NDA 22-576 (ridaforolimus tablets)

Oncologic Drugs Advisory Committee
Briefing Document

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Ridaforolimus Tablets
ODAC Briefing Document

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1. Executive Summary/Overview

Ridaforolimus (also known as AP23573, MK-8669, and formerly known as deforolimus) is a unique non-prodrug analog of rapamycin (sirolimus) that inhibits the mammalian target of rapamycin (mTOR) protein kinase. The company has an active development program for ridaforolimus under IND 72,003 for various forms of solid tissue cancer including sarcoma, lung, breast, endometrial and ovarian cancer.

NDA 22-576 was submitted on August 5, 2011 for the treatment of metastatic soft tissue sarcoma or bone sarcoma as a maintenance therapy for patients who have completed at least 4-cycles of chemotherapy without evidence of disease progression. It is proposed that ridaforolimus be indicated for adult patients and pediatric patients (aged 13 through 17 with a body weight ≥ 100 lb).

Soft tissue and bone sarcoma are rare with approximately 10,500 and 2,700 new diagnoses respectively per year in the US. This submission is based on Protocol 011, a global Phase III randomized, placebo-controlled, double-blind trial of single-agent oral ridaforolimus administered at 40 mg daily times 5 days (q.d. x 5 days/wk) versus oral placebo in patients with metastatic sarcomas who had achieved at least stable disease after 4 or more cycles in 1 to 3 lines of prior chemotherapy. The study enrolled 711 patients, age ≥ 13 years. The primary endpoint of the study was progression free survival (PFS) as assessed by independent radiologic review, and the study was designed to determine whether treatment with ridaforolimus would improve PFS relative to patients treated with placebo. The final analysis of PFS was performed based on a clinical data cut-off date of 25-Oct-2010, which was determined to approximately achieve the target number (516) of PFS events.

The Phase III study was powered to detect a 25% risk reduction in the PFS endpoint as determined by independent radiologic committee (IRC) compared with placebo. The outcome was a 28% overall reduction in risk of progression or death in patients when treated with ridaforolimus vs. placebo. A pre-specified analysis of PFS by site assessment yielded a similar reduction in risk of progression or death. Subgroup analyses of the PFS endpoint revealed that the benefit of ridaforolimus was consistent over age, geographic region, functional performance status, tumor histology, and prior line of therapy. In particular, ridaforolimus exhibited a similar improvement in both bone sarcoma and soft tissue sarcoma subgroups. As assessed by a Kaplan-Meier analysis, the difference in median PFS between the ridaforolimus and placebo group was 3.1 weeks and 7.7 weeks when assessed by IRC and site investigators, respectively. Due to the shape of the Kaplan-Meier curves, the median when assessed by IRC is an underestimate of the effect of ridaforolimus on PFS compared to placebo, with an improvement of approximately 6 weeks in the median estimated by the hazard ratio or parametric modeling. These findings indicate that maintenance treatment of metastatic sarcoma patients with ridaforolimus significantly reduced the risk of disease progression or death.

The secondary endpoints of the study were overall survival (OS), best target lesion response, safety and tolerability, and changes in patient-reported, cancer-related

symptoms. To provide as mature an OS dataset as possible, a pre-specified analysis for OS was performed with a data base cut of 21 January 2012, based upon the protocol requirement of a minimum follow up of 24 months for OS. While the trial was not powered to detect a difference in OS, the Hazard Ratio of 0.93 in favor of ridaforolimus with a median improvement of 5.3 weeks was noted. With the upper bound of the 95% confidence interval of the hazard ratio for OS at 1.12, a detrimental effect of ridaforolimus on survival is largely ruled out. Ridaforolimus treatment was also associated with a statistically significant mean target lesion size reduction of 1.3% compared to a mean target lesion size increase of 10.3 % with placebo..

The overall survival (OS) and target lesion findings support the PFS result and underscore the impact of ridaforolimus on the disease process.

The Phase III study included a dose modification scheme to allow for temporary or permanent dose reductions in patients experiencing adverse events commonly associated with ridaforolimus and other rapamycin analogs, such as mucositis. Patients received on average 74% of the target dosage of ridaforolimus, with only 15% of patients having to discontinue ridaforolimus treatment because of an intolerable side effect. The most common adverse events (AEs) associated with ridaforolimus treatment were stomatitis, fatigue, diarrhea, anemia and thrombocytopenia, all of which are known effects of the mTOR inhibitor class. Stomatitis emerged as the most common reason leading to ridaforolimus treatment discontinuation in this study; however, the rate of discontinuation due to stomatitis was low, at <3% of the patients who were treated with ridaforolimus.

The most common serious adverse events defined as 'reported by ≧l%' of the 343 patients in the P011 ridaforolimus group were pneumonia (2.3%), anemia (2.0%), pneumonitis (1.7%), thrombocytopenia (1.7%), dehydration (1.5%), dyspnea (1.5%), pleural effusion (1.5%), renal failure acute (1.5%), nausea (1.2%), pulmonary embolism (1.2%) and vomiting (1.2%). There were 21 and 16 deaths observed in the ridaforolimus and placebo groups, respectively. Of note, in the ridaforolimus group, respiratory disorder adverse events resulted in 6 deaths while no respiratory-related deaths were observed in the placebo group. .A review of individual case reports concluded that one of the 6 deaths appeared related to pneumonitis from ridaforolimus treatment. The event terms from the other fatal respiratory events suggests that many or most events were due to a worsening of the underlying disease, and were often reported as non-specific terms that occur when patients die of cancer.

P011 also collected data on three patient reported symptoms (pain, cough, and shortness of breath) that are related to both sarcoma progression and adverse events (AEs) using an exploratory questionnaire. Results of an exploratory longitudinal data analysis demonstrated that average symptom scores were between none and mild at baseline and all post-baseline time points in both treatment arms. Differences between the treatment arms were small to moderate, at most 0.24 on a 1 to 4 point scale in favor of placebo, and were likely consistent with the severity and timing of the stomatitis, cough, and dyspnea adverse events observed in P011.

In summary, administration of ridaforolimus as maintenance therapy for patients with metastatic sarcoma resulted in a reduction in the risk of disease progression or death that exceeded the pre-specified target effect size for clinical benefit. There was also significant target lesion size reduction in response to ridaforolimus treatment. While the study was not powered for analysis of overall survival, an analysis that included 67% of the study population yielded a hazard ratio of 0.93 favoring ridaforolimus, and largely rules out a detrimental effect. An exploratory analysis of post-progression survival yielded a hazard ratio of 0.95 favoring ridaforolimus, providing further evidence that treatment with ridaforolimus did not adversely impact subsequent patient management. While a higher AE rate was observed in the ridaforolimus treatment group versus placebo, the AEs were expected based on knowledge of the mTOR inhibitor drug class, and were generally clinically maneagable, addressed by dose modification, and rarely required treatment discontinuation. Although there was a higher incidence of death due to respiratory disorders in the ridaforolimus group, in only one case was the death attributed to ridaforolimus treatment. The overall safety profile of ridaforolimus is similar to that of other rapamycin analogs used in the treatment of cancer patients, and no new safety concerns were identified relative to information known before the initiation of the study.

2. Regulatory History

In March 2005, the IND for oral ridaforolimus was filed with the FDA. In August 2005 the FDA granted orphan drug designation to ridaforolimus for "treatment of soft tissue sarcoma" and "treatment of bone sarcoma."

In November 2006, the FDA granted fast track designation to ridaforolimus for advanced or metastatic soft tissue and bone sarcoma stating that the condition is a serious and life threatening condition that is generally incurable and that the responses observed suggest ridaforolimus may have activity against this disease.

In August 2007, a Special Protocol Assessment (SPA) agreement was reached with the FDA. The Agency concluded that based upon their review, the study design, proposed endpoints (with PFS as the primary endpoint) and planned analysis of the Phase III study (P011) "A Pivotal Trial to Determine the Efficacy and Safety of Ridaforolimus [AP23573] when Administered as Maintenance Therapy to Patients with Metastatic Soft Tissue or Bone Sarcomas" could adequately address the objectives necessary to support a regulatory submission.

In November 2009, a ridaforolimus pre-NDA meeting was held with the FDA to discuss the proposed submission.

In August 2011, the NDA for ridaforolimus as maintenance therapy for metastatic soft tissue or bone sarcoma was filed with the FDA

3. Scientific Background

3.1 Unmet Medical Need in Metastatic Sarcoma

Sarcomas are a rare group of malignant tumors of mesenchymal origin that develop from cells comprising connective tissue structures such as fat, muscle, blood vessels, and nerves, as well as from the skeleton. Sarcomas can be broadly divided into soft-tissue sarcomas and bone sarcomas based on histology and tissue of origin. Bone sarcomas are also commonly referred to as primary malignant bone tumors [1]. The most common soft tissue sarcomas are leiomyosarcoma and liposarcoma and the most common bone sarcoma is osteosarcoma [2].

Patients with metastatic soft-tissue or bone sarcoma face a poor prognosis, with a 5-year survival rate of 15-22% [3; 4]. Except for patients with gastrointestinal stromal tumors, existing treatment options for patients with metastatic disease consist solely of cytotoxic chemotherapy, which has limited activity and considerable toxicity. Examples of available agents that are used as monotherapy or in combination for the treatment of soft-tissue sarcoma include doxorubicin, ifosfamide, docetaxel, gemcitabine, and dacarbazine. In addition to these drugs, vinblastine, cyclophosphamide, and etoposide are used in the treatment of metastatic bone sarcomas [5; 6; 7; 8; 9; 10; 11; 12; 13]. In addition, for most adult sarcomas, doxorubicin is the only FDA-approved drug.

In studies of doxorubicin, which is a DNA-damaging agent and considered one of the most active drugs in the treatment of advanced soft-tissue and bone sarcoma [8; 7; 13], responses occur in 9% to 30% of patients, and median overall survival ranges from 8 to 12 months. Febrile neutropenia occurs in 16% to 19% of patients, Grade 3 or 4 neutropenia in 77%, alopecia in 78%, and cardiac adverse events in approximately 3% to 4% of patients. In large part due to concerns over cumulative cardiac toxicity, median duration of treatment is generally 3 to 4 monthly cycles and rarely exceeds 8 cycles. Approximately 35% of patients experience progression of disease as their best response to doxorubicin.

Newer chemotherapeutics, such as the DNA-damaging agent trabectedin, have yielded little improvement over older treatments such as doxorubicin. In a phase II study comparing two different trabectedin intravenous infusion schedules, median time-to-progression was less than 4 months for both schedules of administration [14].

Despite advances in understanding genetic alterations underlying the development and progression of sarcomas, relatively little progress has been made in translating this information into targeted therapies that avoid the non-specific toxicities of chemotherapy. Other than gastrointestinal stromal tumors, for which the c-kit-inhibitor imatinib mesylate is an effective treatment, there are no non-chemotherapy, targeted treatment options available for patients with soft tissue or bone sarcomas.

3.2 Mammalian Target-of-Rapamycin as a Therapeutic Target in Sarcoma

The mammalian-target of rapamcyin (mTOR) serine/threonine protein kinase is the catalytic subunit of two multi-protein complexes (mTORC1 and mTORC2) that play a central role in cell growth, proliferation, metabolism, tumor metastasis and angiogenesis. Abnormal mTOR activation occurs in a range of solid tumors, including sarcoma [15]. Specifically, upregulation of receptor tyrosine kinases upstream of mTOR, including the insulin-like growth factor receptor, epidermal growth factor receptor, and fibroblast growth factor receptor, has been reported in leiomyosarcomas, osteosarcomas, and synovial sarcomas [16; 17]. Deletion of the genes TSC1 or TSC2, which underly the disease tuberous sclerosis, or of the gene NF1, which underlies neurofibromatosis, results in activation of mTOR. Loss of function of these genes is associated with both benign and malignant sarcomas, including perivascular epithelioid cell tumors (PEComas) [18] and malignant peripheral nerve sheath tumors [19].

Preclinical studies indicate that rapamycin analogs are potent mTOR inhibitors, and are capable of inhibiting the growth of multiple different cancer histologies [20]. With regard to sarcoma, preclinical studies with multiple sarcoma cell lines and tumor xenograft models indicate that the rapamycin analog ridaforolimus is a potent inhibitor of sarcoma proliferation. Rapamycin analogs and other mTOR inhibitors are under clinical development in multiple cancer types. The rapamycin analogs temsirolimus and everolimus have been shown to be effective as monotherapy in the treatment of a variety of cancers, including renal cell cancer, pancreatic neuroendocrine tumors, and subependymal giant cell astrocytoma, with a safety profile distinct from that of chemotherapy, characterized by frequent but manageable stomatitis, hypercholesterolemia, and hyperglycemia, and infrequent but potentially serious side effects such as non-infectious pneumonitis and infections.

3.3 Maintenance Therapy for Sarcoma

Metastatic sarcoma is an incurable disease, and thus patients typically receive multiple lines of chemotherapy until a decline in peformance status precludes further therapy. "Maintenance" therapy of patients with metastatic, incurable cancers has been developed within the past several years in lung and other cancers in an effort to delay cancer progression and prolong disease control after initial control of the disease is achieved with chemotherapy [21; 22]. Maintenance therapy has also been referred to as "consolidation therapy" or "early next-line therapy" and should be distinguished from adjuvant therapy, which involves patients who typically have undetectable metastatic disease and may have a prolonged period of disease control even without treatment. A unique role for maintenance therapy in metastatic sarcoma compared to other malignancies relates to the predominance of anthracyclines in the treatment of this disease, and the need to discontinue anthracyline treatment after a few cycles in order to avoid cumulative cardiac toxicity. Thus, even after an initial favorable response, treatment is discontinued, and patients are followed off therapy until disease progression. The recently completed SArcoma Treatment and Burden of Illness in North America and Europe (SABINE) Study provides information about reasons for chemotherapy treatment

discontinuation in soft-tissue sarcoma patients [23]. The study evaluated treatment for patients who were at least 13 years of age and had metastatic leiomyosarcoma, liposarcoma, synovial sarcoma, or undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma. Patients must not have had disease progression within the first 4 cycles of a line of treatment, thus reflecting a population that could be offered maintenance therapy. Two-hundred-and-thirteen patient records were reviewed from 20 sites in Canada, France, Germany, Italy, the Netherlands, Spain, Sweden, UK, and the US. The results indicated that the mean number of chemotherapy cycles for all lines of therapy was 5.2, with a median of 5 cycles. Reasons for discontinuation of chemotherapy within the line of chemotherapy where favorable response was first observed were: predefined number of cycles given (60%), disease progression (12%), intolerable toxicity (8%), maximum disease control obtained (7%), patient decision (3%), and other (9%).

In addition, the SABINE study included a prospective analysis of health-related quality of life among 120 metastatic soft tissue or bone sarcoma patients who had attained a favourable response to chemotherapy. The results indicated a marked decrease in health-related quality of life in patients who experienced disease progression during a post-treatment observation period [24]. In this study, disease progression was associated with a decrease of 0.21 in EQ-5D utility score, which is well above the estimated clinically meaningful difference of 0.07-0.09 for the EQ-5D instrument [25] and was associated with a 30-point decrease in the EORTC QLC-C30 global quality of life domain, which would be considered a very large change [26]. The 30-point difference on the EORTC QLQ-C30 quality of life domain is comparable to dropping from the 70th to the 30th percentile of health-related quality of life among all cancer patients These data support the need for a maintenance treatment that could be administered in an effort to delay disease progression in patients with metastatic sarcoma.

The administration of an active and tolerable agent in a maintenance setting to extend the benefits of previous chemotherapy and delay subsequent chemotherapy treatments would offer treating physicians and their patients a useful additional management option [27; 28]. Oral, non-chemotherapeutic agents such as ridaforolimus are of particular interest as potential maintenance therapies.

3.4 Progression-Free Survival as the Primary Endpoint in a Sarcoma Maintenance Study

To evaluate clinical benefit in a maintenance treatment approach, progression-free survival (PFS) has been used frequently as the primary clinical trial endpoint [29; 28; 22]. An improvement in PFS in a maintenance setting could be clinically meaningful by delaying cancer-related morbidity associated with cancer progression, by avoiding cumulative chemotherapy toxicity, by delaying toxicities of salvage chemotherapy, and ultimately by improving overall survival (OS). However, in settings where the survival time post-progression is relatively long (e.g. median >12 months), it can be difficult to detect an improvement in OS, even when this is present, due to dilution by random variability in post-progression survival [30]. Notably, a retrospective analysis of palliative chemotherapy results for 488 patients with advanced metastatic and/or

unresectable sarcoma treated with first line chemotherapy at the Royal Marsden Hospital indicated a relatively long post-progression survival time in sarcoma patients. Median time to progression was 3 months, with a median overall survival time of 12 months [31; 32]. Post-progression survival time was even greater in P011, with patients receiving placebo experiencing a 15-month median post-progression survival time (with a total median survival time of 20 months).

These results indicate that to detect a statistically significant and clinically meaningful effect on OS in metastatic sarcoma patients would require a much larger sample size and longer enrollment period than that of P011. For example, to demonstrate a median OS improvement of 5 months (20 months on placebo compared to 25 months on experimental treatment) with a hazard ratio of 0.8 would require approximately 850 death events or over 1100 patients to achieve 90% power. This study would take approximately 6 years to complete, utilizing up to 150 sites and averaging approximately 25 patients per month.

4. Description of Clinical Development Plan

4.1 Overview of the Clinical Development Plan

As of 30-Apr-2011, ridaforolimus has been evaluated in 36 clinical trials, of which 10 trials utilized intravenous (I.V.) ridaforolimus and 26 trials utilized oral (PO) ridaforolimus; including one extension trial for ongoing patients. These trials involved more than 2000 subjects and have included patients with advanced malignancies (N=1995), healthy subjects (N=77), and subjects with noncancer-related hepatic insufficiency (N=10); of which more than 1600 patients have been exposed to at least one dose of ridaforolimus. The efficacy and safety of ridaforolimus in sarcoma patients was demonstrated with two supportive studies (P016 and P018) and the pivotal phase III study (P011) (Table 1).

During the early Phase 1 investigation of I.V. ridaforolimus in solid tumor patients, antitumor activity was observed among patients with sarcomas. Seven patients with various types of sarcomas that had progressed after an average of more than 2 prior chemotherapy regimens received I.V. ridaforolimus (on a daily x 5 schedule every two weeks across various planned dose levels) and were evaluable for response. Two of these patients (with uterine carcinosarcoma and Ewing's sarcoma) had a partial response as their best response, and 6 of the 7 patients were progression free for at least 6 months, suggesting that ridaforolimus could provide sustained antitumor activity in sarcomas.

Based on this encouraging clinical activity in sarcoma patients, a Phase II trial of IV ridaforolimus was conducted in patients with advanced sarcomas in 4 histological cohorts (P018). Overall, the disease control rate (DCR, defined as complete or partial response or prolonged stable disease ≥16 weeks) was 29% in the 212 patients across cohorts.

In order to support the transition from an I.V. to an oral dose form of ridaforolimus, a Phase I/IIa trial in 147 adult patients with refractory or advanced solid tumors was

conducted to evaluate different doses and schedules of oral ridaforolimus (P016). Among the 85 sarcoma patients in this trial treated across all doses and schedules, the DCR (defined the same as in P018) was 27%, supporting that the oral and I.V. formulations of ridaforolimus had comparable activity. Based on these promising data in patients with progressive advanced sarcomas failing prior chemotherapy and an unmet medical need for a treatment to prolong the beneficial effects achieved from a first, second, or third line of chemotherapy, the Phase III pivotal study was conducted to assess the efficacy of ridaforolimus as maintenance therapy in advanced sarcoma patients following a stable or better response to prior standard cytotoxic chemotherapy. Results of this study provide evidence of a 28% overall reduction in risk of progression in patients who received ridaforolimus over patients who received placebo.

Table 1

Sarcoma Clinical Development Plan

Protocol Number	Protocol Title / Short Description	Phase	Route/ Dose	Type of Trial	Number of Subjects Enrolled and Treated[†]
MK-8669-P011	A Pivotal Trial to Determine the Efficacy and Safety of AP23573 when Administered as Maintenance Therapy to Patients with Metastatic Soft-Tissue or Bone Sarcomas	III	Oral/ 40 mg daily x5 every week	Single-Agent Placebo-controlled	702 (343 on ridaforolimus)
MK-8669-P016	Phase I/IIa dose escalation trial to determine the safety, tolerability and maximum tolerated dose of AP23573 when administered orally in patients with refractory or advanced malignancies	I/IIa	Oral/various[‡]	Single-Agent Single-Arm	147 (85 Sarcoma)
MK-8669-P018	Phase II trial of AP23573 (daily x5, IV) in patients with advanced sarcoma	II	IV/ 12.5 mg daily x5 every 2 weeks	Single-Agent Single-Arm	212

[†] Final number of patients enrolled and treated.
[‡] P016 included 24 patients at the 40 mg daily x5 dose and schedule.

4.2 Rationale for Proposed Market Dose

The recommended dose of ridaforolimus for metastatic soft tissue or bone sarcoma is 40 mg by mouth once daily, to be taken for five consecutive days followed by a two-day dosing holiday each week (40 mg daily x 5 days/wk). Human tumor xenograft studies support an intermittent schedule as a means to optimize antitumor activity while minimizing systemic effects. In addition, the xenograft studies identified that higher exposures are associated with increased efficacy [33].

The goal of the Phase I/IIa dose-ranging study (P016) was to identify maximum-tolerated doses (MTDs) for continuous and intermittent administration schedules, and at these doses to identify the administration schedule that gave the maximum exposure (based upon highest dose density [most doses administered in a dosing cycle], cumulative dose, and cumulative exposure [$AUC_{0\text{-}28days}$]). At their MTDs, two regimens had the highest cumulative dose (800 mg over the 28 day cycle), 40 mg daily x 5 and 50 mg daily x 4 as shown in (Table 2). The 40 mg daily x 5 had the highest dose density over the 28 day cycle (20 doses) compared to 50 mg daily x 4 (16 doses). The cumulative exposures appeared similar. While this study was not designed to compare efficacy across the different administration schedules, in the 40 mg daily x 5 days/wk regimen, two (of 13) sarcoma patients achieved partial response as their best overall response, and the DCR was 23% in sarcoma patients at this dose level, indicating that this dose and schedule had activity in patients with advanced sarcomas.

Table 2

Total Predicted Exposures Over the First Cycle ($AUC_{0\text{-}28days}$) for Selected Schedules[§]

Dosing Schedule	n[†]	Dose[‡] density	MTD	Cumulative Dose/ 28 days	Ridaforolimus $AUC_{0\text{-}28days}$ (ng×hr/mL)	
					Mean	SD
daily × 21 days/cycle	11	21	15 mg	315 mg	21404	12566
daily × 28 days/cycle	13	28	10 mg	280 mg	20147	10607
daily × 4 days/week	12	16	50 mg	800 mg	38497	14615
Loading Dose daily × 5 days/week	7	20	Day 1/60mg + Days 2-5/30mg	720 mg	27898	12808
daily × 5 days/week	20	20	40 mg	800 mg	40399	13321

[†] Number of patients for which pharmacokinetic data are available
[‡] Doses administered in a dosing cycle
Dosing schedules listed are those that achieved MTD.
MTD = Maximum Tolerated Dose
[§] Individual simulated profiles with full-compliance dosing (Protocol 016)

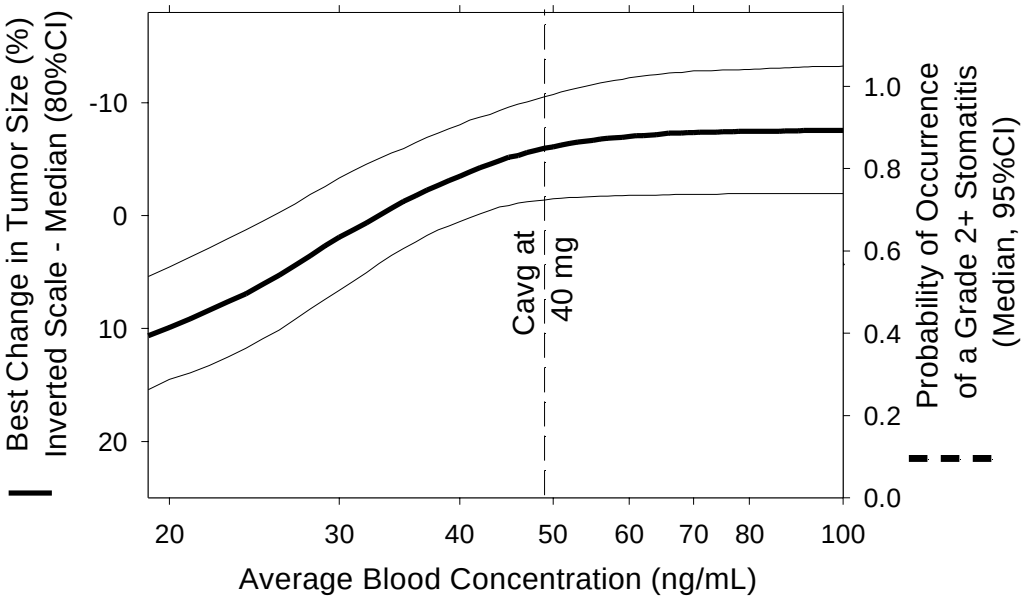
Exploratory PK/PD analysis of efficacy (PK/Efficacy) and tolerability (PK/AE) based on individual average ridaforolimus concentration in P016 further supports the recommended clinical dose and provides insight into the therapeutic window for ridaforolimus and doses which achieve an appropriate balance of efficacy and tolerability (Figure 1). Although PK data were not collected in P011, exposure-response relationships from P016 are expected to be informative of the therapeutic window for ridaforolimus in general. Relatively small sample size (n=59 for PK/Efficacy and n=138 for PK/AE) and

some differences in patient populations (progressing vs stable sarcoma at study entry) are noted as potential limitations. However, taken together the available information from the PK/PD analysis suggests that 40 mg daily x 5 days/wk is an appropriate treatment dose that falls within a therapeutic window associated with favorable benefit to patients and manageable tolerability.

The upper range of the therapeutic window explored through the PK/AE relationship for the probability of occurrence of Grade 2 or greater stomatitis as a function of blood C_{avg} from treatment start to adverse event suggests a steepening of the PK/AE curve at exposure levels above the mean C_{avg} for 40 mg daily x 5 days/wk (dotted line represents PK/AE relationship as depicted in Figure 1). This finding is consistent with the MTD approach taken originally to select the dose for the Phase III sarcoma study (P011) and provides corroborative evidence that tolerability would limit use of doses substantially higher than the proposed 40 mg dose. The majority of patients at exposures double the mean C_{avg} for 40 mg daily x 5 days/wk are predicted to experience dose-limiting stomatitis; therefore, subpopulations, (e.g. patients with moderate hepatic insufficiency) expected to have >2-fold increases in drug exposures are judged as exceeding the therapeutic window and labeling guidance to manage these patients is needed (see Sec 5.).

Figure 1

Therapeutic Window for Ridaforolimus Based on Exploratory PK/PD and PK/Efficacy Models Based on Protocol 016



The lower range of the therapeutic window was explored through the PK/Efficacy relationship in P016 for the best percent change in target lesion measurement (based on RECIST imaging criteria [Response Evaluation Criteria in Solid Tumors]) as a function of blood C_{avg} over Cycle 1 of treatment (solid line represents PK/Efficacy relationship as depicted in Figure 1). This analysis suggests that efficacy is reduced at exposures well below the mean C_{avg} for 40 mg daily x 5 days/wk. At exposures <0.65-fold the mean C_{avg} for 40 mg daily x 5 days/wk the modeling results indicate uncertainty as to whether benefit would be maintained; therefore, subpopulations (e.g., patients on concomitant treatment with CYP3A4 inducers) expected to have <0.65-fold typical drug exposures are judged as falling below the therapeutic window and labeling guidance to manage these patients is needed (see Sec. 5). Thus, the clinical comparability bounds were defined as 0.65 and 2.0.

Thus, the 40 mg daily x 5 days/wk regimen was selected as the recommended clinical dose based upon the results from P016, including exploratory PK/PD assessments, and was confirmed in P011, the Phase III pivotal sarcoma study. The recommended clinical dose is intended to maximize efficacy for the average patient with the understanding that down-dosing may be needed for individual patients to address tolerability issues while still maintaining a level of efficacy.

5. Overview of Clinical Pharmacology

Several clinical pharmacology studies in healthy subjects (N = 77) or patients were completed, including investigation of food effects (N=32 healthy subjects), ADME (N=6 healthy subjects), drug-drug interactions (N=16 patients with advanced cancer, N=30 healthy subjects), hepatic insufficiency (N=10 patients with hepatic insufficiency, N=9 healthy subjects), and the effect of ridaforolimus on QTc interval (N=23 patients with advanced cancer).

5.1 Pharmacokinetics in Humans

Blood ridaforolimus pharmacokinetics (PK) are nonlinear, with less than proportional increases in $AUC_{0-\infty}$ and C_{max}, particularly with oral doses above the intended clinical dose of 40 mg. The mechanism resulting in the nonlinear PK is understood. As with other rapamycin analogs, ridaforolimus exhibits saturable binding to the FK506 binding protein (FKBP) present in erythrocytes. A mechanistic PK model demonstrated that the saturable binding phenomena, consistent with this class of compounds, accounts for observed blood and plasma concentrations across a range of doses. The results indicate a modest increase in the proportion of ridaforolimus in plasma relative to whole blood with increasing dose across the clinically relevant dose range, which accounts for the nonlinearity observed in blood PK. Due to the relatively high blood:plasma ratio for ridaforolimus, the pharmacokinetic findings are based upon whole blood exposures, unless stated otherwise.

Ridaforolimus is eliminated almost entirely through metabolism, nearly exclusively by CYP3A. No metabolites were identified that circulated in excess of 10 percent of parent drug exposure in the human absorption, distribution, metabolism, and excretion (ADME) study (P020). The apparent whole blood terminal elimination half-life ($t_{1/2}$) is approximately 56 hours (P003). Steady-state trough levels are generally approached after 1 week of q.d. x 5 administration, and the accumulation is moderate, with an AUC accumulation ratio of approximately 1.44 and C_{max} accumulation ratio of approximately 1.01. For reference, the bioavailability of ridaforolimus is estimated at approximately 16% on average. Based upon data following intravenous administration, the clearance of ridaforolimus is low (<9 L/hr), and the volume of distribution is large (>100 L).

5.2 Intrinsic and Extrinsic Factor Analysis

Ridaforolimus is anticipated to be involved in drug-drug interactions and was studied in Clinical Pharmacology studies as summarized in Table 3.

Table 3

Summary of Ridaforolimus Drug Interaction Studies Conducted and Dosing Recommendations

DDI Studied	AUC GMR[‡] 90%CI	Comparability Bounds Analyses[§]	Recommendation
Ridaforolimus as a Victim of DDI			
CYP3A and P-gp Inhibitors P006, P045	2.26 (1.24, 4.12)	Did not meet upper bound ≤ 2.	Reduce to 20 mg
	8.57 (6.97, 10.39)	Did not meet upper bound ≤ 2.	Coadministration with strong P-gp and CYP3A inhibitors is not recommended.
CYP3A4 Induction P045	0.57 (0.41, 0.78)	Did not meet the lower bound ≥0.65.	Avoid the use of concomitant strong CYP3A4 inducers; if required, consider increasing the dose to 60 mg.
Ridaforolimus as a Perpetrator of DDI			
CYP3A Substrate P044	1.23 (1.07, 1.40)	Met the primary hypothesis for midazolam AUC within the bounds of 0.5 to 2.0	No dose adjustment.

[‡] Based on individual clinical study reports
[§] Based on the PK-PD analyses

Exploratory analyses suggest there is no clinically meaningful effect on ridaforolimus PK based on gender, age, baseline hematocrit, and limited ethnicity data (Japanese vs. Non-

Japanese). Additionally, exploratory analyses also indicate that there is no direct relationship between body mass index (BMI) (or weight) and pharmacokinetics, suggesting that BMI- (or weight-) based dosing is not warranted.

There was an ~2-fold increase in exposure of ridaforolimus in non-cancer patients with moderate hepatic insufficiency, which necessitates a dose reduction when ridaforolimus is used in patients with moderate hepatic insufficiency. Ridaforolimus was not studied in patients with severe hepatic insufficiency and should not be used in that population.

Only 1.84% of the radioactive dose of ridaforolimus is recovered in the urine, therefore, it is not anticipated that renal insufficiency would alter the pharmacokinetics of ridaforolimus. In addition, compounds known to alter renal function are not expected to affect the pharmacokinetics of ridaforolimus.

There was no clinically meaningful effect of food on ridaforolimus exposure based on the clinical comparability bounds of 0.65 to 2.0 ($AUC_{0-\infty}$ GMR and 90% CI high fat/fasted: 1.46 (1.18, 1.81); light breakfast/fasted: 1.06 (0.85, 1.32)). Therefore, ridaforolimus may be administered without regard to food.

6. Overview of Efficacy

The efficacy of ridaforolimus was evaluated in the pivotal Phase III study (P011), which was a randomized, double-blind, placebo-controlled study of metastatic sarcoma patients treated with oral ridaforolimus or placebo at 40 mg daily x 5 days/wk (40 mg once daily over 5 consecutive days with a 2 day "drug holiday" each week) as a maintenance therapy. The results of the Phase III trial are supplemented by the two non-randomized trials, P016 and P018.

6.1 Supportive Sarcoma Studies - Protocols 018 and 016

For the two supporting sarcoma trials, P016 and P018, the efficacy analysis was based on radiological review at local sites every 8 weeks using RECIST criteria. The efficacy was analyzed by determination of DCR, PFS rate at 6 months, and median PFS and OS as determined by Kaplan-Meier analyses.

6.1.1 Protocol 018: A Phase II Study of I.V. Ridaforolimus in Patients with Advanced Sarcoma

A Phase II study was conducted that utilized an I.V. formulation of ridaforolimus in sarcoma patients who had at least one measurable target lesion. This study was an open-label, uncontrolled, non-randomized, multi-center, Phase II study to assess the safety and anti-tumor activity of ridaforolimus administered intravenously in patients 15 years or older with advanced sarcomas (metastatic and/or 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. Patients were eligible to continue treatment until progression or any of the discontinuation criteria were met.

A Simon's optimal 2-stage design (significance level 0.05, power = 0.90) was used to distinguish a favorable true disease control rate (DCR, defined as complete response, partial response, or stable disease for ≥ 16 weeks) of ≥ 35% from a null rate of ≤15% within each histological cohort. The DCRs met statistical criteria for exclusion of the null hypothesis (requiring DCR ≥ 25%) in 3 of the cohorts: bone sarcoma, leiomyosarcoma, and liposarcoma (Table 4). The DCR rate for the other soft tissue sarcoma cohort was 21.1% (12/57).

Table 4

P018 Disease Control Rates Across Sarcoma Cohorts

Cohort	N	DCR % (n)
Bone Sarcoma	54	31.5% (17)
Leiomyosarcoma	57	33.3% (19)
Liposarcoma	44	29.5% (13)
Other Soft Tissue Sarcoma	57	21.1% (12)
N = Number of patients in the disease cohort		

6.1.2 Protocol 016: A Phase I/IIa, Sequential Cohort, Dose Escalation Trial to Determine the Safety, Tolerability and Maximum Tolerated Dose of Ridaforolimus when Administered Orally in Patients with Refractory or Advanced Malignancies

P016 was a Phase I dose-escalation, non-randomized study of oral ridaforolimus. Patients with advanced solid tumors (including 85 patients with advanced sarcoma) refractory to standard therapies was conducted to assess 7 dose schedules (including continuous and intermittent schedules) to determine the recommended dose for subsequent development. Planned dose increases for each schedule were to proceed in increments of 10 mg per dose until the MTD was determined. The MTD was defined as the dose below the dose that produced dose-limiting toxicities in at least one-third of at least six patients treated within a dose cohort in Cycle 1.

Efficacy parameters across dosing regimens and at the recommended dose are shown in (Table 5). Two of 13 (15.4%) of sarcoma patients treated with the recommended dosing regimen of 40 mg daily x 5 days/wk achieved a best overall response of partial response, and the DCR rate with this dose regimen was 23.1 %. These data suggest comparable

activity for oral and IV ridaforolimus in patients with advanced sarcomas who have progressed on standard treatments.

Table 5

P016 Efficacy Parameters for All Doses and the Recommended Dose

Dose Schedule	N	PR, n (%)	DCR, n (%)	PFS rate at 26 weeks	Median PFS (weeks)
All Schedules	85	2 (2.3%)	23 (27.1%)	29.3%	17.1
40 mg daily x5	13	2 (15.4%)	3 (23.1%)	23.1%	16.1

DCR = Disease Control Rate; PFS = Progression-free Survival; PR = Partial Response; daily x5 = every day for 5 days per week

Because P016 and P018 were single arm studies, historical control data provide a useful reference to place the efficacy results into context. The EORTC Soft Tissue and Bone Sarcoma Group estimated the progression free rate from their clinical trial database to provide reference values for Phase 2 studies in several soft tissue sarcoma populations, in recognition that the biological activity of many anticancer agents used for sarcomas may not translate into formal RECIST responses, but may rather result in stabilization of disease as defined by RECIST. Thus PFR (progression free rate, or the fraction of a study population that is progression free at a given landmark in time) was suggested as a useful endpoint for Phase 2 studies and reference values were provided. The database contained the results of clinical studies in 380 previously treated soft tissue sarcoma patients from 12 clinical trials involving 13 therapeutic regimens. Among patients with previously treated soft tissue sarcoma who received an agent that was deemed to be active (for example, ifosfamide following anthracycline failure), the 6-month PFR was 14% and the median PFS was 8 weeks [34]. The study populations in P016 and P018, in particular the STS cohorts, is reasonably comparable to the EORTC database of previously treated metastatic soft tissue sarcoma patients, and the results of P016 and P018 compare favorably to the historical controls from the EORTC database of agents that are active in previously treated, metastatic soft tissue sarcoma (Table 6).

Table 6

Key Supportive Efficacy Data from Protocols 016 and 018
Compared to a Historical Control Database

	P016 (Sarcoma patients; N = 85)	**P018 (N=212)**	**EORTC Soft Tissue Sarcoma Database [34]**
Progression-Free Survival (weeks) Median (95% CI)	17.1 (14-20)	15.3 (14.3, 16.3)	8
6-month Progression-Free Survival Rate	23%	23.4%	14%
Disease Control Rate	27.1%	28.8%	NR
Overall Survival Median (weeks) (95% CI)	42.7 (29-88)	40.1 (32.1, 51.6)	NR

6.2 Protocol 011—Pivotal Registration Study

6.2.1 Study Design

The pivotal trial (P011) was a multi-center, randomized, Phase III, double-blind, placebo-controlled trial of oral ridaforolimus vs. oral placebo in patients with metastatic sarcoma. The study planned to enroll 650 patients, age ≥ 13 years. Eligible patients included those with metastatic soft-tissue or bone sarcoma who had achieved a complete response, partial response or stable disease as defined by RECIST guidelines, version 1.0, after completion of at least 4 cycles of 1st, 2nd or 3rd line chemotherapy for metastatic sarcoma. Patients were randomly assigned in a 1:1 ratio to receive either ridaforolimus 40 mg q.d. x 5 days per week or placebo by oral administration. Randomization was stratified by geographical region, histological category (soft-tissue or bone sarcoma), and prior treatment (1st line or 2nd/3rd line). Although the management of bone and soft tissue sarcomas may differ in earlier stages of disease, when sarcomas become metastatic, the outcome and management of soft tissue and bone sarcoma is generally similar, and it is appropriate to design a study combining these two groups for the endpoints of P011. Only eligible patients were randomized.

The disease status at study entry was confirmed through an independent radiographic review during the screening period prior to randomization. In addition, histopathology slides were submitted for review within 30 days post randomization to the central pathology review group for confirmation of the patient's sarcoma diagnosis.

Treatment continued until disease progression as defined by RECIST guidelines. Treatment was also discontinued for intolerable adverse events, or at the decision of the patient or treating physician. Crossover from the placebo group to the ridaforolimus treatment group upon documentation of disease progression was not allowed. Patients

were followed after treatment discontinuation for collection of survival information, but details of any therapy administered after progression were not collected.

To evaluate efficacy, disease progression and objective tumor response were assessed by imaging studies every 8 weeks and reviewed by investigators and an independent radiology committee according to RECIST guidelines [35]. Patients were intended to be followed for overall survival for at least 24 months and up to 60 months after randomization (a pre-specified long-term overall survival analysis was conducted in January 2012, 24 months after the last patient was randomized).

The primary endpoint, PFS, was defined as the time from the date of randomization to the date of documented progressive disease, recurrence or death (whichever occurred first). Patients who discontinued treatment without having documented disease progression continued whenever possible to have assessments every 8 weeks until disease progression was documented or another anti-cancer therapy was instituted, whichever came first. All radiological images collected for the purpose of disease assessment, beginning with the baseline scans through the last on-study disease assessment, were reviewed by an Independent Review Committee (IRC). Radiographic images were provided to the IRC with masked patient information; the IRC was blinded to treatment assignment. Secondary supportive analysis for PFS was conducted based on Investigator assessment of disease response. The study was designed so that the final analysis of PFS would occur after approximately 516 PFS events (among the 650 patients randomized) in order to provide approximately 90% power to detect a hazard ratio of 0.75.

The secondary endpoint, OS, was defined as the time from the date of randomization to the date of death. The secondary endpoint, best target lesion response, was defined as the maximum percentage decrease (or minimum percent increase if a decrease did not occur) in the sum of longest diameters of target lesions pre-specified at baseline until disease progression, based on IRC review. To evaluate the secondary endpoint of cancer related symptoms, patients were required to complete a questionnaire on changes in selected symptoms every 4 weeks until Week 16 and every 8 weeks afterwards during treatment and at treatment discontinuation. The questionnaire was not completed after discontinuation of study treatment. The questionnaire had three symptoms categories: pain, cough, and shortness of breath. Each symptom category had 4 severities: none, mild, moderate and severe. The methods for analyzing the symptom data were not pre-specified, and thus all analyses of this endpoint should be considered exploratory.

The study had 5% (two-sided) Type I error for the primary endpoint of PFS that was controlled for the two interim analyses using a group sequential design. Two formal interim analyses for efficacy and safety were planned after approximately one-third (172) and two-thirds (344) of the total expected events (progression or deaths) had occurred and a final analysis after 516 events. The group sequential bounds were conservative in that evidence required to stop the trial early needed to be relatively definitive to reject either the null or alternative hypotheses. The cutoff for final analysis was set to October 25, 2010 to achieve 516 events based on the accumulation of events recorded over time. At that time, all remaining patients imaging studies were reviewed by the IRC, including

patients who remained on study and had not been assessed by investigators as having progressed. Due to a higher than anticipated number of events found by the IRC, the number of events was 552 rather than 516 at the pre-specified cutoff date. The primary analysis included all randomized patients in accordance with the intention-to-treat principle.

Three analyses of overall survival were specified prior to sponsor unblinding: 1) at the time of unblinding (October 25, 2010), 2) February, 2011 and 3) January 21, 2012. The second was revised to April 30, 2011 to allow for additional survival events to be included in the NDA. While cancer related symptoms was described as a secondary endpoint in the objectives of the protocol, the analysis was described in the protocol as exploratory and no method of analysis was suggested.

6.2.2 Patient Characteristics

The pivotal Phase III trial included patients with metastatic soft tissue or bone sarcoma, who achieved response or stable disease after completion of at least 4 cycles of chemotherapy. Table 7 displays the baseline characteristics of the Intent-To-Treat (ITT) population from P011. Baseline characteristics were generally well-balanced between treatment arms.

Table 7

Demographic and Baseline Characteristics
(ITT Population) Protocol 011

	Ridaforolimus (N=347)	Placebo (N=364)
Age		
Age Median (Years)	53.0	52.0
Male	46%	43%
ECOG		
0	50.1%	50.5%
1	49.6%	49.5%
Histological Category[a]		
Soft Tissue	89.3%	91.2%
Bone	10.7%	8.8%
Prior Most Recent Chemotherapy[a]		
First Line	61.1%	61.5%
Second/Third Line	38.9%	38.5%
Number of chemotherapy cycles prior to enrollment (median)	6	6
Independent Pathologist Tumor Grade		
Low	3.7%	5.5%
High	73.8%	73.1%
Cannot be assessed	8.6%	7.7%
Not Applicable	2.3%	2.5%
Missing	11.5%	11.3%
Best response to most recent cytotoxic chemotherapy regimen[b]		
CR	5.5%	4.9%
PR	18.4%	19.2%
SD	74.4%	75.0%
Unknown	0.9%	0.5%
Metastatic Sites [c]		
Lung	64.8%	67.0%
Liver	27.1%	32.1%
Bone	18.2%	15.4%

[a] From stratification. [b] For metastatic disease.
[c] Based on presence of target or non-target lesions in these sites at baseline by IRC
(Database Cutoff Date: 25OCT2010)

Sarcoma histology for the study population based on independent pathology review is shown in Table 8. Independent pathology review for histologic subtype was available for more than 90% of patients; when it was not available, the local diagnosis was used. Patients with the diagnosis of soft tissue or bone sarcoma were eligible, with the exception of patients with certain histopathologic subtypes of sarcomas that derive no benefit from conventional chemotherapies or with distinctly different natural histories, including well differentiated liposarcoma, chondrosarcoma, and gastrointestinal stromal tumor. The proportions of patients enrolled with soft tissue (90%) and bone sarcoma (10%) reflects the general US prevalence of soft tissue and bone sarcoma. The number of patients with bone sarcoma based on initial investigator stratification in

Table 7 (69) is slightly greater than the number of patients with bone sarcoma determined by independent pathology review in Table 8 (63).

Table 8

Sarcoma Histologies after Independent Pathology Review (ITT Population) P011

		Ridaforolimus (N=347)	Placebo (N=364)	Overall (N=711)
Bone Sarcoma				
	Osteosarcoma	25 (7.2%)	25 (6.9%)	50 (7.0%)
	Other†	5 (1.4%)	8 (2.2%)	13 (1.8%)
Soft Tissue				
Leiomyosarcoma	Leiomyosarcoma	113 (32.6%)	118 (32.4%)	231 (32.5%)
Liposarcoma	Liposarcoma	51 (14.7%)	48 (13.2%)	99 (13.9%)
Other Sarcoma	Angiosarcoma	7 (2.0%)	5 (1.4%)	12 (1.7%)
	Desmoplastic Small Round Cell Sarcoma	7 (2.0%)	4 (1.1%)	11 (1.5%)
	Malignant Peripheral Nerve Sheath Tumor	7 (2.0%)	9 (2.5%)	16 (2.3%)
	Myxofibrosarcoma	9 (2.6%)	6 (1.6%)	15 (2.1%)
	Rhabdomyosarcoma	5 (1.4%)	8 (2.2%)	13 (1.8%)
	Solitary Fibrous Tumor	8 (2.3%)	2 (0.5%)	10 (1.4%)
	Spindle Cell Sarcoma	9 (2.6%)	7 (1.9%)	16 (2.3%)
	Synovial Sarcoma	23 (6.6%)	37 (10.2%)	60 (8.4%)
	Undifferentiated Pleiomorphic Sarcoma	27 (7.8%)	28 (7.7%)	55 (7.7%)
	Other†	43 (12.4%)	46 (12.6%)	89 (12.5%)
Other Cancer				
	Other†	5 (1.4%)	12 (3.3%)	17 (2.4%)
Unknown				
	Unknown	3 (0.9%)	1 (0.3%)	4 (0.6%)

† The "Other" sub-categories in the second column include specific diagnoses in fewer than 10 patients each.

6.2.3 Efficacy Results

6.2.3.1 PFS

6.2.3.1.1 Primary Analyses of PFS

P011 met the pre-specified primary endpoint of improvement of PFS (by independent radiologic assessment) compared with placebo. The hazard ratio was 0.72 (95% CI [0.61, 0.85], p=0.0001), indicating a 28% overall reduction in risk of progression or death in patients who received ridaforolimus, exceeding the pre-specified target HR of 0.75 that was determined in collaboration with sarcoma experts during the design of the study to represent meaningful improvement in PFS in this patient population and which was agreed to by FDA in the Special Protocol Assessment. The Kaplan Meier plots of PFS based on IRC assessment and site assessment are shown in Figure 2 and Figure 3, respectively.

Figure 2

Kaplan-Meier Plot of Progression-Free Survival by IRC Assessment (ITT Population)
Protocol 011

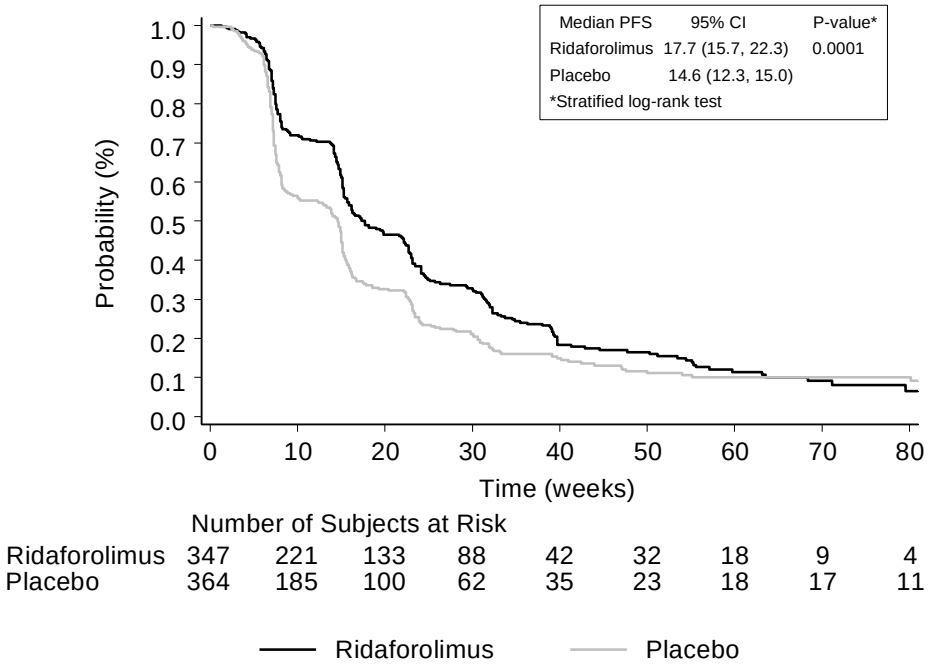
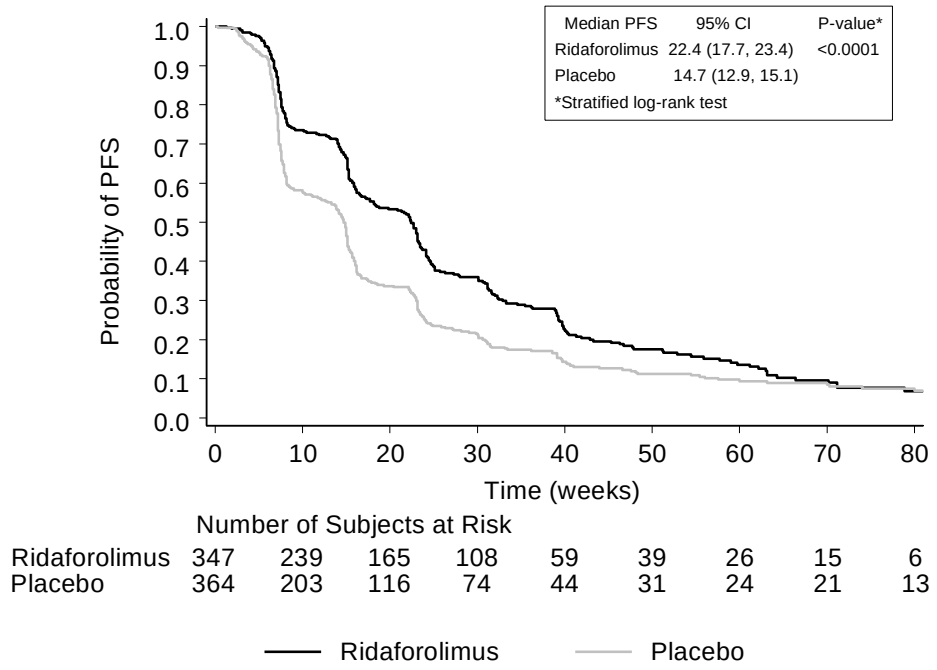


Figure 3

Kaplan-Meier Plot of Progression-Free Survival Primary Analysis
by Investigative Site Assessment (ITT Population)
Protocol 011

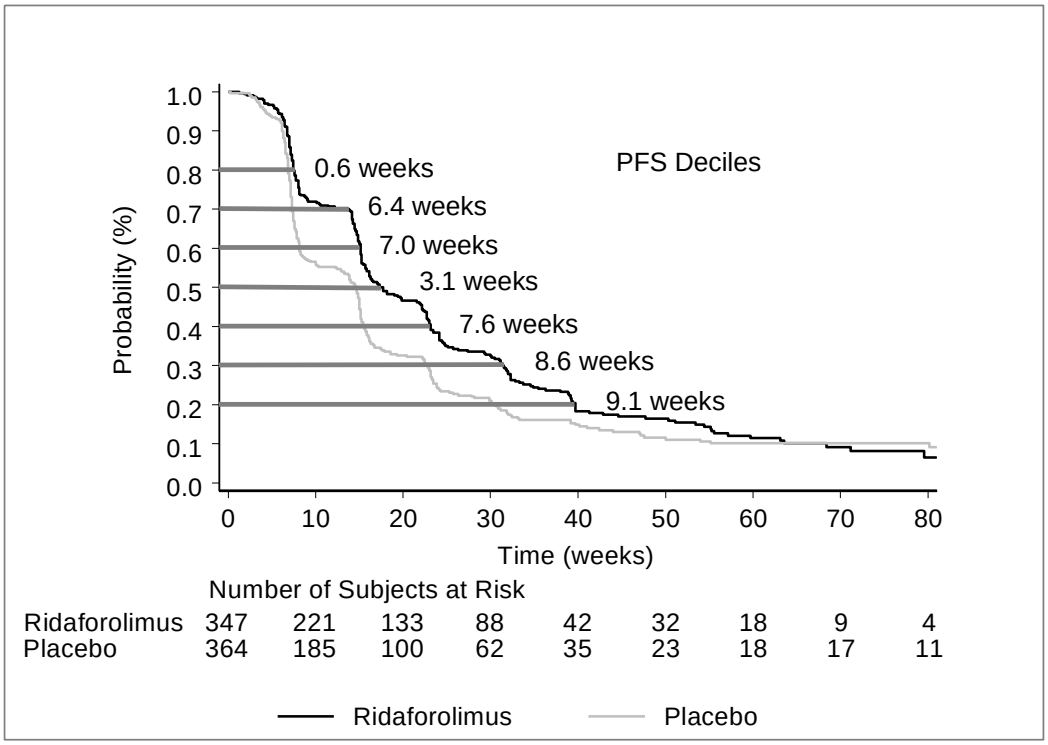


The difference in median estimated PFS between treatment groups for the IRC assessed endpoint is 3.1 weeks in Figure 3, and is likely an underestimate of the true difference between treatment arms. The curves for the ridaforolimus arm and the placebo arm have a scalloped pattern that corresponds approximately to the timing of imaging studies every 8 weeks, and the curves appear to be artifactually close to each other at the median in the IRC assessed PFS curves. With the exception of the median (50^{th} percentile), the absolute difference between treatment arms at each decile along the curve from the 30^{th} to 70^{th} percentiles is 6.4-8.6 weeks (Figure 4). For this reason, the hazard ratio is the single best descriptor of the difference in treatment arms. Based on the HR and median PFS in the control arm, 5.7 weeks is a better estimate of the median treatment effect (calculated

from: 14.6 weeks x 1/0.72). This estimate is in agreement with the supportive analyses of PFS discussed below.

Figure 4

Kaplan-Meier Plot of Progression-Free Survival by IRC Assessment (ITT Population), Illustrating the Difference between Treatment Arms at Each Decile
Protocol 011



6.2.3.1.2 Supportive Analyses of PFS

As exploratory analyses, interval censoring and parametric methods were used to provide additional information on the PFS treatment effect. These analyses took into account the interval censored nature of the data, i.e. the exact date of disease progression was only known to be between disease assessment visits rather than at the time of the scan documenting progression that is used with the Kaplan-Meier method. Thus, interval censored analyses of data generally result in a shorter median than the conventional Kaplan-Meier method. Smoothed PFS curves based on parametric assumptions, including the allowance of non-proportional hazards between treatment groups and interval censoring are presented in (Figure 5). These analyses indicated a more substantial improvement in median PFS compared to the primary analysis method, with a median

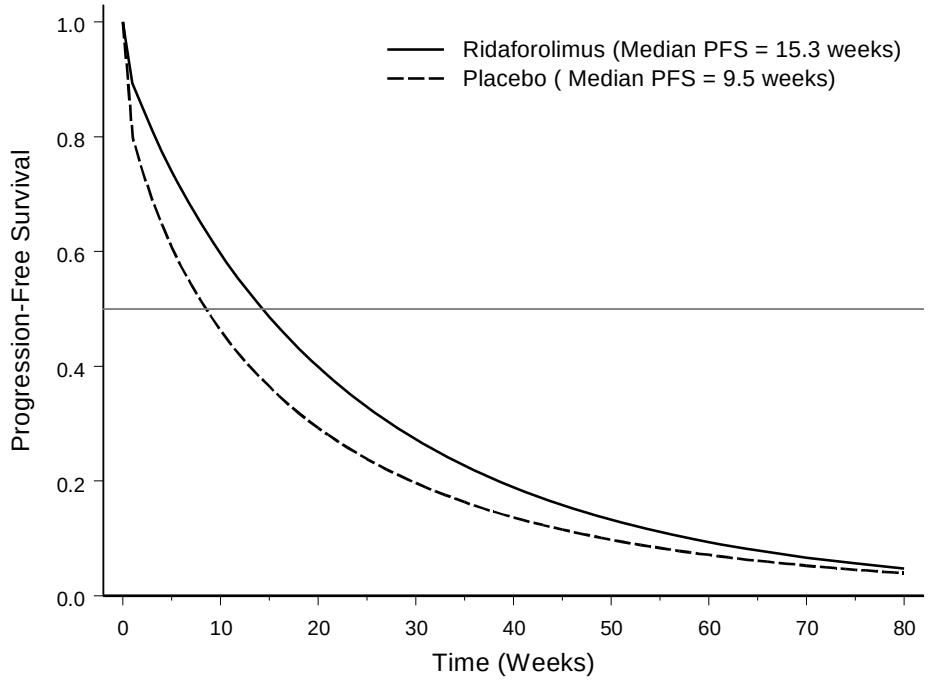
PFS improvement of 5.2 weeks for the interval censored method (12.7 weeks for ridaforolimus vs. 7.5 weeks for placebo) and 5.8 weeks for the parametric method 15.3 weeks for ridaforolimus vs. 9.5 weeks for placebo) by IRC assessment. Both are in good agreement with the estimated median PFS difference from the primary analysis method based on the hazard ratio.

It is also important to note that the Finkelstein (1986) interval censored method [36] has been shown to be robust to data abnormalities such as extremely infrequent assessments and/or imbalance in assessment frequencies between treatment arms [37; 38]. The results based on Finkelstein (1986) are HR=0.75 (95% CI [0.63, 0.89]; p=0.0001) per IRC assessment and HR=0.71 per site assessment (95% CI [0.60, 0.84];p<0.0001), which are supportive of the conclusion from the primary analysis of PFS. Based on these data, it is apparent that the 3.1 week median difference in PFS between the treatment arms is an underestimate of the treatment effect.

To further evaluate the impact of the timing of disease assessment, a supportive analysis to the primary analysis of PFS based on scheduled assessment timing was performed. In this analysis, events documented between scheduled assessments are dated at the next scheduled assessment. Censoring dates for patients without events between scheduled assessments are dated to the next scheduled assessment. To accommodate the one week window around the scheduled assessment that was allowed by the protocol, if the event/censoring date is up to one week later than the scheduled date, it is moved back to the scheduled date. Using this approach, the PFS HR was 0.72 (95% CI [0.61, 0.85]) based on IRC assessment and the HR was 0.69 (95% CI [0.58, 0.81]) based on site assessment. Median improvement was 8 weeks by both IRC and site assessments (24 weeks for ridaforolimus vs. 16 weeks for placebo). This analysis further demonstrates that differences in the timing of disease assessments between treatment arms have minimal impact on the magnitude of the improvement in PFS observed in the ridaforolimus arm.

Figure 5

Parametric Estimate of Progression-Free Survival by IRC Assessment (ITT Population)
Protocol 011

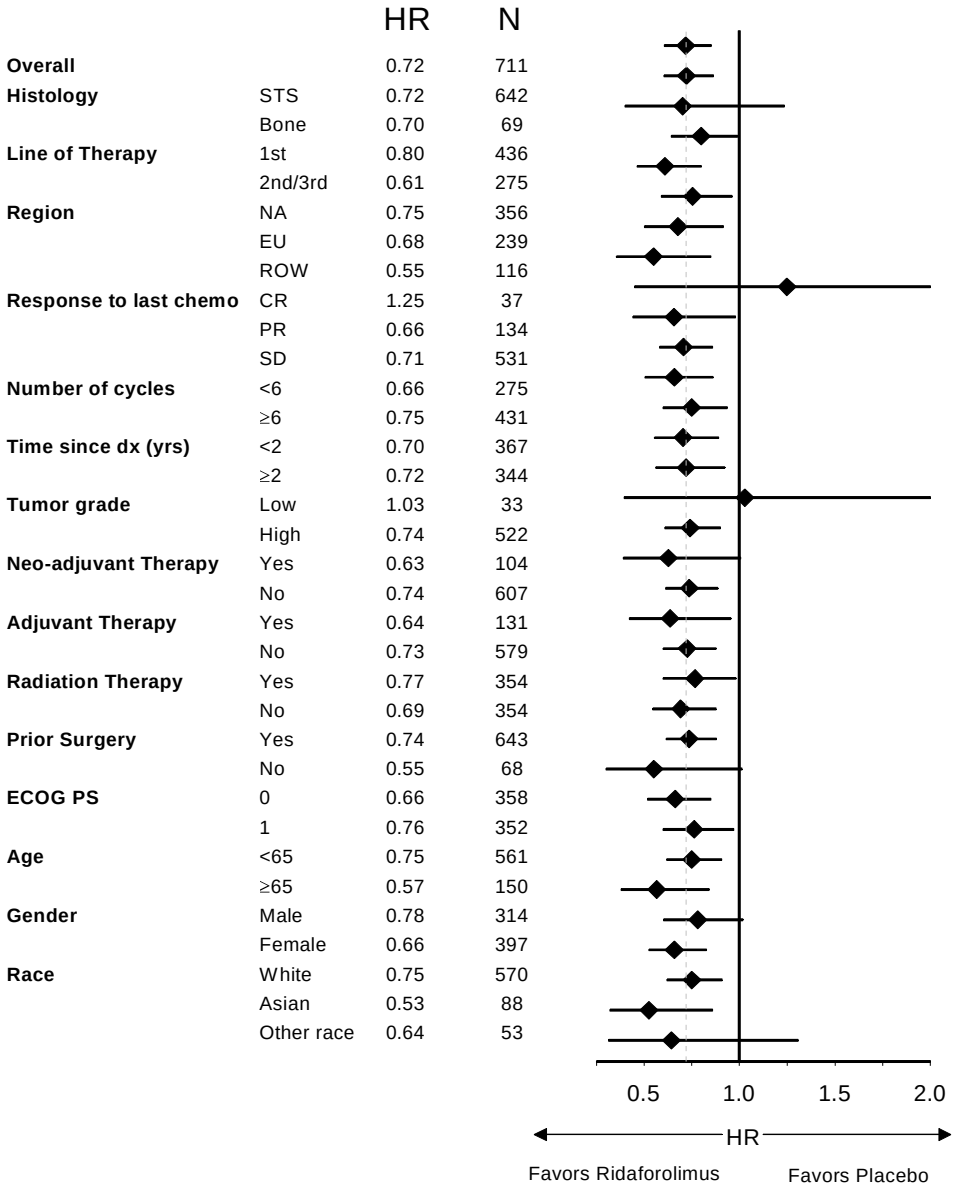


6.2.3.1.3 Subgroup Analysis of PFS

Pre-specified subgroup analyses of the PFS endpoint based on various baseline demographic characteristics also revealed that the benefit of ridaforolimus persisted regardless of baseline characteristics such as age, gender, race, geographic region, functional performance status, tumor histology, prior line of therapy, prior surgery, neoadjuvant or adjuvant therapy (Figure 6). In particular, ridaforolimus exhibited similar PFS benefit in both bone sarcoma and soft tissue sarcoma subgroups based on stratification at randomization (HR: 0.70 vs. 0.72).

Figure 6

Subgroup Analysis of Progression - Free Survival (IRC) (ITT Population) Protocol 011

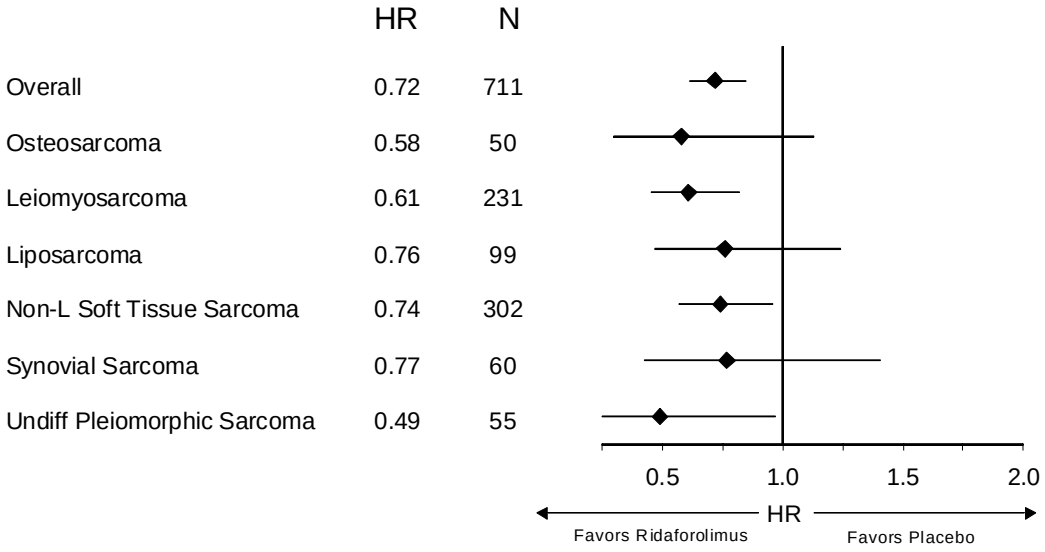


Post-hoc Subgroup Analyses:

Additional post-hoc subgroup analyses were performed to evaluate additional common clinical factors that could potentially influence response to treatment. These analyses include PFS for the histological subtypes of sarcoma based on independent pathology review (Figure 7), and corresponding to the histological subtypes shown in Table 8. In addition, PFS based on sites of metastases or tumor involvement (determined by the presence of target lesions or non-target lesions in a given organ system) on IRC review of baseline imaging studies was determined. Analyses are shown for PFS based on IRC assessment. "Non-L" soft tissue sarcoma indicates other soft tissue sarcomas, except for leiomyosarcoma and liposarcoma. Synovial sarcomas and undifferentiated pleiomorphic sarcomas (formerly known as malignant fibrous histiocytomas) are the two largest subgroups of non-L soft tissue sarcomas. There is high consistency of PFS effect in the subgroups with the overall effect size, and there are no major differences in PFS based on the histologic subtype of sarcoma. Similarly, there are no major differences in PFS based on tumor involvement of lungs (HR 0.71, 95% CI 0.58, 0.87), liver (HR 0.53, 95% CI 0.39, 0.72), bone (HR 0.85, 95% CI 0.55, 1.33) or lymph nodes (HR 0.71 95% CI 0.51, 0.98). It is notable that the PFS HR for the subgroup of patients with liver metastases is 0.53, as this is a subgroup of patients who often have a poor outcome with conventional chemotherapy [39].

Figure 7

Subgroup Analysis of Progression - Free Survival (IRC) based on Sarcoma Histology by Independent Pathology Review (ITT Population) Protocol 011



6.2.3.1.4 Concordance Between IRC Assessment and Site Assessment of Progression and PFS Events

An evaluation of concordance in determining progression events between IRC assessment and investigative site assessment for the 691 patients who were reviewed by IRC is shown in Table 9.

Table 9

Evaluation of Concordance of Progression Events

		IRC Assessment	
	Site Assessment	PD	Non-PD
Ridaforolimus	PD	218†	45
	Non-PD	26	45
Placebo	PD	274‡	43
	Non-PD	12	28

† 137 agreed on timing and occurrence of progression, 76 agreed on PD but IRC has earlier time, 5 agreed on PD but Site has earlier time.
‡ 202 agreed on timing and occurrence of progression, 62 agreed on PD but IRC has earlier time, 10 agreed on PD but Site has earlier time.
PD = progressive disease
(Database Cutoff Date: 25OCT2010)

The discordance in terms of type of event and timing of event between IRC and investigator determined PFS events was calculated (Table 10). While there is a slightly greater percentage of discordance in evaluation of PFS events among the ridaforolimus treatment arm than the placebo treatment arm, overall these results are consistent with the frequency of investigator/IRC discordance in historical randomized controlled studies of cancer therapeutics [40].

Table 10

Discordance of PFS Events

Ridaforolimus (N=347)			Placebo (N=364)		
Type	Timing	Total	Type	Timing	Total
73 (21.0%)	79 (22.8%)	152 (43.8%)	56 (15.4%)	71 (19.5%)	127 (34.9%)

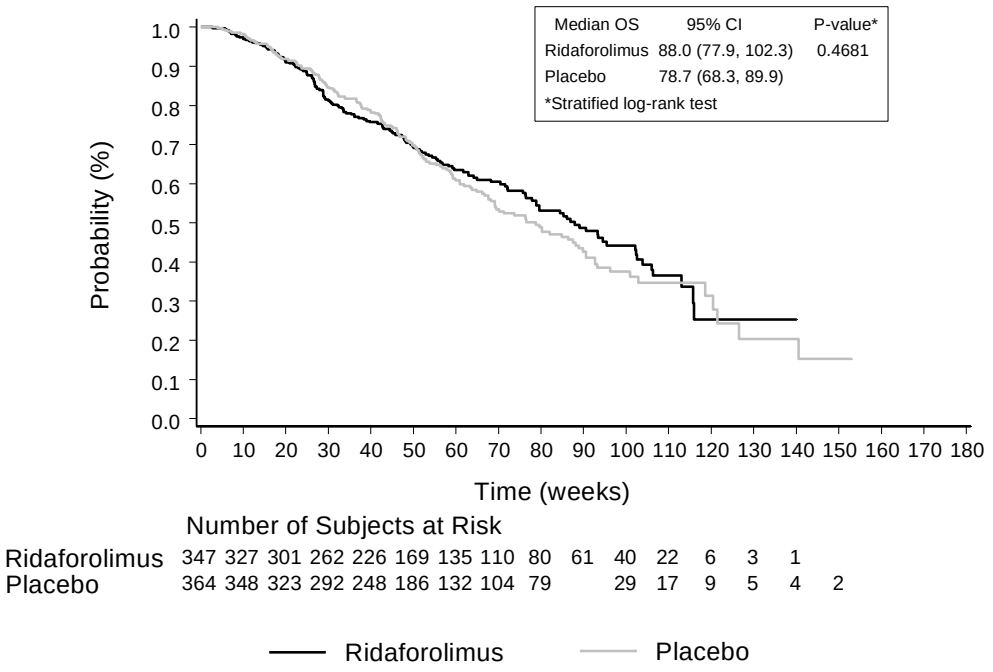
6.2.3.2 Overall Survival (OS)

OS was a prespecified secondary endpoint. However, the study was not powered to detect a difference in overall survival. An analysis of the secondary endpoint of OS was performed based on 313 death events (44% of the ITT population) at the time of the data cut-off for the primary PFS analysis (25-Oct-2010). At that analysis, the HR was 0.92

(95% CI [0.74, 1.15]) favoring the ridaforolimus treatment group with a p-value of 0.4681 based on Log-rank test. The median OS durations were 88 weeks (95% CI [77.9, 102.3]) for patients receiving ridaforolimus and 78.7 weeks (95% CI [68.3, 89.9]) for the placebo group, for a 9.3-week difference favoring the ridaforolimus treatment group based on the median point estimates, however, this result did not achieve statistical significance. The corresponding Kaplan-Meier plot of OS is shown in Figure 8.

Figure 8

Kaplan-Meier Plot of Overall Survival
Protocol 011 (October 25, 2010 data cutoff, 313 deaths)
(ITT Population)

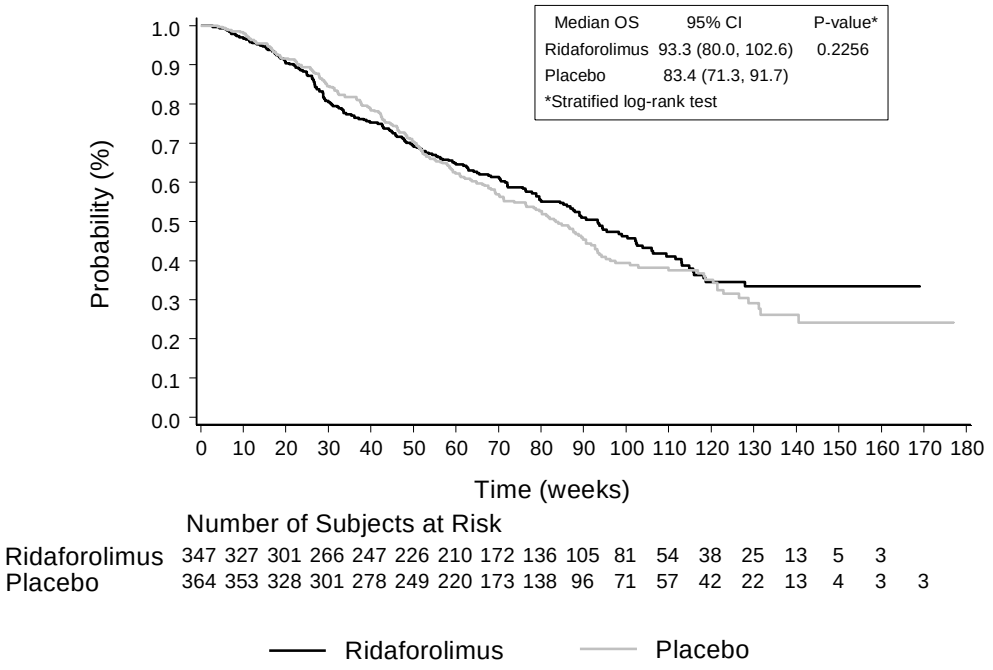


The second prespecified OS analysis was performed with an April 30 2011 data cut-off date at a total of 386 deaths, representing 54% of the ITT population. At this analysis there were 178 deaths in the ridaforolimus treatment group and 208 deaths in the placebo treatment group. The median OS was 93.3 weeks (95% CI [80.0, 102.6]) for patients assigned to ridaforolimus and 83.4 weeks (95% CI [71.3, 91.7]) for patients assigned to placebo, a difference of 9.9 weeks. In this analysis of OS, the HR is 0.88, favoring

ridaforolimus (95% CI [0.72, 1.08]; p=0.2256), though again not achieving statistical significance. The corresponding Kaplan-Meier plot of OS is shown in Figure 9.

Figure 9

Kaplan-Meier Plot of Overall Survival
Protocol 011 (April 30, 2011 data cutoff, 386 deaths)
(ITT Population)



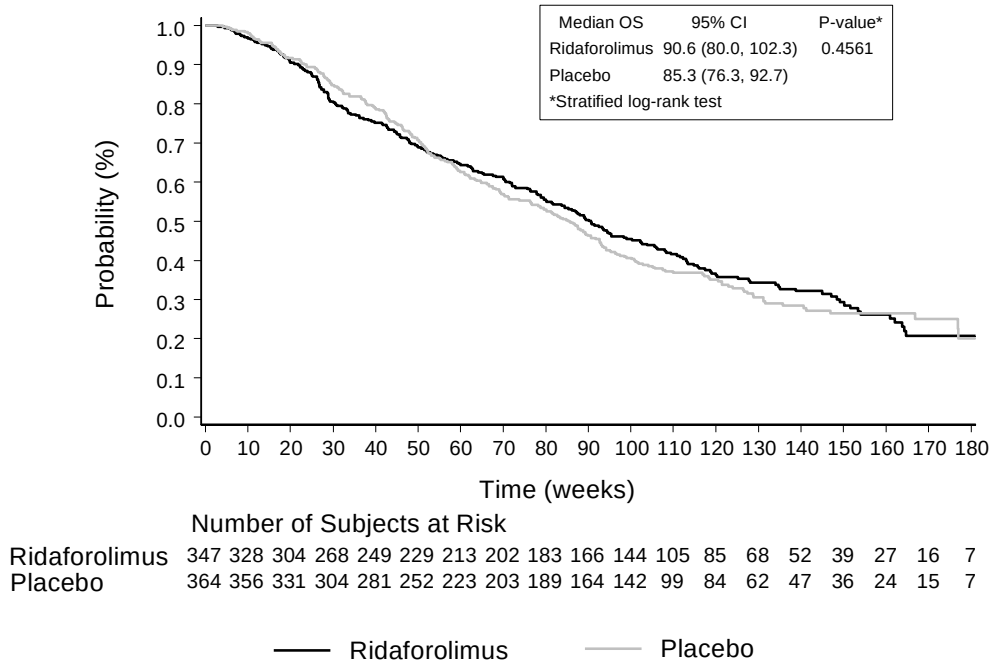
The third prespecified overall survival analysis was performed with a January 21, 2012, data cutoff, two years after the last patient was randomized, and thus includes at least 24 months follow-up on all patients in the ITT population. The analysis includes current follow-up data (patients known to be dead or having a survival follow-up recorded within 90 days of the data cutoff) on a total of 683 (96.1%) patients (329 [94.8%] in the ridaforolimus treatment group and 354 [97.3%] in the placebo treatment group). Survival follow-up was incomplete on 28 (3.9%) patients (18 [5.2%] in the ridaforolimus arm, and 10 [2.7%] in the placebo arm). At the time of the data cutoff, there were 478 deaths, representing 67.2% of the ITT population, with 228 deaths in the ridaforolimus treatment group and 250 in the placebo treatment group.

The median OS was 90.6 weeks (95% CI [80.0, 102.3]) for patients assigned to ridaforolimus and 85.3 weeks (95% CI [76.3, 92.7]) for patients assigned to placebo, a

difference of 5.3 weeks. The HR is 0.93, favoring ridaforolimus (95% CI [0.78, 1.12]; p-value=0.4561). The Kaplan-Meier plot of OS from the January 2012 update is shown in Figure 10. At this latest OS update, with mortality in 67% of the ITT population, the upper bound of the 95% confidence interval is 1.12, and a Bayesian analysis with flat prior distribution showed approximately 80% probability that the HR is < 1. Thus, with mature survival data that is consistent across three pre-specified analyses, a detrimental effect of ridaforolimus on survival is largely ruled out.

Figure 10

Kaplan-Meier Plot of Overall Survival
Protocol 011 (January 2012 data cutoff, 478 deaths)
(ITT Population)



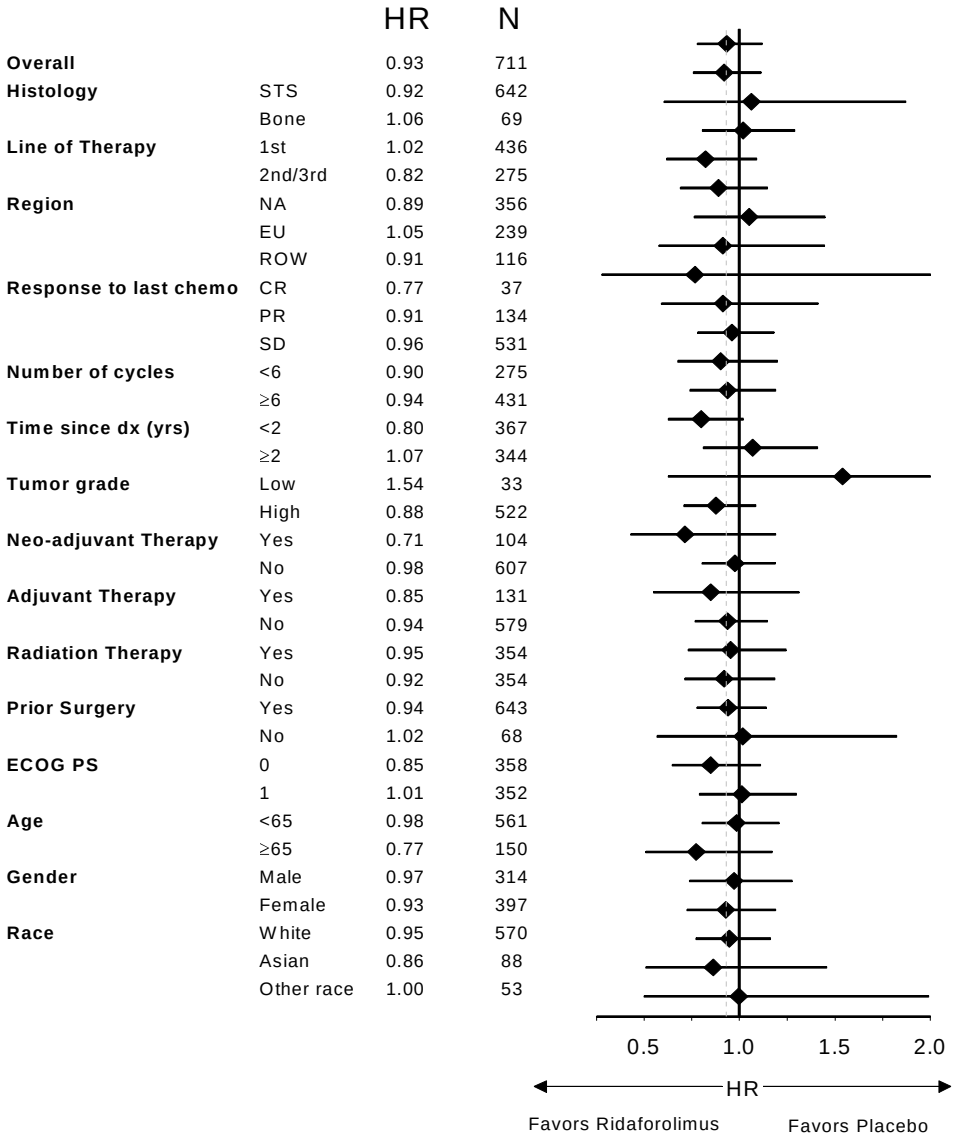
6.2.3.2.1 Subgroup Analysis of OS

An additional analysis of OS was performed to examine the impact of subgroups defined by certain baseline characteristics. Most of the subgroups have a relatively small sample size as shown by their wide confidence intervals in Figure 11 and for this reason, the analysis is displayed based on the OS data cutoff of January 21, 2012, which has the

greatest number of OS events overall and provides a better estimate of the OS in various subgroups. The treatment effect is generally consistent in all subgroups. All CIs cover the estimated overall treatment effect (HR of 0.93). The forest plot of multiple subgroup analyses also suggests that the appearance of observed differences in treatment effect is consistent with random variation. Overall, the subgroup analyses support the conclusion from the primary analysis of OS in the context of random variation. .

Figure 11

Subgroup Analysis of Overall Survival (ITT Population) Protocol 011
Based on the January 2012 OS Analysis



6.2.3.3 Best Target Lesion Response

Best target lesion response, another pre-specified secondary endpoint, 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 tumor measurements. Patients without target lesions at baseline or patients without any post-baseline data in target lesions were not included in this analysis. Based on IRC assessment, the ridaforolimus treatment group showed a mean reduction of 1.3% in target lesion tumor size. In contrast, the placebo treatment group showed a mean increase of 10.3% in target lesion tumor size ($p<0.0001$) (Table 11).

Table 11

Best Target Lesion Response (IRC)

	Ridaforolimus (N=255)	Placebo (N=274)
Average change in tumor size ($p<0.0001$)	↓1.3%	↑10.3%
Tumor growth > 10%	22%	38%
No change (-10% - +10%)	49%	46%
Tumor Shrinkage >10%	29%	17%

These data are in general agreement with the best overall response by RECIST criteria (Table 12), which was performed as a post hoc supportive analysis. While partial responses defined by RECIST (per IRC) were reported in only a small number of patients receiving ridaforolimus (5 patients), the proportion of patients with disease control, defined as objective responses plus stable disease for at least 4 months was 41% in the ridaforolimus arm compared to 29% in the placebo arm ($p = 0.0009$). Conversely, a best response of progressive disease was reported in 43% of patients in the placebo arm compared to 28% in the ridaforolimus arm. Thus, whether analyzed by best response in target lesions or best overall response by conventional RECIST criteria, it is clear that more patients experienced tumor growth in the placebo arm, and more patients achieved stable disease or some degree of tumor shrinkage in the ridaforolimus arm. These results further support the use of ridaforolimus as a maintenance therapy, demonstrating that the response to chemotherapy was maintained among patients receiving ridaforolimus.

Table 12

Best Overall Response (IRC)

	Ridaforolimus (N=347)	Placebo (N=364)
Disease Control Rate (CR/PR + SD ≥ 4 months)	41%	29%
Complete Response	0	0
Partial Response	1% (5 pts)	<1% (2 pts)
Stable Disease ≥ 4 months	39%	28%
Progressive Disease	28%	43%

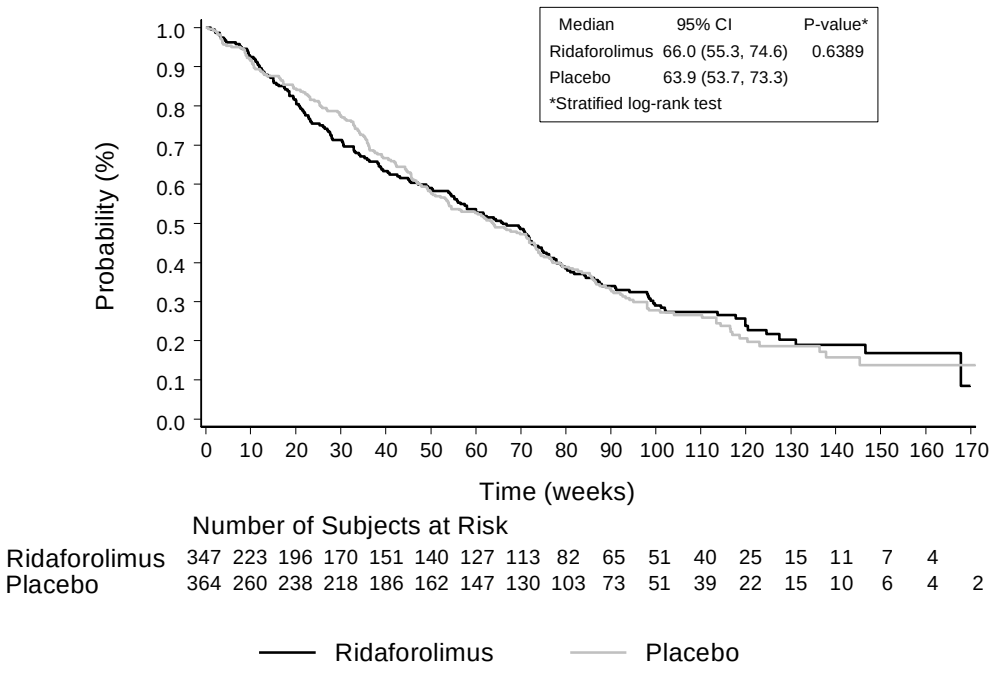
6.2.3.5 Post Progression Survival

The protocol did not collect data on subsequent therapy after disease progression. An exploratory analysis was performed to evaluate post-progression survival in patients receiving ridaforolimus or placebo in order to evaluate the potential effect of treatment on patient outcome after disease progression and subsequent management of the sarcoma. Post-progression survival is defined as the time interval between PD, per IRC assessment, and death. Note that patients without PD by IRC were censored at time 0 and were effectively excluded from the analysis.

Exploratory post-progression survival analyses were performed for the three pre-specified OS analyses, and showed consistent results. The analysis is displayed based on the OS data cutoff of January 21, 2012, which has the greatest number of OS events overall and provides a better estimate of the post-progression survival. Both stratified and unstratified p-values (2-sided) are close to 1. The January 2012 update indicated a HR based on stratified Cox model of 0.95 in favor of ridaforolimus (95% CI [0.78, 1.17]). Following progression, median survival was 66.0 weeks in the ridaforolimus arm and 63.9 weeks in the placebo arm, a difference of 2.1 weeks. A Kaplan-Meier Plot of Time between PD and Death in P011 is shown in Figure 12. This analysis provides evidence that treatment with ridaforolimus did not adversely impact subsequent management of patients with metastatic sarcoma.

Figure 12

Kaplan-Meier Plot of Time between PD and Death
(Data Cutoff January 2012, ITT Population)
Protocol 011



6.3 Efficacy Summary

In summary, supportive studies P016 and P018 initially demonstrated the clinical activity of ridaforolimus across a broad spectrum of sarcoma subtypes and showed a pattern of activity of disease stabilization in patients who had progressive disease on chemotherapy. The pivotal trial, P011, was conducted in patients who had soft tissue or bone sarcoma and stable disease or better after first, second, or third line chemotherapy and showed the following key efficacy findings:

- Progression free survival, per IRC, was improved with ridaforolimus treatment
  - Hazard Ratio = 0.72, p = 0.0001, 95% CI 0.61-0.85
  - High consistency between IRC and investigator assessed PFS (HR = 0.69)
  - High consistency across histological subtypes and various subgroups based on patient demographics and prior treatment history
- Overall survival analysis largely rules out a detrimental effect of ridaforolimus

  - Hazard ratio = 0.93, p = 0.4561, 95% CI 0.78-1.12
  - Based on mortality in 67% of the ITT population at January 21, 2012 data cutoff
- Best target lesion response showed objective evidence of disease control
  - Mean tumor size reduction 1.3% in the ridaforolimus treatment arm
  - Mean tumor size increase of 10.3% in the placebo arm
    - $p < 0.0001$ for the difference
- Exploratory analysis of post-progression survival suggested no detrimental effect of ridaforolimus on subsequent patient management

7. Overview of Safety

The randomized Phase III study (P011) forms the foundation of the safety analysis for this submission. This study provides a direct comparison of ridaforolimus versus a placebo treated group in the target indication utilizing the proposed dosing strategy. For most safety analyses, we did not pool databases across all studies investigating this compound because of the wide range of ridaforolimus doses used, different therapeutic interventions (i.e., single-agent or in combination), different routes of administration, varied patient populations, lack of appropriate controls (i.e. phase II studies did not have a control arm), and the high background rate of adverse events in patients with advanced cancer. Each of these confounding issues would make identification and interpretation of safety signals from a pooled analysis very difficult. Therefore, the pivotal randomized Phase III study (P011) is the focus of the safety evaluation.

The overall safety data indicate that the adverse event (AE) profile of ridaforolimus is generally similar to the known safety profile of other rapamycin analogs used in the treatment of cancer patients, i.e. everolimus (Afinitor®) [41] and temsirolimus (Torisel®) [42]. No safety concerns were identified that have not been previously observed with this class of compounds.

7.1 Safety Evaluation Plan

The safety analysis for this document groups the 37 trials in the ridaforolimus program into three groups based on each trial's relevance and significance with respect to the target indication and population (Appendix 1):

- **Pivotal Phase 3 Study:** The pivotal trial was the randomized Phase III study (P011) in which 343 patients were randomized to ridaforolimus treatment. The results of the P011 study provide the primary supportive evidence to evaluate the safety and therapeutic efficacy of ridaforolimus. The safety database was analyzed with a cutoff date of October 25, 2010 for the original application. A formal safety update report was submitted to FDA with a cutoff date of September 1, 2011. There was a relatively small amount of incremental data after the October 25, 2010 data cutoff, because less than 10% of the safety population remained on study beyond the October 25, 2010 data cutoff. Therefore, in this

document, adverse event tables from the original application with the October 25, 2010 data cutoff are shown.

- **Supportive Sarcoma Studies:** P011 is supported by P016, a Phase I/IIa single arm study of oral ridaforolimus in patients with advanced solid tumors to determine the most suitable dosing regimen and PK profile of oral ridaforolimus, and by the Phase II study P018, which evaluated the efficacy of I.V. ridaforolimus as a salvage therapy for sarcoma patients. A total of 359 patients were treated with ridaforolimus in P016 and P018 combined, of which 297 were sarcoma patients.

- **All Other Studies:** The remaining 34 trials in the ridaforolimus clinical program involved administration of ridaforolimus as a single agent or in combination with other drugs in non-sarcoma cancer patients, or administration in healthy volunteer settings, as well as an extension trial (P038). In the trials that were completed by 25-Oct-2010, there were 495 patients enrolled, of which 476 patients were treated with ridaforolimus as single-agent or in combination with other agents. In some analyses, such as adverse events with a fatal outcome, a pooled analysis of all other completed studies (as of October 25, 2010) is provided. In the trials that were ongoing after 25-Oct-2010, there were approximately 526 patients enrolled and treated, of which 429 patients were treated with ridaforolimus and 97 patients were treated with a comparator agent only. Listings of serious adverse events from ongoing studies were carefully reviewed, submitted in the original application, and updated in the safety update report, but are generally not discussed in this document. These 34 completed or ongoing trials have limited relevance from a safety perspective to the sarcoma indication based upon the tumor type being treated, the wide range of dosages administered, the route of administration, or co-administration of other anti-cancer therapeutics.

The safety population used for analysis includes only those patients who received at least one dose of study medication; therefore all AEs presented are by definition treatment-emergent AEs. There are generally two safety populations thus analyzed:

1) Protocol 011 safety data were analyzed and include, but are not limited to, analysis of common adverse events, deaths, other serious or significant adverse events, analysis of adverse events by organ system, and laboratory abnormalities; a particular focus is provided on those less common but potentially serious adverse events known to be associated with rapamycin analogs such as pneumonitis, gastrointestinal perforation, renal failure, and infections (including opportunistic infections).

    - In some cases, these adverse events of special interest occurred with low frequency in P011, and additional safety information from supporting sarcoma studies (P016/P018) or all other studies is provided.

2) Deaths and serious adverse events were analyzed using studies from the entire ridaforolimus development program.

7.2 Extent of Exposure

P011 included a dose modification scheme to allow for temporary or permanent dose reductions in patients experiencing adverse events. The following dosing adjustment recommendations consider 3 adverse experience (AE) occurrences, and are based on a regimen of 5 consecutive dosing days, followed by 2 days without ridaforolimus/placebo each week (Table 13).

Table 13

Recommended Dose Adjustments in P011 for Selected Adverse Experiences ≥Grade 2* Including Stomatitis**

AE Occurrence†	Action Until Day 5	Days 6-7	Action during next week	Days 6-7	Action during second week or more
First	Decrease the dose of study drug to 10 mg/day (1 tablet).	No Treatment	If the adverse experience is ≤Grade 1 or resolved on Day 1, the dose of study drug may be increased to 40 mg/day (4 tablets). Otherwise, continue at 10 mg/day through Day 5.	No Treatment	If the adverse experience is resolved on Day 1, the dose of study drug may be increased to 40 mg/day (4 tablets). Otherwise, stop study drug until resolution, and resume 40 mg/day.
Second	Decrease the dose of study drug to 10 mg/day (1 tablet).	No Treatment	If adverse experience is resolved on Day 1, the dose of study drug may be increased to 30 mg/day (3 tablets). Otherwise, continue at 10 mg/day through Day 5.	No Treatment	If adverse experience is resolved on Day 1, the dose of study drug may be increased to 30 mg/day (3 tablets). Otherwise, stop study drug until resolution, and resume 30 mg/day.
Third	Decrease the dose of study drug to 10 mg/day (1 tablet).	No Treatment	If adverse experience is resolved on Day 1, the dose of study drug may be increased to 20 mg/day (2 tablets). Otherwise, continue at 10 mg/day through Day 5.	No Treatment	If adverse experience is resolved on Day 1, the dose of study drug may be increased to 20 mg/day (2 tablets). Otherwise, stop study drug until resolution and resume 20 mg/day.

* NCI CTCAE (National Cancer Institute Common Terminology Criteria Adverse Event) Grade
** Pneumonitis adverse events were managed by a different dose adjustment algorithm along with corticosteroids
† "Occurrence" refers to a specific, repeating adverse experience. A "second occurrence" refers to the second episode of the AE following resolution of the first episode to ≤ Grade 1.

In the analysis of the P011 safety population, over 90% of patients in the ridaforolimus treatment group and about 99% of placebo patients received 75% or more of expected treatment. Patients in the ridaforolimus group received an average of 74% of expected total doses over a median duration of 15.7 weeks, whereas the placebo group received 96% of expected total doses over a median duration of 14.7 weeks.

Table 14 provides a comparison of time to discontinuation between treatment groups. The ridaforolimus treatment group median time to discontinuation was longer than placebo, 15.7 weeks compared to 14.7 weeks, respectively. Despite a lower ratio of observed/expected dose (i.e. 74%) in the ridaforolimus treatment group, when time to treatment discontinuation was analyzed as a time-to-event endpoint, patients in the placebo group were noted to have discontinued treatment earlier than patients in the ridaforolimus group (HR 0.85, 95% CI 0.72, 0.99, p=0.0414). This suggests that although patients in the ridaforolimus treatment group had less exposure to planned study treatment, it is due to reduced and delayed dosing for management of AEs, and overall patients were able to remain on treatment with ridaforolimus longer than with placebo.

Table 14

Time to Treatment Discontinuation
(P011 Safety Population)

	N	Number of Events	Number Censored†	Median (weeks) (95% CI)	Hazard Ratio‖ (95% CI)	p-value‡	p-value§
Time to Discontinuation							
Ridaforolimus	343	316	27	15.7 (14.7, 18.9)	0.85 (0.72, 0.99)	0.0414	0.1133
Placebo	359	333	26	14.7 (11.1, 15.3)			
Total	702	649	53				

†: 53 patients had not discontinued at the time of database lock..
‡: 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 Cox Proportional Hazards Model with treatment as a covariate (Ridaforolimus relative to Placebo)
CI= Confidence Interval
(Database Cutoff Date: 25OCT2010)

7.3 Analysis of Adverse Experiences

7.3.1 Adverse Experiences in P011

Overall, AEs were more common and more severe in the ridaforolimus group. While active treatment was associated with more adverse experiences compared to placebo, the majority of these events were manageable and most patients did not discontinue treatment due to these events. It is notable that even in the placebo group, there was a high incidence of grade 3 or higher AEs (25.6%) (Table 15), which highlights the underlying morbidity and the risks associated with a "watch and wait" approach in the management of patients with metastatic sarcoma.

Table 15

Adverse Event Summary
Protocol 011
Safety Population

	P011 Ridaforolimus 40 mg daily x 5 days/week		P011 Placebo	
	n	(%)	n	(%)
Patients in population	343		359	
Any Treatment-Emergent Event	343	(100.0)	336	(93.6)
Severe (Grade ≥3) Treatment-Emergent AE	220	(64.1)	92	(25.6)
Serious Treatment-Emergent AE	124	(36.2)	77	(21.4)
Treatment-Emergent AE Leading to Death	21	(6.1)	16	(4.5)
Treatment-Emergent AE Leading to Withdrawal	50	(14.6)	9	(2.5)
Treatment-Emergent AE Leading to Dose Reduction or Dose Delay	270	(78.7)	45	(12.5)

In P011, the most common AEs in the ridaforolimus treatment group were stomatitis and related terms (78%). The majority of ridaforolimus-treated patients in P011 reported this adverse event as stomatitis (52.2%); however patients also reported adverse events of mucosal inflammation (16.6%), mouth ulceration (6.7%), aphthous stomatitis (4.7%) and tongue ulceration (0.9%). Other AEs occurring in at least 30% of patients in the ridaforolimus treatment group were infections (52%), fatigue (36%), thrombocytopenia (34%), diarrhea (31%), and cough (31%). Note that for the presentation of common adverse events, two adverse events: stomatitis and pneumonitis are not presented as single terms, but as a category of multiple terms (Table 16).

The AEs for which the ridaforolimus treatment group showed more than a 20% difference over the placebo treatment include stomatitis and related terms (difference of 55%), thrombocytopenia (difference of 30%), infections (difference of 26%), and rash (difference of 22%) (Table 16).

Grade 3 and higher AEs which occurred with an incidence ≥ 5% were stomatitis, thrombocytopenia, hyperglycemia, anemia, neutropenia, and infections. It is notable that many of the severe AEs were laboratory-based, and, while important, may not be associated with clinical symptoms. Excluding adverse events that were laboratory-based, severe AEs (Grade ≥ 3) were reported in 48% of patients receiving ridaforolimus compared to 23% of patients receiving placebo. Laboratory abnormalities, whether or not reported as an adverse event, are presented in Table 17 below.

The rates of treatment-emergent AEs (irrespective of causality) resulting in permanent discontinuation were 14.6% and 2.5% for the groups treated with ridaforolimus and placebo, respectively. The most common adverse reactions (irrespective of causality) leading to treatment discontinuation in patients receiving ridaforolimus (in at least 1% of patients) were stomatitis and related events (2.9% of patients), pneumonitis and related events (1.7%), and infections (1.5%). No patients on placebo discontinued due to these events. The remainder of adverse events leading to treatment discontinuations occurred in 1-2 patients for any given event term, and were distributed across several organ classes. Stomatitis was the most common reason for treatment delay or dose reduction in patients receiving ridaforolimus.

Table 16

P011:Adverse Reactions Reported in at Least 10% of Patients Receiving Ridaforolimus Tablets and at a Higher Rate Than Oral Placebo

MedDRA System Organ Class Preferred Term	Ridaforolimus Tablets (N=343)		Oral Placebo (N=359)	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Number of Patients with at least One Adverse Event	100	64	94	26
Gastrointestinal Disorders				
Stomatitis*	78	11	23	<1
Diarrhea	31	3	18	0
Nausea	27	1	25	1
Vomiting	18	1	10	<1
Constipation	16	0	11	<1
Abdominal pain	13	2	11	1
Dry mouth	11	<1	7	0
General Disorders and Administration Site Conditions				
Fatigue	36	3	22	2
Pyrexia	23	<1	8	<1
Edema peripheral	22	1	7	0
Asthenia	17	3	12	1
Respiratory, Thoracic and Mediastinal Disorders				
Cough	31	<1	16	<1
Dyspnea	19	4	9	<1
Oropharyngeal pain	17	<1	4	0
Epistaxis	17	0	1	0
Pneumonitis†	10	3	<1	<1
Musculoskeletal and Connective Tissue Disorders				
Pain in extremity	16	1	9	1
Back pain	12	2	14	1
Arthralgia	11	<1	11	<1

P011:Adverse Reactions Reported in at Least 10% of Patients Receiving Ridaforolimus Tablets and at a Higher Rate Than Oral Placebo (Cont.)

MedDRA System Organ Class Preferred Term	Ridaforolimus Tablets (N=343)		Oral Placebo (N=359)	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Metabolism and Nutrition Disorders				
Decreased appetite	27	<1	10	<1
Hypertriglyceridemia	27	2	9	<1
Hypercholesterolemia	21	<1	4	0
Hyperglycemia	14	7	3	<1
Hypokalemia	14	5	3	<1
Skin and Subcutaneous Tissue Disorders				
Rash	28	<1	6	0
Pruritus	11	<1	4	0
Nervous System Disorders				
Headache	27	1	14	<1
Dysgeusia	16	<1	4	0
Infections and Infestations	52	6	26	3
Urinary tract infection	9	<1	4	<1
Upper respiratory tract infection	6	0	3	0
Influenza	4	0	2	0
Pneumonia	4	1	<1	<1
Sinusitis	4	0	<1	0
Nasopharyngitis	4	0	4	0
Blood and Lymphatic System Disorders				
Thrombocytopenia	34	10	4	1
Anemia	28	7	10	3
Neutropenia	18	6	6	2
Leukopenia	13	2	4	<1
Investigations				
Weight decreased	15	<1	4	0
Cardiac Disorders				
Tachycardia	13	0	4	0

Note: Percentages are based on the number of treated patients in each treatment group.

* Stomatitis includes stomatitis, mucosal inflammation, aphthous stomatitis, mouth ulceration, and tongue ulceration.

† Pneumonitis includes pneumonitis, interstitial lung disease, and alveolitis allergic.

Only treatment-emergent adverse events with a start date on or after the first dose of study treatment are reported.

(Database Cutoff Date: 25OCT2010)

In P011, grading of laboratory test results was based on standard laboratory normal ranges [43]. The laboratory abnormalities with incidence ≥ 50% for all grades in patients taking ridaforolimus in P011 were ALT (SGPT) increased, AST (SGOT) increased, glucose increased, hemoglobin decreased, lymphocytes decreased, phosphorous decreased, platelets decreased, serum triglycerides increased, total cholesterol increased, and white blood cells decreased. In the placebo arm of P011, hemoglobin decreased and lymphocytes decreased were reported in more than 50% of patients. Most laboratory abnormalities were low grade (1-2), and grade 3 or higher laboratory abnormalities were much less frequent, with only lymphocytes decreased, phosphorus decreased, and glucose increased occurring in at least 10% more patients receiving ridaforolimus compared to patients receiving placebo.

The percentage of patients receiving ridaforolimus, with laboratory abnormalities ≥10% and at a greater rate than in patients receiving oral placebo, are presented in Table 17.

Table 17

P011: Laboratory Abnormalities Reported in ≥10% of Patients Receiving Ridaforolimus Tablets and at a Greater Rate Than in Patients Receiving Oral Placebo

Laboratory Test	Ridaforolimus (N=343) %	Oral Placebo (N=359) %
ABSOLUTE NEUTROPHIL COUNT – DECREASED		
All Grades	24	12
Grade ≥3	8	3
ALBUMIN – DECREASED		
All Grades	31	15
Grade ≥3	2	<1
ALKALINE PHOSPHATASE – INCREASED		
All Grades	44	29
Grade ≥3	1	1
ALT (SGPT) – INCREASED		
All Grades	54	26
Grade ≥3	3	<1
AST (SGOT) – INCREASED		
All Grades	56	22
Grade ≥3	<1	0
CALCIUM – DECREASED		
All Grades	40	16
Grade ≥3	<1	<1
CREATININE – INCREASED		
All Grades	17	12
Grade ≥3	<1	0

P011: Laboratory Abnormalities Reported in ≥10% of Patients Receiving Ridaforolimus Tablets and at a Greater Rate Than in Patients Receiving Oral Placebo (Cont.)

Laboratory Test	Ridaforolimus (N=343) %	Oral Placebo (N=359) %
GLUCOSE – INCREASED		
All Grades	68	43
Grade ≥3	12	<1
HEMOGLOBIN – DECREASED		
All Grades	73	54
Grade ≥3	4	<1
LYMPHOCYTES – DECREASED		
All Grades	70	59
Grade ≥3	23	7
PHOSPHOROUS – DECREASED		
All Grades	53	22
Grade ≥3	13	1
PLATELETS - DECREASED		
All Grades	66	18
Grade ≥3	10	3
POTASSIUM - DECREASED		
All Grades	33	8
Grade ≥3	5	<1
SERUM TRIGLYCERIDES - INCREASED		
All Grades	70	44
Grade ≥3	4	<1
SODIUM - DECREASED		
All Grades	18	13
Grade ≥3	3	<1
SODIUM – INCREASED		
All Grades	13	7
Grade ≥3	<1	<1
TOTAL CHOLESTEROL - INCREASED		
All Grades	69	44
Grade ≥3	2	0
WHITE BLOOD CELLS - DECREASED		
All Grades	67	39
Grade ≥3	5	<1

7.3.2 Patient Reported Symptoms

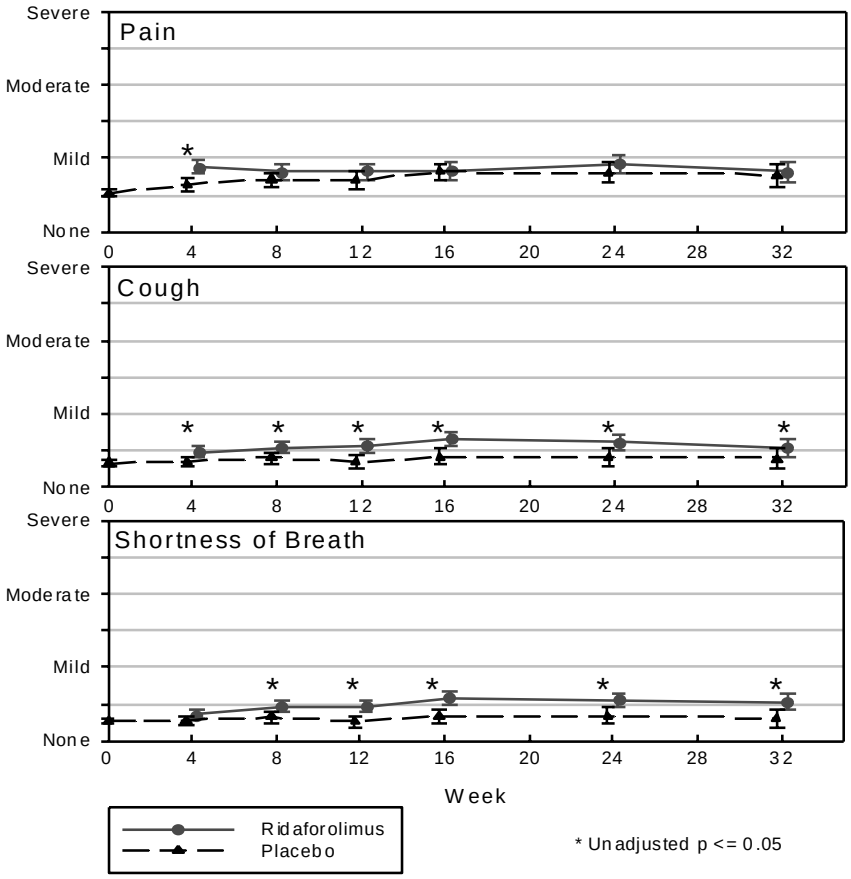
P011 collected exploratory data on three patient reported symptoms (pain, cough, and shortness of breath) that are related to both sarcoma progression and adverse events (AEs). Symptoms were recorded using a simple questionnaire on a 1 to 4 point scale as none, mild, moderate, or severe. Cancer-Related Symptoms Questionnaires were scheduled for administration while patients were still on treatment so no symptom questionnaires were to be filled out after treatment discontinuation. More than 50% of patients completed the symptom questionnaires through week 16; fewer than 1/3 completed questionnaires at 32 weeks and beyond (the number of patients responding to the questionnaire on pain is provided below (Figure 13).

No formal analysis plan for the symptom data was pre-specified in the protocol or statistical analysis plan. Longitudinal data analysis (LDA) [44] was performed using symptom data through week 32. Baseline scores are modeled to be the same between arms, and post-baseline scores are modeled to be dependent on time and treatment. Within each patient, multiple repeated measurements over time are assumed to be correlated, but with no assumption made on the pattern of correlation. Results of the LDA for pain, cough, and shortness of breath are shown in Figure 13.

Average pain scores at baseline and at all post-baseline time points are about mid-way between none (score = 1) and mild (score = 2) for both treatment arms. At most time points, there are no differences between treatment arms. At one time point, week 4, there is a numerically small but statistically significant (95% CI excludes 0) difference in pain scores of 0.23 points in favor of the placebo arm. As the median time to onset of stomatitis in P011 was 11 days, this increase in pain at 4 weeks may be at least in part attributable to stomatitis. The pain scores at week 8 and beyond show no differences between treatment arms, likely representing the resolution of stomatitis and infrequent recurrence of this adverse event.

Figure 13

Longitudinal Data Analysis Modeled Symptom Scores Over Time in P011



Number (ITT%) of Patients Completing Symptoms Questionnaire

		Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 24	Wk 32
Placebo	N	342	315	293	189	178	110	71
	(ITT%)	(94%)	(87%)	(80%)	(52%)	(49%)	(30%)	(20%)
Ridaforolimus	N	330	294	265	210	193	141	97
	(ITT%)	(95%)	(85%)	(76%)	(61%)	(56%)	(41%)	(28%)

For cough, the average scores are again about midway between none and mild at baseline and post-baseline time points, with numerically small, but statistically significant (95% CI excluding 0) differences in symptom scores over time ranging from 0.13 to 0.23 in

favor of placebo at all post-baseline time points except Week 32. The pattern is consistent with adverse event data from P011. Cough, almost all grade 1-2 in severity, was reported as a common adverse event in P011, with 31% of patients in the ridaforolimus arm reporting cough, and 16% of patients on the placebo arm reporting cough.

The findings from the model for shortness of breath are similar to cough, with baseline and post-baseline scores between none to mild, and post-baseline scores with small differences ranging from 0.07 to 0.24 in favor of placebo, which are statistically significant at most time points. This result is also consistent with the adverse event data from P011. Dyspnea (shortness of breath), mostly grade 1-2 in severity, was reported as a common adverse event in P011, with 19% of patients in the ridaforolimus arm reporting dyspnea, and 9% of patients on the placebo arm reporting dyspnea.

In summary, the patient-reported symptom results are consistent with the severity and timing of the stomatitis, cough, and dyspnea AEs observed in P011. The on-treatment symptom scores indicate that patients felt that the severity of these three symptoms was between none and mild on average at baseline and over time. The difference between ridaforolimus and placebo was 0.24 points or less in favor of placebo on a 1 to 4 point scale, but the differences were statistically significant at multiple time points. Based upon the baseline variability in symptom scores, all of these differences are less than 0.5 standard deviation units. While sometimes statistically significant, they never exceed a difference that would be considered likely to be clinically meaningful [45; 46]. The differences are not surprising for the mTOR inhibitor class and are in accordance with the reported AE profile of ridaforolimus for stomatitis (reflected as an increase in patient reported pain at week 4), cough, and dyspnea.

This analysis can only provide information on the change in symptoms before treatment discontinuation, as data collection stopped at treatment discontinuation. This may bias the analysis against ridaforolimus because the potential benefits of delaying disease progression as evidenced in the SABINE study [24]are not completely captured in this study even though symptoms related to AEs are captured. Data collection schedules which stop data collection after treatment discontinuation are hindered by non-random missing data [47]. Important changes in patient outcome that happen after treatment discontinuation, such as the symptoms associated with disease progression, remain unknown based on the data collected.

7.3.3 Deaths

In P011 with 702 treated patients, the total number of adverse events leading to death was 21 (6.1%) in the ridaforolimus treatment group, and 16 (4.5%) in the placebo group (Table 18). Twenty out of the 37 deaths in both arms were classified into the neoplasm or general disorders system organ class (SOC), suggesting worsening of the underlying sarcoma as the cause of the adverse event leading to death. In these two SOCs combined, there were 8 adverse events leading to death in the ridaforolimus treatment group and 12 in the placebo group.

In P011, adverse events leading to death in the respiratory/thoracic SOC were greater in the ridaforolimus arm. There were a total of 6 respiratory/thoracic adverse events leading to death in the ridaforolimus group (1.7% incidence) and none for the placebo treatment group. However, the specific adverse event terms suggest a diverse set of adverse events that are confounded by the underlying malignancy, including pleural effusion (N=2), pulmonary embolism (N=1), dyspnea (N=1), respiratory distress (N=1), and pneumonitis (N=1). All 6 patients with respiratory adverse events leading to death reported lung metastasis at study entry, and only one of these deaths, the death due to pneumonitis, was considered related to study medication by the Investigator. This is also the only reported death due to pneumonitis across the entire ridaforolimus program.

Table 18

Patients With Adverse Events Resulting in Death
(Incidence > 0% in One or More Treatment Groups)
P011 Safety Population

	P011 Ridaforolimus 40 mg daily x 5 days/week		P011 Placebo	
	n	(%)	n	(%)
Patients in Population	343		359	
with one or more adverse events	21	6.1	16	4.5
Cardiac disorders	**2**	**0.6**	**0**	**0.0**
Arrhythmia	1	0.3	0	0.0
Pericardial effusion	1	0.3	0	0.0
Gastrointestinal disorders	**2**	**0.6**	**3**	**0.8**
Duodenal perforation	0	0.0	1	0.3
Gastrointestinal haemorrhage	2	0.6	0	0.0
Intestinal obstruction	0	0.0	1	0.3
Intestinal perforation	0	0.0	1	0.3
General disorders and administration site conditions	**4**	**1.2**	**5**	**1.4**
General physical health deterioration	3	0.9	4	1.1
Performance status decreased	1	0.3	1	0.3
Hepatobiliary disorders	**1**	**0.3**	**1**	**0.3**
Cholangitis	0	0.0	1	0.3
Hepatic failure	1	0.3	0	0.0
Metabolism and nutrition disorders	**1**	**0.3**	**0**	**0.0**
Hypercalcaemia	1	0.3	0	0.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**4**	**1.2**	**7**	**1.9**
Acute monocytic leukaemia	0	0.0	1	0.3
Desmoplastic small round cell tumour	1	0.3	0	0.0
Malignant neoplasm progression	1	0.3	3	0.8
Metastases to central nervous system	1	0.3	1	0.3
Small cell lung cancer stage unspecified	1	0.3	0	0.0
Spindle cell sarcoma	0	0.0	1	0.3
Tumour perforation	0	0.0	1	0.3
Nervous system disorders	**1**	**0.3**	**0**	**0.0**
Grand mal convulsion	1	0.3	0	0.0
Respiratory, thoracic and mediastinal disorders	**6**	**1.7**	**0**	**0.0**

Dyspnoea	1	0.3	0	0.0
Pleural effusion	2	0.6	0	0.0
Pneumonitis	1	0.3	0	0.0
Pulmonary embolism	1	0.3	0	0.0
Respiratory distress	1	0.3	0	0.0

7.3.3.1 Deaths Occurring Early in Treatment—P011

Visual inspection of the Kaplan-Meier curves for overall survival showed an apparent small imbalance of deaths favoring the placebo arm between weeks 24-40. For this reason, a subset of death events comprised of early deaths (defined as deaths occurring up to week 40 of treatment) was assessed for trends (Table 19). There were a total of 159 deaths occurring up to treatment week 40, 82 (23.9%) in the ridaforolimus treatment arm and 77 (21.4%) in the placebo arm. Using alternate data cut-off points of 16, 24, and 32 weeks, there was little numerical difference between the 2 treatment arms up to week 24, while at 32 weeks, the numerical difference between the arms was similar to that observed at week 40 (Table 20). For deaths occurring up to week 40, deaths not attributed to cancer were numerically higher in the ridaforolimus arm compared to placebo (14 versus 8, respectively).

Among the 14 deaths in the ridaforolimus arm not attributed to cancer through week 40, in 6 of these cases there was preceding radiologic documentation of cancer progression by investigator or IRC. Causes of death in these 6 cases were: congestive heart failure, cerebro-vascular stroke, digestive hemorrhage, dyspnea, and unknown (n=2).

Among the 8 deaths in the ridaforolimus arm not attributed to cancer and not preceded by documented cancer progression through week 40, there was one case of fatal pneumonitis. Disease progression with known lung involvement was stated as another possible cause of the event. Among the other 7 cases, in each case the underlying malignancy could have contributed to the death, and there was no pattern suggesting a common causative relationship with ridaforolimus. Causes were general health deterioration, decreased performance status, pericardial effusion, recurrent pleural effusion, GI hemorrhage, pulmonary embolism, and tonic-clonic seizures in the setting of multiple brain metastases.

Thus analyses of the early deaths in P011 show a numerical similarity between the 2 arms through 24 weeks, and at 40 weeks the vast majority of patient deaths in both arms was attributed to cancer or preceded by documented progressive disease. Evaluating the individual cases underlying the slight numerical imbalance in deaths not attributed to cancer in the ridaforolimus arm failed to reveal a consistent causal relationship with ridaforolimus.

Table 19

Analysis of All Deaths up to Week 40
P011

	Ridaforolimus (N = 343)	Placebo (N = 359)
All deaths	82 (23.9%)	77 (21.4%)
Cause of death not attributed to cancer	14 (4.1%)	8 (2.2%)
Cause of death not attributed to cancer and death not preceded by documentation of cancer progression	8 (2.3%)	2 (0.6%)

Table 20

Number of Deaths over Time
P011

	Deaths at 16 wks n (%)	Deaths at 24 wks n (%)	Deaths at 32 wks n (%)	Deaths at 40 wks n (%)
Ridaforolimus (N = 343)	23 (6.7%)	39 (11.4%)	68 (19.8%)	82 (23.9%)
Placebo (N = 359)	21 (5.8%)	38 (10.6%)	60 (16.7%)	77 (21.4%)

7.3.3.2. Deaths Across Entire Ridaforolimus Program (All Completed Trials)

Appendix 2 displays the incidence of AEs resulting in death individually for P011, P016, P018, and also for all completed trials combined as of the established October 25, 2010 data cut-off. There were 117 (9.8%) patients with adverse events leading to death reported in 1197 patients receiving ridaforolimus, alone or in combination with other agents, collectively in these trials. The adverse event of disease progression leading to death was the most common cause of death across all trials (n = 30, 2.5%).

In Protocols 011, 016, and 018 combined, there are 702 total patients in the safety population who received ridaforolimus, of whom collectively 78 (11.1%) had an adverse event with a fatal outcome. Among these 78 deaths, only 5 were considered treatment-related. These 5 adverse events leading to death were all from the ridaforolimus treatment arm in P011, and included two patients with gastrointestinal hemorrhages, and one patient each with pneumonitis, performance status decreased, and general physical health deterioration. Twenty-eight of 147 (19.0%) patients in P016, and 29 of 212 (13.7%) patients in P018 had adverse events leading to death. The most common adverse events leading to death were related to disease progression. In the respiratory disorders category,

there were 3 (2.0%) deaths in P016, and 8 deaths (3.8%) in P018, but none were related to pneumonitis and none were considered related to ridaforolimus treatment.

Three (3) patient deaths were reported by the Investigator as at least possibly related to ridaforolimus across completed clinical trials other than P011 or P016/018, including ventricular dysfunction (n = 1), pneumonia (n = 1), and a complex of pseudomonas septicemia/acute renal failure/myocardial infarction (n = 1). A review of listings of adverse events leading to deaths in the currently ongoing studies across the ridaforolimus program through the 30-Apr-2011 data cutoff (original application) and the 01-Sept-2011 data cutoff (safety update report) revealed qualitatively similar findings to the analysis of P011, P016, P018, and all other completed studies in the ridaforolimus program.

7.3.4. Other Serious Adverse Experiences (All Completed Trials)

Table 21 summarizes the SAEs, irrespective of drug attribution and including fatal events, that occurred in equal to or greater than 1% of the patients in the pivotal Phase III trial (P011), compared with the SAEs experienced in patients in P016 and P018 and the other studies in the ridaforolimus clinical program that were completed prior to the cut-off date of 25-Oct-2010.

In P011, there were 36.2% of patients in the ridaforolimus group and 21.4% of patients in the placebo group who experienced SAEs, a difference of 15% (Table 21). Adverse events from the respiratory/thoracic disorders system, the gastrointestinal system, and the infections SOC were the three most common categories for SAEs in the ridaforolimus arm of P011. These findings are similar to findings across the ridaforolimus clinical program.

In patients receiving ridaforolimus in P011, 7.6% of patients experienced respiratory/thoracic SAEs, compared to 2.8% patients in the placebo treatment group. The MedDRA term of pneumonitis accounted for SAEs in 6 (1.7%) of patients receiving ridaforolimus, and pneumonitis and related events (such as interstitial lung disease) collectively accounted for SAEs in 9 (2.6%) of patients receiving ridaforolimus in P011. Non-specific adverse event terms such as dyspnea accounted for some respiratory/thoracic SAEs, and these could be due to underlying disease, pneumonitis, respiratory infections or other causes. Pleural effusions and pulmonary emboli also accounted for many of the SAEs in this category. These data are consistent with other AE data as well as the known AE profile for other rapamycin analogs (Section 7.4, Figure 15).

Gastrointestinal disorders were the next most common source of SAEs in the ridaforolimus group of P011, occurring in 6.7% of patients receiving ridaforolimus compared to 4.5% of patients receiving placebo. It is notable that stomatitis and related terms was an uncommon cause of SAEs; only 3 (<1%) patients receiving ridaforolimus in P011 experienced SAEs related to stomatitis. Nausea and vomiting, while generally uncommon causes of SAEs, were the only gastrointestinal SAEs occurring in ≥1% of patients receiving ridaforolimus in P011, each reported in 4 (1.2%) patients.

Infections were the third most common SAEs in patients receiving ridaforolimus in P011, with 6.4% of patients receiving ridaforolimus compared to 2.2% of patients receiving placebo experiencing SAEs of infections. The only serious infections occurring in ≥ 1% of patients receiving ridaforolimus in P011 was pneumonia (2.3%), representing the single most reported SAE term for patients receiving ridaforolimus.

Table 21

Patients with Serious Adverse Events
(Incidence for All Grades ≥ 1% in One or More Treatment Groups in P011)
All Completed Trials Safety Population

	P011 Ridaforolimus		P011 Placebo		P016 Ridaforolimus		P018 Ridaforolimus		All Other Completed Trials Ridaforolimus†	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	343		359		147		212		495	
with one or more adverse events	124	36.2	77	21.4	77	52.4	96	45.3	197	39.8
Blood and lymphatic system disorders	**14**	**4.1**	**5**	**1.4**	**0**	**0.0**	**4**	**1.9**	**25**	**5.1**
Anaemia	7	2.0	3	0.8	0	0.0	2	0.9	7	1.4
Thrombocytopenia	6	1.7	1	0.3	0	0.0	1	0.5	7	1.4
Cardiac disorders	**11**	**3.2**	**5**	**1.4**	**5**	**3.4**	**3**	**1.4**	**13**	**2.6**
Gastrointestinal disorders	**23**	**6.7**	**16**	**4.5**	**17**	**11.6**	**19**	**9.0**	**46**	**9.3**
Nausea	4	1.2	1	0.3	1	0.7	1	0.5	4	0.8
Vomiting	4	1.2	1	0.3	2	1.4	2	0.9	7	1.4
General disorders	**14**	**4.1**	**14**	**3.9**	**15**	**10.2**	**21**	**9.9**	**42**	**8.5**
General physical health deterioration	3	0.9	4	1.1	0	0.0	0	0.0	0	0.0
Infections and infestations	**22**	**6.4**	**8**	**2.2**	**21**	**14.3**	**35**	**16.5**	**65**	**13.1**
Pneumonia	8	2.3	2	0.6	6	4.1	5	2.4	16	3.2
Metabolism and nutrition disorders	**15**	**4.4**	**0**	**0.0**	**6**	**4.1**	**6**	**2.8**	**15**	**3.0**
Dehydration	5	1.5	0	0.0	1	0.7	4	1.9	6	1.2
Musculoskeletal and connective tissue disorders	**7**	**2.0**	**4**	**1.1**	**6**	**4.1**	**3**	**1.4**	**7**	**1.4**
Neoplasms	**12**	**3.5**	**20**	**5.6**	**13**	**8.8**	**17**	**8.0**	**7**	**1.4**
Malignant neoplasm progression	1	0.3	5	1.4	0	0.0	0	0.0	0	0.0
Nervous system disorders	**12**	**3.5**	**5**	**1.4**	**2**	**1.4**	**6**	**2.8**	**14**	**2.8**
Renal and urinary disorders	**9**	**2.6**	**1**	**0.3**	**10**	**6.8**	**7**	**3.3**	**10**	**2.0**
Renal failure acute	5	1.5	0	0.0	4	2.7	4	1.9	4	0.8
Respiratory, thoracic and mediastinal disorders	**26**	**7.6**	**10**	**2.8**	**16**	**10.9**	**15**	**7.1**	**33**	**6.7**
Dyspnoea	5	1.5	1	0.3	4	2.7	2	0.9	9	1.8
Pleural effusion	5	1.5	3	0.8	2	1.4	2	0.9	6	1.2
Pneumonitis	6	1.7	1	0.3	1	0.7	0	0.0	1	0.2
Pulmonary embolism	4	1.2	0	0.0	0	0.0	1	0.5	6	1.2
Skin and subcutaneous tissue disorders	**5**	**1.5**	**0**	**0.0**	**0**	**0.0**	**1**	**0.5**	**3**	**0.6**

Every patient is counted a single time for each applicable specific adverse event. A patient with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.

† Alone or in combination with other agents.

7.3.5. Adverse Experiences Associated with mTOR Inhibition – P011

Common or serious adverse events reported for other rapamycin analogs were selected for additional analysis [42; 41] including stomatitis, infections, pneumonitis, renal function impairment, hyperglycemia, and hyperlipidemias. Table 22 displays the incidence of these events in P011. There were no new signals of adverse events unique to ridaforolimus and the event profile is consistent with other rapamycin analogs (see Section 7.4, Figure 15).

Adverse events of special interest are discussed in greater detail below. Gastrointestinal hemorrhage and gastrointestinal perforation were included as adverse events of special interest because they are uncommon, serious, and have been reported at low frequency with other rapamycin analogs [48; 41; 49], but analysis of the data for these two adverse event categories from P011 do not suggest a clear relationship to ridaforolimus treatment.

Table 22

Patients with Other Adverse Events of Special Interest
Protocol 011
Safety Population

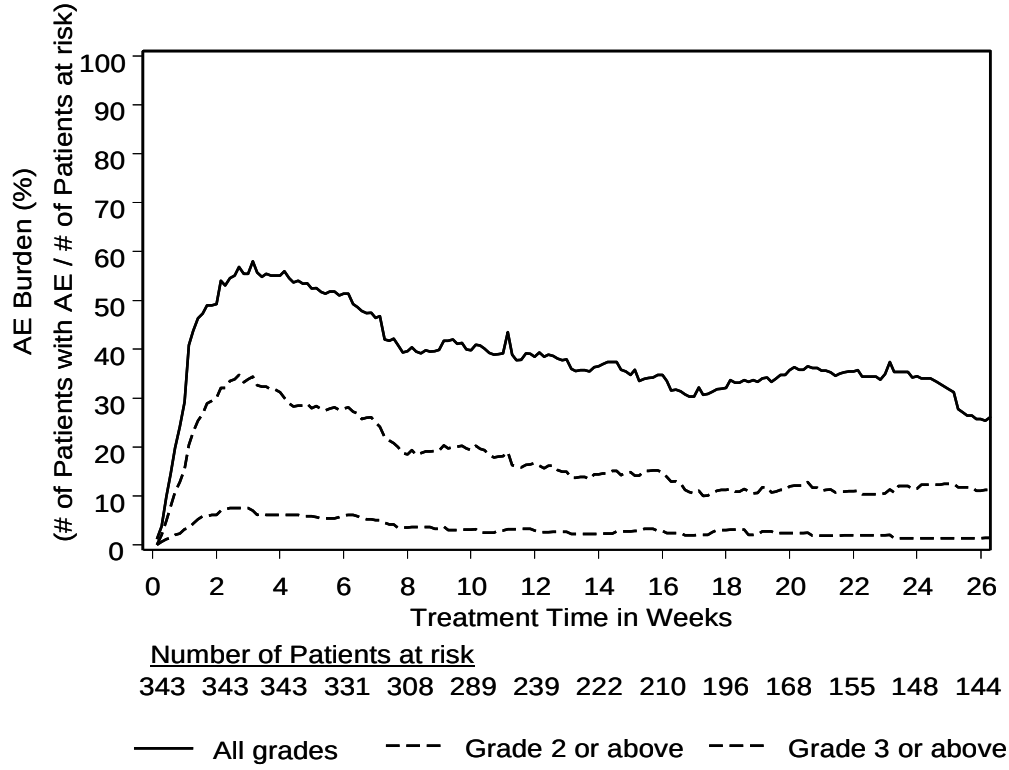
	P011 Ridaforolimus 40 mg daily x 5 days/week				P011 Placebo			
	All Grades		Grade ≥3		All Grades		Grade ≥3	
	n	(%)	n	(%)	n	(%)	n	(%)
	343		343		359		359	
Stomatitis	267	77.8	37	10.8	82	22.8	2	0.6
Hematology Disorders	184	53.6	70	20.4	67	18.7	18	5.0
Infections and infestations	177	51.6	19	5.5	92	25.6	9	2.5
Skin Rash	139	40.5	4	1.2	38	10.6	1	0.3
Hyperlipidemia	131	38.2	9	2.6	41	11.4	2	0.6
Hyperglycemia	62	18.1	25	7.3	10	2.8	2	0.6
Non- infectious Pneumonitis	35	10.2	9	2.6	2	0.6	1	0.3
Liver Function Abnormalities	34	9.9	7	2.0	6	1.7	0	0.0
Renal Insufficiency and Renal Failure	31	9.0	8	2.3	3	0.8	1	0.3
Gastrointestinal Haemorrhage	9	2.6	4	1.2	4	1.1	2	0.6
Gastrointestinal Perforation/Fistula	1	0.3	1	0.3	2	0.6	2	0.6

Stomatitis and Related Terms

To analyze stomatitis, related MedDRA terms were incorporated, including stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration and tongue ulceration (Table 23). In P011, 77.8% of patients in the ridaforolimus group experienced stomatitis or related events compared to 22.8% in the placebo group. The study protocol included a specific algorithm for the management of patients who experienced stomatitis, including bicarbonate mouth rinses, topical analgesic preparations, dose reductions, and dose delays. Patient discontinuations due to stomatitis were only seen in 2.9% of patients and Grade 3 and above stomatitis or related events were reported in only 10.8% of patients in P011 compared to 0.6% of patients in the placebo group, suggesting that the protocol-recommended management was successful in most patients experiencing stomatitis. Figure 14 displays the proportion of patients in the ridaforolimus treatment arm who experienced stomatitis-related adverse events over the treatment period.

Figure 14

Proportion of Patients Receiving Ridaforolimus with Stomatitis Related Adverse Events Over Treatment Period
P011



Although adverse events of stomatitis occurred frequently in P011, they were generally low grade (Grade 1-2) and generally did not become serious or cause patients to withdraw from ridaforolimus treatment in these clinical trials. Most patients experienced stomatitis early in the course of treatment, and once resolved or improved to Grade 1, few patients experienced a recurrence of Grade 2 or higher stomatitis-related event. The onset, duration, and recurrence of stomatitis-related events were assessed from P011 (Table 23). For grade 2 or higher events (the events associated with oral ulcers), the median onset was 11 days, the median duration was 29 days, and 12.5% of patients experienced a recurrence. The median duration of stomatitis-related adverse events of 29 days in patients receiving ridaforolimus in P011 is about twice as long in P011 as in the supporting sarcoma studies, where the median duration was 15.0 days in both P016 and P018. The reason for the longer duration of stomatitis-related events in P011 is uncertain, but may be related to reporting differences because of the longer interval between patient visits in P011 (approximately every 4 weeks) compared to P016 (weekly) and P018 (every 4-10 days). Consistent with this interpretation is the duration of stomatitis in the placebo arm of P011 was 29.5 days, which is virtually identical to the unexpectedly long duration of stomatitis in ridaforolimus treated patients in this protocol.

The totality of these stomatitis data suggest that stomatitis-related events are typically early onset events that, once resolved, do not typically recur.

Table 23

Onset, Duration, and Recurrence of Stomatitis and Related Event
Protocol 011
Safety Population

	P011 Ridaforolimus 40 mg daily x 5 days/week		P011 Placebo	
	n	(%)	n	(%)
Patients in population	343		359	
Patients with Adverse Event of Interest	267	(77.8)	82	(22.8)
Patients with Adverse Event of Interest in Grade 2 or higher	164	(47.8)	12	(3.3)
Time to Onset of First Adverse Event of Interest(median, days)				
All grades	10.0		26.0	
Grade 2 or higher	11.0		50.0	
Duration of First Adverse Event of Interest(median, days)				
All grades	40.0		29.0	
Grade 2 or higher	29.0		29.5	
Patients with Recurrences of Stomatitis				
All grades	76	(22.2)	10	(2.8)
Grade 2 or higher	43	(12.5)	0	

(%) = Number of patients with adverse events of special interest/ Number of patients in population.
Time to onset statistics are based on number of patients with Adverse events of interest.
Recurrence of stomatitis was defined as a new AE at least 7 days after the stop date of the prior episode for this analysis. Otherwise, the duration of both events was combined.

Infections

An increased incidence of infections (e.g. pneumonias) has been reported in cancer patients treated with rapamycin analogs. Data from P011 are presented in Table 24. Infections were common in both the ridaforolimus and placebo group of P011 and occurred in 51.6% of patients (all grades), and 5.5% of patients (Grade 3 and above) in the ridaforolimus treatment group compared to 25.6% of patients (all grades) and 2.5% of patients (Grade 3 and above) in the placebo group. Among the more commonly reported infections in P011, most were Grade 1 or 2; and only pneumonia (4 patients, 1.2%) was reported as severe (Grade 3 and above) in more than a single patient receiving ridaforolimus. Only urinary tract infection and upper respiratory tract infection occurred in more than 5% of patients treated with ridaforolimus in P011. There were no fatal adverse events from infections in either treatment arm of P011. Patients with active infection requiring systemic treatment were excluded from the protocol. The SPONSOR recommends that treatment be interrupted for patients experiencing ≥ Grade 2 active infection and resumed when the infection resolved. Only 5 (1.5%) of patients discontinued study treatment with ridaforolimus due to an infection, suggesting that almost all infections were medically manageable while patients remained on the study.

Grade 1 and Grade 2 oral candidiasis was reported in 2.3% of patients treated with ridaforolimus in P011 compared to 0.6% of patients in the placebo group. Severe (Grade 3 or higher) opportunistic infections were uncommon. There were 2 patients with severe fungal infections (one candidiasis, one fungal infection not otherwise specified) in the ridaforolimus treatment group compared to 1 patient with bronchopulmonary aspergillosis in the placebo group. In addition, 1 patient in the ridaforolimus treatment group had pneumocystis jiroveci pneumonia. There were no cases of treatment-emergent mycobacterial infections reported.

Oral herpes was reported in 2.9% of patients treated with ridaforolimus in P011 compared to 0.6% of patients in the placebo group. Severe (Grade 3 and above) viral infections were uncommon, with one case of severe herpes zoster in each arm of P011, and one case of severe parainfluenza virus infection in the ridaforolimus treatment group of P011.

Another important category of severe infections, systemic bacterial infections (of Grade 3 and above), were uncommon in P011, including septic shock in 1 patient in the ridaforolimus treatment group and neutropenic sepsis and Escherichia sepsis in 1 patient each in the placebo group.

Similarly in P016 and P018, patients experienced a similar proportion of infections, 49.0% and 50.5%, respectively, in all grades, but with a slightly greater incidence of patients reporting Grade 3 and above (11.6% and 15.6%) infection adverse events. The infections reported in these trials are generally similar to the types of infections seen in P011.

In P016 and P018, one patient was reported with systemic candida infection and one patient reported a severe fungal pneumonia. Both of these patients recovered following an interruption in study therapy. There were no treatment-emergent mycobacterial infections, nor were severe viral infections reported. There were systemic bacterial infections reported in P016/018, including 2 patients with systemic Streptococcus, and 1 patient each with systemic Enterococcus, Escherichia, Klebsiella, and Staphylococcus infections, as well as systemic bacterial infections without a specified organism, including bacteremia (n = 1), bacterial sepsis (n = 3) sepsis (n = 9), septic shock (n = 3) and urosepsis (n = 1) in P016 and P018, collectively.

Overall, while infections were observed in patients treated with ridaforolimus, most infections were mild (Grade 1-2), and. few infections resulted in discontinuation of therapy in P011, P016, and P018, suggesting that most infections were medically manageable while patients remained on study treatment.

Table 24

Adverse Event Summary
Patients with Infections and Related Terms
Safety Population
Protocol 011

	P011 Ridaforolimus 40 mg daily x 5 days/week		P011 Placebo	
	n	(%)	n	(%)
Patients in population	343		359	
Any Treatment-Emergent Event	177	(51.6)	92	(25.6)
Severe (Grade ≥3) Treatment-Emergent AE	19	(5.5)	9	(2.5)
Serious Treatment-Emergent AE	22	(6.4)	8	(2.2)
Treatment-Emergent AE Leading to Death	0	(0.0)	0	(0.0)
Treatment-Emergent AE Leading to Withdrawal	5	(1.5)	0	(0.0)
Treatment-Emergent AE Leading to Dose Reduction or Dose Delay	34	(9.9)	3	(0.8)

Non-Infectious Pneumonitis and Related Terms

Non-infectious pneumonitis, which may become a serious event that sometimes results in death, is a well-known side effect of rapamycin analogs used in the treatment of cancer patients, and can usually be managed effectively by close monitoring, interruption in treatment, initiation of corticosteroids, and other supportive measures. The natural history of non-infectious pneumonitis can result in interventions that would qualify it as a serious adverse events, and sometimes results in death. Similar to stomatitis, the P011 protocol

included a specific algorithm of dose reductions, dose withholdings, and use of corticosteroids for the management of patients who experienced pneumonitis (Table 25).

Table 25

Recommended Dose Adjustments to Manage Non-Infectious Pneumonitis – P011

Grade*	Description	Treatment	Dose Modification
1	Asymptomatic, radiographic	• No intervention • Consider diagnostics to exclude infectious causes • Continue treatment with study drug	No change in dose
2	Symptomatic, not interfering with activities of daily living	Depending on severity of symptoms: • Consider interruption of study drug • Consult pulmonologist • Consider diagnostics to exclude infectious causes • Consider corticosteroids	Depending on duration of pneumonitis symptoms: • If improvement to Grade ≤1 in ≤2 weeks, resume study drug treatment at current dose • If improvement to Grade ≤1 in 2 to 4 weeks, resume study drug at 10 mg lower than current dose • If no improvement to Grade ≤1 within 4 weeks, discontinue study drug
3	Symptomatic, interfering with activities of daily living, supplemental oxygen required	• Interrupt treatment with study drug • Consult pulmonologist • Diagnostics to exclude infectious causes • Corticosteroids if infectious cause excluded (e.g., oral prednisone 20 g once-daily or intravenous methyl-prednisolone 60 mg every 6 hours) • For impending respiratory distress, concomitant treatment with antibiotics and corticosteroids is recommended	Discontinue study drug permanently
4	Life-threatening; ventilatory support indicated		
* NCI CTCAE Grade			

To analyze non-infectious pneumonitis, related MedDRA terms were incorporated, including pneumonitis, alveolitis, interstitial lung disease, acute interstitial pneumonitis, allergic alveolitis, lung infiltrate, and pulmonary toxicity (Table 26). In P011, the incidence of these events in the ridaforolimus group was 10.2%, with events Grade 3 and above in 2.6% of patients, compared to 0.6% for all grades and 0.3% for Grade 3 and above in the placebo group.

In the P016 and P018 trials, the incidence of these events was 7.5% and 2.4% respectively, with Grade 3 and above events occurring in less than 1% of patients in each study.

Out of 702 ridaforolimus-treated patients in P011, P016, and P018 combined, there were 51 patients who experienced non-infectious pneumonitis (7.3%). The gender and age of patients with non-infectious pneumonitis was approximately similar to the overall study populations. Only 2 patients in the placebo group of P011 experienced a pneumonitis event. Among patients who had an adverse event of pneumonitis or related terms, the median time to onset was 107 days (SD 77) from the initiation of ridaforolimus. There were 17 patients with the highest severity at Grade 1, 23 at Grade 2, 10 at Grade 3, none at Grade 4, and 1 at Grade 5. Among the 51 ridaforolimus patients who experienced pneumonitis in P011, 20 (39.2%) received corticosteroid treatment. Among the 20 patients who received corticosteroid treatment, there was 1 patient with a diagnosis of pneumonitis whose outcome was listed as continuing, 2 patients with a diagnosis of pneumonitis whose outcomes were resolved with sequelae, and 1 patient who had a fatal outcome. The remaining 16 patients had an outcome of resolved. Pneumonitis was diagnosed clinically, and Grade 1 pneumonitis (defined in CTCAE as asymptomatic) was frequently detected incidentally by imaging studies conducted to assess tumor status. Chest CTs were not required for pneumonitis surveillance. Patients with pneumonitis who were asymptomatic did not require corticosteroid treatment. Among the 51 ridaforolimus patients who experienced non-infectious pneumonitis, this was considered a serious adverse event in 10 patients, and only 6 (1.7%) of patients in the ridaforolimus treatment group of P011 discontinued from the study as a result of pneumonitis. A single patient in the placebo group of P011 discontinued from the study due to pneumonitis.

Table 26

Adverse Event Summary
Patients with Non-infectious Pneumonitis and Related Terms
Safety Population
Protocol 011

	P011 Ridaforolimus 40 mg daily x 5 days/week		P011 Placebo	
	n	(%)	n	(%)
Patients in population	343		359	
Any Treatment-Emergent Event	35	(10.2)	2	(0.6)
Severe (Grade ≥3) Treatment-Emergent AE	9	(2.6)	1	(0.3)
Serious Treatment-Emergent AE	9	(2.6)	1	(0.3)
Treatment-Emergent AE Leading to Death	1	(0.3)	0	(0.0)
Treatment-Emergent AE Leading to Withdrawal	6	(1.7)	1	(0.3)
Treatment-Emergent AE Leading to Dose Reduction or Dose Delay	26	(7.6)	0	(0.0)

Hyperlipidemia and Related Terms

Hyperlipidemias, including hypertriglyceridemia and hypercholesterolemia have been reported for ridaforolimus and other rapamycin analogs. Hyperlipidemia was more frequent in the ridaforolimus treatment group than in the placebo group in P011 (38.2% vs. 11.4%), as was the incidence of Grade 3 and higher AEs (2.6% vs. 0.6%). Most hyperlipidemia events were assessed by Investigators as related to treatment, regardless of treatment arm. There were no notable differences in the frequency and severity of hyperlipidemia events in P016 and P018. Across P011, P016, and P018, there was a single serious adverse event from hyperlipidemia (in P011), there were no hyperlipidemia adverse events leading to death, and only 1 patient in P016 discontinued study treatment due to a hyperlipidemia adverse event.

In totality, hyperlipidemia events were reported frequently, but were generally mild to moderate in severity and rarely became serious or resulted in discontinuation of study treatment. Patients were able to continue on study treatment, and physicians were advised to manage their patients with lipid-lowering agents, such as statins or fibrates, as needed.

Hyperglycemia and Related Terms

Hyperglycemia has been reported with rapamycin analogs, including ridaforolimus, and was reported more frequently in the ridaforolimus-treatment group. Hyperglycemia and related clinical adverse events, such as blood glucose increased, glucose tolerance impaired, diabetes mellitus, and diabetic ketoacidosis; occurred in 18.1% of patients in the ridaforolimus-treatment group compared to 2.8% of patients in the placebo group of P011. The clinical adverse events of hyperglycemia (14.3%), diabetes mellitus (2.9%), and type 2 diabetes mellitus (0.9%), mostly Grade 1-2 events, accounted for most hyperglycemic related adverse events in patients treated with ridaforolimus in P011. A similar percentage of these adverse events (19.0%) occurred with oral ridaforolimus treatment in P016, but there was a somewhat higher incidence (30.7%) reported with I.V. ridaforolimus in P018. Grade 3 and above hyperglycemia occurred with similar frequency across P011, P016, and P018, occurring in 8.8% of patients in P016, 5.2% of patients in P018, and 7.3% of patients in the ridaforolimus-treatment group of P011. Across P011, P016, and P018, 9 patients experienced serious hyperglycemic events, including 2 patients with diabetic ketoacidosis with a prior history of diabetes mellitus and both were reported to have resolved.

Upon medical review of the 9 serious hyperglycemic events, it was determined that patients with an underlying history of frank diabetes, hyperglycemia from metabolic syndrome, or glucose intolerance may be more susceptible to serious hyperglycemia and related adverse events. For such patients, appropriate anti-diabetic agents, such as metformin, sulfonylurea, dipeptidyl peptidase-4 inhibitor, or insulin should be considered for hyperglycemia.

Based on the above data, it is apparent that most patients with hyperglycemic events are medically manageable, have resolution of the adverse event, and are able to continue on

study treatment. Hyperglycemia is manageable with careful monitoring of fasting blood glucose levels and glycosylated hemoglobin prior to initiation of ridaforolimus therapy and on a routine basis thereafter. Use of oral anti-hyperglycemic medications and patient education related to diet is encouraged to control elevations in blood glucose.

Gastrointestinal Hemorrhage

Gastrointestinal perforation and gastrointestinal hemorrhage have been reported in cancer patients receiving rapamycin analogs [48; 49]. To analyze adverse events related to gastrointestinal hemorrhage, related MedDRA terms were grouped, including gastrointestinal hemorrhage, rectal hemorrhage, anal hemorrhage, hemorrhoidal hemorrhage, gastric hemorrhage, hematemesis, hematochezia, melena, small intestinal hemorrhage, and upper gastrointestinal hemorrhage. These events were observed in 2.6% of patients (all grades) in the ridaforolimus treatment group and 1.1% of patients in the placebo group of the Phase III trial (P011), in 7.5% of patients in P016, and in 1.4% of patients in P018.

In P011, 4 (1.2%) patients in the ridaforolimus group experienced serious adverse events of gastrointestinal or rectal hemorrhage that were also considered to be severe (Grade 3 and above), while 2 (0.6%) patients in the placebo group experienced SAEs and severe events of small intestinal hemorrhage or gastric hemorrhage. While no patients in the placebo group withdrew from P011 as a result of gastrointestinal hemorrhage, there were 2 (0.6%) patients treated with ridaforolimus who discontinued study treatment due to this event. A similar discontinuation rate was seen in the P016 and P018 trials with only 1 patient discontinuing in each protocol. In P011, there were 2 deaths reported (0.6%) in the ridaforolimus treatment group compared to none (0%) in the placebo group as a result of this event. P016 reported 1 fatal event of gastrointestinal hemorrhage and P018 had no deaths related to this event.

Because thrombocytopenia is a common adverse event occurring among ridaforolimus-treated patients, a medical review of the 10 patients in the P011, P016, and P018 clinical studies who received ridaforolimus and reported SAEs of gastrointestinal hemorrhage was undertaken to assess if thrombocytopenia might have been a contributing factor. Among the 702 patients collectively treated with ridaforolimus from P011, P016, and P018, 10 (1.4%) patients reported SAEs of gastrointestinal hemorrhage and related terms compared to 2 (0.6%) gastrointestinal hemorrhages reported among the 359 patients in the placebo group. Only 1 ridaforolimus-treated patient is reported to have had a gastrointestinal hemorrhage secondary to thrombocytopenia (platelets count 22,000/L, Grade 4 at the time of the event).

It is important to note that multiple confounding factors are associated with the reported serious adverse events of gastrointestinal hemorrhage. Several patients were taking aspirin, non-steroidal anti-inflammatory agents, or anti-coagulants such as warfarin or fluindione, and many patients had sarcomas anatomically involving the abdomen such as uterine leiomyosarcoma, gastrointestinal stromal tumors, other sarcomas arising from a truncal location, or metastatic disease to the abdomen or abdominal viscera. Based on

these observations, and the relatively low frequency across P011 and P016/018, it is difficult to draw conclusions about a causal relationship between ridaforolimus treatment and gastrointestinal hemorrhage.

Gastrointestinal Perforation

Gastrointestinal perforations are considered to be serious adverse events associated with another rapamycin analog, temsirolimus [41]. MedDRA preferred terms were incorporated and include search terms such as intestinal perforation and duodenal perforation for analysis. While uncommon, these adverse events occurred slightly more frequently in the placebo group (0.6%) than in the ridaforolimus treatment group (0.3%) in P011. A single event of intestinal perforation was observed in a patient treated with ridaforolimus, compared to a duodenal perforation and one intestinal perforation occurring in patients receiving placebo in P011.

In P016/018, there were 6 patients with serious gastrointestinal perforation related events representing an incidence of about 0.3-0.9% across these three trials. While no fatal events were reported in the ridaforolimus treatment group in P011, two deaths were reported in the placebo group. Results were similar in P016/018 with no deaths reported in P016 and one death reported in P018. No patients withdrew from the study in P011 due to gastrointestinal perforation or related events, however in P016/018, one patient each withdrew from the study.

Because gastrointestinal perforations are so uncommon, a careful search for this class of adverse events was performed across the ridaforolimus program, including ongoing and other completed trials (with data cutoff of 30-Apr-2011). From this dataset of more than 2,000 patients and healthy subjects enrolled on ridaforolimus clinical trials, there were 23 patients who reported gastrointestinal perforation related adverse events. Four (4) of these 23 patients were not exposed to ridaforolimus (of approximately 456 patients collectively on control arms of randomized studies), including two (2) patients in the placebo group in P011 and two (2) patients who were not exposed to ridaforolimus from a control arm of an earlier study. Nineteen (19) patients who were exposed to ridaforolimus (of approximately 1,626 patients/subjects exposed to ridaforolimus across all studies, collectively) reported gastrointestinal perforations and related adverse event terms. Thus, in the advanced cancer patient populations enrolled on ridaforolimus studies, approximately 1% of patients exposed to ridaforolimus and approximately 1% of patients who were not exposed to ridaforolimus reported gastrointestinal perforations and related adverse event terms.

Based on these data, it is apparent that gastrointestinal perforations and related disorders are uncommon and occur sporadically across studies of advanced cancer patients enrolled into ridaforolimus clinical trials. These events occurred at a low frequency in both ridaforolimus and placebo in P011. Gastrointestinal perforation related events were also reported in two other randomized studies (for prostate cancer patients and endometrial cancer patients), and also occurred with the same approximate frequency in patients exposed to ridaforolimus or the control treatment in these two studies. Six of these

patients with GI perforations occurred in a single study (P010). In this study, P010, a phase I study of ridaforolimus combined with bevacizumab, a higher frequency of gastrointestinal perforations was reported (6 of 17 patients). Bevacizumab is known to increase the incidence of gastrointestinal perforation, with this event reported to occur in up to 2.4% of bevacizumab-treated patients [50]. Across most studies, very few gastrointestinal perforations were considered by the investigator to be related to study therapy with ridaforolimus (or related to control therapy in those cases occurring in patients not exposed to ridaforolimus). Instead, most events occurred in patients with abdominal or pelvic tumors, such as sarcomas or endometrial cancers, where invasion of the gastrointestinal tract may result in perforation, fistula formation, or an abdominal (pelvic) abscess. In some cases, patients with gastrointestinal perforations had a history of diverticular disease or had a clear cut alternative explanation (procedural complication of colonoscopy). It is thus unclear based on these data whether perforations in the ridaforolimus program are occurring at higher frequency in patients receiving ridaforolimus than would be expected in an advanced cancer population, except in the context of the ridaforolimus-bevacizumab combination. In conclusion, the available data do not demonstrate a clear relationship between treatment with ridaforolimus monotherapy and gastrointestinal perforation.

Renal Function Impairment

To analyze adverse events related to renal function impairment, related MedDRA terms were incorporated, including renal insufficiency, acute renal failure, increased creatinine, azotemia, and renal impairment. In the ridaforolimus treatment group of the Phase III study, renal function impairment events of all grades were reported in 9.0% of patients, and were Grade 3 and above events in 2.3% of patients. The corresponding percentages for the placebo group were 0.8% for all grades and 0.3% for Grade 3 and above. In P016, 10.2% of patients had renal impairment events of any grade with 6.8% having Grade 3 and above events. In P018, there were 9.4% of patients with renal impairment events in all grades and 3.8% of patients with Grade 3 and above events. The laboratory based adverse events of blood creatinine increased and hypercreatininemia, all Grade 1-2 events, accounted for most of the renal function impairment adverse events in P011.

Across Protocols 011, 016, and 018, there were 22 patients with serious renal function impairment adverse events, representing an incidence of approximately 2.3% to 5.4% across the three trials. It is important to note that 16 of the 22 patients (72.7%) reported an outcome of recovered or resolved for the event, indicating that permanent renal damage did not occur in most cases. Four (4) patients in the ridaforolimus group discontinued study drug due to a renal function impairment event in P011 and there were no fatal renal function impairment events reported for in this group. Similar incidences of discontinuations due to renal function impairment events were reported in P016 and P018 (1.4% and 1.9%, respectively). Based on these data, it is apparent that most patients with renal function impairment had resolution of the adverse event and were able to continue on study treatment.

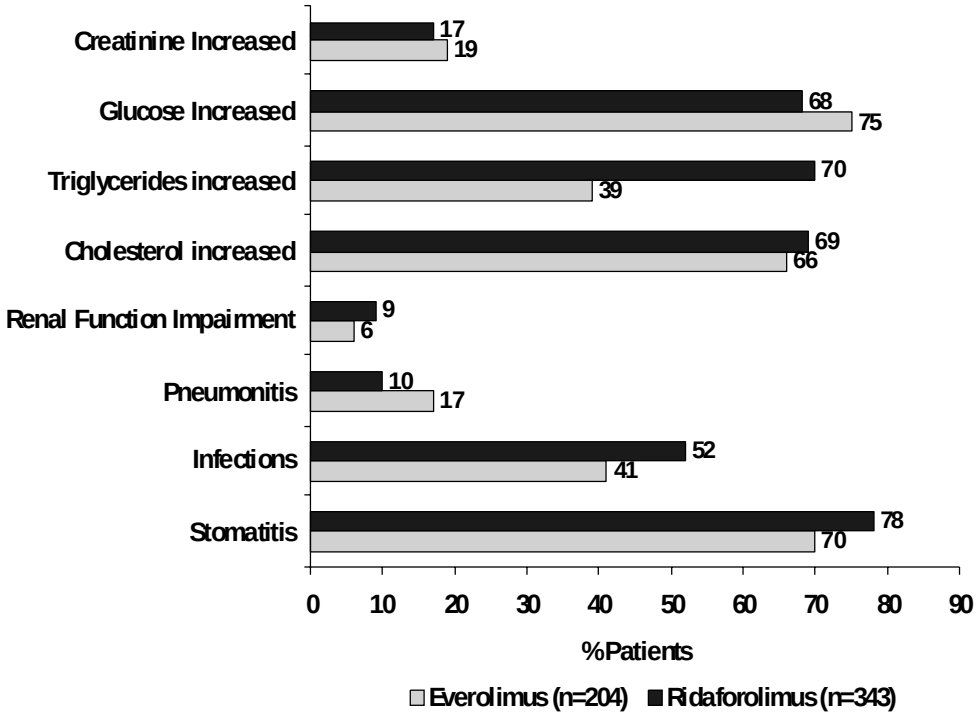
These results suggest that similar to other rapamycin analogs, renal impairment is uncommon but a potentially serious side effect of ridaforolimus treatment.

7.4. Safety Comparison with Other Rapamycin Analogs

The safety and tolerability profile of ridaforolimus is generally similar to the two rapamycin analogs used in the treatment of cancer patients, namely everolimus and temsirolimus, including the frequency and severity of most adverse events [42; 41]. It should be appropriately noted that this comparison is across clinical studies with relevant differences in study design and execution, including different tumor types. Three important types of adverse events reported for the rapamycin analogs, stomatitis, pneumonitis, and renal function impairment, illustrate the similarities in the incidence and severity of adverse events between the two oral rapamycin analogs ridaforolimus and everolimus (Figure 15). The most common and dose limiting adverse event for rapamycin analogs is stomatitis and related terms. The incidence for ridaforolimus in P011 (77.8%) is similar to everolimus in pancreatic neuroendocrine tumors (70%) or subependymal giant cell astrocytoma (86%). Pneumonitis and related terms was reported in 10.2% of patients receiving ridaforolimus in P011 and 14% to 17% of patients treated with everolimus for renal cell cancer and pancreatic neuroendocrine tumors, with severe pneumonitis in 2.6% of patients receiving ridaforolimus in P011 compared to 3% to 4% of patients treated with everolimus in its two pivotal randomized studies. Renal function impairment is difficult to compare (because of potential differences in the methods of analysis and reporting), but for patients receiving ridaforolimus in P011, 9.0% of patients reported clinical adverse events of renal function impairment, mostly blood creatinine increased and hypercreatinemia, with 2.3% of patients reporting Grade 3 and Grade 4 clinical adverse events. For patients receiving everolimus for pancreatic neuroendocrine tumors or renal cell cancer, the laboratory abnormality of increased creatinine is noted in 19.0% to 50.0%, with 1.0% to 2.0% Grade 3 and Grade 4. As these examples of key adverse events illustrate, the adverse event profile of ridaforolimus appears to be generally comparable to that of other rapamycin analogs for the treatment of cancer.

Figure 15

Comparable Toxicities of Ridaforolimus and Everolimus†
(All Grades)



† A randomized, controlled trial of Afinitor versus placebo in patients with advanced pancreatic neuroendocrine tumors [51]

7.5. Overall Safety Conclusion

When used for the maintenance treatment of patients with advanced sarcomas at 40 mg q.d. x 5 days/wk, ridaforolimus is associated with more adverse events compared with placebo, including more serious and severe AEs. However the majority of these adverse experiences are manageable with AE leading to treatment discontinuation occurring in only 14.6% of patients treated with ridaforolimus, and a longer median time on treatment (time to treatment discontinuation) was observed for patients treated with ridaforolimus compared to placebo.

Most adverse events leading to death were due to the underlying sarcoma and progressive disease. Review of the individual cases indicated a single ridaforolimus related death due to pneumonitis that was attributed to ridaforolimus treatment, while all other cases failed to demonstrate a consistent causative relationship with ridaforolimus, and were heavily confounded by other medical conditions including the underlying metastatic disease.

The most common AE was stomatitis, which was consistent with an increased pain score in patient reported symptoms. Other serious adverse events such as infections, pneumonitis, hyperlipidemia, hyperglycemia, gastrointestinal hemorrhage/perforation, and renal function impairment were similar in frequency and severity to other rapamycin analogs.

8. Pediatric Population

8.1. Intravenous Ridaforolimus in Pediatrics (PN028)

In the open label, multi-center Phase I dose escalation trial of pediatric patients with recurrent/refractory solid tumors, including lymphoma and tumors of the central nervous system (P028), I.V. ridaforolimus was administered once daily over 5 consecutive days every other week. Dose levels were 8, 10, 13 and 16 mg/m^2/day (maximum doses of 10, 12.5, 18.75 and 18.75 mg, respectively). Results were published in abstract form at the 2010 ASCO meeting. A total of 15 patients, age 2 to 16 years, were enrolled; 3 were male and 12 were female. Tumor types included 6 CNS, 8 sarcoma, and 1 nephroblastoma. Response was assessed by RECIST criteria and toxicity assessed according to CTCAE, v3.0. Review of safety information show there were no dose-limiting toxicities up to the maximum administered dose of 16 mg/m^2/day. Most AEs were low or moderate grade (≤Grade 2), reversible, and easily managed. Related grade 3/4 toxicities in >10% of patients were reversible myelosuppression, electrolyte disturbances, transaminitis, hyperglycemia, anorexia, nausea, vomiting, acidosis, and pain. A total of 19 Serious Adverse Events (SAEs) were reported in 10 of the patients. Only 3 SAEs (anemia, fever, mucositis) were reported by investigators as related to ridaforolimus; all three were expected. This suggests that the safety profile of ridaforolimus in children is not significantly different than the adult population. Following 5 once-daily ridaforolimus 30 min infusions to patients aged 4-16 years old: 1.) Ridaforolimus trough concentrations appeared to approach steady state in both blood and plasma for the majority of individuals where trough data were available; 2.) Mean accumulation when comparing concentrations 24 hours after dosing was ~1.4-1.7 and ~1.2-3.0 –fold for blood and plasma, respectively; 3.) Mean apparent terminal t½ were 38.1-66.2 hr and 22.7-31.3 hr in blood and plasma, respectively, which is comparable to the observed t½ in adults. The best observed response was stable disease.

In the Phase II study of I.V. ridaforolimus (P018) in patients with advanced sarcoma, pediatric patients ≥ 15 years of age were eligible, and 2 patients (1 age 16, and 1 age 17) were enrolled in the study. No untoward adverse events were reported in these patients.

8.2. Efficacy Among Pediatric Patients in P011

In the pivotal Phase III sarcoma trial (P011), information for the pediatric population is available for patients age 13 to 17. In other studies, enrollment of subjects less than 18 years of age was not allowed apart from the two studies listed above (P018 and P028).

P011 enrolled patients 13 years of age and above as long as their weight was at least 45.4 kg or 100 pounds. There were 12 patients 13 to 17 years of age enrolled in the study. Seven (7) of the patients were in the ridaforolimus treatment group, 4 with bone sarcoma and 3 with STS. The other 5 pediatric patients were in the placebo group, 4 with bone sarcoma and 1 with STS. Among the 7 patients treated with ridaforolimus, 1 with osteosarcoma had PR with tumor shrinkage of 64%, 4 had SD with PFS durations of 23, 20, 48, and 19 weeks, respectively, and 2 had PD. In contrast, among the 5 patients in the placebo group, 1 had SD with PFS duration of 20 weeks, and 4 had PD. These results suggest that the benefit of ridaforolimus in the pediatric population of 13 to 17 years of age is consistent with the adult population.

8.3. Safety Among Pediatric Patients in P011

The adverse events experienced by the 12 pediatric patients in P011 were generally consistent with those experiences by the population of patients age 18 and above. Three patients on ridaforolimus had the following grade 3 or higher adverse experiences (AEs): thrombocytopenia, liver injury, intestinal perforation, and intra-abdominal hemorrhage. The grade 3 thrombocytopenia and liver injury AEs were considered by investigators to be probably related to study medication. Two ridaforolimus-treated patients had serious adverse events: one patient with intestinal perforation and intra-abdominal hemorrhage; one patient with infectious pneumonia. Neither serious AE was considered treatment-related. The intestinal perforation and hemorrhage occurred in a 17-year-old female patient with a solitary fibrous tumor of the trunk who had previously undergone a hemicolectomy for intestinal disease and had progressive disease (PD) at the time of the perforation. Four patients required dose reductions (3 due to mucositis); the PR and the longest-duration SD were among the 4 patients requiring dose adjustment. The mean (range) BSA in patients requiring dose reduction was 1.7 (1.41-2.26), compared to 1.63 (1.45-1.81) in those that did not, suggesting that the patients' size did not influence the need for dose adjustment. Pharmacokinetic analyses were not performed in patients treated on PN011.

8.4 Summary and Conclusions for Pediatric Patients

Overall, while the sample size is small, no additional safety concerns are noted in the 13 to 17 age group treated with 40 mg qd x 5 when compared with the adult population. There is an ongoing Phase I study of oral ridaforolimus (MK-8669 PN056) in children between the ages of 6 and 18 years.

9. Benefits and Risks Conclusions

Patients with metastatic soft tissue or bone sarcomas are usually initially treated with anthracycline-based chemotherapy. This represents a challenging clinical scenario as the majority of sarcoma patients who do not progress during this or subsequent chemotherapy-based treatments have to undergo a treatment hiatus, as prolonged treatment is infeasible due to concerns over cumulative anthracycline cardiac toxicity, or other cumulative, intolerable toxicities. Analyses of health-related quality of life in metastatic sarcoma patients who experience disease progression during a post-treatment observation period indicate that these patients experience a marked decrease in quality-of-life, as assessed by both EQ-5D and EORTC QLC-C30 instruments.

P011 was designed to evaluate the efficacy and safety of ridaforolimus as a maintenance treatment in patients with metastatic soft-tissue or bone sarcoma who had achieved a complete response, partial response or stable disease after completion of at least 4 cycles of first, second, or third line chemotherapy.

9.1. Efficacy

P011 met the pre-specified primary endpoint of at least a 25% reduction in the risk progression or death compared to placebo. The PFS hazard ratio was 0.72 (95% CI [0.61, 0.85], p=0.0001), indicating a 28% overall reduction in risk of progression or death in patients who received ridaforolimus. In terms of absolute measures of the benefit of ridaforolimus on PFS, the shape of the Kaplan-Meier curves indicates that the difference in medians (3.1 weeks by the IRC analysis) is not an accurate assessment of absolute benefit. With the exception of the median (50^{th} percentile), the absolute difference between treatment arms at each decile along the curve from the 30^{th} to 70^{th} percentiles is 6.4-8.6 weeks (Figure 4). For this reason, the hazard ratio is the single best descriptor of the difference in treatment arms. Based on the IRC-determined hazard ratio and median PFS in the control arm, 5.7 weeks is a better estimate of the improvement in median PFS conferred by ridaforolimus treatment (calculated from: 14.6 weeks x 1/0.72). This estimate is in agreement with supportive analyses of PFS discussed in Section 6.2.3.1.2. This median difference is similar to the 8 week median difference that a 25% PFS hazard reduction was expected to yield, based on pre-specified study assumptions. Indeed, since the pre-specified study assumptions overestimated the median PFS time for the placebo group, the adjusted observed median PFS improvement of ~ 6 weeks represents a greater relative improvement in median PFS than was targeted prior to study initiation (39% versus 33% improvement in PFS).

The results of the primary PFS analysis are supported by similar results obtained from multiple additional pre-specified analyses of PFS, including sensitivity analyses of PFS using alternate censoring rules, as well as pre-specified subgroup analyses of PFS based on various baseline characteristics. The subgroup analyses indicated that the benefit of ridaforolimus persisted regardless of age, gender, race, geographic region, functional performance status, tumor histology, prior line of therapy, prior surgery, and neoadjuvant

or adjuvant therapy. In particular, ridaforolimus exhibited similar PFS benefit in both bone sarcoma and soft tissue sarcoma subgroups.

In addition, the improvement in PFS conferred by ridaforolimus treatment was supported by an improvement in tumor growth control based on best target lesion response and best overall response analyses.

While the study was not powered for analysis of overall survival, an analysis that included 67% of the study population yielded a hazard ratio of 0.93 favoring ridaforolimus, and largely rules out a detrimental effect. An exploratory analysis of post-progression survival yielded a hazard ratio of 0.95 favoring ridaforolimus, providing further evidence that treatment with ridaforolimus did not adversely impact subsequent patient management.

9.2. Safety

Adverse effects observed with ridaforolimus in P011 and in other studies of ridaforolimus as monotherapy and in combination with other anti-cancer agents are similar to those of the related rapamycin analogs temsirolimus and everolimus – no new or unexpected safety signals were observed in the study relative to previously known safety information about ridaforolimus or other rapamycin analogs. Similar to other rapamycin analogs, in P011 patients treated with ridaforolimus commonly experienced mucositis, but with supportive measures and appropriate dose interruptions or reductions, most patients were able to continue therapy. In P011, only 15% of patients discontinued ridaforolimus because of a side effect.

While in the P011 study there were more deaths associated with a respiratory-related adverse event in patients treated with ridaforolimus versus placebo, there was only one respiratory-related death attributed to ridaforolimus in the study. This death was attributed to pneumonitis, and is the only case of fatal pneumonitis reported among all completed and ongoing ridaforolimus studies. The risk of pneumonitis in patients who are given rapamycin analogs is well-known by oncologists and is generally manageable with dose modification and corticosteroids.

9.3. Overall Benefit-Risk

For metastatic sarcoma patients, who live in fear of the inevitable progression of their disease during planned chemotherapy breaks, the availability of an orally administered, effective maintenance treatment to extend the benefits of previous chemotherapy and delay the need for subsequent chemotherapy treatments represents an important therapeutic advance.

The adverse effects associated with ridaforolimus are well-known in the context of rapamycin analogs that approved for the treatment of cancer patients and are manageable with dose reduction and appropriate supportive care. When viewed in the context of the effectiveness of ridaforolimus in extending progression-free survival, and thus delaying disease progression and the need for subsequent chemotherapy, many patients and

physicians would consider the benefits of ridaforolimus maintenance therapy to outweigh the risk of adverse effects.

The results of P011 support the use of ridaforolimus as a maintenance treatment for patients with metastatic soft tissue sarcoma or bone sarcoma who have completed at least 4 cycles of chemotherapy without evidence of disease progression.

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11. Appendices

Appendix 1

Completed and Ongoing Ridaforolimus Clinical Trials as of 25-Oct-2010

Protocol Number	Protocol Title / Short Description	Phase	Route	Type of Trial	Number of Subjects Enrolled and Treated[†]	Trial Status	CSR
Pivotal study							
MK-8669-P011	A Pivotal Trial to Determine the Efficacy and Safety of AP23573 when Administered as Maintenance Therapy to Patients with Metastatic Soft-Tissue or Bone Sarcomas	III	Oral	Single-Agent Placebo-controlled	702	Completed	Full
Supportive studies							
MK-8669-P016	Phase I/IIa dose escalation trial to determine the safety, tolerability and maximum tolerated dose of AP23573 when administered orally in patients with refractory or advanced malignancies	I/IIa	Oral	Single-Agent Single-Arm	147	Completed	Full
MK-8669-P018	Phase II trial of AP23573 (QDx5, IV) in patients with advanced sarcoma	II	IV	Single-Agent Single-Arm	212	Completed	Full
All Other studies							
MK-8669-P001	Phase I dose escalation trial to determine the safety, tolerability, and maximum tolerated dose of weekly administration of AP23573 (QW) in patients with refractory or advanced malignancies	I	IV	Single-Agent Single-Arm	46	Completed	Full
MK-8669-P002	A Phase II Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Study the Efficacy and Safety of Bicalutamide with or without Deforolimus in Men with Asymptomatic, Metastatic Castrate-Resistant Prostate Cancer	II	Oral	Combination Comparator	21	Ongoing	Protocol synopsis, SAEs
MK-8669-P003	A Phase I Study of MK-8669 in Patients with Metastatic or Locally Advanced Solid Tumors	I	Oral	Single-Agent Single-Arm	13 Japanese patients only	Completed	Full
MK-8669-P004	Phase I Combination Study of MK-8669 (Deforolimus) and MK-0646 in Patients with Advanced Cancer	I	Oral	Combination Single-Arm	87	Enrollment Completed[‡]	Protocol synopsis, SAEs

Completed and Ongoing Ridaforolimus Clinical Trials as of 25-Oct-2010 (Cont.)

Protocol Number	Protocol Title / Short Description	Phase	Route	Type of Trial	Number of Subjects Enrolled and Treated†	Trial Status	CSR
MK-8669-P007	A Randomized Phase II Trial of Ridaforolimus (AP23573; MK-8669) Compared to Progestin in Female Adult Patients with Advanced Endometrial Carcinoma Following One Line of Chemotherapy	II	Oral	Single-Agent Comparator	120	Ongoing	Protocol synopsis, SAEs
MK-8669-P009	A Phase II Trial of Oral Deforolimus in Combination with Trastuzumab for Patients with HER-2 positive Trastuzumab-Refractory Metastatic Breast Cancer	II	Oral	Combination Single-Arm	34	Ongoing	Protocol synopsis, SAEs
MK-8669-P010	A Phase I Trial of Oral Deforolimus (AP23573; MK-8669), an mTOR Inhibitor, in Combination with Bevacizumab for Patients with Advanced Cancers	I	Oral	Combination Single-Arm	17	Completed	Abbreviated
MK-8669-P012	Phase Ib pharmacokinetic and pharmacodynamic study to define the optimal dose for combining AP23573 (QW) with capecitabine	I	IV	Single-Agent Single-Arm	32	Completed	Full CSR
MK-8669-P013	Phase I dose escalation trial to determine the safety, tolerability, and MTD of dailyx5 administration of AP23573 (QDx5, IV) in patients with refractory or advanced malignancies	I	IV	Single-Agent Single-Arm	32	Completed	Full
MK-8669-P014	Phase Ib pharmacokinetic and pharmacodynamic study to define the optimal dose for combining AP23573 (QW) with paclitaxel	I	IV	Single-Agent Single-Arm	29	Completed	Full CSR
MK-8669-P015	Phase Ib dose escalation trial to determine the safety, tolerability, and maximum tolerated dose of oral AP23573 (QDx4, QDx14) in combination with doxorubicin (every 3 weeks)	I	Oral	Combination Single-Arm	37	Completed	Abbreviated
MK-8669-P017	Phase II study of the efficacy and safety of AP23573 (QW) in patients with taxane-resistant androgen-independent prostate cancer	II	IV	Single-Agent Single-Arm	38	Completed	Abbreviated
MK-8669-P019	Phase II trial of AP23573 (QDx5, IV) in female adult patients with recurrent or metastatic endometrial cancer	II	IV	Single-Agent Single-Arm	45	Completed	Abbreviated

Completed and Ongoing Ridaforolimus Clinical Trials as of 25-Oct-2010 (Cont.)

Protocol Number	Protocol Title / Short Description	Phase	Route	Type of Trial	Number of Subjects Enrolled and Treated†	Trial Status	CSR
MK-8669-P021	A Randomized Discontinuation Phase II Trial of Deforolimus in Non-Small Cell Lung Cancer (NSCLC) Patients with KRAS Mutations	II	Oral	Single-Agent Comparator	65	Ongoing	Protocol synopsis, SAEs
MK-8669-P023	Phase I sequential ascending dose trial of AP23573 (QDx5, IV) in patients with progressive or recurrent glioma	I	IV	Single-Agent Single-Arm	10	Completed	Abbreviated
MK-8669-P024	Phase II trial of AP23573 (QDx5, IV) in patients with relapsed or refractory hematologic malignancies	II	IV	Single-Agent Single-Arm	57	Completed	Protocol synopsis, SAEs
MK-8669-P028	A Phase I study of intravenous AP23573 administered QDx5 every other week in pediatric patients with advanced solid tumours	I	IV	Single-Agent Single-Arm	15	Completed	Protocol synopsis, SAEs
MK-8669-P030 (Banyu)	Phase II trial of AP23573 (QDx5, PO) in Japanese patients with advanced sarcoma for maintenance	II	Oral	Single-Agent Single-Arm	28	Ongoing	Protocol Synopsis, SAE
MK-8669-P038	An Extension Trial of Deforolimus (AP23573; MK-8669), an mTOR Inhibitor, for Patients with Advanced Cancer	I	IV or Oral	Single-Agent Extension	7	Ongoing	Protocol synopsis, SAEs
MK-8669-P039	A Phase II Study of Ridaforolimus in Patients with Metastatic and/or Locally Advanced Recurrent Endometrial Cancer.	II	Oral	Single-Agent Single-Arm	34	Enrollment Completed‡	Protocol synopsis, SAEs
MK-8669-P041	A Phase 2 randomized study of the combination of Ridaforolimus and Dalotuzumab	II	Oral	Combination Comparator	0	Ongoing	Protocol synopsis, SAEs
MK-8669-P049	A Phase 1 dose defining study of the combination of Ridaforolimus with AKT inhibitor MK-2206 or Notch inhibitor MK-0752	I	Oral	Combination Comparator	0	Ongoing	Protocol synopsis, SAEs
MK-8669-P050	A Phase 2 biomarker study of the combination of Ridaforolimus and Dalotuzumab	Ib	Oral	Combination Single-Arm	3	Ongoing	Protocol synopsis, SAEs
MK-8669-P051	A Phase 1 dose defining study for the combination of Ridaforolimus and Cetuximab in solid tumors	I	Oral	Combination Single-Arm	1	Ongoing	Protocol synopsis, SAEs

Completed and Ongoing Ridaforolimus Clinical Trials as of 25-Oct-2010 (Cont.)

Protocol Number	Protocol Title / Short Description	Phase	Route	Type of Trial	Number of Subjects Enrolled and Treated†	Trial Status	CSR
MK-8669-P052	A Phase 1 dose defining study for the combination of Ridaforolimus and vorinostat in renal cell carcinoma	I	Oral	Combination Single-Arm	0	Ongoing	Protocol synopsis, SAEs
Clinical Pharmacology Studies							
MK-8669-P005	An Open-Label, 2-Part, Randomized, Single Oral Dose, 3-Period Crossover Study to Evaluate the Food Effects of the Deforolimus (AP23573; MK-8669 Enteric Coated Tablet in Healthy Young Male Subjects	I	Oral	Single Dose	14	Completed	Abbreviated
MK-8669-P006	An Open-Label, 2-Period, Fixed Sequence Study to Assess the Effects of Multiple Oral Doses of Diltiazem (CARDIZEM™ CD), a Moderate CYP3A4 Inhibitor, on the Single-Dose Pharmacokinetics of Deforolimus (AP23573; MK-8669) in Healthy Young Male Subjects	I	Oral	Single Dose	10	Completed	Full
MK-8669-P020	A Study to Investigate the Absorption, Metabolism, Excretion, and Mass Balance of a Single Dose of Deforolimus (AP23573; MK8669)	I	Oral	Single Dose	6	Completed	Full
MK-8669-P037	A Clinical Trial to Assess the Effect of Deforolimus (AP23573; MK-8669) on QTc Interval in Patients	I	Oral	Part 1 Single Dose Part 2 Multiple Dose	22	Completed	Full
MK-8669-P042	A Single Dose Study to Evaluate the Effect of Food on Pharmacokinetics of Ridaforolimus (AP23573; MK-8669) in Healthy Young Male Subjects	I	Oral	Single Dose	18	Completed	Full
MK-8669-P044	A Study to Evaluate the Effect of Multiple Doses of Ridaforolimus (AP23573; MK-8669) on the Single Dose Pharmacokinetics of Midazolam in Patients	I	Oral	Multiple Dose	16	Completed	Full

Completed and Ongoing Ridaforolimus Clinical Trials as of 25-Oct-2010 (Cont.)

Protocol Number	Protocol Title / Short Description	Phase	Route	Type of Trial	Number of Subjects Enrolled and Treated†	Trial Status	CSR
MK-8669-P045	A 2-Part Study to Assess the Effects of Multiple Oral Doses of Rifampin and Ketoconazole on the Single-Dose Pharmacokinetics of Ridaforolimus	I	Oral	Single Dose	20	Completed	Full
MK-8669-P046	A Single Dose Study to Investigate the Pharmacokinetics of Ridaforolimus in Patients (non-cancer) with Hepatic Insufficiency	I	Oral	Single Dose	18	Completed	Full

† Enrolled and treated as of data cut-off 25-Oct-2010

‡ Includes studies with patients on active treatment, safety follow-up, or database lock occurring after 25-Oct-2010 with CSRs pending

CSR = Clinical Study Report; NA = Not Applicable; SAE = Serious Adverse Event

Appendix 2

Patients With Adverse Events Resulting in Death
(Incidence > 0% in One or More Treatment Groups)
All Completed Trials (25-Oct-2011 Data Cutoff)

	P011 Ridaforolimus 40 mg daily x 5 days/week		P016 Ridaforolimus All Dose Levels		P018 Ridaforolimus 12.5 mg IV daily 5 days/2weeks		All Other Completed Trials Ridaforolimus All Dose Levels[†]	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients in Population	343		147		212		495	
with one or more adverse events	21	6.1	28	19.0	29	13.7	39	(7.9)
Blood and lymphatic system disorders	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**1**	**(0.2)**
Leukocytosis	0	0.0	0	0.0	0	0.0	1	(0.2)
Cardiac disorders	**2**	**0.6**	**3**	**2.0**	**1**	**0.5**	**3**	**(0.6)**
Arrhythmia	1	0.3	0	0.0	0	0.0	0	(0.0)
Cardiac arrest	0	0.0	1	0.7	0	0.0	0	(0.0)
Cardio-respiratory arrest	0	0.0	2	1.4	0	0.0	1	(0.2)
Cardiopulmonary failure	0	0.0	0	0.0	1	0.5	0	(0.0)
Myocardial infarction	0	0.0	0	0.0	0	0.0	1	(0.2)
Pericardial effusion	1	0.3	0	0.0	0	0.0	0	(0.0)
Ventricular dysfunction	0	0.0	0	0.0	0	0.0	1	(0.2)
Gastrointestinal disorders	**2**	**0.6**	**1**	**0.7**	**1**	**0.5**	**2**	**(0.4)**
Duodenal perforation	0	0.0	0	0.0	0	0.0	0	(0.0)
Gastrointestinal haemorrhage	2	0.6	1	0.7	0	0.0	0	(0.0)
Gastrointestinal perforation	0	0.0	0	0.0	1	0.5	0	(0.0)
Intestinal obstruction	0	0.0	0	0.0	0	0.0	1	(0.2)
Intestinal perforation	0	0.0	0	0.0	0	0.0	0	(0.0)
Small intestinal obstruction	0	0.0	0	0.0	0	0.0	1	(0.2)
General disorders and administration site conditions	**4**	**1.2**	**6**	**4.1**	**12**	**5.7**	**17**	**(3.4)**
Asthenia	0	0.0	0	0.0	1	0.5	0	(0.0)
Disease progression	0	0.0	5	3.4	9	4.2	16	(3.2)
General physical health deterioration	3	0.9	0	0.0	0	0.0	0	(0.0)
Multi-organ failure	0	0.0	1	0.7	1	0.5	1	(0.2)
Pain	0	0.0	0	0.0	1	0.5	0	(0.0)
Performance status decreased	1	0.3	0	0.0	0	0.0	0	(0.0)
Pyrexia	0	0.0	0	0.0	1	0.5	0	(0.0)
Hepatobiliary disorders	**1**	**0.3**	**0**	**0.0**	**0**	**0.0**	**0**	**(0.0)**

Patients With Adverse Events Resulting in Death
(Incidence > 0% in One or More Treatment Groups)
All Completed Trials
(Cont.)

	P011 Ridaforolimus 40 mg daily x 5 days/week		P016 Ridaforolimus All Dose Levels		P018 Ridaforolimus 12.5 mg IV daily 5 days/2weeks		All Other Completed Trials Ridaforolimus All Dose Levels[†]	
	n	(%)	n	(%)	n	(%)	n	(%)
Hepatobiliary disorders	**1**	**0.3**	**0**	**0.0**	**0**	**0.0**	**0**	**(0.0)**
Cholangitis	0	0.0	0	0.0	0	0.0	0	(0.0)
Hepatic failure	1	0.3	0	0.0	0	0.0	0	(0.0)
Infections and infestations	**0**	**0.0**	**1**	**0.7**	**2**	**0.9**	**8**	**(1.6)**
Escherichia sepsis	0	0.0	0	0.0	0	0.0	1	(0.2)
Pneumonia	0	0.0	0	0.0	1	0.5	2	(0.4)
Pseudomonal sepsis	0	0.0	0	0.0	0	0.0	1	(0.2)
Respiratory tract infection	0	0.0	0	0.0	0	0.0	1	(0.2)
Sepsis	0	0.0	0	0.0	1	0.5	2	(0.4)
Septic shock	0	0.0	1	0.7	0	0.0	0	(0.0)
Sinusitis	0	0.0	0	0.0	0	0.0	1	(0.2)
Metabolism and nutrition disorders	**1**	**0.3**	**0**	**0.0**	**0**	**0.0**	**0**	**(0.0)**
Hypercalcaemia	1	0.3	0	0.0	0	0.0	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**4**	**1.2**	**12**	**8.2**	**5**	**2.4**	**5**	**(1.0)**
Acute monocytic leukaemia	0	0.0	0	0.0	0	0.0	0	(0.0)
Acute myeloid leukaemia	0	0.0	0	0.0	0	0.0	1	(0.2)
Adenocarcinoma	0	0.0	3	2.0	0	0.0	0	(0.0)
Breast cancer metastatic	0	0.0	1	0.7	0	0.0	0	(0.0)
Chondrosarcoma	0	0.0	1	0.7	0	0.0	0	(0.0)
Desmoplastic small round cell tumour	1	0.3	0	0.0	0	0.0	0	(0.0)
Leiomyosarcoma	0	0.0	1	0.7	0	0.0	0	(0.0)
Leiomyosarcoma metastatic	0	0.0	1	0.7	0	0.0	0	(0.0)
Malignant fibrous histiocytoma	0	0.0	1	0.7	0	0.0	0	(0.0)
Malignant neoplasm progression	1	0.3	0	0.0	0	0.0	0	(0.0)
Metastases to central nervous system	1	0.3	1	0.7	1	0.5	0	(0.0)
Metastases to lung	0	0.0	0	0.0	2	0.9	0	(0.0)
Mueller's mixed tumour	0	0.0	1	0.7	0	0.0	0	(0.0)
Neoplasm malignant	0	0.0	0	0.0	0	0.0	2	(0.4)

Patients With Adverse Events Resulting in Death
(Incidence > 0% in One or More Treatment Groups)
All Completed Trials
(Cont.)

	P011 Ridaforolimus 40 mg daily x 5 days/week		P016 Ridaforolimus All Dose Levels		P018 Ridaforolimus 12.5 mg IV daily 5 days/2weeks		All Other Completed Trials Ridaforolimus All Dose Levels[†]	
	n	(%)	n	(%)	n	(%)	n	(%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**4**	**1.2**	**12**	**8.2**	**5**	**2.4**	**5**	**(1.0)**
Pancreatic carcinoma	0	0.0	0	0.0	0	0.0	1	(0.2)
Retroperitoneal neoplasm	0	0.0	0	0.0	1	0.5	0	(0.0)
Sarcoma	0	0.0	0	0.0	1	0.5	0	(0.0)
Small cell lung cancer stage unspecified	1	0.3	1	0.7	0	0.0	0	(0.0)
Spindle cell sarcoma	0	0.0	1	0.7	0	0.0	0	(0.0)
Tumour haemorrhage	0	0.0	0	0.0	0	0.0	1	(0.2)
Tumour perforation	0	0.0	0	0.0	0	0.0	0	(0.0)
Nervous system disorders	**1**	**0.3**	**0**	**0.0**	**0**	**0.0**	**0**	**(0.0)**
Grand mal convulsion	1	0.3	0	0.0	0	0.0	0	(0.0)
Renal and urinary disorders	**0**	**0.0**	**2**	**1.4**	**1**	**0.5**	**2**	**(0.4)**
Renal failure	0	0.0	2	1.4	0	0.0	0	(0.0)
Renal failure acute	0	0.0	0	0.0	1	0.5	2	(0.4)
Respiratory, thoracic and mediastinal disorders	**6**	**1.7**	**3**	**2.0**	**8**	**3.8**	**6**	**(1.2)**
Acute respiratory failure	0	0.0	0	0.0	0	0.0	1	(0.2)
Dyspnoea	1	0.3	0	0.0	1	0.5	1	(0.2)
Hypoxia	0	0.0	0	0.0	1	0.5	0	(0.0)
Pleural effusion	2	0.6	0	0.0	0	0.0	1	(0.2)
Pneumonia aspiration	0	0.0	0	0.0	0	0.0	1	(0.2)
Pneumonitis	1	0.3	0	0.0	0	0.0	0	(0.0)
Pulmonary embolism	1	0.3	0	0.0	0	0.0	0	(0.0)
Respiratory arrest	0	0.0	1	0.7	0	0.0	1	(0.2)
Respiratory distress	1	0.3	0	0.0	0	0.0	0	(0.0)
Respiratory failure	0	0.0	2	1.4	6	2.8	1	(0.2)

Every patient is counted a single time for each applicable specific adverse event. A patient with multiple adverse events within a system organ class is counted a single time for that system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.

Only the highest reported grade of a given adverse event is reported for the individual patient if multiple identical events occur.

[†] Alone or in combination with other agents.

All other Completed Trials - data cut-off date 25-Oct-2010 P001, P003, P005, P006, P010, P012, P013, P014, P015, P017, P019, P020, P023, P024, P028, P037, P042, P044, P045, P046