A pilot phase 2 study of albumin-bound sirolimus nanoparticles, ABI-009, in patients with metastatic, unresectable, low or intermediate grade neuroendocrine tumors of the lung or gastroenteropancreatic system

Investigational Product:	**ABI-009**
Protocol Number:	**NET-001**
Study Phase:	**Pilot Phase 2**
Sponsor Name / Address:	**Ochsner Clinic Foundation** 1514 Jefferson Highway New Orleans, LA 70121
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Protocol Versions	Date
Amendment v3.0:	November 13, 2019
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PROTOCOL SYNOPSIS

INVESTIGATIONAL PRODUCT	ABI-009, sirolimus protein-bound nanoparticles for injectable suspension (albumin bound), sirolimus (formerly *nab*-rapamycin), nanoparticle albumin-bound rapamycin
TITLE	A pilot phase 2 study of albumin-bound sirolimus nanoparticles, ABI-009, in patients with metastatic, unresectable, low or intermediate grade neuroendocrine tumors of the lung or gastroenteropancreatic system
PROTOCOL NUMBER	NET-001
PHASE	Pilot Phase 2
STUDY OBJECTIVES	**Objectives** • The primary objective of this pilot phase 2 study is to evaluate the preliminary efficacy of ABI-009 in patients with grade 1 and 2 neuroendocrine tumors (NETs) of the gastroenteropancreatic system or lung, as measured by disease control rate (DCR) at 6 months • The secondary objective is to evaluate the safety and toxicity profile of ABI-009 and the overall response rate (ORR)
STUDY ENDPOINTS	**Endpoints** **Primary Endpoint** • Disease control rate at 6 months, assessed by investigator using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 **Secondary endpoint** • Safety • Overall response rate (ORR)
STUDY DESIGN and DOSE-FINDING RULES	This study is a prospective, single arm, single institution pilot phase 2 study to evaluate the efficacy and safety ABI-009 in patients with gastroenteropancreatic NET (GEPNETs) or NET of the lung and prior exposure to everolimus. ABI-009 will be given weekly for 2 weeks followed by a week of rest (qw2/3) in a 21-day cycle (on D1 and 8). The study will be conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCPs).
NUMBER OF PATIENTS	Up to 10 evaluable patients will be enrolled.
INCLUSION CRITERIA	A patient will be eligible for inclusion in this study only if all of the following criteria are met at screening:

	1. Unresectable or metastatic patients with typical or atypical carcinoid tumors of the lung or low or intermediate grade GEPNETS. 2. Patients must have measurable disease per RECIST 1.1. 3. Patients must have progressed on everolimus or been intolerant to everolimus as defined as discontinued for any adverse reactions other than allergic reaction. 4. Patients, ≥18 years old, must have Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1. 5. Concurrent use of somatostatin analogs (SSAs) is allowed if currently used for symptom control. 6. Adequate liver function: a. Total bilirubin ≤1.5 x upper limit of normal (ULN) mg/dL b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN (<5 x ULN if the patient has liver metastases). 7. Adequate renal function: a. Serum creatinine ≤2 x ULN or creatinine clearance ≥50 ml/min (Cockcroft-Gault). 8. Adequate biological parameters: a. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L b. Platelet count ≥100,000/mm^3 (100 × 10^9/L) c. Hemoglobin ≥8 g/dL (transfusions are allowed if clinically indicated) 9. Fasting serum triglyceride ≤300 mg/dL; fasting serum cholesterol ≤350 mg/dL. 10. Male or non-pregnant and non-breast feeding female: • Females of child-bearing potential must agree to use effective contraception without interruption from 28 days prior to starting IP throughout 3 months after last dose of IP and have a negative serum pregnancy test (β-hCG) result at screening and agree to ongoing pregnancy testing during the course of the study, and after the end of study treatment. A second form of birth control is required even if she has had a tubal ligation. • Male patients must practice abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study and throughout 3 months after last dose of IP. A second form of birth control is required even if he has undergone a successful vasectomy. 11. Life expectancy of >3 months, as determined by the investigator. 12. Ability to understand and sign informed consent. 13. Willingness and ability to comply with scheduled visits, laboratory tests, and other study procedures.

EXCLUSION CRITERIA	A patient will not be eligible for inclusion in this study if any of the following criteria apply: 1. Patients currently undergoing anti-cancer therapy for neuroendocrine tumors (other than SSAs for symptoms). 2. History of allergic reactions to compounds of similar chemical or biologic composition to ABI-009. 3. Known active uncontrolled or symptomatic central nervous system (CNS) metastases. A patient with controlled and asymptomatic CNS metastases may participate in this study. As such, the patient must have completed any prior treatment for CNS metastases ≥28 days (including radiotherapy and/or surgery) prior to start of treatment in this study and should not be receiving chronic corticosteroid therapy for the CNS metastases. 4. Active gastrointestinal bleeding. 5. Uncontrolled serious medical or psychiatric illness. 6. Patients with a "currently active" second malignancy other than non-melanoma skin cancers, carcinoma in situ of the cervix, resected incidental prostate cancer (staged pT2 with Gleason Score ≤ 6 and postoperative PSA <0.5 ng/mL), or other adequately treated carcinoma-in-situ are ineligible. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥1 year). 7. Recent infection requiring systemic anti-infective treatment that was completed ≤14 days prior to enrollment (with the exception of uncomplicated urinary tract infection or upper respiratory tract infection). 8. Uncontrolled diabetes mellitus as defined by HbA1c >8% despite adequate therapy. 9. Unstable coronary artery disease or myocardial infarction during preceding 6 months. 10. Patients with history of interstitial lung disease and/or pneumonitis, or pulmonary hypertension. 11. Use of strong inhibitors and inducers of CYP3A4 within the 14 days prior to receiving the first dose of ABI-009. Additionally, use of any known CYP3A4 substrates with narrow therapeutic window (such as fentanyl, alfentanil, astemizole, cisapride, dihydroergotamine, pimozide, quinidine, terfanide) within the 14 days prior to receiving the first dose of ABI-009. 12. Known Human Immunodeficiency Virus (HIV). 13. Known active Hepatitis B or Hepatitis C.
DURATION OF TREATMENT AND STUDY PARTICIPATION	The study is expected to take approximately 24 months from first patient enrolled to last patient follow-up. The study will take 12 months to enroll all subjects and an estimated 12 months of treatment per subject or until treatment is no longer tolerated. End of Treatment (EOT) for a patient is defined as the date of the last dose of ABI-009. End of Treatment Visit for a patient is when safety assessments and

	procedures are performed after the last treatment, which must occur within 1 month after the last dose of ABI-009. The End of Study (EOS) defined as either the date of the last visit of the last patient to complete the study, or the date of receipt of the last data point from the last patient that is required for primary, secondary, and/or exploratory analysis, as pre-specified in the protocol. Follow-up period begins after the EOT Visit. All patients that discontinue study drug and have not withdrawn full consent to participate in the study will continue in the follow-up phase for survival or initiation of new anticancer therapy. Follow up will continue approximately every 12 weeks (±3 weeks), until death, withdrawal of consent, start of new anticancer therapy, or the study closes, whichever is the earliest. This evaluation may be made by record review and/or telephone contact.
STUDY DRUG ADMINISTRATION	Patients will receive 75 mg/m^2 ABI-009 weekly for 2 weeks followed by a week of rest (qw2/3, 21-day cycle) by IV infusion over 30 minutes. Patients will continue on therapy until disease progression, unacceptable toxicity, until in the opinion of the investigator the patient is no longer benefiting from therapy, or at the patient's discretion.
KEY EFFICACY ASSESSMENTS	Efficacy will be assessed every 9 weeks by investigators using CT scans (or MRI if CT is contraindicated) and RECIST v1.1. Descriptive statistics and cox proportional hazards will be used in this analysis. Matching patients based on demographics and other cofounders such as disease primary site, site of metastatic disease and Ki-67 proliferative index as indicated on the original pathology report will be utilized to try to create a comparison group to identify possible differences.
KEY SAFETY ASSESSMENTS	Safety and tolerability will be monitored through continuous reporting of treatment-emergent and treatment-related adverse events (AEs), AEs of special interest, laboratory abnormalities, and incidence of patients experiencing dose modifications, dose delay/dose not given, dose interruptions, and/or premature discontinuation of ABI-009 due to an AE. All AEs will be recorded by the investigator from the time the patient signs informed consent until 28 days after the last dose of IP. Adverse events will be graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Physical examination, vital signs, laboratory assessments (eg, serum chemistry, hematology), and ECOG performance status will be monitored. All serious AEs (regardless of relationship to ABI-009) will be followed until resolution. Local laboratory analysis will be performed as per study schedule.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase (SGPT)
ANC	absolute neutrophil count
AST	aspartate transaminase (SGOT)
AUC	area under the time-concentration curve
BSA	body surface area
C_{max}	maximum plasma drug concentration
C_{min}	minimum plasma drug concentration
CBC	complete blood count
CEA	carcinoembryonic antigen
CI	confidence interval
CNS	central nervous system
CR	complete response
CT	computed tomography
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DCR	disease control rate
DOR	duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
CRF	electronic case report form
EOS	end of study
EOT	end of treatment
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	Imunohistochemistry
IND	investigational new drug

IP	investigational product
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
MRI	magnetic resonance imaging
MTD	maximum-tolerated dose
mTOR	mammalian target of sirolimus
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PD	progressive disease
PF rate	Progression-free rate
PFS	Progression-free survival
PR	partial response
PTEN	protein tyrosine phosphatase
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
TBL	total bilirubin level
ULN	upper limit of normal

Term	Definition/Explanation
Study Day 1	First day that protocol-specified IP is administered to the patient.
End of Treatment	The date of the last dose of ABI-009 for an individual patient.
End of Treatment Visit	For a patient is when safety assessments and procedures are performed after the last treatment, which should occur within 1 week (±3 days) after the last dose of ABI-009.
Follow-up Period	The time period after the End of Treatment Visit. All patients that discontinue study drug and have not withdrawn full consent to participate in the study will continue in the follow-up phase for survival and initiation of new anticancer therapy. Follow up will continue approximately every 12 weeks (±3 weeks), or more frequently as needed, until death, withdrawal of consent, or the study closes, whichever is the earliest. This evaluation may be made by record review and/or telephone contact.
End of Study	Either the date of the last visit of the last patient to complete the study, or the date of receipt of the last data point from the last patient that is required for primary, secondary, and/or exploratory analysis, as pre-specified in the protocol.
Primary Analysis	For this study will occur after all patients have either completed the study or completed 12 months of treatment. Patients who are still active at the time of the primary analysis may continue on study until disease progression or medication intolerance is observed.
Efficacy Analysis Dataset	All enrolled patients with measurable tumor per RECIST v1.1 at baseline who received at least 1 dose of ABI-009 and had a follow-up CT / PET (or MRI) (modified treated population).
Safety Analysis Set	All enrolled patients who receive at least 1 dose of ABI-009 (treated population).
Per-protocol Analysis Set	All enrolled patients who do not have any prospectively defined protocol violations.
Disease control rate at 6 months	Disease control rate at 6 months is the proportion of patients who have partial or complete response or stable disease at 6 months.
Overall response rate	The proportion of patients who achieve a confirmed partial response or complete response per RECIST 1.1. Response rates based on a local radiologic assessment.

Duration of response	The time from when criteria of response are first met until the first observation of disease progression per RECIST v1.1 or death due to any cause, whichever comes first.
Progression-free survival	The time from the first dose date to the first observation of a disease progression, assessed radiologically, or death due to any cause.
Overall survival	The time from the first dose date to the date of death due to any cause.

1. INTRODUCTION

1.1. Neuroendocrine Tumors of the Gastroenteropancreatic System or Lung

Neuroendocrine tumors (NETs) are a group of rare and heterogeneous malignancies, most commonly arise from neuroendocrine cells of the gastrointestinal tract (particularly pancreas and small bowel), followed by lung, liver, and thymus (Yao 2008). While most NETs are more indolent than other epithelial malignancies, poorly differentiated NETs can become aggressive and resistant to therapy. In a population analysis from SEER registry, the median survival for high-grade (3 and 4) NETs with localized, regional, and distant disease were 34, 14, and 5 months, respectively (Yao, Hassan 2008). The 10-year survival rate for any grade NETs is approximately 46% (Hallet 2015).

Because of their rarity and heterogeneity, nonspecific presentation symptoms, unique indolent biology, and lack of awareness, diagnosis can be delayed up to 7 years. The incidence of NETs has been increasing in recent years, doubling between 1994 and 2009, in part due to improved detection and greater clinician and patient awareness (Hallet, Law 2015).

1.2. Treatment Options in Neuroendocrine Tumors

When possible, surgery for is performed with the intent to cure or remove as much tumor as possible (debulking). Somatostatin analogues (SSAs) are highly effective for controlling the symptoms of hormone release by carcinoid and pancreatic NETs (pNETs), but their anti-tumor efficacy is modest. Interferon has utility in NETs, especially in combination with SSA. Combination chemotherapy using temozolomide and capecitabine has shown efficacy in various NETs (Strosberg 2011). Recently the FDA has approved radionuclide therapy with Lu-177 in patients with gastroenteropancreatic neuroendocrine tumors (GEPNETs) based off a study comparing high dose SSA to Lu-177 which indicated impressive PFS with Lu-177 compared to the SSA (Strosberg 2017).

The management of NETs is still challenging, and effective and safe therapeutic options are needed for the treatment of these tumors. Targeted therapies, such as sunitinib and everolimus produced promising efficacy in clinical trials. Subsequently, both therapeutics were approved by the United States (US) Food and Drug Administration (FDA); sunitinib is approved for pNETs and everolimus is approved for NETs of gastrointestinal (GI) or lung origin (Novartis-Gleevec 2017, Novartis 2017).

1.2.1. mTOR Inhibition in Neuroendocrine Tumors

Preclinical evidence has shown that the PI3K/AKT/mTOR signaling pathway plays a central role in the pathogenesis and progression of NETs (Manfredi 2015, Chan 2017). In accordance with preclinical evidence, clinical studies with everolimus (RADIANT 1-4 trials) demonstrated its safety and efficacy, which was a major advance in the treatment for NETs. The tolerability profile of everolimus has been consistent across clinical studies. The most adverse events (AEs) have been mild or moderate in severity, with grade 3/4 anemia and hyperglycemia occurring about 5% of patients.

The RADIANT trials (Pusceddu 2017)

RADIANT 1 was a phase 2 open label trial in patients with metastatic pNET, who have progressed on chemotherapy. Patients received either everolimus 10 mg alone or everolimus + octreotide. The combination arm had a 7-month longer median progression-free survival (PFS, 9.7 vs 16.7 months). RADIANT 3 was a subsequent phase 3 trial in patients with advanced low or intermediate grade pNET receiving everolimus 10 mg alone or placebo. In this study, the median PFS was 11 vs 4.6 months, respectively, HR 0.35 [95% CI 0.27-0.45], p< 0.001.

RADIANT 2 was a phase 2 study in patients with NETs and carcinoid syndrome, receiving either everolimus 10 mg + octreotide or placebo + octreotide. The median PFS was 16.4 vs 11.3, respectively, HR 0.77 [95% CI 0.059-1.00], p=0.026. RADIANT 4 was a subsequent phase 3 trial in patients with pulmonary or gastrointestinal NETs, with low grade well-differentiated disease, receiving everolimus 10 mg alone or placebo. Similar to RADIANT 3, in RADIANT 4 median PFS was nearly 3x longer in the combination arm (11 vs 3.9 months, HR 0.48 [95% CI 0.35-0.67], p<0.00001). Tumor shrinkage occurred in 64% vs 26%, in the everolimus versus placebo groups respectively (Pusceddu, Verzoni 2017).

While the optimal treatment sequence and patient population for mTOR inhibitors are still to be investigated, given the RADIANT trial results, everolimus might be a particularly suitable for 1st-line treatment for patients with grade 2 pNET and rapidly evolving disease and high disease burden, given the antiproliferative efficacy and tolerability profile of everolimus. On the other hand, in patients with G1 pNET with low tumor burden and indolent disease, everolimus may be more useful as a second-line therapy, after treatments with SSAs (Pusceddu, Verzoni 2017).

1.3. ABI-009 Background

1.3.1. Sirolimus and Rapalogs

Sirolimus (rapamycin) is a protein kinase inhibitor that is approved for immunosuppression in renal transplant patients and is under investigation for various cancer treatment. Sirolimus and its analogs (rapalogs) function as allosteric inhibitors of mTORC1. Rapalogs are currently used in the treatment of advanced renal cell carcinoma and other tumors (Dowling 2010).

Although sirolimus is an efficacious mTOR inhibitor, it has poor solubility, low oral bioavailability, and produces DLTs, including mucositis and stomatitis (O'Donnell 2008, Yuan 2009). Marketed sirolimus analogs are temsirolimus and everolimus. Temsirolimus, a prodrug of sirolimus requiring conversion to sirolimus in vivo, is approved for the treatment of kidney cancer. Everolimus is approved for pediatric and adult patients with subependymal giant cell astrocytoma, advanced hormone receptor-positive HER2-negative breast cancer in combination with exemestane, progressive NET of pancreatic or lung origin, subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis, and advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib (Hanna 2008, Molina 2011, Yao 2011, Baselga 2012, Thompson 2012).

Oral sirolimus and currently available rapalogs induce common side effects including hypertension, maculopapular rash (75%), mucositis (50%), asthenia (40%), nausea (43%), thrombocytopenia, metabolic abnormalities and more rarely pneumonitis (8%, 3% grade 3) sometimes fatal (de Oliveira 2011, Albiges 2012, Qi 2013). The most frequently occurring grade

3 or 4 adverse events (AEs) were hyperglycemia (17%), hypophosphatemia (13%), anemia (9%), and hypertriglyceridemia (6%) (Zhou 2010).

A novel mTOR inhibitor, ABI-009 (albumin-bound sirolimus nanoparticles, *nab*-rapamycin), is a solvent-free, intravenous (IV) form of sirolimus and has relatively high bioavailability. Dose-limiting toxicities (DLT) including mucositis/stomatitis that were observed with other mTOR inhibitors were not dose-limiting with ABI-009 (Gonzalez-Angulo 2013). The particularly safe toxicity profile of ABI-009 offers a promising new therapeutic for NETs.

1.3.2. ABI-009 (sirolimus, formerly *nab*-Rapamycin)

The novel nanoparticle albumin-bound sirolimus (formerly *nab*-rapamycin, ABI-009) is freely dispersible in saline and is suitable for IV administration, and has produced both a favorable safety profile and evidence of efficacy in patients with metastatic solid tumors (Gonzalez-Angulo, Meric-Bernstam 2013).

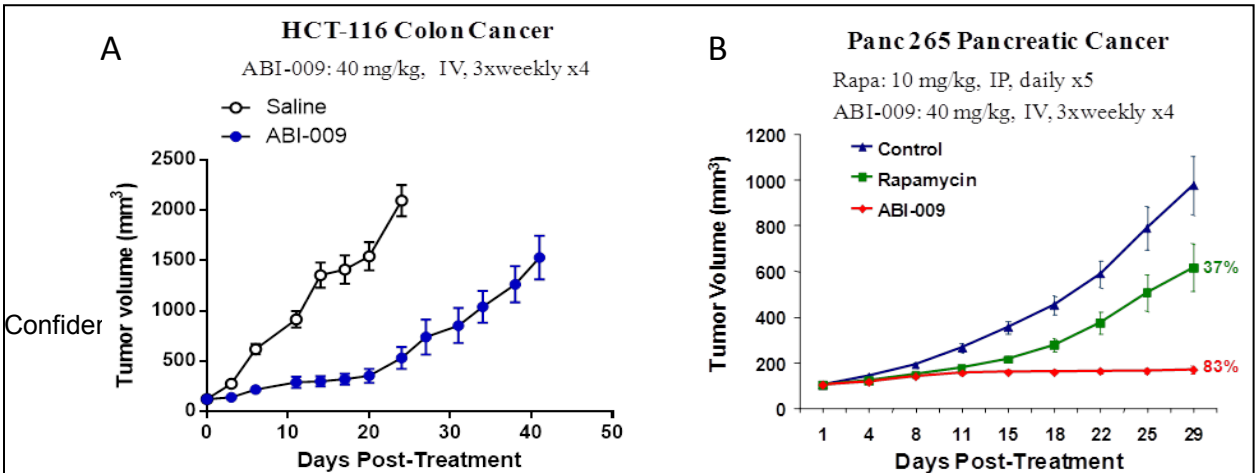
Nanoparticle albumin-bound or *nab*® technology (Abraxis BioScience, a wholly-owned subsidiary of Celgene Corporation) when applied to hydrophobic molecules, such as paclitaxel (*nab*-paclitaxel; Abraxane®), has led to improved drug delivery, safety, and efficacy in various solid tumors vs conventional paclitaxel formulation (Gradishar 2005). This suggests that the *nab* form of sirolimus may also produce similar advantages over the standard sirolimus.

The *nab* technology may enhance tumor penetration and accumulation via the albumin receptor-mediated (gp60) endothelial transcytosis. Albumin is highly soluble, has long plasma half-life, broad binding affinity, and accumulates in tumors, making it an ideal candidate for drug delivery (Kremer 2002, Kratz 2008). Albumin circulating in the bloodstream can interact with gp60 to initiate caveolae-mediated transcytosis to reach tumor cells (Schnitzer 1992, Schnitzer 1995). Indeed, *nab*-paclitaxel transcytosis across the epithelial monolayer was dependent on caveolae formation (Desai 2006). In accordance with these observations, at equal doses, *nab*-paclitaxel showed greater selectivity to tumors compared with solvent-based paclitaxel, which is likely attributed to the biologically active ingredient albumin and lack of solvent (Desai, Trieu 2006).

1.3.3. Preclinical Studies with ABI-009

Preclinical primary pharmacology studies in vivo demonstrated significant antitumor activity of ABI-009 as a single agent administered IV at 40 mg/kg, 3 times weekly for 4 weeks, across different tumor xenograft models in nude mice (see Figure 1A and B, below), including colorectal and pancreatic cancer (De 2007, Desai 2009, Trieu 2009, Cirstea 2010, Kennecke 2011). This dose level correlates to approximately 120 mg/m^2 in human. These findings are consistent with published information on sirolimus as an mTOR inhibitor and the role of mTOR in tumor growth (Fasolo 2012).

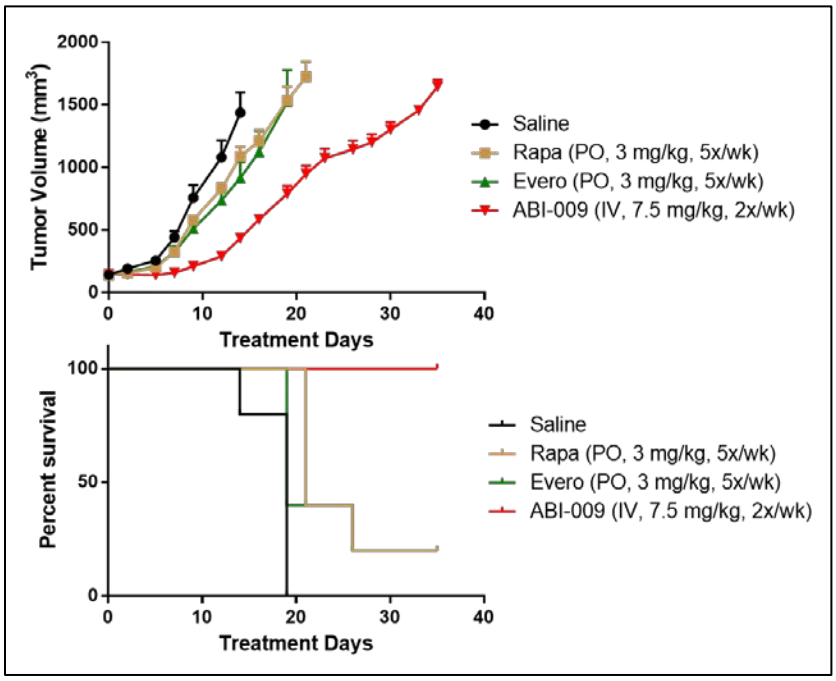
Figure 1: Antitumor Activity of ABI-009 in Colon and Pancreatic Cancer Tumor Xenografts



Confider

A recent preclinical study demonstrated significantly greater antitumor activity and prolonged survival with ABI-009 administered IV compared with equal weekly dosing of oral sirolimus and oral everolimus (Aadi internal data, Figure 2). In athymic mice bearing UMUC3 human bladder cancer xenografts, ABI-009 was administered IV at 7.5 mg/kg, 2x weekly (total weekly dose: 15 mg/kg), whereas sirolimus and everolimus were administered PO at 3 mg/kg/day, 5 days per week to achieve the same weekly total dose. The tumor growth inhibition (TGI) was 69.6% with ABI-009, significantly greater than oral sirolimus (TGI 24.3%; $P < 0.00001$ vs ABI-009, ANOVA) and oral everolimus (TGI 36.2%; $P = 0.0023$ vs ABI-009, ANOVA). The median OS was also significantly longer with ABI-009 (not reached) compared with oral sirolimus (21 days; $P < 0.05$, log rank test) and oral everolimus (19 days; $P < 0.05$, log rank test). Results from this preclinical study clearly demonstrate superior therapeutic efficacy of ABI-009 to oral mTOR inhibitors in this setting.

Figure 2: ABI-009 Administered IV Compared with Equal Weekly Dosing of Oral Sirolimus and Oral Everolimus



Preclinical pharmacokinetic (PK) studies in rats showed that IV ABI-009 exhibited linear PK with respect to dose and large volume of distribution (Vz), due to efficient tissue extraction of sirolimus from the central blood compartment (De, Trieu 2007). Shortly after dosing, tissue sirolimus level was 3-5 folds higher than that of blood, indicating efficient extraction. The terminal half-life of ABI-009 was long in rats, ranging from 13.4 - 25.8 hours and resulted in significant blood level at 48 hours (~10 ng/mL) and 120 hours (>1 ng/ml). Consistent with

sirolimus literature (Sehgal 2003), excretion of ABI-009 was primarily through the fecal route (68.57 - 69.99%) with minimum contribution from the renal route (7.73 - 8.84%).

The safety and toxicity of ABI-009 were evaluated in a series of preclinical studies. In a Good Laboratory Practice (GLP) repeat-dose toxicity study in male and female rats, ABI-009 administered IV was well tolerated at doses up to 90 mg/kg (equivalent to 540 mg/m^2 human dose) when delivered every 4 days for 3 cycles. Nonclinical toxicology studies of ABI-009 showed no new or unexpected toxicity compared to what is already known for sirolimus and other rapalogs (Pfizer 2011, Pfizer 2011, Novartis 2017).

1.3.4. Clinical Studies with ABI-009

In a phase 1 dose-finding, tolerability, and PK study conducted at MD Anderson Cancer Center (Protocol CA401, NCT00635284), ABI-009 was well tolerated with evidence of responses and stable disease (SD) in various solid tumors including renal cell carcinoma, bladder cancer, and colorectal cancer, all of which typically overexpress mTOR (Gonzalez-Angulo, Meric-Bernstam 2013). Twenty-six patients were treated with 45, 56.25, 100, 125, or 150 mg/m^2 ABI-009 per week for 3 weeks, followed by a week of rest (28-day cycle, qw3/4). ABI-009 was administered IV. The maximum-tolerated dose (MTD) was established at 100 mg/m^2.

Nineteen patients were evaluable for efficacy. One patient in the 45 mg/m^2 (95 mg actual sirolimus dose) cohort, diagnosed with adenocarcinoma of the kidney and with bone and intrathoracic metastases, had a confirmed partial response (PR). The target lesion of this patient was reduced by 35.1% and the duration of response lasted 183 days. Two (11%) patients (at doses 45 and 125 mg/m^2, with actual sirolimus doses of 88 mg and 193 mg, respectively) had an overall tumor evaluation of SD (confirmed): 1 patient with mesothelioma had SD for 365 days and 1 patient with a NET in the left axillary node had SD for 238 days.

In the phase 1 study described above, for all cohorts and all grades, 25 of 26 (96%) patients experienced at least 1 AE. The most common AEs were mucosal inflammation (10 patients, 38%), fatigue (7 patients, 27%), rash (6 patients, 23%), diarrhea (6 patients, 23%), and nausea (5 patients, 19%). Most of these AEs were grade 1/2 events, with only 3 grade 3 nonhematologic AEs (2 elevated AST and 1 dyspnea). Specifically, at the MTD of 100 mg/m^2, all 7 patients experienced at least 1 AE of any grades, and the most common AEs were mucositis and fatigue (5 patients, 71% each). Four (15%) patients experienced at least 1 treatment-related serious AE (SAE), including arrhythmia (grade 2) and mood alteration (grade 3) both in the 125 mg/m^2 cohort, vomiting (grade 3) in the 45 mg/m^2 cohort, and dyspnea (grade 3) in the 100 mg/m^2 cohort.

The most common hematologic AEs, for all cohorts and grades, were thrombocytopenia (58%), followed by hypokalemia (23%), and anemia and hypophosphatemia (19% each), and neutropenia and hypertriglyceridemia (15% each). Most of these events were grade 1/2, and only 1 grade 4 hematologic event occurred (thrombocytopenia in the 150 mg/m^2 arm). At the MTD, the only hematologic AE was a grade 3 anemia. In this clinical study, 16 of 26 patients (62%) had treatment-related adverse events (TRAEs) requiring a week dose delay.

Currently, there are several ongoing trials investigating the safety and efficacy of single-agent ABI-009 in various disease areas, including a trial in patients with malignant perivascular epithelioid tumors (PEComas), a rare type of soft-tissue tumors (NCT02494570). The particularly

safe toxicity profile of ABI-009 allows this mTOR inhibitor to be combinable with other therapeutics and a trial in patients with advanced STS is currently evaluating the combination of ABI-009 and nivolumab (NCT03190174).

1.4. Rationale for Investigating ABI-009 in Neuroendocrine Tumors of the Gastroenteropancreatic System or Lung

Based on results from the phase 1 study with single agent ABI-009 (Section 1.3.4, NCT00635284), the safety profile, evidence of antitumor activity and SD in various solid tumors, particularly in the patients with pNET and mesothelioma, as well as the tumor xenograft study demonstrating improved therapeutic potential of ABI-009 vs oral sirolimus or everolimus, we propose this pilot phase 2 study of ABI-009 for patients with GEPNET or NET of the lung. Particularly, the preclinical data showing improved tumor growth inhibition and survival with ABI-009 vs everolimus, dose for dose (Figure 2) and the potentially enhanced tumor penetration of the therapeutic by the *nab*-technology (described in 1.3.2.), ABI-009 may result in disease control even after everolimus failure. The goal of this phase 2 pilot study is to demonstrate that ABI-009 is safe and produce promising efficacy to warrant a full phase 2 study in patients who progressed on or failed everolimus treatment.

1.5. Rationale for the Schedule of Administration for ABI-009

A slightly different schedule, 2 of 3 weekly administration, has been selected in the present study than was studied in the first-in-human (FIH) phase 1 study (NCT00635284). Additionally, to improve safety, the original starting dose was reduced from 100 mg/m^2 (MTD) to 75 mg/m^2 , with the option to escalate to the MTD after completing 2 cycles of continuous treatment at their originally assigned dose level and upon meeting the criteria as follows:

- No observation of Grade > 2 adverse event(s) considered related to study treatment
- Meet the hematological requirements as outlined in section 6.2
- Ongoing clinical benefit: Patients must have no clinical signs or symptoms of progressive disease
- No clinically significant safety or tolerability concern in the opinion of the investigator

The rationale for the modification to the dose and schedule of administration of a dose of 100 mg/m^2 (MTD) is to further improve the tolerance of ABI-009. In the FIH phase 1 study, 19.4% of doses were missed at doses ≤100 mg/m^2. Most of the missing doses (83%) occurred at day 15, corresponding to the 3rd administration within a cycle. Thus, the present study will examine 100 mg/m^2 ABI-009 given weekly for 2 weeks followed by a week off. This change in schedule will not substantially impact the total drug received by the patients. In a period of 6 months (24 weeks) of treatment, the 2/3 schedule will allow 16 administrations, while the 3/4 schedule will allow 18 administrations.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

- The primary objective of this pilot phase 2 study is to evaluate the preliminary efficacy of ABI-009 in patients with grade 1 and 2 neuroendocrine tumors (NETs) of the gastroenteropancreatic system or lung, as measured by disease control rate (DCR) at 6 months
- The secondary objectives are to evaluate the safety and toxicity profile of ABI-009 as well as the Overall Response Rate (ORR)

2.2. Endpoints

Primary Endpoint

- Disease control rate at 6 months, assessed by investigator using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Secondary Endpoints

- Safety and toxicity
- ORR: partial or complete response per RECIST v1.1

2.3. Study Design

This study is a prospective pilot phase 2, single arm, single center, open-label, evaluate the efficacy and safety ABI-009 in patients with gastroenteropancreatic NET (GEPNETs) or NET of the lung and prior exposure to everolimus. ABI-009 at 75 mg/m^2 will be given IV weekly for 2 weeks followed by a week of rest (qw2/3) in a 21-day cycle (on D1 and 8).

The study will be conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCPs).

2.4. Study Duration, End of Study, End of Treatment, End of Treatment Visit, Follow-up Period

The study is expected to take approximately 24 months from first patient enrolled to last patient follow-u.p The study will take approximately 12 months to enroll all patients and an estimated 12 months of treatment per patient, or until treatment is no longer tolerated.

End of Treatment (EOT) for a patient is defined as the date of the last dose of ABI-009. End of Treatment Visit for a patient is when safety assessments and procedures are performed after the last treatment, which must occur within 1 month after the last dose of ABI-009.

The End of Study (EOS) defined as either the date of the last visit of the last patient to complete the study, or the date of receipt of the last data point from the last patient that is required for primary, secondary, and/or exploratory analysis, as pre-specified in the protocol.

The follow-up period begins after the EOT Visit. All patients that discontinue study drug and have not withdrawn full consent to participate in the study will continue in the follow-up phase for survival or initiation of new anticancer therapy. Follow up will continue approximately every 12 weeks (±3 weeks), until death, withdrawal of consent, start of new anticancer therapy, or the study closes, whichever is the earliest. This evaluation may be made by record review and/or telephone contact.

3. STUDY POPULATION

3.1. Number of Patients

The sample size for pilot phase 2 will be up to 10 evaluable patients.

3.2. Inclusion Criteria

A patient will be eligible for inclusion in this study only if all of the following criteria are met during screening:

1. Unresectable or metastatic patients with typical or atypical carcinoid tumors of the lung or low or intermediate grade GEPNETS.
2. Patients must have measurable disease per RECIST 1.1.
3. Patients must have progressed on everolimus or been intolerant to everolimus as defined as discontinued for any adverse reactions other than allergic reaction.
4. Patients, ≥18 years old, must have Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1.
5. Concurrent use of somatostatin analogs (SSAs) is allowed if currently used for symptom control.
6. Adequate liver function:
   a. Total bilirubin ≤1.5 x upper limit of normal (ULN) mg/dL
   b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN (<5 x ULN if the patient has liver metastases).
7. Adequate renal function:
   a. Serum creatinine ≤2 x ULN or creatinine clearance >50 ml/min (Cockcroft-Gault).
8. Adequate biological parameters:
   a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
   b. Platelet count ≥100,000/mm^3 (100×10^9/L)
   c. Hemoglobin ≥8 g/dL.
9. Fasting serum triglyceride ≤300 mg/dL; fasting serum cholesterol ≤350 mg/dL.
10. Male or non-pregnant and non-breast feeding female:
    - Females of child-bearing potential must agree to use effective contraception without interruption from 28 days prior to starting IP throughout 3 months after last dose of IP and have a negative serum pregnancy test (β-hCG) result at screening and agree to ongoing pregnancy testing during the course of the study, and after the end of study treatment. A second form of birth control is required even if she has had a tubal ligation.
    - Male patients must practice abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study and throughout 3 months after last dose of IP. A second form of birth control is required even if he has undergone a successful vasectomy.
11. Life expectancy of >3 months, as determined by the investigator.
12. Ability to understand and sign informed consent.
13. Willingness and ability to comply with scheduled visits, laboratory tests, and other study procedures.

3.3. Exclusion Criteria

A patient will not be eligible for inclusion in this study if any of the following criteria apply during screening:

1. Patients currently undergoing anti-cancer therapy for neuroendocrine tumors (other than SSAs for symptoms).
2. History of allergic reactions to compounds of similar chemical or biologic composition to ABI-009.
3. Known active uncontrolled or symptomatic central nervous system (CNS) metastases. A patient with controlled and asymptomatic CNS metastases may participate in this study. As such, the patient must have completed any prior treatment for CNS metastases 28 days (including radiotherapy and/or surgery) prior to start of treatment in this study and should not be receiving chronic corticosteroid therapy for the CNS metastases.
4. Active gastrointestinal bleeding.
5. Uncontrolled serious medical or psychiatric illness.
6. Patients with a "currently active" second malignancy other than non-melanoma skin cancers, carcinoma in situ of the cervix, resected incidental prostate cancer (staged pT2 with Gleason Score ≤6 and postoperative PSA <0.5 ng/mL), or other adequately treated carcinoma-in-situ are ineligible. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥1 year).
7. Recent infection requiring systemic anti-infective treatment that was completed ≤14 days prior to enrollment (with the exception of uncomplicated urinary tract infection or upper respiratory tract infection).
8. Uncontrolled diabetes mellitus as defined by HbA1c >8% despite adequate therapy.
9. Unstable coronary artery disease or myocardial infarction during preceding 6 months.
10. Patients with history of interstitial lung disease and/or pneumonitis, or pulmonary hypertension.
11. Use of strong inhibitors and inducers of CYP3A4 within the 14 days prior to receiving the first dose of ABI-009. Additionally, use of any known CYP3A4 substrates with narrow therapeutic window (such as fentanyl, alfentanil, astemizole, cisapride, dihydroergotamine, pimozide, quinidine, terfanide) within the 14 days prior to receiving the first dose of ABI-009.
12. Known Human Immunodeficiency Virus (HIV).
13. Known active Hepatitis B or Hepatitis C.

4. TABLE OF EVENTS

The schedule of assessments in Table 1 outlines the specific time points for study assessments.

Table 1. Schedule of Assessments

Assessments [a]	Baseline Screening [b]	Treatment Phase 21-day (3-week) Cycles Days			End of Treatment (EOT) Visit [d]	Follow-up [d]
		1	8	15[c]		
Informed Consent	x					
Demographics / Medical History [e]	x					
I/E Criteria	x					
Pregnancy Test [f]	x				x	
Physical Exam	x	x	x	x	x	
Vital Signs, Height, and Weight [g]	x	x	x	x	x	
Prior / Concomitant Medications and Procedures	x	x	x	x	x	
CBC/Differential	x	x	x	x	x	
Chemistry Panel	x	x	x	x	x	
Fasting Lipids and Fasting Cholesterol	x	Even Cycles				
Sirolimus level [h]		C2, C3 and C4	C1, C2, C3 and C4	C1, C2, C3 ad C4		
ECOG Performance Status	x	x			x	
CT [i]	x	Every 9 weeks from 1st dose during the 1st year, then every 12 weeks until disease progressions or last treatment				
ABI-009 Infusion [j]		x	x			
Adverse Event Assessment	Continuous from the signing of the informed consent to 28 days after last study treatment					
Survival						x

[a] All visits are allowed to occur in a window of ±3 days unless otherwise specified.

[b] Baseline screening visit will be done within 28 days prior to study treatment Day 1.

[c] Day 15 evaluations are required only during Cycles 1 and 2 to obtain additional safety and laboratory evaluations, then, based on investigator discretion, patients may opt to take 'visit holidays' on D15.

[d] End of Treatment-phase (EOT) Visit should be within 1 month of last study treatment. Follow up will be every 12 weeks, after EOT or last visit till study closes or withdrawal of consent, via phone call.

[e] Collect reports of tumor molecular profiling, if available.

[f] For all female patients of childbearing potential, a serum pregnancy test will be done at screening. A urine pregnancy test will be repeated within 72 hours before first treatment if the serum pregnancy test occurred >72 hours before dosing, and at EOT. Pregnancy tests conducted after screening will be recorded in the source documentation only.

[g] Height is measured only at screening. BSA will be capped at 2 m^2 for dose calculation.

[h] Sirolimus levels are done locally and for all patients to determine trough levels: C1 D8 prior to dosing and on the D15 visit, and in C2 through C4 D1 and 8 prior to dosing and on D15 visit.

[i] Baseline imaging should be done as close to C1 D1 as possible, then every 9 weeks (±1 week) from first treatment during the 1^{st} year, and every 12 weeks thereafter through disease progressions, regardless of missed or out of window doses. If a patient discontinued treatment other than disease progression, scan should be done at EOT visit. MRI is allowed, if CT is contra-indicated for a patient. The same mode of imaging at screening must be used consistently throughout the study. If functional imagining, including GA68 PET/CT were done as SOC, they may be collected if they were conducted within 60 days prior to enrollment and/or 60 days after last treatment.

[j] ABI-009 must be administered after all study specific assessments are done in a visit.

5. PROCEDURES

5.1. Screening Evaluations

This study will be conducted at 1 US center. Each patient who enters into the screening period for the study receives a unique patient identification number before any study-related procedures are performed. This number will be used to identify the patient throughout the clinical study and must be used on all study documentation related to that patient.

The patient identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a patient is rescreened.

Before patients may be entered into the study, the study funder requires a copy of the sites' written IRB approval of the protocol, informed consent form, and all other patient information and/or recruitment material, if applicable. A signed and dated Institutional Review Board (IRB) approved informed consent form (latest approved version) must be obtained from each patient prior to performing any study-specific procedures. All patients must personally sign and date the consent form before commencement of study-specific procedures. Adverse events are to be collected for a patient once they have signed the informed consent.

Screening evaluations will be performed for all patients to determine study eligibility. These evaluations must be obtained ≤28 days prior to enrollment. Any questions regarding patient eligibility should be directed to the investigator or designees for approval.

The following procedures are to be completed during the screening period, after signed informed consent has been obtained, designated in the Schedule of Assessments, Table 1.

- Demographics (date of birth, sex, race, and ethnicity)
- Medical /cancer history, prior/concomitant medications and procedures evaluation: all medications taken ≤28 days prior to screening
    - Collect reports of tumor molecular profiling, if available
- Physical examination as per standard of care (including physical exam, ECOG performance status assessment)
- Vital signs (blood pressure, pulse, respiration rate, temperature, height, weight)
- Local Laboratory Assessments: chemistry, complete blood count (CBC), differential, platelet count, pregnancy test (women of child-bearing potential, includes tubal ligations), fasting cholesterol and fasting lipids
- CT scans (or MRI, if CT is contraindicated) should be done as close to C1D1 as possible
- Adverse event assessment

A patient is considered eligible when the investigator decides that the patient has met all eligibility criteria and documents this in the patient's medical record..

For laboratory assessments, see Table 2 for analyte listing.

5.2. Treatment Period

A patient is considered enrolled on study Day 1 when ABI-009, is first administered. ABI-009 must be administered after all other protocol-specified pre-dosing assessments have been performed. Patients will continue therapy until disease progression, unacceptable AE, withdrawal of consent, or withdrawal by the investigator.

5.2.1. Day 1 Assessment

The following assessments will be performed on Day 1 of each cycle, unless otherwise specified:

- Physical examination
- Vital signs, including weight
- Concomitant medication and procedures evaluation
- CBC, differential
- Clinical chemistry panel
- Fasting lipids and fasting cholesterol (every even cycles)
- Sirolimus level, C2 through C4 (for trough level) prior to dosing
- ECOG performance status
- Adverse events assessment

Day 1 evaluations for Cycle 1 may be omitted if screening evaluations are performed within 72 hours of Cycle 1 Day 1.

5.2.2. Day 8 Assessment

The following assessments will be performed on Day 8 of each cycle, unless otherwise specified:

- Physical evaluation
- Vital signs, including weight
- Concomitant medication and procedures evaluation
- CBC, differential
- Clinical chemistry panel
- Sirolimus level, C1 through C4 (for trough levels) prior to dosing
- Adverse event assessment

5.2.3. Day 15 Assessment

The following assessments will be performed on Day 15 in Cycles 1 and 2, there after this visit is optional:

- Physical evaluation
- Vital signs, including weight
- Concomitant medication and procedures evaluation
- CBC, differential
- Clinical chemistry panel
- Sirolimus level, C1 through C4 (for trough levels) prior to dosing
- Adverse event assessment

Table 2. Analyte Listing

Chemistry	Hematology	Other Labs
Sodium	WBC	Pregnancy test
Potassium	RBC	Total Cholesterol
Bicarbonate	Hemoglobin	HDL
Chloride	Hematocrit	LDL
Total protein	MCV	Triglyceride
Albumin	MCH	Sirolimus
Calcium	MCHC	
Magnesium	RDW	
Phosphorus	Platelets	
Glucose	Differential:	
BUN	-Neutrophils	
Creatinine	-Lymphocytes	
Total bilirubin	-Monocytes	
Alkaline phosphatase	-Eosinophils	
AST (SGOT)	-Basophils	
ALT (SGPT)		
Amylase		
Lipase		

5.2.4. Response Assessment

Tumor response will be assessed by CT (or MRI, if CT is contra-indicated) scan of the chest, abdomen, and pelvis (CAP) per institutional guidelines; image preparation and evaluation will follow the specifications provided in the RECIST version 1.1. The same modality (CT or MRI) must be used at screening and throughout the study.

CT or MRI scans to be performed at the following frequency during the study:

- Screening, preferable as close to C1 D1 as possible
- followed by every 9 weeks for the first year; then every 12 weeks until disease progression. End of Treatment Visit CT (or MRI) should be performed only for those patients that discontinue treatment for a reason other than disease progression.

An unscheduled scan for suspected disease progression may be performed at any time. However, adherence to the planned imaging schedule is critical regardless of dose delays or unscheduled or missed assessments. Determination of disease progression and clinical management of patients on study will be assessed at the local site.

5.3. End of Treatment Visit Assessment

The EOT Visit is a safety follow-up visit that is to be performed within 1 month after the last dose of ABI-009. All efforts should be made to conduct this visit. If it is not possible to conduct the EOT Visit, documentation of efforts to complete the visit should be provided.

The following procedures will be completed at the EOT Visit as designated in the Schedule of Assessments (Table 1):

- Physical examination
- Vital signs, including weight
- Concomitant medications and procedures evaluations

- Pregnancy test (urine test is sufficient)
- CBC /differential
- Chemistry panel
- ECOG performance status
- Imaging Assessment: CT/PET (or MRI) is to be performed at the EOT visit only for those patients that discontinue treatment for a reason other than disease progression per RECIST v1.1

5.4. Sirolimus Trough Levels

Assays for sirolimus will be performed on patients in the dose-finding (phase 1) portion of the study, who received ABI-009 during C1 through C4, to determine trough levels, assessed via local lab:

- Cycle 1: D8 prior to dosing, and on the D15 visit
- Cycle 2 through Cycle 4: D1 and 8 prior to dosing, and on D15 visit

5.5. Follow-up Period for Survival and Initiation of Anticancer Therapy

Post-treatment survival time will be monitored approximately every 12 weeks (±3 weeks) from EOT Visit or more frequently as needed, until death, withdrawal of consent, or the study closes, whichever is earliest. This evaluation may be by record review and/or telephone contact.

6. DESCRIPTION OF STUDY TREATMENTS

6.1. ABI-009 Dosage, Administration, and Schedule

Treatment cycles are 21 days in duration and patients are treated until disease progression or unacceptable toxicities. Patients will receive ABI-009 75 mg/m^2 (IV infusion over 30 minutes, +10 min) weekly for 2 weeks followed by a week of rest (2/3 weekly schedule). The schedule 2 weeks out of a 3-weekly schedule will allow the patient to have 1-week rest, when most of the toxicities occur, based on experience in the phase 1 study of ABI-009 (Protocol CA401). The starting dose may be escalated from 75 mg/m^2 to 100 mg/m^2 only after completing 2 cycles of continuous treatment at their originally assigned dose level and upon meeting the criteria as follows:

- No observation of Grade > 2 adverse event(s) considered related to study treatment
- Meet the hematological requirements as outlined in section 6.2
- Ongoing clinical benefit: Patients must have no clinical signs or symptoms of progressive disease
- No clinically significant safety or tolerability concern in the opinion of the investigator

Dose reduction levels are allowed from 75 mg/m^2: 60, 45, and 30 mg/m^2 in incremental order. A physician must be available at the time of administration of IP on dosing days that correspond to study visits. Supportive care per the institution's normal standard of care including concomitant medications can be provided at the investigator's discretion.

The subject's weight on Cycle 1 Day 1 will be considered the baseline weight for drug dosing. BSA will be calculated at baseline and recalculated if the weight changes by 10%. BSA will be capped at 2m^2.

6.2. ABI-009 Dose Modification and Stopping Rules

If, treatment cannot be administered on the planned visit date, ABI-009 may be administered ± 2 days from the scheduled date. Prior to ABI-009 administration on Day 1 of each cycle, patients must meet the following hematological requirements:

- ANC ≥1.5 x 10^9/L
- Platelet count ≥100 x 10^9/L
- Hemoglobin ≥8 g/dL (transfusions are allowed if clinically indicated)

The treatment will be on hold up to 14 days until the patient has fulfilled these criteria.

Day 1 Dose Missed

If the dose held or missed was to be given on Day 1 of the next cycle, that next cycle will not be considered to start until the day the first dose is actually administered to the patient (ie, D1-D8-Rest, X-D1-D8-Rest, etc).

Day 8 Dose Is Missed

That week becomes the week of rest. Next dose (if counts and chemistries permit) becomes Day 1 of a new cycle (ie, D1-D8-Rest, D1-X, D1-D8-Rest, etc).

The maximum delay between a missed scheduled dose and the next one (whichever dose was missed) should not be longer than 14 days. When there is evidence of clinical benefit or in the

opinion of the principal investigator the patient's best interest is to continue therapy, treatment may be restarted after ≥21 days.

Doses will be reduced for hematologic and other toxicities, according to criteria below. Dose reductions will occur sequentially (60, 45, and 30 mg/m^2), there should be no direct reduction by 2 dose levels. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in this section:

- General guidelines for clinically significant toxicities related to study treatment

And

- Specific guidelines for adverse events of special interest, which are events that have been observed with higher frequency or severity.

In the event of clinically significant AE in any part of the study (Table 4), treatment may be withheld, and supportive therapy administered as clinically indicated. If the toxicity or event is not grade 3/4 and resolves to baseline or grade 1 in less than or equal to 14 days of stopping therapy, then treatment may be restarted. Dose reduction of ABI-009 should be considered as clinically indicated.

If the toxicity does not resolve to at least grade 1 in less than 14 days, withdrawal from treatment with the IP is recommended. However, if, in the opinion of the investigator, further treatment would benefit the patient, treatment can continue with at least 1 dose level dose reduction, per Table 3.

Table 3: Dose Level Modification Guidelines

Dose level	**ABI-009 Dose/Schedule**
+1 (optional dose escalation)	100 mg/m^2 (if criteria in section 6.1 is met)
0	**Initial Dose: 75mg/m^2**
-1 (first dose reduction)	20% reduction of initial dose of 75 mg/m^2: 60 mg/m^2
-2 (second dose reduction)	25% reduction from 60 mg/m^2: 45 mg/m^2
-3 (third dose reduction)	33% reduction from 45 mg/m^2: 30 mg/m^2

If an AE resolves to grade 1 or baseline at the reduced dose level, and no additional toxicities are seen during the following cycle of study treatment at the reduced dose, the dose may be increased to the previous dose level. The dose of ABI-009 will not be increased to the previous dose level if a second AE requiring dose reduction occurs.

Any patient meeting the criteria for Hy's Law case (ie, severe drug-induced liver injury) will be considered a Adverse Event. A Hy's Law case is defined as: AST or ALT values of ≥3 x ULN AND with serum total bilirubin level (TBL) of >2 x ULN without signs of cholestasis and with no other clear alternative reason to explain the observed liver-related laboratory abnormalities.

ABI-009 dose modification guidelines are outlined in Table 3**.** for clinically significant toxicities that are deemed related. The dosing schedule is described in the Schedule of Assessments Table 1.

Table 4. Dose Modification Algorithms for Adverse Events Possibly Related to ABI-009

System/Organ	Adverse Event	CTCAE Grade v5.0	Dose modification Algorithm
Mucosa [a]	Stomatitis, mucosal inflammation	Grade 2	Hold ABI-009 until resolution to grade 1 or baseline and restart at the same dose for 1st occurrence; for subsequent occurrences, drug will be restarted at a reduced dose; provide supportive care as clinically indicated.
		Grade ≥3	Hold ABI-009 until resolution to grade 1 or baseline and restart at the same dose for 1st occurrence for subsequent occurrences, drug will be restarted at a reduced dose; provide supportive care as clinically indicated.
Skin and Subcutaneous Tissue Disorders	Skin rash	Grade 2	Tolerable: Continue ABI 009 at full dose, monitor as clinically indicated.
			Intolerable: Hold ABI-009 until resolution to grade 1 or baseline and restart at the same dose for 1st occurrence; for subsequent occurrences, drug will be restarted at a reduced dose; provide supportive care as clinically indicated.
		Grade ≥3	Hold ABI-009 until resolution to grade 1 or baseline; for subsequent events, drug will be restarted at a reduced dose; provide supportive care as clinically indicated.
Gastrointestinal Disorders	Diarrhea despite optimal medication	Grade 2	Hold ABI-009 until resolution to grade 1 or baseline and restart at the same dose for 1st occurrences; for 2nd and subsequent events, drug will be restarted at a reduced dose; provide supportive care as clinically indicated.
		Grade ≥3	Hold ABI-009 until resolution to grade 1 or baseline; for subsequent events, drug will be restarted at a reduced dose; provide supportive care as clinically indicated.

Metabolic disorders	Hyperlipidemia (cholesterol, triglycerides)	Grade 3	If this is persistent for 2 months, reduce by 1 dose level at start of next cycle.
		Grade 4	If this is persistent for 1 month, reduce by 1 dose level at start of next cycle.
	Hyperglycemia	Grades 1 and 2	Start at home 2x/day glucose monitoring; initiate medical management.
		Grade 3	Initiate medical management; If recurrent post ABI-009 despite adequate medical management, reduce by 1 dose level.
		Grade 4	Initiate medical management, hold ABI-009 until grade 2 or less, restart 1 dose level lower
Hematologic toxicity	Thrombocytopenia, Neutropenia, Anemia	Grade 2	ABI-009 can be administered if the following hematological requirements: ANC >1.5 x 10^9/L, platelets >100 x 10^9/L and hemoglobin ≥8 g/dL.
		Grade ≥3	Hold ABI-009 immediately for the remainder of that cycle. Repeat blood collection within 3 days. ABI-009 can resume once meeting following requirements: absolute ANC >1.5 x 10^9/L, platelet count > 100 x 10^9/L and hemoglobin ≥8 g/dL. For 2nd and subsequent events, drug will be restarted at a reduced dose; G-CSF may be given as deemed indicated.
Respiratory events	Pneumonitis, bronchiolitis obliterans, and/or organizing pneumonia	Grade 2	Hold ABI-009 immediately for up to 3 weeks until resolved to ≤ grade 1, then reduce by 1 dose level. If it is still a grade 2 after 3 weeks, discontinue treatment. If > grade 2 recurs after resuming ABI-009 at a reduced dose level, discontinue treatment. For noninfectious pneumonitis, if cough is troublesome, prescribe corticosteroids.
		Grade ≥3	Permanently remove patient from protocol treatment. For grade 3 noninfectious pneumonitis, prescribe corticosteroids if infection is ruled out. Hold ABI-009 until recovery to ≤ grade 1; may restart within 3 weeks at reduced dose level if evidence of clinical benefit. Patients

			will be withdrawn from the study if they fail to recover to ≤ grade 1 within 3 weeks. For grade 4 noninfectious pneumonitis, permanently discontinue ABI-009.

[a] Prophylactic approaches to prevent stomatitis such as steroid mouthwash (10 mL dexamethasone 0.1 mg/mL oral solution four times daily) could be considered for those who develop or at risk for stomatitis.

6.3. Hepatotoxicity Stopping Rules

Patients with abnormal hepatic laboratory values (ie, ALP, AST, ALT, total bilirubin TBL) and/or signs/symptoms of hepatitis may meet the criteria for withholding or permanent discontinuation of ABI-009 as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

6.3.1. Criteria for Permanent Discontinuation of ABI-009 Due to Potential Hepatotoxicity

ABI-009 should be discontinued permanently and the patient should be followed for possible drug-induced liver injury (DILI), if **ALL** of the criteria below are met:

- TBL >2 x upper limit of normal (ULN) or INR >1.5 x ULN
- AND increased AST or ALT from the relevant baseline ≥3 x ULN.
- AND no other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:
  - Hepatobiliary tract disease
  - Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, Cytomegalovirus, Herpes Simplex Virus, Varicella, Toxoplasmosis, and Parvovirus)
  - Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia.
  - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
  - Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
  - Alpha-one antitrypsin deficiency
  - Alcoholic hepatitis
  - Autoimmune hepatitis
  - Wilson's disease and hemochromatosis
  - Nonalcoholic Fatty Liver Disease including Steatohepatitis (NASH)
  - Non-hepatic causes (eg, rhabdomylosis, hemolysis)

6.3.2. Criteria for Conditional Withholding of ABI-009 Due to Potential Hepatotoxicity

For patients who do not meet the criteria for permanent discontinuation of ABI-009 and have no underlying liver disease, and eligibility criteria requiring normal transaminases and TBL at

baseline or patients with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of ABI-009:

- Elevation of either AST or ALT according to the following schedule:

Baseline AST or ALT value	AST or ALT elevation
Any	>8 x ULN at any time
Any	>5 x ULN but <8 x ULN for ≥2 weeks
Any	>5 x ULN but <8 x ULN and unable to adhere to enhanced monitoring schedule
Any	≥3 x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice).

- OR: TBL >3 x ULN at any time
- OR: ALP >8 x ULN at any time

ABI-009 should be withheld pending investigation into alternative causes of DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, and ALP) and/or elevated TBL is discovered and the laboratory abnormalities resolve to normal or baseline.

6.3.3. Overdose

On a per dose basis, an overdose is defined as 10% over the protocol-specified dose of ABI-009 assigned to a given patient, regardless of any associated AEs or sequelae.

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate of 30 minutes for each infusion.

7. STUDY DRUG MANAGEMENT

7.1. Description of Study Drugs

7.1.1. ABI-009 Packaging, Labeling, and Storage

ABI-009 will be supplied to the sponsor in single-use vials as lyophilized product. Each single-use 50-mL vial will contain 100 mg sirolimus and approximately 800 mg of human albumin as a stabilizer. Each vial will be labeled according to country-specific regulatory requirements for labeling of IPs.

Unopened vials of ABI-009 should be stored in a refrigerator (2°-8°C; 36°-46°F) in original cartons to protect from light. Reconstituted ABI-009 may be stored for up to 4 hours at 2-8°C (36°- 46°F), followed by 4 hours at room temperature (<25°C) in the IV bag. Both unopened vials of ABI-009 and reconstituted ABI-009 should be stored in an area free of environmental extremes and must be accessible only to study personnel.

Temperature records for ABI-009 must be made available to Aadi Bioscience or designee for verification of proper study drug storage.

7.2. ABI-009 Accountability, Disposal, and Compliance

For ABI-009, only completely unused study drug vials should be retained by the site until a representative from Aadi Bioscience or designee has completed an inventory. Partially used and completely used vials should be destroyed according to the site's guidelines, and their disposition should be recorded on the Investigational Drug Accountability Record Form.

For ABI-009, the investigator or designee shall record the dispensing of study drug to patients and any remaining study drug after dosing in a study drug accountability record. The study drug record will be made available to Aadi Bioscience or designated personnel for the purpose of accounting for the study drug supply. Inspections of the study drug supply for inventory purposes and assurance of proper storage will be conducted as necessary. Any significant discrepancy will be recorded and reported to Aadi Bioscience or their designee and a plan for resolution will be documented.

Accurate recording of all ABI-009 administration will be made in the appropriate section of the patient's CRF and source documents. The investigator or designee is responsible for accounting for all study-specific IP either administered or in their custody during the course of the study.

7.3. ABI-009 Reconstitution and Use

NOTE: It is not a requirement to use filter needles in the preparation, or in-line filters during the administration of ABI-009. In any event, filters of pore size less than 15 microns (15 µm) must not be used.

ABI-009 will be reconstituted by appropriate study personnel following the Pharmacy Manual and administered to the patient in the study site (see below). The investigator will calculate the BSA of the patient in order to determine the total amount of ABI-009 to be administered. The BSA will be capped at 2 m^2.

7.4. Receipt and Return of ABI-009

The process for handling the receipt and return of the study drug supplies are described in the Pharmacy Manual.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

All concomitant treatments, including blood and blood products, must be reported on the CRF. Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 8.2.

Concomitant therapies are to be collected from the signing of informed consent through the EOT Visit. Use of prohibited medications and procedures will be evaluated and documented during screening and on study. Therapy name including indication, dose, frequency, route, start date and stop date will be recorded on each patient's CRF(s).

Concurrent use of somatostatin analogs can be used for symptom control. Initial dosing as well as any dose adjustments will be documented.

8.1. Permitted Medications and Procedures

The investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the CRF. The minimum requirement is that drug name, dose, and the dates of administration are to be recorded. Additionally, a complete list of all prior cancer therapies will be recorded in the CRF.

Patients should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. G-CSF growth factors may be administered at the discretion of the investigator, consistent with institutional guidelines.

Extreme precaution must be taken with contraceptives (either combined or progesterone only), as it is not known if there is the potential of inhibition/induction of enzymes that affect the metabolism of estrogens and/or progestins. For patients that are able to have children, two methods of contraceptives should be used, one of which should be a barrier contraceptive.

8.2. Prohibited Medications and Procedures

The use of certain medications, and illicit drugs within 5 half-lives or 28 days, whichever is shorter prior to the first dose of study drug and for the duration of the study will not be allowed. If a prohibited medication is required for single use (such as for a procedure) while study drug is held, the investigator can approve such use.

The following medications or non-drug therapies are prohibited:

- Other anti-cancer therapy while on treatment in this study (other than somatostatin analogs if used for symptom control).
- Antiretroviral drugs (patients with known HIV are ineligible for study participation).
- Herbal remedies (eg, St. John's wort) unless approval is granted by the medical monitor.
- Sirolimus is metabolized primarily by CYP3A4. Drugs that are strong inhibitors or inducers of CYP3A4 may only be used under special circumstances (eg, as a single use for a procedure) while treatment with study drug is interrupted. The list may be modified based on emerging data.

- Use of any known CYP3A4 substrates with narrow therapeutic window (such as fentanyl, alfentanil, astemizole, cisapride, dihydroergotamine, pimozide, quinidine, terfanide) that are contra-indicated in the opinion of the investigator, within the 14 days prior to receiving the first dose of ABI-009.
- Use of strong inhibitors and inducers of CYP3A4 within the 14 days prior to receiving the first dose of ABI-009

9. STATISTICAL CONSIDERATIONS

9.1. Study Endpoints

Primary Endpoint:

- Disease control rate at 6 months, assessed by investigator using Response Evaluation Criteria In Solid Tumors (RECIST) v1.1.

Secondary Endpoints:

- ORR
- Safety

9.2. Safety Analysis

The safety analysis set includes all treated patients.

Safety and tolerability will be monitored through continuous reporting of treatment-emergent and treatment-related AEs, AEs of special interest (Table 4), laboratory abnormalities that are clinically significant, and incidence of patients experiencing dose modifications, dose delay/dose not given, dose interruptions, and/or premature discontinuation of IP due to an AE. All AEs will be recorded by the investigator from the time the patient signs informed consent until 28 days after the last dose of IP. Adverse events will be graded by NCI CTCAE v5.0. Clinically significant labs will be determined by the investigator.

Physical examination, vital signs, laboratory assessments (eg, serum chemistry, hematology), and ECOG performance status will be monitored. All SAEs (regardless of relationship to IP) will be followed until resolution. Local laboratory analysis will be performed as per study schedule.

9.3. Efficacy Analysis

The Efficacy Analysis Set includes all enrolled patients with measurable tumor per RECIST v1.1 at baseline who received at least 1 dose of ABI-009 and had a follow-up CT (or MRI).

Efficacy will be assessed by investigators using CT scans and RECIST v1.1.

The DCR at 6 months is the proportion of patients who achieve complete response (CR) or partial response (PR) or stable disease (SD) at 6 months.

9.4. Sample Size Considerations

In this pilot phase 2 study, up to 10 evaluable patients should be sufficient to provide preliminary information for efficacy and safety of ABI-009 in this patient population.

9.5. Primary Analysis

For this study will occur after all patients have either completed the study or completed at least 12 months of treatment. Patients who are still active at the time of the primary analysis may continue on study until disease progression or medication intolerance is observed.

10. MONITORING, RECORDING AND REPORTING OF ADVERSE EVENTS

10.1. Toxicities of ABI-009

ABI-009 is a formulation of sirolimus. No unexpected toxicities not already known for sirolimus (Rapamune®) or the sirolimus prodrug, temsirolimus (Torisel®), were identified in the nonclinical toxicity studies, or observed in the phase 1 studies for ABI-009.

More details on the known precautions, warnings, and AEs of sirolimus and rapalogs are found in the Rapamune® and Torisel® Package Inserts (Pfizer 2011, Pfizer 2011).

10.2. Evaluation of Adverse Events

The investigator must assign the following AE attributes:

- AE diagnosis or syndrome(s), if known (if not known, signs or symptoms)
- Dates of onset and resolution (if resolved)
- Severity [and/or toxicity per protocol]
- Assessment of relatedness to the IP
- Assessment of relatedness to protocol-required procedures
- Expectedness
- Action taken

The AE toxicity grading scale used will be the NCI CTCAE v5.0.

10.3. Serious Adverse Events

10.3.1. Definition of Serious Adverse Events

An SAE is defined as an AE that meets at least 1 of the following serious criteria:

- fatal
- life-threatening (places the patient at immediate risk of death)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An AE would meet the criterion of “requires hospitalization” if the event necessitated an in-patient admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as an SAE under the criterion of “other medically important serious event”. Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury, or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

Since the criteria for the CTCAE grading scale differs from the regulatory criteria for SAEs, if AEs correspond to grade 4 “life threatening” CTCAE grading scale criteria (eg, laboratory abnormality reported as grade 4 without manifestation of life-threatening status), it will be left to the investigator’s judgment to also report these abnormalities as SAEs. For any AE that applies to this

situation, comprehensive documentation of the event's severity status must be recorded in the patient's medical record.

10.3.2. Reporting Procedures for Serious Adverse Events

All SAEs that are treatment-related must be reported by the investigator to their IRB in writing, and to the FDA within 7 days as required by law.

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. All SAEs must be reported to Aadi Bioscience Drug Safety or designee within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time of signing of the informed consent form to 28 days after the last dose of IP), and those made known to the investigator at any time thereafter that are suspected of being related to IP.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a patient died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Aadi Bioscience Drug Safety as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Aadi Bioscience Drug Safety.

Where required by local legislation, the investigator is responsible for informing the IRB of the SAE and providing them with all relevant initial and follow-up information about the event. The investigator must keep copies of all SAE information on file including correspondence with Aadi Bioscience and the IRB.

10.4. Pregnancy and Breast-feeding Reporting

If a pregnancy occurs in a female patient, or female partner of a male patient, while the patient is taking protocol-required therapies, report the pregnancy to Aadi Bioscience as specified below. In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur up to 3 months after the last dose of protocol-required therapies.

The investigator will follow the female patient until completion of the pregnancy, and must notify Aadi Bioscience Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form. If a lactation case occurs while the female patient is taking protocol-required therapies, report the lactation case to Aadi Bioscience as specified below. In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur up to 1 week after the last dose of protocol-required therapies.

11. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

11.1. Discontinuation from Investigational Product

The following events are considered sufficient reasons for discontinuing a patient from the IP:

- AE(s) (that are intolerable)
- Disease progression
- Physician decision
- Withdrawal of consent (from treatment only)
- Death
- Lost to follow up
- Protocol violation
- Other (to be specified on the CRF)

The reason for treatment discontinuation should be recorded in the CRF and in the source documents.

11.2. Discontinuation from the Study

The following events are considered sufficient reasons for discontinuing a patient from the study:

- Withdrawal of consent
- Death
- Lost to follow up
- Protocol violation
- Other (to be specified on the CRF)

The reason for study discontinuation should be recorded in the CRF and in the source documents.

At the time of withdrawal, it should be determined whether the patient is withdrawing from treatment alone, or from treatment and collection of further data (e.g., survival). Every effort should be made to collect survival data after patient withdraws from treatment.

Patients have the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

11.3. Investigator or Sponsor Decision to Withdraw or Terminate Patient's Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a patient(s) from Investigational Product and/or other protocol required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Patients may be eligible for continued treatment with Aadi Bioscience's IP and/or other protocol required therapies by a separate protocol or as provided for by the local country's regulatory mechanism.

12. REGULATORY OBLIGATIONS

12.1. Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the investigator to Aadi Bioscience. The written informed consent document is to be prepared in the language(s) of the potential patient population.

Before a patient's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or the IP is administered.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the patient.

If a potential patient is illiterate or visually impaired, the investigator must provide an impartial witness to read the informed consent form to the patient and must allow for questions. Thereafter, both the patient and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

12.2. Institutional Review Board

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by Aadi Bioscience before recruitment of patients into the study and shipment of Aadi Bioscience's IP.

The investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB of deviations from the protocol or SAEs occurring at the site and other AE reports received from Aadi Bioscience, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB approval /renewal throughout the duration of the study. Copies of the investigator's reports and the IRB continuance of approval must be sent to Aadi Bioscience.

12.3. Patient Confidentiality

The investigator must ensure that the patient's confidentiality is maintained for documents submitted to Aadi Bioscience.

- Patients are to be identified by a unique patient identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRF demographics page, in addition to the unique patient identification number, include the age at time of enrollment.
- For SAEs reported to Aadi Bioscience, patients are to be identified by their unique patient identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).

- Documents that are not submitted to Aadi Bioscience (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the patient to permit such individuals to have access to his/her study-related records, including personal information.

12.4. Protocol Amendments

If investigator amends the protocol, agreement from Aadi Bioscience must be obtained. The IRB must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IRB to Aadi Bioscience.

12.5. Termination of the Study

Both Aadi Bioscience and the investigator reserve the right to terminate the investigator's participation in the study according to the study contract. The investigator is to notify the IRB in writing of the study's completion or early termination and send a copy of the notification to Aadi Bioscience.

13. DATA HANDLING AND RECORDKEEPING

13.1. Data/Documents

The investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed, and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy; and the laboratories, as well as copies of CRFs or CD-ROM.

13.2. Data Management

Data will be collected via CRF and entered into the clinical database. These data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

13.3. Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including patients not receiving protocol-required therapies) as stipulated in the protocol for each patient in the study. For patients who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 1), the investigator can search publicly available records (where permitted) to ascertain survival status.

This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

14. QUALITY CONTROL AND QUALITY ASSURANCE

14.1. Study Monitoring, Audits and Inspections

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and institution's compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable Ochsner compliance and quality assurance offices.

15. PUBLICATIONS

The results of this study may be published in a medical publication, journal, or may be used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Selection of first authorship will be based on several considerations, including, but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in a study.

16. REFERENCES

Albiges, L., F. Chamming's, B. Duclos, M. Stern, R. J. Motzer, A. Ravaud and P. Camus (2012). "Incidence and management of mTOR inhibitor-associated pneumonitis in patients with metastatic renal cell carcinoma." Ann Oncol **23**(8): 1943-1953.

Baselga, J., M. Campone, M. Piccart, H. A. Burris, 3rd, H. S. Rugo, T. Sahmoud, S. Noguchi, M. Gnant, K. I. Pritchard, F. Lebrun, J. T. Beck, Y. Ito, D. Yardley, I. Deleu, A. Perez, T. Bachelot, L. Vittori, Z. Xu, P. Mukhopadhyay, D. Lebwohl and G. N. Hortobagyi (2012). "Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer." N Engl J Med **366**(6): 520-529.

Chan, D. L., E. Segelov and S. Singh (2017). "Everolimus in the management of metastatic neuroendocrine tumours." Therap Adv Gastroenterol **10**(1): 132-141.

Cirstea, D., T. Hideshima, S. Rodig, L. Santo, S. Pozzi, S. Vallet, H. Ikeda, G. Perrone, G. Gorgun, K. Patel, N. Desai, P. Sportelli, S. Kapoor, S. Vali, S. Mukherjee, N. C. Munshi, K. C. Anderson and N. Raje (2010). "Dual inhibition of akt/mammalian target of rapamycin pathway by nanoparticle albumin-bound-rapamycin and perifosine induces antitumor activity in multiple myeloma." Mol Cancer Ther **9**(4): 963-975.

de Oliveira, M. A., E. M. F. Martins, Q. Wang, S. Sonis, G. Demetri, S. George, J. Butrynski and N. S. Treister (2011). "Clinical presentation and management of mTOR inhibitor-associated stomatitis." Oral Oncol **47**(10): 998-1003.

De, T., V. Trieu, Z. Yim, J. Cordia, A. Yang, B. Beals, S. Ci, L. Louie and N. Desai (2007). Nanoparticle albumin-bound (nab) rapamycin as an anticancer agent. Proceedings of the 98th American Association for Cancer Research Annual Meeting (AACR), Los Angeles CA, AACR.

Desai, N., O. D'Cruz and V. Trieu (2009). Potent antitumor effects of nab-rapamycin (ABI-009) in combination with kinase inhibitors erlotinib and perifosine. Proceedings of the 100th American Association for Cancer Research Annual Meeting (AACR), Denver CO, AACR.

Desai, N., V. Trieu, Z. Yao, L. Louie, S. Ci, A. Yang, C. Tao, T. De, B. Beals, D. Dykes, P. Noker, R. Yao, E. Labao, M. Hawkins and P. Soon-Shiong (2006). "Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel." Clin Cancer Res **12**(4): 1317-1324.

Dowling, R. J., I. Topisirovic, B. D. Fonseca and N. Sonenberg (2010). "Dissecting the role of mTOR: lessons from mTOR inhibitors." Biochim Biophys Acta **1804**(3): 433-439.

Fasolo, A. and C. Sessa (2012). "Targeting mTOR pathways in human malignancies." Curr Pharm Des **18**(19): 2766-2777.

Gonzalez-Angulo, A. M., F. Meric-Bernstam, S. Chawla, G. Falchook, D. Hong, A. Akcakanat, H. Chen, A. Naing, S. Fu, J. Wheler, S. Moulder, T. Helgason, S. Li, I. Elias, N. Desai and R. Kurzrock (2013). "Weekly nab-Rapamycin in patients with advanced nonhematologic malignancies: final results of a phase I trial." Clin Cancer Res **19**(19): 5474-5484.

Gradishar, W. J., S. Tjulandin, N. Davidson, H. Shaw, N. Desai, P. Bhar, M. Hawkins and J. O'Shaughnessy (2005). "Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer." J Clin Oncol **23**(31): 7794-7803.

Hallet, J., C. H. Law, M. Cukier, R. Saskin, N. Liu and S. Singh (2015). "Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes." Cancer **121**(4): 589-597.
Hanna, S. C., S. A. Heathcote and W. Y. Kim (2008). "mTOR pathway in renal cell carcinoma." Expert Rev Anticancer Ther **8**(2): 283-292.
Kennecke, H., M. Rahman, S. Yip, R. Woods, D. Schaeffer and I. Tai (2011). Effect of nab-rapamycin versus rapamycin in colorectal cancer cell lines and associations with KRAS and PI3K mutations. Proceedings of the 47th American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, IL,, J Clin Oncol
Kratz, F. (2008). "Albumin as a drug carrier: design of prodrugs, drug conjugates and nanoparticles." J Control Release **132**(2): 171-183.
Kremer, P., G. Hartung, U. Bauder-Wust, H. H. Schrenk, A. Wunder, S. Heckl, U. Zillmann and H. Sinn (2002). "Efficacy and tolerability of an aminopterin-albumin conjugate in tumor-bearing rats." Anticancer Drugs **13**(6): 615-623.
Manfredi, G. I., A. Dicitore, G. Gaudenzi, M. Caraglia, L. Persani and G. Vitale (2015). "PI3K/Akt/mTOR signaling in medullary thyroid cancer: a promising molecular target for cancer therapy." Endocrine **48**(2): 363-370.
Molina, A. M., D. R. Feldman, M. H. Voss, M. S. Ginsberg, M. S. Baum, D. R. Brocks, P. M. Fischer, M. J. Trinos, S. Patil and R. J. Motzer (2011). "Phase 1 trial of everolimus plus sunitinib in patients with metastatic renal cell carcinoma." Cancer **118**(7): 1868-1876.
Novartis-Gleevec (2017). Sutent Prescribing Information.
Novartis (2017). Everolimus (Afinitor) Prescribing Information.
O'Donnell, A., S. Faivre, H. A. Burris, 3rd, D. Rea, V. Papadimitrakopoulou, N. Shand, H. A. Lane, K. Hazell, U. Zoellner, J. M. Kovarik, C. Brock, S. Jones, E. Raymond and I. Judson (2008). "Phase I pharmacokinetic and pharmacodynamic study of the oral mammalian target of rapamycin inhibitor everolimus in patients with advanced solid tumors." J Clin Oncol **26**(10): 1588-1595.
Pfizer (2011). Prescribing Information: TORISEL Kit (temsirolimus) injection, for intravenous infusion only.
Pfizer (2011). Rapamune Prescribing Information.
Pusceddu, S., E. Verzoni, N. Prinzi, A. Mennitto, D. Femia, P. Grassi, L. Concas, C. Vernieri, G. Lo Russo and G. Procopio (2017). "Everolimus treatment for neuroendocrine tumors: latest results and clinical potential." Ther Adv Med Oncol **9**(3): 183-188.
Qi, W. X., Y. J. Huang, Y. Yao, Z. Shen and D. L. Min (2013). "Incidence and risk of treatment-related mortality with mTOR inhibitors everolimus and temsirolimus in cancer patients: a meta-analysis." PLoS One **8**(6): e65166.
Schnitzer, J. E. (1992). "gp60 is an albumin-binding glycoprotein expressed by continuous endothelium involved in albumin transcytosis." Am J Physiol **262**(1 Pt 2): H246-254.
Schnitzer, J. E., P. Oh, B. S. Jacobson and A. M. Dvorak (1995). "Caveolae from luminal plasmalemma of rat lung endothelium: microdomains enriched in caveolin, Ca(2+)-ATPase, and inositol trisphosphate receptor." Proc Natl Acad Sci U S A **92**(5): 1759-1763.
Sehgal, S. N. (2003). "Sirolimus: its discovery, biological properties, and mechanism of action." Transplant Proc **35**(3 Suppl): 7S-14S.
Strosberg, J., G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P. L. Kunz, M. H. Kulke, H. Jacene, D. Bushnell, T. M. O'Dorisio, R. P. Baum, H. R. Kulkarni, M. Caplin, R. Lebtahi, T.

Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Oberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J. L. Erion, P. Ruszniewski, D. Kwekkeboom, E. Krenning and N.-T. Investigators (2017). "Phase 3 Trial of (177)Lu-Dotatate for Midgut Neuroendocrine Tumors." N Engl J Med **376**(2): 125-135.
Strosberg, J. R., R. L. Fine, J. Choi, A. Nasir, D. Coppola, D. T. Chen, J. Helm and L. Kvols (2011). "First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas." Cancer **117**(2): 268-275.
Thompson, L. A., M. Kim, S. D. Wenger and C. L. O'Bryant (2012). "Everolimus: a new treatment option for advanced pancreatic neuroendocrine tumors." Ann Pharmacother **46**(9): 1212-1219.
Trieu, V., S. Ran, L. Volk, A. Stutzman, O. D'Cruz and N. Desai (2009). CNS safety, antitumor activity, and antiangiogenic activity of nab-rapamycin (ABI-009). Proceedings of the 100th American Association for Cancer Research Annual Meeting (AACR), Denver CO, AACR.
Yao, J. C., M. Hassan, A. Phan, C. Dagohoy, C. Leary, J. E. Mares, E. K. Abdalla, J. B. Fleming, J. N. Vauthey, A. Rashid and D. B. Evans (2008). "One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States." J Clin Oncol **26**(18): 3063-3072.
Yao, J. C., M. H. Shah, T. Ito, C. L. Bohas, E. M. Wolin, E. Van Cutsem, T. J. Hobday, T. Okusaka, J. Capdevila, E. G. de Vries, P. Tomassetti, M. E. Pavel, S. Hoosen, T. Haas, J. Lincy, D. Lebwohl, K. Oberg and T. T. S. G. Rad001 in Advanced Neuroendocrine Tumors (2011). "Everolimus for advanced pancreatic neuroendocrine tumors." N Engl J Med **364**(6): 514-523.
Yuan, R., A. Kay, W. J. Berg and D. Lebwohl (2009). "Targeting tumorigenesis: development and use of mTOR inhibitors in cancer therapy." J Hematol Oncol **2**: 45.
Zhou, H., Y. Luo and S. Huang (2010). "Updates of mTOR inhibitors." Anticancer Agents Med Chem **10**(7): 571-581.