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.

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2. Synopsis

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC. MK-8669 Ridaforolimus (formerly deforolimus), Tablet Sarcoma	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Pivotal Trial to Determine the Efficacy and Safety of [redacted] when Administered as Maintenance Therapy to Patients with Metastatic Soft-Tissue or Bone Sarcomas #011

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter, 23 countries and 186 sites worldwide including the US, Europe, and Asia

PUBLICATION(S): n/a

PRIMARY THERAPY PERIOD: 23-Oct-2007 until the 25-Oct-2010 data cut-off, with patients still ongoing.

CLINICAL PHASE: III

DURATION OF TREATMENT: Patients continued on study until disease progression or unresolved clinically significant study treatment related toxicity

- **OBJECTIVE(S):** Primary Objective: To compare progression-free survival (PFS) of patients who have achieved complete response (CR), partial response (PR) or stable disease (SD) following 1st, 2nd or 3rd line chemotherapy when treated with ridaforolimus versus placebo.

Secondary Objectives:

- To compare the overall survival (OS) of patients when treated with ridaforolimus versus placebo.
- To compare the best target lesion response of patients receiving ridaforolimus versus placebo.
- To assess changes in cancer-related symptoms in those patients treated with ridaforolimus compared to those treated with placebo.
- To determine the safety and tolerability of ridaforolimus

STUDY DESIGN: The study was a multicenter, randomized, Phase III placebo-controlled, double-blind trial

SUBJECT/PATIENT DISPOSITION:

	Ridaforolimus	Placebo	Overall
SCREENING FAILURES:			140
RANDOMIZED:	347	364	711
Male (14-92)	158	156	314
Female (14-85)	189	208	397
DISCONTINUED:	318	331	649
Clinical adverse experience	50	9	59
Progressive Disease (includes clinical progressive disease)	231	309	540
Withdrew Consent	13	4	17
Other	24	9	33

DOSAGE/FORMULATION NOS.: Patients took four tablets once daily of ridaforolimus (10 mg each) or matching placebo, 5 days per week continuously, without interruption (40 mg qdx5/week of ridaforolimus). Each enteric-coated tablet (ECT) contained 10 mg of ridaforolimus active ingredient. Other ingredients were lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate, and butylated hydroxytoluene (BHT), copovidone, methacrylic acid copolymer, triethyl citrate, and talc.

Drug	Potency	Dosage Form	Formulation No. (Mfg Lot #)	Control No. (package batch No.)
Ridaforolimus	10 mg	ECT	[redacted]	
Placebo	10 mg	ECT		

ECT= enteric coated tablet
Mfg = manufacturing
No = number
mg = milligram

DIAGNOSIS/INCLUSION CRITERIA: Male or female patients aged 13 years or older with a documented histological diagnosis of soft-tissue or bone sarcoma that has metastasized and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Ongoing CR, PR, or SD per Response Evaluation Criteria in Solid Tumors (RECIST) after a minimum of any 1st, 2nd, or 3rd line prior cytotoxic chemotherapy, where randomization is within or equal to 12 weeks since previous chemotherapy.

EVALUATION CRITERIA:

Efficacy: The assessment of tumor response was based on the evaluations performed every 8 weeks after baseline using RECIST criteria. Evidence of progressive disease (PD) may have been obtained at these scheduled visits, or obtained from disease evaluations conducted between scheduled visits, prompted by symptoms. An adequate assessment was defined as one in which sufficiently clear radiographic images were obtained so that changes in target lesions may be observed, or the presence of new lesions determined. The Independent Review Committee (IRC) assessment of disease response was used for the analysis of PFS and best target lesion response. The investigator assessment of disease response was used in secondary, supportive analyses for PFS.

Safety: Safety and tolerability were assessed by a clinical and statistical review of adverse events (AEs) and laboratory values. AEs were graded according to the NCI Common Terminology Criteria for Adverse Events, Version 3.0. All AEs are reported regardless of relation to study treatment.

STATISTICAL PLANNING AND ANALYSIS:

Approximately 650 patients were to be randomized to study treatment in a 1:1 ratio. It was projected that approximately 516 events (among the 650 patients randomized) would need to be observed in order to provide approximately 90% power to detect a 25% effect size based on a 0.75 hazard ratio (HR). A 25% effect size implied extending the median PFS from 6 months to 8 months (or from 9 months to 12 months). [redacted]

The overall alpha for the primary endpoint PFS was to be less than or equal to 0.025 for a one-sided test. The proportion of patients lost to follow up was assumed to be less than 10%. The power projection was based on the assumption that the hazard rates were proportional.

RESULTS:

Safety

Exposure analysis showed that patients assigned to ridaforolimus were able to tolerate treatment and on average received 74% of the prescribed ridaforolimus dose. Moreover, the ridaforolimus treatment group median time to discontinuation was longer than placebo, 15.7 weeks compared to 14.7 weeks, respectively. Overall, the treatment groups are comparable, though more ridaforolimus treatment group patients discontinued due to an AE, and more placebo patients discontinued due to PD.

The most common AEs, occurring in at least 25% of patients in the ridaforolimus treatment group, were stomatitis (52.2%), fatigue (35.6%), thrombocytopenia (33.5%), diarrhea (31.5%), cough (30.6%), rash (28.3%), anemia (27.7%), nausea (27.1%), hypertriglyceridaemia (27.1%), headache (27.1%), and decreased appetite (26.8%).

In this cancer population, 93.6% of patients in the placebo treatment group experienced an AE. The AEs for which the ridaforolimus treatment group showed more than a 20% difference over the placebo treatment group were in order or greatest difference; stomatitis (difference of 38.3%), thrombocytopenia (difference of 29.9%), and rash (difference of 22.2%).Severe (Grade 3 or above) AEs with the greatest difference between treatment groups were thrombocytopenia (difference of 9.1%), stomatitis (difference of 7.6%), and hyperglycaemia (difference of 6.4%).

Even in patients not receiving ridaforolimus approximately 2 in 3 experienced a treatment-related AE. The treatment-related AEs in which the ridaforolimus treatment group showed more than a 20% difference over the placebo treatment group were stomatitis (difference of 37.1%) and thrombocytopenia (difference of 30.1%).

The most common serious AEs in the ridaforolimus treatment group by System Organ Class (SOC)

were respiratory/thoracic disorders at 7.6%, followed by gastrointestinal (GI) disorders (6.7%), and infections (6.4%). The single most reported serious adverse event (SAE) in the ridaforolimus treatment group was pneumonia with 2.3% of patients having reported events versus 0.6% of patients in the placebo treatment group.

The 5 treatment-related SAEs resulting in death were all in the ridaforolimus treatment group and were GI haemorrhage (2), pneumonitis (1), performance status decreased (1), and general physical health deterioration (1). Deaths in the placebo and ridaforolimus treatment groups were generally comparable across SOCs except for the respiratory/thoracic disorders SOC deaths. There were a total of 6 respiratory/thoracic disorders SOC deaths in the ridaforolimus treatment group versus 0 for the placebo treatment group. All 6 patients reported lung metastasis at study entry. One (1) of these deaths (pneumonitis) was considered related to study medication by the investigator.

Stomatitis (2.3%) emerged as the most common reason leading to study medication discontinuation in this study.

An AE summary table and a count table of AEs reported in greater than 10% of patients in any treatment group is provided below.

Summary of Adverse Events (Safety Population)

	Ridaforolimus (N=343)	Placebo (N=359)	Difference in Percentages
	Patients. n (%)	Patients. n (%)	Ridaforolimus versus Placebo % (95% CI)
Any Treatment-Emergent Adverse Event	343 (100.0)	336 (93.6)	6.4 (4.3, 9.4)
Severe (Grade ≥ 3) Treatment-Emergent AE	220 (64.1)	92 (25.6)	38.5 (31.5, 45.1)
Serious Treatment-Emergent AE	124 (36.2)	77 (21.4)	14.7 (8.0, 21.3)
Treatment-Emergent AE Leading to Death	21 (6.1)	16 (4.5)	1.7 (-1.7, 5.2)
Treatment-Emergent AE Leading to Study Drug Discontinuation	50 (14.6)	9 (2.5)	12.1 (8.2, 16.4)
Any Treatment-Emergent Treatment-Related AE	334 (97.4)	231 (64.3)	33.0 (27.9, 38.3)
Severe (Grade ≥ 3) Treatment-Emergent Treatment-Related AE	157 (45.8)	16 (4.5)	41.3 (35.6, 47.0)
Serious Treatment-Emergent Treatment-Related AE	46 (13.4)	7 (1.9)	11.5 (7.8, 15.7)
Treatment-Emergent Treatment-Related AE Leading to Death	5 (1.5)	0 (0.0)	1.5 (0.4, 3.4)
Treatment-Emergent Treatment-Related AE Leading to Study Drug Discontinuation	37 (10.8)	2 (0.6)	10.2 (7.2, 14.0)

Note: Percentages are based on the number of patients in each treatment group.
Only treatment-emergent adverse events with a start date on or after the first dose of study drug are reported.
CI=Confidence Interval, calculated using Mietinnen and Nurminen method.
Treatment-Related: Considered by the investigator to be possibly, probably, or definitely related to study therapy.
(Database Cutoff Date: 25OCT2010)

Patients with Adverse Events in All Grades and in Grade 3 and Above
(Incidence for All Grades ≥ 10% in One or More Treatment Groups)
(Safety Population)

MedDRA System Organ Class Preferred Term	Ridaforolimus (N=343)		Placebo (N=359)	
	All Grades Patients. n (%)	Grade ≥ 3 Patients. n (%)	All Grades Patients. n (%)	Grade ≥ 3 Patients. n (%)
Number of Patients with at least One Adverse Event	**343 (100.0)**	**220 (64.1)**	**336 (93.6)**	**92 (25.6)**
Gastrointestinal disorders	**306 (89.2)**	**63 (18.4)**	**223 (62.1)**	**22 (6.1)**
Stomatitis	179 (52.2)	27 (7.9)	50 (13.9)	1 (0.3)
Nausea	93 (27.1)	5 (1.5)	90 (25.1)	5 (1.4)
Diarrhoea	108 (31.5)	10 (2.9)	66 (18.4)	0 (0.0)
Vomiting	63 (18.4)	4 (1.2)	36 (10.0)	2 (0.6)
Constipation	55 (16.0)	0 (0.0)	38 (10.6)	1 (0.3)
Abdominal pain	45 (13.1)	7 (2.0)	40 (11.1)	4 (1.1)
Dry mouth	38 (11.1)	1 (0.3)	24 (6.7)	0 (0.0)
General disorders and administration site conditions	**250 (72.9)**	**41 (12.0)**	**181 (50.4)**	**22 (6.1)**
Fatigue	122 (35.6)	10 (2.9)	80 (22.3)	7 (1.9)
Pyrexia	80 (23.3)	1 (0.3)	27 (7.5)	1 (0.3)
Asthenia	59 (17.2)	12 (3.5)	42 (11.7)	4 (1.1)
Oedema peripheral	75 (21.9)	4 (1.2)	26 (7.2)	0 (0.0)
Mucosal inflammation	57 (16.6)	8 (2.3)	16 (4.5)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	**213 (62.1)**	**37 (10.8)**	**119 (33.1)**	**9 (2.5)**
Cough	105 (30.6)	2 (0.6)	58 (16.2)	1 (0.3)
Dyspnoea	66 (19.2)	15 (4.4)	31 (8.6)	2 (0.6)
Oropharyngeal pain	58 (16.9)	1 (0.3)	14 (3.9)	0 (0.0)
Epistaxis	59 (17.2)	0 (0.0)	4 (1.1)	0 (0.0)
Musculoskeletal and connective tissue disorders	**162 (47.2)**	**21 (6.1)**	**163 (45.4)**	**16 (4.5)**
Back pain	42 (12.2)	6 (1.7)	52 (14.5)	4 (1.1)
Pain in extremity	54 (15.7)	5 (1.5)	31 (8.6)	5 (1.4)
Arthralgia	39 (11.4)	1 (0.3)	38 (10.6)	2 (0.6)
Metabolism and nutrition disorders	**227 (66.2)**	**61 (17.8)**	**97 (27.0)**	**11 (3.1)**
Decreased appetite	92 (26.8)	2 (0.6)	35 (9.7)	2 (0.6)
Hypertriglyceridaemia	93 (27.1)	8 (2.3)	32 (8.9)	2 (0.6)
Hypercholesterolaemia	73 (21.3)	1 (0.3)	16 (4.5)	0 (0.0)
Hyperglycaemia	49 (14.3)	23 (6.7)	9 (2.5)	1 (0.3)
Hypokalaemia	47 (13.7)	16 (4.7)	10 (2.8)	1 (0.3)
Skin and subcutaneous tissue disorders	**202 (58.9)**	**9 (2.6)**	**78 (21.7)**	**1 (0.3)**
Rash	97 (28.3)	2 (0.6)	22 (6.1)	0 (0.0)
Pruritus	38 (11.1)	1 (0.3)	14 (3.9)	0 (0.0)
Nervous system disorders	**166 (48.4)**	**14 (4.1)**	**111 (30.9)**	**10 (2.8)**
Headache	93 (27.1)	4 (1.2)	51 (14.2)	2 (0.6)

Patients with Adverse Events in All Grades and in Grade 3 and Above
(Incidence for All Grades ≥ 10% in One or More Treatment Groups)
(Safety Population)

MedDRA System Organ Class Preferred Term	Ridaforolimus (N=343)		Placebo (N=359)	
	All Grades Patients. n (%)	Grade ≥ 3 Patients. n (%)	All Grades Patients. n (%)	Grade ≥ 3 Patients. n (%)
Dysgeusia	55 (16.0)	1 (0.3)	13 (3.6)	0 (0.0)
Infections and infestations	**177 (51.6)**	**19 (5.5)**	**92 (25.6)**	**9 (2.5)**
Blood and lymphatic system disorders	**190 (55.4)**	**71 (20.7)**	**68 (18.9)**	**18 (5.0)**
Anaemia	95 (27.7)	25 (7.3)	35 (9.7)	10 (2.8)
Thrombocytopenia	115 (33.5)	35 (10.2)	13 (3.6)	4 (1.1)
Neutropenia	62 (18.1)	19 (5.5)	22 (6.1)	6 (1.7)
Leukopenia	46 (13.4)	8 (2.3)	15 (4.2)	2 (0.6)
Investigations	**103 (30.0)**	**9 (2.6)**	**40 (11.1)**	**1 (0.3)**
Weight decreased	51 (14.9)	1 (0.3)	16 (4.5)	0 (0.0)
Psychiatric disorders	**66 (19.2)**	**2 (0.6)**	**61 (17.0)**	**8 (2.2)**
Cardiac disorders	**74 (21.6)**	**9 (2.6)**	**36 (10.0)**	**3 (0.8)**
Tachycardia	43 (12.5)	0 (0.0)	16 (4.5)	0 (0.0)
Vascular disorders	**48 (14.0)**	**3 (0.9)**	**49 (13.6)**	**2 (0.6)**
Renal and urinary disorders	**55 (16.0)**	**11 (3.2)**	**26 (7.2)**	**1 (0.3)**
Injury, poisoning and procedural complications	**39 (11.4)**	**4 (1.2)**	**27 (7.5)**	**4 (1.1)**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**23 (6.7)**	**12 (3.5)**	**37 (10.3)**	**15 (4.2)**

Note: Percentages are based on the number of treated patients in each treatment group.
Only treatment-emergent adverse events with a start date on or after the first dose of study drug are reported.
(Database Cutoff Date: 25OCT2010)

Efficacy: The study met its primary endpoint of improvement in PFS, demonstrating a statistically significant 28% reduction of risk in disease progression or death (PFS HR=0.72; p=0.0001 two-sided) by ridaforolimus compared to placebo in patients with advanced sarcoma who had achieved at least SD after 1-3 lines of chemotherapy. For the PFS endpoint, the stratified analysis by IRC assessment was the primary analysis of this endpoint. The unstratified analysis, the analyses by site assessment, sensitivity analyses, analyses in Per Protocol (PP) and Modified Intent to Treat (MITT) populations and other supportive analyses including various covariate adjusted analyses, all supported the conclusion from the primary analysis. To evaluate the magnitude of the benefit of a 28% risk reduction, improvement in median PFS and PFS rate at fixed time points were reviewed. The analysis by site assessment showed a greater improvement in median PFS (22.4 vs. 14.7 weeks) than the analysis by IRC (17.7 vs. 14.6 weeks) while the HRs were similar. Examination of the Kaplan-Meier plots suggests the difference at the single point of median might not be a good representation of the treatment effect. Exploratory analyses using interval censoring and parametric methods showed a more substantial improvement in median than the primary analysis (12.7 vs. 7.5 weeks by interval censored estimate for IRC assessment; 15.3 vs 9.5 weeks by parametric estimate for IRC assessment). Based on IRC assessment, ridaforolimus showed substantial improvement in 3-month PFS rate (70.3% vs. 54.1% or 30% relative improvement) and 6-month PFS rate (34.3% vs. 22.7% or 51% relative improvement). At 9 and 12 months, the relative improvement was about 39%. These additional measurements of PFS improvement demonstrated that

the 28% risk reduction is of clinical meaningful magnitude. Subgroup analyses were performed based on histology, line of therapy, geographic region and other demographic and prognostic factors. The forest plots of the HRs across the subgroup analyses suggests that the treatment effect is generally consistent in all subgroups. Overall, the subgroup analyses support the conclusions from the primary analysis of PFS.

Secondary efficacy endpoints specified in the protocol included OS, best target lesion response, and cancer-related symptoms. In the secondary endpoint of OS, the HR was 0.92 (95% CI [0.74, 1.15], p=0.4681), favoring ridaforolimus. The improvement by ridaforolimus in median OS was greater than 2 months (88.0 vs. 78.7 weeks). The Kaplan-Meier curves do not separate substantially. The observed trend is that any potential treatment effect of ridaforolimus on OS improves over time. While not conclusive, these analyses suggest that ridaforolimus has a positive trend in extending OS compared to placebo.

Best target lesion response was one of the pre-specified secondary endpoints. This response was defined as the maximum percentage decrease (or minimum percent increase if a decrease does not occur) in the sum of longest diameters of target lesions pre-specified at baseline until disease progression. Based on IRC assessment, the ridaforolimus treatment group showed a 1.3% reduction (SD 24.7) in target lesion tumor size. In contrast, the placebo treatment group showed a 10.3% increase (SD 36.8) in target lesion tumor size. The (two-sided) p-value based on Wilcoxon Rank Sum Test was <0.0001. This indicates that tumor growth was better controlled in the ridaforolimus treatment group than in the placebo treatment group. This is another indicator of potential therapeutic benefit. The best overall response using RECIST criteria was also analyzed. Ridaforolimus demonstrated improvement (IRC: 40.6% vs. 28.6%, p=0.0009) in Clinical Benefit Response rate, defined as the proportion of patients achieving CR, PR, or SD ≥4 months.

Cancer-related symptoms were one of the secondary endpoints for this study and based on collected data, the vast majority of patients who stayed on therapy were free of severe symptoms in both treatment groups. However, there was a large amount of missing data mainly because of treatment discontinuation due to PD. There was more missing data in the placebo group over time. Given the large amount of missing data that is likely informative, the analysis of the cancer-related symptoms is inconclusive.

Post-progression survival, defined as the time interval between PD, per IRC assessment, and death, which captures the interval of time after disease progression including the subsequent management of the advanced sarcoma, provides a measure of the impact of ridaforolimus on the outcome of subsequent sarcoma management after disease progression. An exploratory analysis on post-progression survival was performed to evaluate the use of ridaforolimus as a maintenance therapy. The HR based on a stratified Cox model was 1.00 (95% CI [0.78, 1.28]), suggesting that ridaforolimus as a maintenance therapy does not have detrimental effect on subsequent management of sarcoma patients.

[redacted]

Progression-Free Survival
(ITT Population)

	N	Number of PFS Events	Number Censored	PFS (weeks) Median (95% CI)	Hazard Ratio§ (95% CI)	p-value†	p-value‡
IRC Assessment							
Ridaforolimus	347	261	86	17.7 (15.7, 22.3)	0.72 (0.61, 0.85)	0.0001	0.0012
Placebo	364	291	73	14.6 (12.3, 15.0)			
Total	711	552	159				
Site Assessment							
Ridaforolimus	347	278	69	22.4 (17.7, 23.4)	0.69 (0.58, 0.81)	<.0001	<.0001
Placebo	364	319	45	14.7 (12.9, 15.1)			
Total	711	597	114				

†: Log-rank test, stratified over histology (bone vs. soft-tissue sarcoma) and prior chemotherapy (lst line vs. 2nd/3rd line)
‡: Unstratified log-rank test
§: Based on a stratified[1] Cox Proportional Hazards Model with treatment as a covariate (Ridaforolimus relative to Placebo)
IRC= Independent Review Committee PFS= Progression Free Survival CI=Confidence Interval
(Database Cutoff Date: 25OCT2010)

CONCLUSIONS: In conclusion, this global phase III prospective, randomized, placebo-controlled clinical trial has demonstrated that, overall, ridaforolimus has a favorable risk-benefit profile as a maintenance therapy for sarcoma patients who have achieved CR, PR, or SD from 1-3 lines of chemotherapy. The totality of all the supporting evidence is summarized in the following key points:

1. PFS benefit with a HR 0.72, 95% CI of (0.61, 0.85), or 28% hazard reduction for progression or death, that is statistically significant and clinically meaningful. The finding was robust as confirmed by various supportive analyses.
2. Consistent PFS benefit across subgroups defined by demographic and prognostic factors.
3. Positive trend in extending OS (HR=0.88, 95% CI [0.72, 1.08]).
4. Best target lesion response indicating ridaforolimus controls tumor growth better than placebo (mean of best change = -1.3% vs. +10.3%, $p<0.0001$). Analysis of best overall response showed that ridaforolimus demonstrated improvement (IRC: 40.6% vs. 28.6%, $p=0.0009$) in Clinical Benefit Response rate i.e. the proportion of patients achieving CR, PR, or SD for at least 4 months.
5. Analysis of cancer related symptoms was inconclusive.
6. Exploratory analysis on post-progression survival suggesting no detrimental effect on subsequent management of sarcoma after use of ridaforolimus as a maintenance therapy.
7. Favorable toxicity profile compared to conventional cytotoxic chemotherapy and comparable to other rapamycin analogs.

AUTHORS:	(Clinical Scientist)	(Statistician)	(Clinical Monitor)
	[redacted]		