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

Name of Sponsor/Company: ARIAD Pharmaceuticals, Inc **Name of Finished Product:** Ridaforolimus ([redacted]; MK-8669, formerly deforolimus) **Name of Active Ingredient:** [redacted] Drug Product	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Title of Study: A Phase II Study of [redacted], an mTOR Inhibitor, in Patients with Advanced Sarcoma		
Principal Investigators: [redacted]		
Study center(s): Seventeen sites participated in this study. Fourteen sites were in the United States, 2 in France, and 1 in Belgium. [redacted]. [redacted] Belgium [redacted] France [redacted] France		

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Name of Finished Product: Ridaforolimus (MK-8669, formerly deforolimus)		
Name of Active Ingredient:		

Publications (reference):

Dodion P, Haluska F, Rivera V, Lehnert M, Ebbinghaus S. New drug development in sarcoma: exploration of novel targets, particularly the mammalian target of rapamycin (mTOR) pathway. Molecular Therapeutics of Cancer Session [Keynote address]. BIT'S 2nd Annual World Cancer Congress-2009; 2009 Jun 22. 8669_1021. Beijing, China, 2011.

Hartford CM, Desai AA, Janisch L, Karrison T, Rivera VM, Berk L, et al. A phase I trial to determine the safety, tolerability, and maximum tolerated dose of deforolimus in patients with advanced malignancies. Clin Cancer Res 2009;15(4):1428-34.

Sessa C, Tosi D, Vigano L, Albanell J, Hess D, Maur M, et al. Phase lb study of weekly mammalian target of rapamycin inhibitor ridaforoliums (MK-8669) with weekly paclitaxel. Ann Oncol 2009:11-8.

Sonis S, Treister N, Chawla S, Demetri G, Haluska F. Preliminary characterization of oral lesions associated with inhibitors of mammalian target of rapamycin in cancer patients. Cancer 2009:19-24.

Chawla SP, Sankhala KK, Chua V, Menendez LR, Eilber FC, Eckardt JJ, et al. A phase II study of AP23573 (an mTOR inhibitor) in patients (pts) with advanced sarcomas. J Clin Oncol (Meeting Abstracts) 2005;23(16S):9068.

Sankhala KK, Chawla SP, Lagaru A, Dellamaggiora R, Chua V, Daly S, et al. Early response evaluation of therapy with (an mTOR inhibitor) in sarcoma using [18F]2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) scan [abstract] [Abstract]. J Clin Oncol 2005 ASCO Annual Meeting Proceedings 2005;23(16S Pt I of II):9028.

Chawla SP, Blay J-Y, Staddon AP, D'Amato GZ, Tolcher AW, Sankhala KK, et al. A phase II trial of a novel mTOR inhibitor, in patients (pts) with advanced soft tissue or bone sarcoma. AACR-NCI-EORTC International Conference, 2011:268.

Rivera VM, Berk L, Chawla SP, Daly ST, Sankhala KK, Clackson T, et al. Analysis of potential biomarkers of activity in a Phase II trial in sarcoma patients [abstract]. AACR-NCI-EORTC International Conference Molecular Targets and Cancer Therapeutics; 2005 Nov 14-18. Philadelphia (PA), 2005:174.

Chawla SP, Tolcher AW, Sankhala KK, Staddon AP, Bedrosian CL, Demetri GD. Updated interim results of a phase 2 study of the MTOR inhibitor in patients (PTS) with advanced sarcomas of soft tissue or bone [Abstract 447]. CTOS 11th Annual Meeting; 2005 Nov 19. 8669_1022. Florida, 2011:29.

Name of Sponsor/Company: ARIAD Pharmaceuticals, Inc	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Ridaforolimus ([redacted] MK-8669, formerly deforolimus)		
Name of Active Ingredient: AP23573 Drug Product		

Sankhala K, Chawla SP, Tolcher AW, Chua V, Daly ST, Bedrosian CL, et al. Early imaging with [18F]2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) scans as a predictor of [redacted] activity in patients (PTS) with advanced sarcomas [Abstract 488]. CTOS 11th Annual Meeting; 2005 Nov 19. Florida, 2011:30.

Chawla SP, Tolcher AW, Staddon AP, Schuetze SM, D'Amato GZ, Blay JY, et al. Updated results of a phase II trial of [redacted] a novel mTOR inhibitor, in patients (pts) with advanced soft tissue or bone sarcomas [Abstract]. J Clin Oncol (2006 ASCO Annual Meeting Proceedings Part I) 2006;24(18S):9505.

Chawia S, Tolcher A, Sankhala KK, Amato GZD, Schoffski P, Staddon AP, et al. Updated results of a phase 2 trial of the novel MTOR inhibitor AP23573 in patients with advanced soft-tissue or bone sarcoma [Abstract 665]. 12th Annual CTOS Meeting; 2006 Nov 2. Venice, Italy, 2006:55.

Chawla S, Blay J-Y, Sankhala KK, D'Amato GZ, Schoffski P, Staddon AP, et al. 12th Annual CTOS Meeting; Clinical characteristics and outcomes of advanced sarcoma patients who achieved clinical benefit response (CBR) while receiving [redacted] in a phase 2 trial; November 2-4, 2006. 2006 Nov 2. 8669_1008, 2006.

Studied period (years):	**Phase of development:**
Date first subject first visit: 11-Oct-2004 Date last subject last visit: 24-Nov-2008	Phase II

Objectives:

Primary:

- Assess the efficacy of ridaforolimus in patients with advanced sarcoma when administered once daily for 5 consecutive days every 2 weeks (QDx5 days every 2 weeks)

Secondary:

- Assess the safety and tolerability of this study drug regimen
- Evaluate secondary efficacy endpoints, such as time to tumor progression, progression-free survival, overall survival, and duration of response
- Examine ridaforolimus blood levels and experimental parameters that may predict or indicate response to mTOR inhibition, such as effects on plasma VEGF levels and markers of tumoral PI3K/mTOR-pathway activity

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Name of Active Ingredient: [redacted] Drug Product		

Methodology: This study was an open-label, uncontrolled, non-randomized, multicenter, Phase II study to assess the safety and anti-tumor activity of ridaforolimus administered intravenously (I.V.) in patients 15 years or older with advanced sarcomas (metastatic and unresectable soft tissue or bone sarcoma). The study included 4 parallel, histological cohorts (leiomyosarcoma, liposarcoma, bone sarcoma, and "other" soft tissue sarcoma). Eligible patients were given a fixed dose of 12.5 mg ridaforolimus administered I.V. over 30 minutes once daily for five consecutive days every 2 weeks (QDx5 days every 2 weeks). Patients were eligible to continue treatment until any of the discontinuation criteria were met.

Number of subjects (planned and analyzed): Up to approximately 176 patients (44 per cohort) were planned for enrollment; 216 were enrolled and 212 were treated with ridaforolimus and analyzed for safety and anti-tumor activity.

Main criteria for eligibility:

Inclusion Criteria

1. Patients ≥ 15 years of age (≥ 18 years, where applicable due to local laws) with metastatic and/or unresectable sarcomas of the following histological subgroups: bone sarcoma (such as osteosarcoma and Ewing's sarcoma), leiomyosarcoma, liposarcoma, any "other" soft tissue sarcoma except GIST. Patients with well-differentiated liposarcoma or desmoid tumors had to demonstrate progressive disease within the previous 6 months.

   Patients under the age of 18 years were to have received available alternative treatment approaches that provide therapeutic benefit prior to being considered for enrollment into this trial.

2. Presence of at least 1 measurable lesion that:

   - Could be accurately measured in at least 1 dimension with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral computerized tomography (CT) scan (or otherwise at least twice the reconstruction interval for CT or magnetic resonance imaging [MRI] scans).
   - Previously irradiated lesions were considered to be measurable provided: 1) there has been documented progression of the lesion(s) since completion of radiotherapy, and 2) the criteria for measurability as outlined above are met.

3. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1
4. Minimum life expectancy of 3 months

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5. Adequate renal and hepatic function
6. Adequate bone marrow function
7. Serum cholesterol < 350 mg/dL and triglycerides < 400 mg/dL
8. Male and female patients who were not surgically sterile or postmenopausal had to agree to use reliable methods of birth control for the duration of the study until 30 days after the last dose of study drug
9. Able to understand and give written informed consent

Exclusion Criteria

1. Women who were pregnant or lactating
2. Presence of active brain metastases
3. Prior therapy with rapamycin analogues or tacrolimus
4. Prior anticancer treatment (chemotherapy, radiotherapy, hormonal, immunotherapy, biological response modifiers, signal transduction inhibitors, etc) within 4 weeks prior to the first dose of ridaforolimus; the interval is ≥ 2 weeks for signal transduction inhibitors with a half-life known to be < 24 hours, and is ≥ 6 weeks for nitrosourea or mitomycin.

   The following exceptions were allowed: hormonal therapy (e.g., megestrol acetate) for appetite stimulation; nasal, ophthalmic, and topical glucocorticoid preparations; a stable dose of corticosteroids for at least two weeks; low dose maintenance steroid therapy for other conditions; physiologic hormone replacement therapy (e.g., thyroid supplementation for thyroid deficiency or oral replacement glucocorticoid therapy for adrenal insufficiency)
5. Ongoing toxicity associated with prior anticancer therapy (except peripheral neuropathy of ≤ Grade 1 by NCI toxicity criteria)
6. Another primary malignancy within the past three years (except for non-melanoma skin cancer and cervical carcinoma in situ)
7. Known or suspected hypersensitivity to drugs formulated with polysorbate 80 (Tween) or any other excipient contained in the study drug
8. Known Grade 3 or 4 hypersensitivity to macrolide antibiotics (e.g., clarithromycin, erythromycin, azithromycin)

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9. Significant uncontrolled cardiovascular disease
10. Active infection requiring systemic therapy
11. Known human immunodeficiency virus (HIV) infection
12. Treatment with any investigational agent within 4 weeks prior to the first dose of ridaforolimus
13. Concurrent treatment with immunosuppressive agents other than prescribed corticosteroids at stable doses for ≥ 2 weeks prior to first planned dose of study drug
14. Inadequate recovery from any prior surgical procedure or having undergone any major surgical procedure within 2 weeks prior to the first dose of ridaforolimus

    Patients having undergone recent placement of a central venous access port were considered eligible if they had recovered. Study drug was not to be administered until the wound had healed.
15. Presence of any other life-threatening illness or organ system dysfunction which, in the opinion of the Investigator, would have either compromised the patient's safety or interfered with evaluating the safety of the study drug

Test product, dose and mode of administration, batch number:

Drug Product and diluent, 12.5 mg, administered I.V. over 30 minutes ± 5 minutes once daily for 5 days every 2 weeks in a 28-day cycle (two 2-week courses equals 1 cycle)

Drug Product lot numbers:

Diluent lot numbers:

Duration of treatment:

A minimum of 2 consecutive cycles of ridaforolimus were planned, for a total duration of 8 weeks (two 2-week courses equals 1 cycle). If tolerated, treatment could continue until any of the discontinuation criteria were met.

Reference therapy, dose and mode of administration, batch number:

None

Criteria for evaluation:

Efficacy: Clinical benefit response, defined as complete or partial response or prolonged stable

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disease ≥ 16 weeks; time to disease progression; progression-free survival, overall survival, duration of response, and quality of life assessment (Functional Assessment of Cancer Therapy [FACT-G] questionnaire)

Safety: Adverse events, change from baseline in physical examination, weight, slit-lamp ophthalmologic examination, vital signs, clinical laboratory assessments (hematology, serum chemistry, and urinalysis), 12-lead electrocardiogram (ECG)

Drug concentration measurements: Whole blood concentrations of ridaforolimus were to be measured in samples collected before and within 5 minutes following the end of I.V. infusion on Day 1 and Day 5 of Cycle 1 and before infusion on Day 15 of Cycle 1. Whole blood concentrations of ridaforolimus were to be measured in samples before I.V. infusion on Day 1 of Cycle 2.

[redacted]

Statistical methods:
Sample size calculation: The study employed a Simon's optimal 2-stage design (significance level 0.05, power = 0.90] to distinguish a favorable true clinical benefit response rate of ≥ 35% from a null (uninteresting) rate of ≤ 15% within each histological cohort. Nineteen (19) patients were to be enrolled into each histological cohort. If at the end of Study Stage 1, 3 or fewer occurrences of clinical benefit response were observed in a cohort, further enrollment into that cohort was to be discontinued. If 4 or more clinical benefit responses were observed within any given histological cohort, approximately 26 additional patients were to be enrolled into that cohort (yielding an estimated total of 44 evaluable patients per cohort). If 11 or more clinical benefit responses were observed among 44 evaluable patients, the regimen was to be considered effective based on the Study Stage 2 decision rule of the Simon 2-stage design. This design has a probability of 0.684 of stopping the enrollment early if the study drug was ineffective, a significance level of 0.048 and a power of 0.905. This means that if the drug was not effective there is a 0.048 chance of concluding that it was effective. Conversely, if the drug was effective, there is a probability of 0.095 of concluding that it was not effective.

During trial implementation, the following changes were made: the "other sarcoma" cohort continued to Study Stage 2 with 3 responses and additional patients beyond 44 evaluable patients per cohort were enrolled in all cohorts during stage 2.

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Statistical methods (continued):

Statistical Analyses: For each histological cohort, the clinical benefit rate was to be determined based on all treated patients (as opposed to evaluable patients, i.e. patients, who received 2 cycles of treatment and had one assessment as originally stated in the protocol). Patients were to be classified as
"clinical benefit" responders if they had a complete or partial response or if they had prolonged stable disease ≥ 16 weeks. Secondary endpoints included progression-free survival, overall survival, pharmacodynamics, ridaforolimus blood concentrations, and quality of life (QOL) assessments. Originally the time to disease progression and duration of response were to be assessed and estimated. The final statistical analysis did not include these assessments.

The Simon's 2-stage design employs a 1-sided test of significance. All other statistical tests performed were 2-sided controlling for the type I error level at 0.05, unless otherwise specified. Summary statistics (number of patients, mean, minimum, median, maximum, standard deviation) were used to summarize all of the continuous variables.

Descriptive data were summarized using the mean, median, standard deviation, minimum, and maximum for continuous variables, and using counts and percentages for discrete variables. Summary statistics are presented for baseline vital signs and clinically significant changes. Adverse events were coded by body system and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 7.1.

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SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

- The clinical benefit response results for 3 of the cohorts were found to be statistically significantly greater than the null hypothesis rate of 15% ($p < 0.05$; binomial test with a null hypothesis of a 15% rate). The CBR rate for the bone sarcoma cohort was 17/54 (31.5%; $p < 0.05$), 19/57 (33.3%; $p < 0.05$) for the leiomyosarcoma cohort and 13/44 (29.5%; $p < 0.05$) for the liposarcoma cohort. The CBR rate for the other sarcoma cohort was 12/57 (21.1%; not statistically significantly greater than the null hypothesis rate of 15%). Because the CBR rates were comparable among cohorts, additional post-hoc analyses were performed using pooled data from all of the cohorts.
- A total of 61 (28.8%) patients overall achieved CBR.
- Four (2%) patients achieved a confirmed partial response; 2 patients with osteosarcoma, 1 with spindle cell desmoplastic sarcoma, and 1 with fibrous hystiocytoma. Three (1%) patients achieved unconfirmed PR (1 with osteosarcoma, 1 with small round cell desmoplastic sarcoma, and 1 with unclassifiable soft tissue sarcoma); these 3 patients are counted as SD in the present report.
- Overall, 125 (59%) patients achieved stable disease as best overall response; 30 (56%) in the bone sarcoma cohort; 39 (68%) with leiomyosarcoma; 25 (57%) with liposarcoma; and 31 (54%) with other sarcoma.
- The median progression free survival was 15.3 weeks (range: 14.3-16.3 weeks). The overall progression-free survival rate at 6 months (26 weeks) was 23.4%, with a range of 20.2% - 25.6% across cohorts.
- The median overall survival was 40.1 weeks.

PHARMACODYNAMIC RESULTS AND DRUG CONCENTRATION MEASUREMENTS:

- The detected ridaforolimus in blood confirmed that the patients were exposed to ridaforolimus. Among all the patients, the mean ridaforolimus concentration for samples collected within 5 minute post intravenous infusion on Day 1 and Day 5 of Cycle 1 were 570.4 and 511.3 ng/mL, respectively. The mean ridaforolimus concentration for samples collected prior to intravenous infusion on Day 5 and Day 15 of Cycle 1 were 136.5 and 11.8 ng/mL, respectively. The mean ridaforolimus

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concentration for samples collected prior to intravenous infusion on Day 1 of Cycle 2 was 11.9 ng/mL.

- Fresh tumor biopsies could be obtained from 2 patients to measure p-S6 activity. A greater than two-fold decrease in p-S6 was observed 24 hours postdose in both patients, indicating inhibition of mTOR activity in the target tissue.
- An analysis of plasma samples collected prior to and at multiple time points after dosing with ridaforolimus did not show any effect of ridaforolimus on VEGF levels across all patients and doses. There was also no correlation between pre-dose VEGF levels and CBR.
- An analysis of signaling proteins upstream and downstream of mTOR did not show a correlation between the levels of any single marker and clinical outcome.

SAFETY RESULTS:

The safety conclusions for this trial are as follows:

- All 212 (100%) patients treated in the study reported at least 1 treatment emergent adverse event.
- A total of 208 (98.1%) patients reported at least 1 treatment emergent adverse event that was considered by the Investigator to be at least possibly related to treatment with ridaforolimus.
- Adverse events occurred with similar frequency and severity in the bone sarcoma, leiomyosarcoma, liposarcoma, and "other sarcoma" cohorts.
- The most frequently reported treatment-related events (occurring in 20% or more of patients overall) were fatigue, stomatitis, anemia, rash, hypertriglyceridemia, nausea, mucosal inflammation, and thrombocytopenia.
- [redacted]
- Treatment-related Grade 3-4 events considered to be at least possibly related to study drug occurred in 38.7 % patients. Grade 3 anemia (7.5%) was the single treatment related Grade 3-4 event to occur in > 5% patients.
- Oral adverse events (mucositis, stomatitis and related events) were frequent: 45.3% of

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all patients in the treated population experienced stomatitis and 29.7% experienced mucosal inflammation. The majority of the oral disorder events were mild or moderate in severity.

- Rash and similar dermatologic events were frequent (rash considered related to ridaforolimus was reported in 36.8% of all patients in the treated population). Most skin disorder events were mild to moderate in severity with no events of Grade 3 or 4 severity.
- Metabolic disorders events were frequent (43.9% of patients experienced hypertriglyceridemia; 29.7% experienced hyperglycemia; and 26.4% experienced hypercholesterolemia). Most events of metabolic disorders were mild or moderate in severity.
- Adverse events of pneumonitis were reported in 2.4% of patients and were assessed by the Investigator as related to treatment with ridaforolimus in 1.4% of patients.
- Frequent hematologic adverse events were anemia (37.3 % of patients), thrombocytopenia (24.1%), and neutropenia (11.8 %). The incidence of Grade 3 events were 7.5% for anemia, 4.2% for thrombocytopenia, and 1.4% for neutropenia. The incidence of Grade 4 events was 4.2% for thrombocytopenia and 1.4% for neutropenia. The incidence of clinically significant decrease was 19.8% for hemoglobin, 12.7% for absolute neutrophil count, and 6.1% for platelet count.
- Twenty-eight (28) patients died within 30 days of last dose of study drug. None of the reported deaths were considered related to study treatment.
- Serious adverse events (SAEs) were reported in 96 (45.3%) patients and SAEs considered to be related to study drug were reported in 20 (9.4%) patients.
- Adverse events led to drug discontinuation in 21.2% patients and to dose modification or interruption (i.e., reduction and /or temporary interruption and / or delay) in 38.7% patients.
- No safety signal emerged from the review of vital signs pre- and post-infusion, or of ECG assessments over time.

CONCLUSION:

Study [redacted]04-202 (MK-8669-018) demonstrates antitumor activity of ridaforolimus in patients with advanced or metastatic sarcomas; results were similar across four histological

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subgroups: bone sarcomas, leiomyosarcomas, liposarcomas and "other" soft tissue sarcomas. The clinical benefit response results for 3 of the cohorts (bone sarcomas, leiomyosarcomas, liposarcomas) was found to be statistically significantly greater than the null hypothesis rate of 15% ($p < 0.05$; binomial test with a null hypothesis of a 15% rate).

The results from this study suggest that the predominant clinical benefit of ridaforolimus in this patient population is disease stabilization.

The detected ridaforolimus in blood collected prior to and at the end of intravenous infusion both confirmed that the patients were exposed to study drug.

Most adverse events were mild or moderate in severity and adverse events occurred with similar frequency and severity in the various histological subtypes.

The activity and overall safety profile demonstrated in this study warrant further evaluation of ridaforolimus in patients with advanced sarcoma.

Date of the report:
05-May-2010