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, Oral Prostate Ca.	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Phase II Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Study the Efficacy and Safety of Bicalutamide With or Without Ridaforolimus in Men With Asymptomatic, Metastatic Castrate-Resistant Prostate Cancer — #002

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: 10 sites in the US, 5 sites in Colombia, 2 sites in Peru and 23 sites in 9 EU countries including United Kingdom, Italy, Spain, Belgium, Denmark, Finland, Holland, Sweden, and Poland.

[redacted]

PUBLICATION(S): NA

PRIMARY THERAPY PERIOD: 6-Jan-2009 to 11-May-2011 | **CLINICAL PHASE:** IIa

DURATION OF TREATMENT:

Patients could have remained on assigned treatment until the development of intolerable side effects or evidence of disease progression based on biochemical, radiographic, or clinical assessment. Patients may have voluntarily withdrawn from the study at any time, or may have been taken off study for severe toxicity or if in the judgment of the investigator or the medical monitor it was in the best interest of the patient to do so. All patients were followed for survival outcome.

OBJECTIVE(S):

Primary:

1) To determine the efficacy of the combination of ridaforolimus and bicalutamide compared to placebo and bicalutamide by Prostate-Specific Antigen (PSA) decline within 12 weeks, a surrogate measurement of overall survival efficacy in prostate cancer therapy trials; 2) To determine the safety and tolerability of ridaforolimus when combined with bicalutamide.

Secondary:

1) To determine the efficacy of the combination of ridaforolimus and bicalutamide compared to placebo and bicalutamide by PSA response rate, by progression free survival (PFS) analysis; and time to PSA progression, 2) To evaluate the pharmacokinetic profile of ridaforolimus when administered in combination with bicalutamide.

STUDY STATUS: Terminated

STUDY DESIGN:

The base protocol (PN002) is a Phase II multi-center, randomized, double-blind, placebo-controlled trial, designed to study the efficacy and safety of the anti-androgen, bicalutamide with or without ridaforolimus in men with asymptomatic, metastatic, castrate-resistant prostate cancer. Eligible patients were randomly assigned to receive oral ridaforolimus and bicalutamide or a matched placebo and bicalutamide. The protocol was amended to add in the safety lead-in at the reduced starting dose of ridaforolimus to further evaluate the PK parameters. Patient visits were every 4 weeks, and imaging with a bone scan and CT of the abdomen and pelvis was performed at baseline and every 12 weeks on study. PSA was measured at baseline, 6 weeks, 12 weeks, and then every 4 weeks thereafter on study. Patients were designed to remain on blinded study treatment until biochemical, radiographic, or clinical evidence of disease progression.

SUBJECT/PATIENT DISPOSITION:

	MK-8669 30mg and bicalutamide	MK-8669 40mg and bicalutamide	Placebo and bicalutamide
RANDOMIZED:	11	4	7
Male	11	4	7
Age Range	58 to 72	72 to 79	60 to 82
COMPLETED:	0	0	0
Adverse event	3	3	2
Progressive Disease	7	0	3
Physician Decision	1	0	0
Patient Withdrew	0	1	1
Protocol Violation	0	0	1

Data Source [redacted]

DOSAGE/FORMULATION NOS:

Ridaforolimus was administered as an oral formulation, and was supplied as 10 mg enteric coated tablets. No dosing adjustment was allowed based on body weight. The ridaforolimus dose was is 40 mg (base protocol) or 30 mg (amendment -01) daily x 5 for five consecutive days each week. Bicalutamide was given at the standard dose of 50 mg daily. Lot numbers for ridaforolimus 10 mg enteric-coated tablets were [redacted]

During the safety lead-in only, the dosing of ridaforolimus and bicalutamide was staggered to enable evaluation of the pharmacokinetic profile of ridaforolimus before and after starting the bicalutamide. Bicalutamide was still given at the standard dose of 50 mg daily. Ridaforolimus was given on Day 1 only for the first week, and was given five consecutive days each week starting from the second week.

DIAGNOSIS/INCLUSION CRITERIA:

Patients 18 years of age or older with histologically confirmed adenocarcinoma of the prostate, with evidence of evidence of metastatic disease at protocol entry or at the time of prior hormonal manipulation, or disease progression despite castrate levels of testosterone following orchiectomy or therapy with a luteinizing-hormone releasing hormone (LHRH) agonist or antagonist with a PSA > 7 ng/mL; an ECOG performance ≤ l; and adequate hematologic, renal, and hepatic function and provide written informed consent were eligible to enroll. [redacted]

EVALUATION CRITERIA:

Safety Measurements

During the safety lead-in, patients were assessed on a weekly basis for the first 35 days of study treatment with ridaforolimus and bicalutamide for the occurrence of dose limiting toxicities (DLTs). The safety measurements included physical examination, assessment of vital signs, weight, ECOG performance status, complete blood counts, serum chemistry, serum lipids, chest x-rays, and assessment and recording of clinical and laboratory adverse events. Adverse events were graded according to NCI-CTCAE v3.0.

Efficacy Measurements

Efficacy measurements included the PSA decline within 12 weeks (a surrogate measurement of overall survival efficacy in prostate cancer therapy trials), PSA response rate, PFS, time to PSA progression and overall survival. The confirmation of response was to be evaluated by physical examination, radiological measurement, and performance status. Response and progression were to be evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) definition.

Pharmacokinetic Measurements

During the safety lead-in, the pharmacokinetic profile of ridaforolimus was assessed with and without bicalutamide to assess for a potential drug-drug interaction. Patients who were eligible for treatment received a single oral dose of ridaforolimus at the starting dose of 30 mg on Day 1, and blood was drawn to evaluate ridaforolimus pharmacokinetics at the following times relative to ridaforolimus dosing: pre-dose, 30 minutes, 1, 2, 4, 6-8, and 24 hours post-dose. After the 24 hour post-dose PK sample had been drawn, patients were treated with bicalutamide daily from Day 2 to Day 7. From Day 8, patients began to receive the combination of bicalutamide and ridaforolimus, and blood was drawn for ridaforolimus pharmacokinetics at pre-dose and 30 minutes, 1, 2, 4, 6-8, and 24 hours post-dose relative to ridaforolimus administration on Day 8. In addition, a trough PK sample was obtained before ridaforolimus administration on Day 15 and Day 22.

[redacted]

STATISTICAL PLANNING AND ANALYSIS:

Summary statistics and analyses were provided by dose level cohort and where appropriate, overall. All patients receiving at least one dose of ridaforolimus and/or bicalutamide combination were considered evaluable for safety.

The primary analysis of the primary endpoint was to be performed using stratified Miettinen and Nurminen method to determine whether treatment with ridaforolimus plus bicalutamide would increase the fraction of patients with a 30% decline in the PSA within 12 weeks relative to placebo plus bicalutamide. The decline would be determined by the lowest post-baseline PSA value within the first 12 weeks. The analysis was not achieved due to early study termination.

The adverse event incidence rates and the frequency of study drug-related adverse events, categorized by severity grades are described. Listings of laboratory test results collected at baseline and during the study were generated. Clinically significant changes in laboratory test results from baseline are presented by grade.

An interim analysis for safety was planned by the SPONSOR after 10 evaluable patients had completed the DLT observation period at the 30 mg dose level. The decision to proceed to randomized enrollment was to be made by the SPONSOR with the supporting data.

[redacted]

RESULTS:

Pharmacokinetics

Analysis of pharmacokinetic (PK) data did not indicate a clinically relevant drug-drug interaction of ridaforolimus with bicalutamide.

During the safety lead-in, ridaforolimus pharmacokinetics was assessed with and without bicalutamide. In the pharmacokinetic evaluation the single-dose PK profiles of ridaforolimus after administration of a single oral dose of 30 mg were compared between Day 1 (ridaforolimus only) and Day 8 (ridaforolimus with co-administration of bicalutamide).

Average blood concentration profiles following a single 30 mg oral dose of ridaforolimus alone or following concomitant administration of multiple doses of 50 mg bicalutamide with a single 30 mg dose of ridaforolimus showed high similarity (Figure 2-1). There is evidence of some degree of carry-over of ridaforolimus blood levels from Day 1 to Day 8 pre-dose, which is due to the limited duration of washout between Day 1 and Day 8. The mean blood ridaforolimus pre-dose Day 8 level was 2.81ng/mL (range: 0.55-13.2 ng/mL). The impact of this carry-over effect was very limited and no correction was done for the PK evaluation, because the pre-dose Day 8 levels were generally < 10% of Day 8 Cmax levels.

[redacted]

[redacted]

Although this study was not powered to detect small differences in ridaforolimus exposure with or without co-administration of bicalutamide, the PK results indicate that the impact of bicalutamide on AUC0-24 and Cmax of ridaforolimus was small and not clinically relevant.

Safety

Prior to the protocol amendment, a safety interim analysis was performed after the first 11 patients were randomized and treated (4 treated with ridaforolimus and bicalutamide and 7 treated with placebo and bicalutamide). All 4 patients treated with ridaforolimus and bicalutamide experienced Grade 3 mucositis or stomatitis. Based on the results of the safety interim analysis conducted using a standing internal data monitoring committee of the Sponsor, a protocol amendment was issued. The amendment reduced dose of ridaforolimus from 40mg to 30mg, and 11 additional patients were treated with the combination of ridaforolimus and bicalutamide in an open label single arm safety lead-in to further assess the safety profile of the combo.

A total of 22 patients enrolled and were treated in the trial, 11 in the first safety lead-in and 11 in the second safety lead-in. A total of 15 patients received ridaforolimus plus bicalutimide, 4 patients at the 40 mg ridaforolimus dose level and 11 at the 30 mg ridaforolimus dose level. Seven (7) patients received placebo plus bicalutimide. Out of these 22 patients, majority of the patients were white (86.4%). The age ranged from 58.0 -82.0. Majority of the patients (9 ridaforolimus plus bicalutimide in treatment group and 5 in placebo plus bicalutimide group) had a stage IV prostate cancer. [redacted]

In the ridaforolimus plus bicalutimide treatment group, all 15 patients had at least one adverse event (AE). A total of 93.3% patients had at least one AE considered by the investigator to be related to study medication. A total of 8 patients (53.3%) had serious adverse events (SAEs) and 4 patients (26.7%) had serious drug-related AEs [redacted]

[redacted]

[redacted]

The most common AEs in ≥ 20% of patients who received ridaforolimus plus bicalutimide were, fatigue (73.3%), diarrhoea (53.3%), mucosal inflammation (46.7%), decreased appetite (46.7%), hypercholesterolaemia (40.0%), oedema peripheral (40.0%), stomatitis (40.0%), rash (40.0%), nausea (33.3%), dysgeusia (33.3%), pneumonitis (33.3%), hypertriglyceridaemia (26.7%), garma-glutany transferase increased (20.%), white blood count decreased (20.0%), hyperglacemia (20.0%), back pain (20.0%), pain in extremity (20.0%), headache (20.0%) and dyspnoea (20.0%) [redacted]

Treatment-related AEs occurring in ≥ 20% of patients who received ridaforolimus plus bicalutimide were fatigue (53.3%), mucosal inflammation (46.7%), stomatitis (40.0%), hypercholesterolaemia (40.0%), rash (40.0%), decreased appetite (33.3%), dysgeusia (33.3%), hypertriglyceridaemia (26.7%), pneumonitis (33.3%), epistaxis (20.0%), and diarrhea (20.0%). Most drug-related AEs were Grade 1 or Grade 2. There were three cases of Grade 3 mucosal inflammation, one case of Grade 3 stomatitis, one case of Grade 3 pneumonitis and one case of Grade 4 pneumonitis [redacted]

Three (3) DLTs were reported in the 11 patients in the second safety lead-in at 30 mg dose level of ridaforolimus [redacted] Dose-limiting Grade 2 stomatitis leading to dose reduction was reported in 2 patients and Grade 3 hyperglycemia lasting > 3 days was reported in 1 patient. Based on the results of the safety lead-in, the study met the predefined termination requirement per protocol. The decision was made by the Sponsor in July 2010, and the study was closed to new subject enrollment but allowed patients in the study to continue on the study if the investigator believed they were deriving clinical benefit, until they met study discontinuation criteria.

A total of 8 of the 15 patients (53.3%) who received the combination of ridaforolimus plus bicalutimide experienced SAEs. Four (4) of these patients had SAEs that the investigator reported as at least possibly related to study medication [redacted] Two (2) patients had treatment-related Grade 3 SAEs of mucosal inflammation which resulted in discontinuation of study drug. These patients eventually recovered. One (1) patient experienced treatment-related SAEs of dehydration and pneumonitis which later resolved. Another patient experienced treatment-related SAEs of hyperglycemia and pneumonitis resulting in discontinuation of study drug.

Nine (9) patients discontinued the study as a result of AEs, 7 of which received the combination of ridaforolimus plus bicalutimide. Among 7 patients who received ridaforolimus plus bicalutimide, 5 patients discontinued the study due to treatment related AEs: 2 with mucosal inflammation (both Grade 3), 1 with pneumonitis (Grade 2), 1 with hyperglycaemia (Grade 3), and 1 with hypertriglyceridemia (Grade 2) [redacted]

Note: Due to a discrepancy of data entry at Inform, the Disposition table indicates that there are eight (8) patients who discontinued the study as a result of AEs, and 6 of which received ridaforolimus and bicalutimide combination therapy.

One treatment-emergent death (within 30 days of taking study drug) has been reported: 1 patient in the placebo plus bicalutimide group died on 14-Sep-2009 due to natural causes. This patient received their final dose of ridaforolimus on 24-Jul-2009. The investigator considered the death not related to study drug [redacted]

Efficacy

Since the trial did not start the randomized enrollment portion, only an exploratory analysis of PSA decline was performed on the 22 patients who enrolled in the trial as safety lead-in patients. Four (4) out of 15 patients (26.7%) who enrolled into the ridaforolimus plus bicalutimide group exhibited 30% PSA decline within 12 weeks of the treatment, all these 4 patients were in ridaforolimus 30 mg plus bicalutamide group.

Summary of 30% PSA Decline within 12 Weeks
All Patients as Treated Population

	MK-8669 30mg and bicalutamide		MK-8669 40mg and bicalutamide		MK-8669 total (30mg and 40mg combined)		Placebo and bicalutamide	
	n	%	n	%	n	%	n	%
Patients in Population	11		4		15		7	
30% PSA decline within 12 weeks[†]	4	36.4	0	0.0	4	26.7	0	0.0

[†] Defined as a ≥30% PSA decline from baseline within the first 12 weeks of study treatment. Decline is determined by the lowest post-baseline PSA value within the first 12 weeks. Patients without first 12 weeks PSA measurements are treated as non-responders.

CONCLUSIONS:

Ridaforolimus 30 or 40 mg q.d. x 5 days/wk combined with bicalutamide 50mg q.d was not tolerable in prostate cancer patients.

There is no indication of a clinically relevant drug-drug interaction between ridaforolimus and bicalutamide.

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* We would like to acknowledge [redacted] for the conduct of the PK evaluation for this study.