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 SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC.
MK-8669
ridaforolimus, Tablet
Endometrial

CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: A Randomized Phase II Trial of Ridaforolimus ([redacted] MK-8669) Compared to Progestin in Female Adult Patients With Advanced Endometrial Carcinoma #007V1

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. [redacted]

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter 36 sites: United States (5), Canada (4), Chile (2), United Kingdom (5), Spain (8), Italy (3), Czech Republic (5), France (2), Germany (1), and India (1). [redacted]

PUBLICATION(S): N/A

PRIMARY THERAPY PERIOD: 19-Sep-2008 to 07-Jun-2012 **CLINICAL PHASE:** IIb

DURATION OF TREATMENT: The total duration of a patient's participation was expected to be approximately 24 months and 2 weeks, which included a 2-week screening period, 6 cycles of study drug administration, and total follow-up for 24 months after randomization for survival. The actual duration of each patient's participation varied since patients could continue to receive study drug until documentation of disease progression or other discontinuation criteria were met.

OBJECTIVE(S):

Primary Objective:

- To compare progression-free survival (PFS) of patients with advanced, recurrent or metastatic endometrial cancer who have received one, but not more than two, prior lines of chemotherapy either as adjuvant therapy or treatment for advanced disease as defined in in the protocol [redacted] and then treated with ridaforolimus or progestin.

Secondary Objectives:

- To compare the proportion of patients receiving ridaforolimus versus progestin who are progression-free at 16 weeks and 26 weeks post randomization as assessed using modified RECIST guidelines.
- To compare the overall survival (OS) of patients receiving ridaforolimus versus progestin.
- To compare the best response rate of patients receiving ridaforolimus versus progestin.
- To assess the safety and tolerability of oral ridaforolimus in this patient population.

[redacted]

STUDY DESIGN: This trial was a randomized, open-label, active control Phase 2 multi-center study designed to evaluate the effect of oral ridaforolimus versus progestin on progression-free survival in patients with advanced endometrial cancer. The trial was to test the hypothesis that ridaforolimus would improve the progression-free survival of treated patients in comparison to those treated with progestin. Approximately 150 patients were to be enrolled at multiple centers. Patients were to be stratified by histology (papillary serous carcinoma and clear cell carcinoma versus others) and region (US and ex-US). Eligible patients were to be randomized 1:1 to receive ridaforolimus or progestin. Ridaforolimus was to be administered orally at a dose of 40 mg QD for five consecutive days followed by a two-day holiday, each week. Medroxyprogesterone acetate was to be administered at a dose of 200 mg orally daily. Megestrol acetate was to be administered at a dose of 160 mg orally daily. A 4-week (28-day) period was defined as a cycle of treatment.

Disease response was to be assessed according to modified RECIST (version 1.0) guidelines every eight weeks. Response assessments were performed by investigators and by an independent central image review. Safety was to be assessed by routine physical and laboratory evaluations. Patients were expected to receive a minimum of 2 cycles of study drug and were to receive additional cycles of study drug if they continue to have at least stable disease and are tolerating therapy. All patients were to be followed for 24 months after randomization for survival follow-up. [redacted].

SUBJECT/PATIENT DISPOSITION:

	Ridaforolimus		Comparator		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	64		66		130	
Study Disposition						
DISCONTINUED	64	(100.0)	66	(100.0)	130	(100.0)
Adverse Event	21	(32.8)	4	(6.1)	25	(19.2)
Clinically Progressive Disease (Physician Judgment)	5	(7.8)	5	(7.6)	10	(7.7)
Death	2	(3.1)	0	(0.0)	2	(1.5)
Investigator Decision	1	(1.6)	1	(1.5)	2	(1.5)
Other	3	(4.7)	0	(0.0)	3	(2.3)
Patient Withdrew	7	(10.9)	7	(10.6)	14	(10.8)
Progressive Disease	24	(37.5)	47	(71.2)	71	(54.6)
Protocol Violation	1	(1.6)	0	(0.0)	1	(0.8)
Termination of the Trial by the Sponsor	0	(0.0)	2	(3.0)	2	(1.5)

Each subject is counted once for Study Disposition based on the latest corresponding disposition record.

Data Source: [redacted]

DOSAGE/FORMULATION NOS.: Patients were to take ridaforolimus once daily as oral tablets for 5 consecutive days followed by a 2-day dosing holiday each week (QDx5/week) at a dose of 40 mg per day. Patients randomized to the comparator arm were to receive progestin. Progestin was to be administered as oral medroxyprogesterone tablets 200 mg PO daily or megestrol tablets 160 mg PO daily, and supplied locally by the Investigator. Dose modifications were to be permitted for management of treatment-related adverse events. The formulation numbers for ridaforolimus used for this study can be found below in Table 1.

Table 1

Dosage and Formulation Numbers

Drug	Potency	Dosage Form	Formulation No. (Mfg. Lot #)	Control No. (Package Batch No.)
MK-8669	10 mg	ECT		
MK-8669	10 mg	ECT		
MK-8669	10 mg	ECT		
MK-8669	10 mg	ECT		
MK-8669	10 mg	ECT		
MK-8669	10 mg	ECT		

Data Source: [N/A]

DIAGNOSIS/INCLUSION CRITERIA: Patients ≥18 years of age diagnosed with unresectable stage III or IVa, or metastatic (stage IVb), or recurrent histologically-confirmed endometrial cancer. Endometrial cancer was to include all carcinomas, including endometrioid carcinoma, papillary serous carcinoma, clear cell carcinoma, and carcinosarcomas. Leiomyosarcomas were not to be included.

EVALUATION CRITERIA:

Efficacy measurements: Disease progression and objective tumor response was assessed by independent review according to RECIST guidelines. All patients were to be followed for survival. The primary endpoint was progression-free survival, defined as the time from the date of randomization to the date of documented progressive disease, recurrence or death (whichever occurs first). Disease progression and objective tumor response was assessed according to RECIST guidelines. The PFS success rate was to be established for all patients.

Safety measurements: Safety assessments included routine physical examinations, laboratory evaluations, and interim history. Adverse events were graded according to U.S. NCI Common Terminology Criteria for Adverse Events.

STATISTICAL PLANNING AND ANALYSIS: The primary endpoint was progression-free survival (PFS), defined as the time from the date of randomization to the date of documented progressive disease, recurrence or death (whichever occurs first). Disease progression and objective tumor response were assessed according to RECIST guidelines. [redacted]

RESULTS: The study had an interim analysis (IA) with a data cut-off date of August 31, 2010. The IA showed that based on independent radiologists review that patients with advanced endometrial carcinoma treated with ridaforolimus substantially improved Progression Free Survival (PFS) compared with that of patients who were treated with the comparator. Since the interim PFS analysis crossed the pre-defined efficacy boundary for the IA (PFS HR< 0.545), the enrollment was discontinued and patients already enrolled were allowed to continue in the study until disease progression (or other discontinuation criteria). Independent radiology review was decommissioned after the IA was completed, therefore PFS and objective response rate (ORR) data by independent radiology review was not available subsequent to the data cutoff for the IA, and the interim analysis may be considered the "final" analysis for the PFS and ORR endpoints. Overall survival (OS) and safety data continued to be collected until final study data base lock (09-Aug-2012). [redacted]

Demographics: All 130 randomized patients are included in the ITT population. Two patients, one in each treatment arm, did not receive study drug which makes a total of 128 patients in the 'As Treated' population (APaT). There were a total of 130 patients, 64 in the ridaforolimus arm and 66 in the comparator arm. The majority of the patients were white (90.8%), and the median age was 66 years old (range 37.0-81.0). The primary diagnosis was endometrioid cancer (53.8%) and papillary serous endometrial carcinoma (26.2%). [redacted]

Efficacy: Data on PFS from the IA are presented in Table 2 and Table 3 (data cutoff 31-Aug-2010). Table 2 below provides PFS data by independent radiology review. The median PFS was 1.9 months for the comparator arm (progestin or chemotherapy of investigator's choice), and 3.6 months for ridaforolimus arm. The hazard ratio for the difference between treatment arms was 0.53 (p=0.008) based on independent review. Table 3 provides PFS data based on Investigator evaluation. The median PFS was 1.9 months for the comparator arm, and 5.6 months for the ridaforolimus arm. The hazard ratio for the difference between treatment arms was 0.39 (p<0.001) by investigator assessment. Table 4 summarizes the key secondary objective, overall survival (OS), from the final analysis (database lock 09-Aug-2012). The median OS was 42.0 weeks for the comparator arm, and 43.6 weeks for the ridaforolimus arm. The hazard ratio for the difference between treatment arms was 1.06 (p=0.604). Data on ORR from the IA are presented in Table 5 and Table 6 (data cutoff 31-Aug-2010). Table 5 presents the ORR based upon independent radiologist's review. The ORR was 4.3% in the comparator arm and 0.0% in the ridaforolimus arm. Table 6 presents the ORR based upon investigator review which shows that ORR was 4.3% in the comparator arm and 8.3% in the ridaforolimus arm. [redacted]

Table 2

Summary of Progression-Free Survival (PFS) [†] Based on Independent Radiology Review
(FAS, Cox Regression Model)
(Interim Analysis)

	Ridaforolimus (N=48)	Comparator (N=47)	Ridaforolimus Versus Comparator		
			Hazard Ratio[‡]	95% CI for Hazard Ratio[‡]	p-Value[‡]
Number (%) of PFS Events	26 (54.2)	32 (68.1)	--	--	--
Person-Months	163	106	--	--	--
Event Rate/100 Person-Months (%)	15.9	30.2	--	--	--
Median PFS (Months)[§]	3.6	1.9	0.53	(0.31,0.90)	0.008
95% CI for Median PFS[§]	(2.7,7.3)	(1.9,2.3)	--	--	--
Number (%) PFS Events at 4 Months[§]	19 (39.6)	28 (59.6)	--	--	--

[†] Progression-free survival is defined as disease progression, or death, whichever occurs first.

[‡] From Cox model test case, as treatment effect is tested. P-Value is one-sided for testing H_0: HR ≥ 1 versus H_1: HR < 1.

[§] From product-limit (Kaplan-Meier) method for censored data.

Data Source: [redacted]

Table 3

Summary of Progression-Free Survival (PFS) [†] Based on Investigator Evaluation
(FAS, Cox Regression Model)
(Interim Analysis)

	Ridaforolimus (N=48)	Comparator (N=47)	Ridaforolimus Versus Comparator		
			Hazard Ratio[‡]	95% CI for Hazard Ratio[‡]	p-Value[‡]
Number (%) of PFS Events	24 (50.0)	34 (72.3)	--	--	--
Person-Months	175	113	--	--	--
Event Rate/100 Person-Months (%)	13.7	30.0	--	--	--
Median PFS (Months)[§]	5.6	1.9	0.39	(0.23,0.66)	0.000
95% CI for Median PFS[§]	(4.4,6.8)	(1.8,2.7)	--	--	--
Number (%) PFS Events at 4 Months[§]	11 (22.9)	32 (68.1)	--	--	--

[†] Progression-free survival is defined as disease progression, or death, whichever occurs first.

[‡] From Cox model test case, as treatment effect is tested. P-Value is one-sided for testing H_0: HR ≥ 1 versus H_1: HR < 1.

[§] From product-limit (Kaplan-Meier) method for censored data.

Data Source: [redacted]

Table 4

Summary of Overall Survival
(ITT Population)

	Ridaforolimus (N=64)	Comparator (N=66)	Ridaforolimus Versus Comparator		
			Hazard Ratio[†]	95% CI for Hazard Ratio[†]	p-Value[‡]
Death (%)	46 (71.9)	47 (71.2)	--	--	--
Median Survival (Weeks)[§]	43.6	42.0	1.06	(0.70,1.59)	0.604
95% CI for Median Survival[§]	(35.1,53.9)	(32.7,53.1)	--	--	--
Number (%) Deaths at 16 Weeks[§]	11 (17.2)	10 (15.2)	--	--	--

[†] Based on Cox regression model with treatment as a covariate (Ridaforolimus versus Comparator). The model is stratified over histology (papillary serous carcinoma and clear cell carcinoma versus all others).

[‡] One-sided p-value based on stratified [2] log-rank test.

[§] From product-limit (Kaplan-Meier) method for censored data.

Data Source: [redacted]

Table 5

Number (%) of Patients with Objective Response[†] Based on Independent Radiology Review
(FAS)
(Interim Analysis)

			Ridaforolimus Versus Comparator		
	Ridaforolimus (N=48)	Comparator (N=47)	Difference of Rates[‡] (%)	95% CI for Differences[‡] (%)	p-Value[‡]
Number of Patients with Objective Response	0	2	--	--	--
Objective Response Rate (%)	(0.0)	(4.3)	-4.3	(-14.3,3.4)	0.925
95% Exact CI for Objective Rate (%)	(0.0,0.0)	(0.5,14.5)	--	--	--

[†] Objective response consists of confirmed complete response and confirmed partial response.

[‡] From stratified Miettinen and Nurminen's method. One-sided p-Value for testing. H_0: Difference ≤ 0 versus H_1: Difference > 0.

Data Source: [redacted]

Table 6

Number (%) of Patients with Objective Response[†] Based on Investigator Evaluation
(FAS)
(Interim Analysis)

			Ridaforolimus Versus Comparator		
	Ridaforolimus (N=48)	Comparator (N=47)	Difference of Rates[‡] (%)	95% CI for Differences[‡] (%)	p-Value[‡]
Number of Patients with Objective Response	4	2	--	--	--
Objective Response Rate (%)	(8.3)	(4.3)	4.1	(-7.1,16.0)	0.208
95% Exact CI for Objective Rate (%)	(2.3,20.0)	(0.5,14.5)	--	--	--

[†] Objective response consists of confirmed complete response and confirmed partial response.

[‡] From stratified Miettinen and Nurminen's method. One-sided p-Value for testing. H_0: Difference ≤ 0 versus H_1: Difference > 0.

Data Source: [redacted]

Safety: Table 7 below provides an overall summary of adverse events. One or more adverse experiences were reported for 62 (98.4%) patients in the ridaforolimus arm and 61 (93.8%) patients in the comparator arm. The most frequently occurring events of clinical interest for the ridaforolimus arm were grade 2 mucosal inflammation (25.4%), grade 3 hyperglycemia (14.3%), and grade 2 stomatitis (14.3%). The most frequently occurring events of clinical interest for the comparator arm were grade 1 hydronephrosis (3.1%), grade 1 hyperglycemia (1.5%), and grade 3 renal failure (1.5%). In the ridaforolimus arm 61 patients (96.8%) and 38 patients (58.5%) in the comparator arm had adverse events considered by the investigator to be drug related. The most frequently reported events considered by the investigator to be drug related in the ridaforolimus arm was grade 2 mucosal inflammation (25.4%), grade 1 diarrhea (19.0%), and grade 2 stomatitis 14.3%). The most frequently reported events considered by the investigator to be drug related in the comparator arm were grade 2 fatigue (10.8%), grade 1 nausea (7.7%), and grade 1 anemia (6.2%).

A total of 36 patients (57.1%) patients in the ridaforolimus arm compared to 22 patients (33.8%) in the comparator arm had serious events. Of the 36 patients in the ridaforolimus arm, 17 patients (27%) had serious events that were considered drug related by the investigator. Of the 22 patients in the comparator arm, 2 patients (3.1%) had serious events that were considered by the investigator to be drug related. The most frequently reported serious drug related events in the ridaforolimus arm was grade 3 diarrhea (4.8%) and grade 1 pyrexia (3.2%). In the comparator arm, grade 4 pulmonary embolism (1.5%) and grade 4 hypoglycemia (1.5%) were the most frequently reported serious drug related events. [redacted]

Twelve deaths were reported during the study, of these deaths, 7 patients (11.1%) were in the ridaforolimus arm and 5 patients (7.7%) in the comparator arm. The most frequently reported event resulting in death in both arms was neoplasm malignant (disease progression). None of the deaths reported in this study were considered by the investigator to be drug related. [redacted]

Table 7

Adverse Event Summary
(APaT)

	Ridaforolimus		Comparator	
	n	(%)	n	(%)
Patients in population	63		65	
with one or more adverse events	62	(98.4)	61	(93.8)
with no adverse event	1	(1.6)	4	(6.2)
with drug-related[†] adverse events	61	(96.8)	38	(58.5)
with serious adverse events	36	(57.1)	22	(33.8)
with serious drug-related adverse events	17	(27.0)	2	(3.1)
who died	7	(11.1)	5	(7.7)
discontinued[‡] due to an adverse event	21	(33.3)	3	(4.6)
discontinued due to a drug-related adverse event	14	(22.2)	1	(1.5)
discontinued due to a serious adverse event	10	(15.9)	2	(3.1)
discontinued due to a serious drug-related adverse event	3	(4.8)	1	(1.5)

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

Data Source: [redacted]

CONCLUSIONS:

- There was a statistically significant improvement in progression free survival (PFS) in patients treated with ridaforolimus compared to progestrin or chemotherapy based upon independent radiology review.
  - This observation was consistent between the independent radiology review and the investigator's evaluation.
- There was no significant difference in Objective Response Rate (ORR) between ridaforolimus and standard therapy.
- There was no significant difference in OS between ridaforolimus and the comparator arm.
- Patients treated with ridaforolimus had adverse events that were consistent with the known safety profile of ridaforolimus.

Authors: [redacted]