2 Synopsis

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC. MK-8669 ECT, enteric-coated granules and uncoated granules Sarcoma	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Single Dose Biocomparison Study to Assess Two Pediatric Formulations of MK-8669 to the Provisional Market Formulation in Healthy Subjects #060

INVESTIGATOR/STUDY CENTER(S): ***PPD***

PUBLICATION(S): None

PRIMARY THERAPY PERIOD: 02-Oct-2011 through 15-Jan-2012. The frozen file date was 09-Mar-2012.

CLINICAL PHASE: I

DURATION OF TREATMENT:
A single oral dose of MK-8669 (ridaforolimus) was administered on Day 1 of 4 treatment periods. There was at least a 2 week washout between treatment doses, followed by a follow-up visit approximately 14 days after the last dose of study drug. The total duration of the study was to be approximately 10 weeks, including prestudy and poststudy evaluations.

OBJECTIVE(S):
Primary:
1. To evaluate the whole blood pharmacokinetics and comparative bioavailability ($AUC_{0-\infty}$, C_{max}, T_{max}, and apparent $t_{1/2}$) of 2 new granule formulations of ridaforolimus compared to the provisional market 10 mg enteric-coated tablet (ECT) in healthy subjects.
2. To compare the whole blood pharmacokinetic data ($AUC_{0-\infty}$, C_{max}, T_{max}, and apparent $t_{½}$) following single 40 mg ridaforolimus enteric-coated and uncoated granules administration in the fed state with a high-fat breakfast and fasted states in healthy young male subjects.

HYPOTHESIS(ES):
Primary: At least 1 of the new formulations is comparable in pharmacokinetic to the ECT (i.e., the true geometric mean ratio [GMR] for the $AUC_{0-\infty}$ is contained within [0.70, 1.43]).
ESTIMATION: The effect of administration of a single 40 mg ridaforolimus enteric-coated and uncoated granules dose in the fed state with a high-fat breakfast and fasted state on blood $AUC_{0-\infty}$ and C_{max} of ridaforolimus will be estimated.

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STUDY DESIGN: This was an open-label, randomized, 4-period, partially fixed-sequence, crossover study to compare the pharmacokinetic profile of the provisional market formulation ECT to 2 potential ridaforolimus granule formulations [enteric-coated granules and uncoated granules]. The effect of a high-fat meal on 40 mg ridaforolimus pharmacokinetics of both enteric-coated and uncoated granules was also evaluated. Twenty one (21) healthy male subjects were enrolled in this study to ensure 18 completed. In Periods 1 to 3, subjects were randomized to receive 1 of 3 oral treatments (A, B, and C) in the fasted state. Treatment A: 40 mg ridaforolimus ECT (4 x 10 mg ECT); Treatment B: 40 mg ridaforolimus enteric-coated granules; Treatment C: 40 mg ridaforolimus uncoated granules. In Period 4, subjects were to be administered either Treatment B (40 mg enteric-coated granules) following a high-fat meal or Treatment C (40 mg uncoated granules) following a high-fat meal. A period may have been repeated, if deemed necessary by the Sponsor. In fact, a total of 7 subjects that were designated to receive a single 40 mg dose of enteric-coated granules or uncoated granules with a high-fat breakfast, actually received a light meal. These subjects underwent another study period (Period 4A) in which the treatment was repeated with a high-fat breakfast. Each period was 14 days in duration; single-dose administration was followed by at least a 2 week washout period between doses. Blood samples for whole blood ridaforolimus pharmacokinetics were collected at selected time points. Safety and tolerability were monitored throughout the study.

SUBJECT DISPOSITION:

ENTERED: Total	21
Male (age range)	21 (19 to 51 yrs)
COMPLETED:	17
DISCONTINUED: Total	4
Clinical adverse experience	0
Laboratory adverse experience	0
Other	4[†]

[†]One (1) subject did not return for dosing in Period 3 and 3 subjects withdrew from the study due to family emergencies.

DOSAGE/FORMULATION NOS.: The 40 mg dose of ridaforolimus was administered as 4 x 10 mg ECT (Treatment A), 40 mg enteric-coated granules (Treatment B) and 40 mg ridaforolimus uncoated granules (Treatment C). Treatments B and C were provided in glass vials, each vial containing 500 mg powder blend (10 mg ridaforolimus strength) and 5.0 mL of potable water that was added. The vial was recapped and shaken vigorously for 15 seconds. The subjects drank the entirety of the suspended dose directly from the glass vial. Each subject was given four (4) 10 mg vials.

Drug	Potency	Formulation No.	Dosage Form	Control No.
MK-8669	10 mg	CCI		
MK-8669	10 mg			
MK-8669	10 mg			

DIAGNOSIS/INCLUSION CRITERIA:
Healthy male subjects between 18 and 55 years of age, with a body mass index (BMI) ≥ 20 and ≤ 32 kg/m^2.

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EVALUATION CRITERIA:

PHARMACOKINETICS:

Whole blood samples for determination of ridaforolimus concentrations were collected at predose and specified time points over 168 hours following the ridaforolimus dose in each treatment period. The whole blood pharmacokinetic parameters ($AUC_{0-\infty}$, C_{max}, T_{max}, the apparent terminal $t_{½}$, AUC_{0-last}, and T_{last}) of ridaforolimus were calculated in Periods 1, 2, and 3 after administration of a single 40 mg dose of ridaforolimus ECT, ridaforolimus enteric-coated granules or ridaforolimus uncoated granules under fasted conditions. The whole blood pharmacokinetic parameters ($AUC_{0-\infty}$, C_{max}, T_{max}, the apparent terminal $t_{½}$, AUC_{0-last}, and T_{last}) of ridaforolimus were also calculated in Periods 4 and a repeated Period 4 (Period 4A) after administration of a single 40 mg dose of ridaforolimus enteric-coated granules or ridaforolimus uncoated granules following a high-fat breakfast or light meal. The presentation and statistical analyses of AUC_{0-last} and T_{last} supporting parameters were added prior to the final analyses. Additionally, a blood sample for future biomedical research was collected predose in 1 period only.

EVALUATION CRITERIA (continued):

SAFETY: Physical examinations and laboratory safety tests were obtained at prestudy, prior to each dose, 24 hours post each dose, and at poststudy. Electrocardiograms (ECGs) were obtained at prestudy and poststudy. Orthostatic vital sign measurements (blood pressure and heart rate) were obtained at prestudy and poststudy and semirecumbent vital signs (blood pressure and heart rate) were measured predose and at selected postdose time points in each period. Subjects were monitored for adverse experiences throughout the study.

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STATISTICAL PLANNING AND ANALYSIS:

METHODS:

For the primary hypothesis, all confidence intervals (CI) constructed for pharmacokinetic parameters were based on the least-squares means (LS means) and variance components arising from a linear mixed-effects model appropriate for a 3-period, randomized, crossover study with fixed effects for treatment and period. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between different treatment measurements within the same subject. Subjects' whole blood $AUC_{0-\infty}$ values for each treatment were natural-log (ln) transformed prior to analysis. A stepwise approach was used to address the primary hypothesis, that at least 1 of the new formulations was comparable to the ECT. This stepwise approach was supported by preclinical testing of both formulations which suggested that the geometric mean ratio (GMR) for the $AUC_{0-\infty}$ of uncoated granules compared to ECT would not be contained within [0.70, 1.43] if the GMR for the $AUC_{0-\infty}$ of enteric-coated granules compared to ECT is not contained within [0.70, 1.43]. To complete the first step of this test, the 90% CI for whole blood $AUC_{0-\infty}$ GMR (enteric-coated granules/ECT) was obtained from the above linear mixed-effects model and was compared to the pre-specified bounds of [0.70, 1.43]. If the 90% CI for the GMR (enteric-coated granules/ECT) fell within the bounds, testing was continued with the uncoated granules versus ECT. If the 90% CI for the GMR (enteric-coated granules/ECT) did not fall within the bounds, testing with the uncoated granules versus ECT was not to be continued. However, for completeness, both sets of GMR and 90% CIs were provided. The hypothesis was supported if the 90% CI for the GMR was contained within [0.70, 1.43] for at least 1 formulation.

Additionally, whole blood C_{max} values were analyzed in a similar fashion for supportive purposes.

For the food effect, secondary estimation, subjects' whole blood $AUC_{0-\infty}$ and C_{max} values following administration of a single 40 mg dose of ridaforolimus enteric-coated granules administered in the fed and fasted states were ln-transformed and analyzed using a linear mixed-effects model. The model contained a fixed effect for fed - fasted states, and a random effect for subject. To estimate the effect of food on the whole blood pharmacokinetics of the 40 mg ridaforolimus enteric-coated granules, the LS means and corresponding 90% CIs for the differences in ln-transformed $AUC_{0-\infty}$ and C_{max} (Fed - Fasted) were calculated from the model using the mean square error and referencing a t-distribution. The mean differences on the log-scale and confidence limits were exponentiated to obtain the $AUC_{0-\infty}$ and C_{max} GMRs and 90% CIs (Fed / Fasted).

The effect of food on the whole blood $AUC_{0-\infty}$ and C_{max} following administration of the 40 mg ridaforolimus uncoated granules, was analyzed in a similar fashion.

The other pharmacokinetic parameters (T_{max}, apparent terminal $t_{½}$, AUC_{0-last}, and T_{last}) were summarized using descriptive statistics.

As an exploratory analysis, summary statistics were presented for AN 0015 through AN 0021 by treatment for whole blood pharmacokinetic parameters of ridaforolimus calculated in Periods 4 and 4A after administration of a single 40 mg dose of ridaforolimus enteric-coated granules or ridaforolimus uncoated granules following a light meal and a high-fat breakfast, respectively.

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RESULTS:

PHARMACOKINETICS:

The table below presents the pharmacokinetic results of ridaforolimus following the administration of a single dose of 40 mg ridaforolimus as ECT (Treatment A), enteric-coated granules (Treatment B) and uncoated granules (Treatment C) to healthy adult male subjects under fasting conditions. $AUC_{0-\infty}$ was 34% lower with enteric-coated granules (Treatment B) compared to the marketed ECT formulation (Treatment A) (GMR [90% CI] of 0.66 [0.48, 0.90]). The 90% CI for $AUC_{0-\infty}$ GMR for the enteric-coated granule/ECT comparison did not fall within the pre-specified bounds of [0.70, 1.43] and therefore the primary hypothesis was not supported. $AUC_{0-\infty}$ was 13% lower with uncoated granules (Treatment C) compared to the marketed ECT formulation (Treatment A) (GMR [90% CI] of 0.87 [0.73, 1.04]). Although it was not part of the formal hypothesis testing, the 90% CI for $AUC_{0-\infty}$ GMR for the uncoated granule/ECT comparison fell within the pre-specified bounds of [0.70, 1.43]. C_{max} was 3% lower with enteric-coated granules (Treatment B) compared to the marketed ECT formulation (Treatment A) (GMR [90% CI] of 0.97 [0.70 – 1.35]). However, C_{max} was 19% higher with uncoated granules (Treatment C) compared to the marketed ECT formulation (Treatment A) (GMR [90% CI] of 1.19 [0.99, 1.43]). Based on the mean whole blood concentration-time profiles of the 3 formulations of ridaforolimus, both granule formulations demonstrated earlier absorption (median T_{max} = 2.00 hr for both granule formulations) compared to the marketed ECT formulation (median T_{max} = 6.00 hr).

Summary of Whole Blood Pharmacokinetics of Ridaforolimus Following the Administration of a Single Dose of 40 mg Ridaforolimus as ECT (Treatment A, Fasted), Enteric-Coated Granules (Treatment B, Fasted), and Uncoated Granules (Treatment C, Fasted) in Healthy Adult Male Subjects

	ECT, Fasted			Enteric-Coated Granules, Fasted			Uncoated Granules, Fasted			Enteric-Coated Granules, Fasted / ECT, Fasted			Uncoated Granules, Fasted / ECT, Fasted		
Pharmacokinetic Parameter	**N**	**GM**	**95% CI**	**N**	**GM**	**95% CI**	**N**	**GM**	**95% CI**	**GMR**	**90% CI**	**Pseudo Within Subject %CV†**	**GMR**	**90% CI**	**Pseudo Within Subject %CV†**
$AUC_{0-□}$‡ (ng•hr/mL)	19	2387 05	(1850 18, 3079 70)	19	1571 17	(1222 71, 2018 94)	18¶	2075 12	(1857 33, 2318 45)	0 66	(0 48, 0 90)	55 521	0 87	(0 73, 1 04)	31 746
C_{max}‡ (ng/mL)	19	148 51	(114 87, 191 99)	19	144 72	(110 06, 190 31)	19	176 67	(163 25, 191 19)	0 97	(0 70, 1 35)	58 104	1 19	(0 99, 1 43)	32 839
T_{max}§ (hr)	19	6 00	(3 00, 10 00)	19	2 00	(1 00, 6 00)	19	2 00	(1 00, 3 00)						
Apparent terminal $t_{½}$‖ (hr)	19	64 0	7 47	19	66 4	7 75	18¶	65 3	5 67						

† Pseudo Within-Subject %CV = 100*sqrt[(σ 2 A + σ 2 B - 2 σ AB)/2], where σ 2 A and σ 2 B are the estimated variances on the log scale for the two treatment groups, and σ AB is the corresponding estimated covariance, each obtained from the linear mixed effects model
Pseudo Within-Subject %CV was also estimated from the estimated (co)variances of σ 2 A, σ 2 C, and 2σ AC
‡ Back-transformed least squares mean and confidence interval from mixed effects model performed on natural log-transformed values
§ Median (min, max) reported for T_{max}
‖ Harmonic mean, jack-knife SD reported for apparent terminal $t_{½}$
¶ ***PPD*** did not complete Period 1, Treatment C and was excluded from statistical analysis for apparent terminal $t_{½}$ and $AUC_{0-□}$

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RESULTS (continued):

PHARMACOKINETICS (continued):

The tables below summarize the pharmacokinetics of ridaforolimus following the administration of a single dose of 40 mg ridaforolimus as enteric-coated granules (Treatment B) and uncoated granules (Treatment C) to healthy adult male subjects in the fed state following a high-fat breakfast and in the fasted state. $AUC_{0-\infty}$ was 30% lower with enteric-coated granules (Treatment B) (GMR [90% CI] of 0.70 [0.52 - 0.93]) and 25% lower with the uncoated granules (Treatment C) (GMR [90% CI] of 0.75 [0.68 - 0.84]) after administration with a high-fat breakfast compared to administration in a fasted state. Similarly, C_{max} was 56% lower with enteric-coated granules (Treatment B) (GMR [90% CI] of 0.44 [0.31 - 0.64]) and 47% lower with the uncoated granules (Treatment C) (GMR [90% CI] of 0.53 [0.44 - 0.62]) after administration with a high-fat breakfast compared to administration in a fasted state. Median T_{max} was delayed for both granule formulations after administration of a high-fat meal compared to the administration in a fasted state (median T_{max} = 4.00 hr after high-fat breakfast versus median T_{max} = 2.00 hr in a fasted state).

Summary of Whole Blood Pharmacokinetics of Ridaforolimus Following the Administration of a Single 40 mg Dose of Ridaforolimus as Enteric-Coated Granules (Treatment B) Under Fasted and Fed (High-Fat Breakfast) States in Healthy Adult Male Subjects

	Enteric-Coated Granules, Fasted			Enteric-Coated Granules, Fed			Enteric-Coated Granules, Fed / Fasted		
Pharmacokinetic Parameter	**N**	**GM**	**95% CI**	**N**	**GM**	**95% CI**	**GMR**	**90% CI**	**rMSE†**
$AUC_{0-\infty}$‡ (ng•hr/mL)	7	1949.56	(1505.06, 2525.34)	7	1359.27	(1049.36, 1760.71)	0.70	(0.52, 0.93)	0.274
C_{max}‡ (ng/mL)	7	189.94	(130.14, 277.22)	7	83.90	(57.48, 122.45)	0.44	(0.31, 0.64)	0.353
T_{max}§ (hr)	7	2.00	(1.00, 3.00)	7	4.00	(3.00, 6.00)			
Apparent terminal $t_{½}$‖ (hr)	7	66.6	5.47	7	74.4	11.8			

† rMSE: Square root of conditional mean squared error (residual error) from the linear mixed-effects model.
rMSE*100% approximates the within-subject %CV on the raw scale.
‡ Back-transformed least squares mean and confidence interval from mixed-effects model performed on natural log-transformed values.
§ Median (min, max) reported for T_{max}.
‖ Harmonic mean, jack-knife SD reported for apparent terminal $t_{½}$.

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RESULTS (continued):
PHARMACOKINETICS (continued):

Summary of Whole Blood Pharmacokinetics of Ridaforolimus Following the Administration of a Single 40 mg Dose of Ridaforolimus as Uncoated Granules (Treatment C) Under Fasted and Fed (High-Fat Breakfast) States in Healthy Adult Male Subjects

	Uncoated Granules, Fasted			Uncoated Granules, Fed			Uncoated Granules, Fed / Fasted		
Pharmacokinetic Parameter	**N**	**GM**	**95% CI**	**N**	**GM**	**95% CI**	**GMR**	**90% CI**	**rMSE†**
$AUC_{0-\infty}$‡ (ng•hr/mL)	10	2211.29	(1814.93, 2694.21)	10	1664.81	(1366.40, 2028.38)	0.75	(0.68, 0.84)	0.129
C_{max} ‡ (ng/mL)	10	178.16	(146.12, 217.23)	10	93.55	(76.73, 114.07)	0.53	(0.44, 0.62)	0.204
T_{max} § (hr)	10	2.00	(1.00, 2.05)	10	4.00	(3.00, 6.00)			
Apparent terminal $t_{½}$ ‖ (hr)	10	65.9	6.42	10	66.1	7.79			

† rMSE: Square root of conditional mean squared error (residual error) from the linear mixed-effects model.
rMSE*100% approximates the within-subject %CV on the raw scale.
‡ Back-transformed least squares mean and confidence interval from mixed-effects model performed on natural log-transformed values.
§ Median (min, max) reported for T_{max}.
‖ Harmonic mean, jack-knife SD reported for apparent terminal $t_{½}$.

As an exploratory analysis, the summary statistics were presented for those subjects that received a single 40 mg dose of ridaforolimus enteric coated granules or uncoated granules following a light meal. AUC GM of the ratios comparing the light meal to the fasting condition was 0.67 for the enteric coated granules and 0.72 for the uncoated granules. Although this analysis was based on only 2 and 4 subjects, respectively, the food effect appeared similar between the meal types (high-fat breakfast and light meal).

SAFETY:
Ridaforolimus ECT, enteric-coated granules, and uncoated granules were generally well tolerated in the healthy male subjects in this study following administration in both fed and fasted states. No serious clinical adverse experiences were reported and no subject discontinued because of an adverse experience. Nine (9) subjects reported a total of 27 clinical adverse experiences, 8 of which were considered possibly drug-related by the Investigator. Five (5) of the 21 subjects reported the most common adverse experience, headache, with the majority reporting the event following treatment with ECT (Treatment A) in the fasted state. All remaining adverse experiences were reported by 2 of the 21 subjects or less. All of the adverse experiences were considered mild in intensity with the exception of 1 episode of moderate tongue ulceration following treatment with enteric-coated granules in the fasted state, and was also considered possibly related to the study treatment. All adverse experiences resolved. There was no safety concerns observed in the safety laboratory, vital signs, or ECG safety assessments.

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CONCLUSIONS:

1. The ridaforolimus $AUC_{0-\infty}$ value is 34% lower when administered as 40 mg enteric-coated granules and 13% lower when administered as 40 mg uncoated granules compared to the ECT. The primary hypothesis was not supported since the 90% CI for $AUC_{0-\infty}$ GMR for the enteric coated granule/ECT comparison (0.66 [0.48 – 0.90]) did not fall within the pre-specified bounds of [0.70, 1.43]. Although not part of the formal hypothesis testing, the 90% CI for $AUC_{0-\infty}$ GMR for the uncoated granule/ECT comparison (0.87 [0.73 – 1.04]) was within the pre-specified bounds of [0.70, 1.43).
2. The ridaforolimus C_{max} value is 3% lower when administered as 40 mg enteric-coated granules and 19% higher when administered as 40 mg uncoated granules compared to the ECT. The C_{max} GMRs and corresponding 90% CIs for both new formulations compared to the marketed formulation were 0.97 [0.70 – 1.35] (enteric-coated granules/ECT) and 1.19 [0.99 – 1.43] (uncoated granules/ECT).
3. A high-fat meal delayed absorption and overall exposure of the 2 granule formulations compared to fasted state. For the enteric-coated granule formulation, median T_{max} is delayed by approximately 2 hours and $AUC_{0-\infty}$ and C_{max} are 30% and 56% lower, respectively, after administration with a high-fat breakfast compared to administration in a fasted state. Similarly, for the uncoated granule formulation, median T_{max} is delayed by approximately 2 hours and $AUC_{0-\infty}$ and C_{max} are 25% and 47% lower, respectively, after administration with a high-fat breakfast compared to administration in a fasted state.
4. Overall in terms of GMRs and variability under fasted and fed conditions, the uncoated granule formulation performs better than the enteric-coated granule formulation. Furthermore, the uncoated granule formulation exhibits comparable bioavailability and more consistent exposure compared to the ECT formulation.
5. Single doses of 40 mg ridaforolimus ECT, enteric-coated granules, and uncoated granules administered in the fasted and fed state are generally well tolerated by healthy male subjects.