK-0533 Protocol 005 was a study conducted in patients with T2DM on diet and exercise therapy which began as a Phase IIa, multicenter, randomized, double-blind, parallel-arm, adaptive design, active-controlled, 12-week study with a pre-defined enrollment target of randomizing 80 patients in a 1:1 ratio to once daily oral administration of MK-0533 30 mg or pioglitazone 45 mg. A planned Phase IIa interim analysis (IA) was performed once 110 patients completed four weeks of double-blind therapy. (Note: While 112 patients were randomized in MK-0533 Protocol 005, the IA included 110 patients. Two patients did not complete four weeks of double-blind therapy prior to the IA and were not included in this analysis.) This IA compared the change from baseline in fasting plasma glucose (FPG) and total body water (TBW) between the two treatment groups. As specified in the protocol, the study adapted to a Phase IIb, five-arm, active- and placebo-controlled, 12-week study with the pre-defined enrollment target of randomizing an additional 500 patients in a 1:1:1:1:1 ratio to once-daily oral administration of placebo (pbo), MK-0533 5 mg, MK-0533 15 mg, MK-0533 30 mg, or pioglitazone 45 mg. Patients randomized prior to the Phase IIa IA continued on their originally assigned therapy until they completed the 12-week double-blind study period. The overall study design is shown in Figure 2-1.

Figure 2-1

Study Design



The design of the Phase IIa and IIb portions of this study differed only in the number of dose arms for each portion of the study. Therefore, for both the Phase IIa and IIb portions of this study, each patient had 7 clinic visits over approximately 14 weeks including a 1-week screening period, a 1-week placebo run-in period, and a 12-week treatment period. A telephone contact was performed 14 days after the last dose of study drug to assess for serious adverse experiences. The overall study design is available in Section 2.4 of the Protocol (Appendix [16.1.1]).

An additional Phase IIb interim analysis was performed once 234 patients from the Phase IIb cohort completed 12 weeks of double-blind therapy. The IA from Phase IIb evaluated the efficacy and safety profiles of MK-0533 5 mg, MK-0533 15 mg, and MK-0533 30 mg vs. both placebo and pioglitazone 45 mg. Based on the results of the Phase IIb interim analysis, which showed that none of the MK-0533 doses tested in Protocol 005 demonstrated both glycemic and body fluid benefits compared to pioglitazone 45 mg, the study was terminated. The decision to terminate this study was not due to any new safety concerns with MK-0533. The complete Phase IIb Interim Analysis Results Memo can be found in Appendix [16.1.9.5].

Both the Phase IIa and Phase IIb interim analyses were performed by the standing internal data monitoring committee (siDMC) monitoring this study [16.1.9.2].

SUBJECT/PATIENT DISPOSITION (Phase IIa):

	MK-0533 30 mg	Pioglitazone 45 mg	Total
RANDOMIZED:[†]	56	56	112
Male (age range)	30 (40-70)	31 (35-70)	61 (35-70)
Female (age range)	26 (21-70)	25 (43-69)	51 (21-70)
COMPLETED:	46	43	89
DISCONTINUED:	10	13	23
Adverse experience	2	6	8
Lack of efficacy	2	2	4
Lost to follow-up	0	0	0
Other	1	1	2
Withdrew consent	2	4	6
Deviation from protocol	3	0	3

SUBJECT/PATIENT DISPOSITION (Phase IIb):

	MK-0533 5 mg	MK-0533 15 mg	MK-0533 30 mg	Pioglitazone 45 mg	Placebo	Total
RANDOMIZED:	47	46	47	47	47	234
Male (age range)	34 (36-70)	19 (40-67)	23 (33-65)	24 (42-68)	27 (39-63)	127 (33-70)
Female (age range)	13 (35-65)	27 (32-66)	24 (36-69)	23 (23-69)	20 (30-69)	107 (23-69)
COMPLETED:	45	42	40	42	36	205
DISCONTINUED:	2	4	7	5	11	29
Adverse experience	0	0	3	0	2	5
Lack of efficacy	0	1	0	1	3	5
Lost to follow up	1	0	1	0	2	4
Other	0	1	0	2	2	5
Withdrew consent	1	1	2	2	0	6
Deviation from protocol	0	1	1	0	2	4

[†] See [16.2.4] and [16.4.1.1] for patient demographics, [16.2.2] for protocol deviations, [16.2.1] for discontinued patients, and [16.4.3.2] for overall disposition of patients.

DOSAGE/FORMULATION NOS.: During Phase IIa, MK-0533 30 mg or pioglitazone 45 mg was administered orally (tablet) once daily. During Phase IIb, placebo (pbo), MK-0533 5 mg, MK-0533 15 mg, MK-0533 30 mg, or pioglitazone 45 mg was administered orally (tablet) once daily. Compliance with study drug can be found in [16.2.5].

Clinical Supplies

Drug Name	Formulation No.
MK-0533 PBO (5 mg, 10 mg) image MK-0533 5 mg image MK-0533 10 mg image Pioglitazone HCl PBO 45 mg image Pioglitazone HCl 45 mg image	[redacted]

DIAGNOSIS/INCLUSION CRITERIA: Diagnosis – Patients with T2DM. Patients ≥18 and ≤70 years of age with inadequate glycemic control (A1C ≥7.0% and ≤10%) who have not taken any antihyperglycemic agents (AHA) for ≥12 weeks prior to screening. Patients were not to have their prior AHAs discontinued solely for the purpose of qualifying for the study. A complete list of inclusion and exclusion criteria can be found in Section 2.3 of the protocol (Appendix [16.1.1]).

EVALUATION CRITERIA:

The study protocol, amendments and protocol clarification letters are found in Appendix [16.1.1]. Sample case report forms are found in Appendix [16.1.2.1]. See [16.1.7.1; 16.1.7.2] for computer-generated allocation schedules. The schedule of clinical observations and laboratory measurements is shown in the Study Flow Chart, located in Section 1.7 of the protocol (Appendix [16.1.1]).

EFFICACY MEASUREMENTS: Primary Endpoint: Fasting plasma glucose (FPG). Secondary Endpoints: A1C*, PK (pharmacokinetics), total cholesterol, TG, HDL-C, LDL-C, non-HDL-C, and TSQM (Treatment Satisfaction Questionnaire for Medication).

SAFTEY MEASUREMENTS: Safety measurements included monitoring of adverse experiences (including adverse experiences of edema), increased LFTs, CHF, clinical evaluation (including vital signs, body weight, physical examination, waist circumference and ankle circumference); adverse experiences of CHF, peripheral edema and impaired hepatic function (as indicated either by increased LFTs, or when considered an adverse experience by the investigator) were categorized as Events of Clinical Interest (ECIs); laboratory assessment included TBW, ECW, AST, ALT, CPK, chemistry (including sodium, potassium, chloride, bicarbonate, calcium, phosphate, albumin, alkaline phosphatase, uric acid, total serum protein, total bilirubin, BUN, and creatinine), hematology (including hemoglobin, hematocrit, mean corpuscular hemoglobin volume, white blood cell count and differential, platelet count, and absolute neutrophil count [ANC]), urine dipstick/microscopy; and electrocardiography (ECG).

* Early in the Phase IIa (2-arm) cohort, a change was made in the instrumentation used to analyze A1C. Validation of the assay was performed by the central laboratory, the results of which confirmed that the new and old instruments reported equivalent results. The site validation report can be found in Appendix [16.1.10.1].

STATISTICAL PLANNING AND ANALYSIS:

To address the primary hypothesis, the between-group difference in mean change from baseline in FPG at Week 24 was assessed via a repeated measures analysis of covariance (RM ANCOVA) model. This model included terms for treatment, week (treated as categorical variable), baseline FPG value, the interaction between week and treatment, and the interaction between week and baseline FPG value. An unconstructed variance-covariance model was used to capture the correlation between repeated measurements.

Other continuous efficacy endpoints, total body water (TBW), extracellular water (ECW), and body weight were analyzed using the above ANCOVA method described for FPG substituting the relevant baseline value as the covariate.

Safety and tolerability were assessed by a review of safety parameters, including adverse experiences (AEs), laboratory safety parameters, vital signs, physical examination (including ankle circumference) and ECG. The analysis of safety parameters followed a multi-tiered approach. Additional detail is available in the Statistical Analysis Plan (SAP), found in Appendix [16.1.9.1].

RESULTS:

EFFICACY: Table 2-1 shows that at Week 12, none of the MK-0533 doses demonstrated both glycemic and body fluid benefits compared to pioglitazone 45 mg. As specified in the protocol, the study was terminated.

Table 2-1

Primary Analysis Results at Week 12

Treatment Group[†]	FPG (mg/dL)		TBW (Liter)	
	LS Mean	95% CI	LS Mean	95% CI
Placebo	-2.2	(-12.0, 7.5)	0.5	(-0.3, 1.4)
MK-0533 5 mg	-25.3	(-34.2, -16.4)	0.1	(-0.6, 0.8)
MK-0533 15 mg	-20.5	(-29.7, -11.4)	0.4	(-0.3, 1.2)
MK-0533 30 mg	-39.6	(-49.0, -30.2)	0.4	(-0.4, 1.2)
Pioglitazone 45 mg	-35.4	(-44.5, -26.3)	0.6	(-0.2, 1.4)
MK-0533 30 mg (Phase IIa)	-30.7	(-39.2, -22.2)	1.2	(0.5, 1.9)
Pioglitazone 45 mg (Phase IIa)	-27.1	(-35.7, -18.5)	0.5	(-0.3, 1.2)

[†] Treatment group in the Phase IIb cohort unless specified otherwise.

Data Source: [16.4.4.3]

The completer Phase IIa portion of the study can be found in Appendix [16.1.9.3]. The Phase IIb interim analysis criteria can be found in Appendix [16.1.9.4]. The complete Phase IIb Interim Analysis Results Memo and supporting patient data for both cohorts can be found in the Interim Analysis Results Memo (Appendix [16.1.9.5]). Individual efficacy response data can be found in [16.2.6]. Patients excluded from the efficacy analysis can be found in [16.2.3].

SAFETY: MK-0533 was generally well tolerated during both the Phase IIa (two-arm) and Phase IIb (five-arm) cohorts. No deaths were reported. There were no serious drug-related adverse experiences.

A summary of adverse experiences can be found in Table 2-2. For a listing of patients who reported adverse experiences in both cohorts, see Appendix 2.1 of the Interim Analysis Results Memo (Appendix [16.1.9.5]).

Phase IIa

In the Phase IIa cohort, the frequency of adverse experiences was lower in the MK-0533 30 mg group than in the pioglitazone 45 mg group. During Phase IIa, the incidence of patients who discontinued due to an adverse experience was lower in the MK-0533 30 mg group than in the pioglitazone 45 mg group. A listing of patients who discontinued due to an adverse experience is shown in Table 2-3.

Discontinuations Due to Drug-Related Adverse Experiences

In the Phase IIa cohort, one patient (1.8%) in the MK-0533 30 mg group and three patients (5.4%) in the pioglitazone 45 mg group discontinued due to drug-related adverse experiences (Table 2-2). These adverse experiences were mild to moderate in intensity. No specific adverse experience term leading to discontinuation was reported in more than one patient in either treatment group. A more detailed description of these four patients who discontinued due to drug-related adverse experiences follows.

[redacted] The patient contacted the site on Day 52 to report left ankle swelling and pain, which had become progressively worse over the prior day. The patient was advised to stop study drug on Day 52, and the patient never resumed taking study drug. The patient was examined by the reporting investigator on Day 54. No abnormal findings were noted upon physical examination, and the patient walked without any discomfort. The cardiovascular examination was normal.

[redacted] The patient discontinued study drug on Day 60 due to the upper abdominal pain. The patient's upper abdominal pain and diarrhea resolved on Day 61, and she discontinued from the study on Day 69.

[redacted] On Day 15, the patient first experienced drug-related adverse experiences of dizziness and hypotension (both described as severe in intensity), and the patient continued in the study. On Day 21, the patient again experienced the drug-related adverse experiences of dizziness and hypotension, both mild in intensity. The patient discontinued study drug on Day 22 as a result of the drug-related adverse experience of hypotension.

[redacted] That same day, the patient also experienced the adverse experience of flatulence (also described as moderate in intensity), which was not considered to be related to study drug. On Day 15, the patient experienced the drug-related adverse experience of weight increased (described as moderate in intensity). The patient's flatulence resolved on Day 57. The patient discontinued study drug as a

result of the drug-related adverse experience of abdominal distension on Day 62. The patient's abdominal distension resolved at the time of the final scheduled study visit on Day 69.

Serious Adverse Experiences

There were two serious adverse experiences reported during the Phase IIa portion of this study. [redacted] Both adverse experiences were determined by the investigator not to be related to study drug.

A listing of patients who reported serious adverse experiences in both cohorts (Phase IIa and IIb) is displayed in Table 2-4.

Narratives for all serious adverse experiences are provided in Appendix [16.2.7.1].

Events of Clinical Interest

In this study, adverse experiences of congestive heart failure (CHF), peripheral edema and impaired hepatic function (as indicated by increased AST and/or ALT values, or when considered an adverse experience by the investigator) were considered Events of Clinical Interest (ECIs) for this study. A summary of ECIs by System Organ Class (SOC) is displayed in Table 2-5. Although a patient may have had two or more ECIs, the patient is counted only once within a SOC. The same patient may be counted in multiple SOCs.

ECIs were reported for 8 patients in the Phase IIa cohort. There were no differences in the overall frequency of ECIs reported for the MK-0533 30 mg and pioglitazone 45 mg groups.

Drug-related ECIs were reported for 4 patients in the Phase IIa cohort. Table 2-6 displays a summary of these drug-related ECIs. There were no differences in the overall frequency of drug-related ECIs reported for the MK-0533 30 mg and pioglitazone 45 mg groups in Phase IIa.

During Phase IIa, ECIs of peripheral edema were reported most frequently. All ECIs of peripheral edema reported during the Phase IIa cohort belong to the General Disorders and Administration Site Conditions SOC. These ECIs ranged from mild to moderate in intensity. [redacted]

Narratives for all ECIs are provided in Appendix [16.2.7.1]. Individual subject data listings for all patients are provided in Appendix [16.2.8; 16.4.1; 16.4.2; 16.4.3; 16.4.4; 16.4.5].

Phase IIb

During the Phase IIb cohort, the frequency of adverse experiences was lower in the placebo group, MK-0533 5 mg group, and MK-0533 15 mg group when compared with the MK-0533 30 mg group and pioglitazone 45 mg group. In the Phase IIb cohort, more patients in the placebo group and MK-0533 30 mg group discontinued due to an adverse experience than in the MK-0533 5 mg, MK-0533 15 mg and pioglitazone 45 mg groups. A listing of patients who discontinued due to an adverse experience is displayed in Table 2-3.

Discontinuations Due to Drug-Related Adverse Experiences

In the Phase IIb cohort, one patient in the MK-0533 30 mg group discontinued due to a drug-related adverse experience (Table 2-2). [redacted] On Days 47 and 48, the patient experienced a drug-related adverse experience of hypoglycemia (both AEs of hypoglycemia described as mild in intensity). The reporting investigator noted that the patient experienced general malaise and vertigo as symptoms during both episodes of hypoglycemia. The patient discontinued from the study due to hypoglycemia on Day 49.

Serious Adverse Experiences

There was one serious adverse experience (erysipelas) during the Phase IIb cohort, which was considered by the investigator not to be related to study drug. [redacted] A listing of patients who reported serious adverse experiences in both cohorts is displayed in Table 2-4.

Narratives for all serious adverse experiences are provided in Appendix [16.2.7.1].

Events of Clinical Interest

ECIs were reported for 25 patients in the Phase IIb cohort. There were fewer overall ECIs reported for the placebo , MK-0533 5 mg, and MK-0533 15 mg groups when compared with the MK-0533 30 mg and pioglitazone 45 mg groups.

Drug-related ECIs were reported for 12 patients in the Phase IIb cohort. Table 2-6 displays a summary of drug-related ECIs. Fewer overall drug-related ECIs were reported for the placebo, MK-0533 5 mg, and MK-0533 15 mg groups when compared with the MK-0533 30 mg and pioglitazone 45 mg groups.

During Phase IIb, ECIs of peripheral edema were reported most frequently. Most of the ECIs of peripheral edema reported during the Phase IIb cohort belong to the General Disorders and Administration Site Conditions SOC. These ECIs ranged from mild to moderate in intensity. A small number of ECIs of peripheral edema belong to the Eye Disorders SOC. [redacted] Both ECIs were described as mild in intensity and related to study drug. Both patients recovered while on study drug. All seven ECIs of overdose, as defined in Section 3.4.3 of the Protocol [16.1.1], were asymptomatic. [redacted] The patient reported via telephone contact that she observed a swelling of her lower left leg, and noticed an indentation mark when she applied pressure with her finger to the skin on her lower left leg. There were no other symptoms associated with the patient's edema. The patient was advised by the reporting investigator to elevate her feet while sitting or laying in bed. At the scheduled study completion visit on Day 84, it was learned that the patient stopped study drug from Day 62 through Day 79. During that time, the patient's edema did not diminish. The patient resumed taking study drug on Day 80. The patient contacted the site on Day 85 to report that her edema had resolved. The reporting investigator felt that the patient's pitting edema was not related to study drug.

Narratives for all ECIs are provided in Appendix [16.2.7.1]. Individual subject data listings for all patients are provided in Appendix [16.4.1; 16.4.2; 16.4.3; 16.4.4; 16.4.5].

Table 2-2

Adverse Experience Summary
All Patients as Treated

	Placebo		MK-0533 5 mg		MK-0533 15 mg		MK-0533 30 mg		Pioglitazone 45 mg		MK-0533 30 mg (Phase IIa)		Pioglitazone 45 mg (Phase IIa)	
	(N=47)		(N=47)		(N=46)		(N=47)		(N=47)		(N=56)		(N=56)	
Event Category	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Number (%) of patients:														
With one or more adverse experiences	16	(34.0)	16	(34.0)	14	(30.4)	24	(51.1)	19	(40.4)	21	(37.5)	29	(51.8)
With no adverse experience	31	(66.0)	31	(66.0)	32	(69.6)	23	(48.9)	28	(59.6)	35	(62.5)	27	(48.2)
With drug-related adverse experiences	5	(10.6)	3	(6.4)	3	(6.5)	7	(14.9)	6	(12.8)	11	(19.6)	10	(17.9)
With serious adverse experiences	1	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.8)	0	(0.0)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)	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)	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	2	(4.3)	0	(0.0)	0	(0.0)	3	(6.4)	0	(0.0)	2	(3.6)	6	(10.7)
Discontinued due to drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)	1	(1.8)	3	(5.4)
Discontinued due to serious adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

N=Number of randomized and treated patients in each treatment group.
Although a patient may have had two or more adverse experiences the patient is counted only once in a category. The same patient may appear in different categories.
All treatment groups are from Phase IIb, unless otherwise noted.

Data Source: [16.2.7; 16.4.3.1]

Table 2-3

Adverse Experiences
Patients who Discontinued due to Adverse Experiences
All Patients as Treated

Site Number	AN	Gender	Race	Age (yrs)	Phase	Therapy	Total Daily Dose	Relative Day of Onset	Adverse Experiences	Duration of Adverse Exper-iences	Days in Study	Intensity	Ser-ious	Drug Relation-ship[†]	Outcome
Table Redacted Pages Removed															

Table 2-4

Adverse Experiences
Patients with Serious Adverse Experiences
All Patients as Treated

Site Number	AN	Gender	Race	Age (yrs)	Phase	Therapy	Total Daily Dose	Relative Day of Onset	Adverse Experiences	Duration of Adverse Exper-iences	Days in Study	Intensity	Drug Relation-ship†	Action Taken	Outcome
[redacted]															

† Drug Relationship: rel = drug related, not rel= not drug related

Data Source: [16.2.7; 16.4.3.1]

Table 2-5

Number (%) of Patients with ECI Adverse Experiences
(Incidence >= 0% in One or More Treatment Groups) by System Organ Class
All Patients as Treated

	Placebo		MK-0533 5 mg		MK-0533 15 mg		MK-0533 30 mg		Pioglitazone 45 mg		MK-0533 30 mg (IIA)		Pioglitazone 45 mg (IIA)	
	(N=47)		(N=47)		(N=46)		(N=47)		(N=47)		(N=56)		(N=56)	
Event Category	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Number (%) of patients:														
With one or more adverse experiences	3	(6.4)	3	(6.4)	3	(6.5)	8	(17.0)	8	(17.0)	4	(7.1)	4	(7.1)
With no adverse experience	44	(93.6)	44	(93.6)	43	(93.5)	39	(83.0)	39	(83.0)	52	(92.9)	52	(92.9)
Eye disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(2.1)**	**1**	**(2.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Eyelid oedema	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.1)	1	(2.1)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	**2**	**(4.3)**	**0**	**(0.0)**	**3**	**(6.5)**	**5**	**(10.6)**	**6**	**(12.8)**	**4**	**(7.1)**	**3**	**(5.4)**
Ankle oedema	1	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)	2	(4.3)	1	(1.8)	0	(0.0)
Dependent oedema	0	(0.0)	0	(0.0)	1	(2.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Foot oedema	0	(0.0)	0	(0.0)	1	(2.2)	1	(2.1)	0	(0.0)	2	(3.6)	1	(1.8)
Leg oedema	1	(2.1)	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema hands	1	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)	0	(0.0)
Oedema lower limb	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.1)	1	(2.1)	0	(0.0)	0	(0.0)
Oedema peripheral	0	(0.0)	0	(0.0)	1	(2.2)	1	(2.1)	0	(0.0)	0	(0.0)	1	(1.8)
Pitting oedema	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.1)	2	(4.3)	1	(1.8)	1	(1.8)
Infections and infestations	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.8)**
Viral infection	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1[†]	(1.8)

Number (%) of Patients with ECI Adverse Experiences
(Incidence >= 0% in One or More Treatment Groups) by System Organ Class
All Patients as Treated (Cont.)

	Placebo		MK-0533 5 mg		MK-0533 15 mg		MK-0533 30 mg		Pioglitazone 45 mg		MK-0533 30 mg (IIA)		Pioglitazone 45 mg (IIA)	
	(N=47)		(N=47)		(N=46)		(N=47)		(N=47)		(N=56)		(N=56)	
Event Category	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**2**	**(4.3)**	**1**	**(2.2)**	**2**	**(4.3)**	**2**	**(4.3)**	**0**	**(0.0)**	**0**	**(0.0)**
Overdose	0	(0.0)	2	(4.3)	1	(2.2)	2	(4.3)	2	(4.3)	0	(0.0)	0	(0.0)
Investigations	**1**	**(2.1)**	**1**	**(2.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(2.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Alanine aminotransferase increased	1	(2.1)	1	(2.1)	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)	0	(0.0)
Aspartate aminotransferase increased	0	(0.0)	1	(2.1)	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)	0	(0.0)

N=Number of randomized and treated patients in each treatment group.

Percent calculation is derived from number of patients in the category divided by the number of patients in the analysis population.

Although a patient may have had two or more adverse experiences the patient is counted only once in a category. The same patient may appear in different categories.

† [redacted]

Data Source: [16.2.7; 16.4.3.1]

Table 2-6

Number (%) of Patients with ECI Adverse Experiences
(Incidence >= 0% in One or More Treatment Groups) by System Organ Class
Patients with Drug-Related Adverse Experiences – All Patients as Treated

	Placebo		MK-0533 5 mg		MK-0533 15 mg		MK-0533 30 mg		Pioglitazone 45 mg		MK-0533 30 mg (IIA)		Pioglitazone 45 mg (IIA)	
	(N=47)		(N=47)		(N=46)		(N=47)		(N=47)		(N=56)		(N=56)	
Event Category	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Number (%) of patients:														
With drug-related adverse experiences	2	(4.3)	0	(0.0)	1	(2.2)	4	(8.5)	5	(10.6)	2	(3.6)	2	(3.6)
With no drug-related adverse experience	45	(95.7)	47	(100.0)	45	(97.8)	43	(91.5)	42	(89.4)	54	(96.4)	54	(96.4)
Eye disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(2.1)**	**1**	**(2.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Eyelid oedema	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.1)	1	(2.1)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	**2**	**(4.3)**	**0**	**(0.0)**	**1**	**(2.2)**	**3**	**(6.4)**	**5**	**(10.6)**	**2**	**(3.6)**	**2**	**(3.6)**
Ankle oedema	1	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)	2	(4.3)	1	(1.8)	0	(0.0)
Foot oedema	0	(0.0)	0	(0.0)	1	(2.2)	1	(2.1)	0	(0.0)	1	(1.8)	1	(1.8)
Leg oedema	1	(2.1)	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema hands	1	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)	0	(0.0)
Oedema lower limb	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.1)	1	(2.1)	0	(0.0)	0	(0.0)
Pitting oedema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)	1	(1.8)

N=Number of randomized and treated patients in each treatment group.
Percent calculation is derived from number of patients in the category divided by the number of patients in the analysis population.
Although a patient may have had two or more adverse experiences the patient is counted only once in a category. The same patient may appear in different categories.

Data Source: [16.2.7; 16.4.3.1]

CONCLUSIONS: At the doses tested, MK-0533: (1) does not demonstrate both glycemic and body fluid benefits compared to pioglitazone 45 mg; (2) is generally well tolerated.

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