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A phase 1/2 study of nab-Sirolimus with pazopanib (VOTRIENT®) in patients with advanced nonadipocytic soft-tissue sarcomas

Investigational Product	**nab-Sirolimus**
Protocol Number	**10015**
Study Phase:	**1/2**
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SPONSOR-INVESTIGATOR SIGNATURE PAGE

Signature of Sponsor-Investigator	**dd/mm/yyyy**
Lee D. Cranmer, MD, PhD	
Printed Name of Sponsor-Investigator	
Institution Name: University of Washington	
By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Aadi Bioscience representatives, the Declaration of Helsinki, ICH Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

PROTOCOL SYNOPSIS

INVESTIGATIONAL PRODUCT	Nab-Sirolimus, ABI-009, sirolimus protein-bound nanoparticles for injectable suspension (albumin bound), *nab*-rapamycin, nanoparticle albumin-bound rapamycin
FDA APPROVED STUDY AGENT	Pazopanib (VOTRIENT®), is a kinase inhibitor indicated for the treatment of subjects with 1) advanced renal cell carcinoma, and 2) advanced soft tissue sarcoma (STS) who have received prior chemotherapy
INDICATION	Previously treated subjects with advanced (metastatic or locally advanced) nonadipocytic STS, for which surgery is not an option
TITLE	A phase 1/2 study of nab-Sirolimus (ABI-009, *nab*-rapamycin) with pazopanib (VOTRIENT®) in subjects with advanced nonadipocytic soft-tissue sarcomas
PROTOCOL NUMBER	CC10015
PHASE OF DEVELOPMENT	1/2
STUDY OBJECTIVES	**Objectives in Phase 1** **Primary** • To identify the recommended phase 2 dose (RP2D) of nab-Sirolimus given intravenously (IV) plus continuous daily oral pazopanib, for subjects with nonadipocytic STS **Secondary** • To evaluate the safety profile of the nab-Sirolimus plus pazopanib combination therapy in advanced nonadipocytic STS **Objectives in Phase 2** **Primary** • To evaluate the efficacy of the combination of nab-Sirolimus and pazopanib at the RP2D **Secondary** • To evaluate the safety profile and to further evaluate the efficacy of nab-Sirolimus plus pazopanib combination therapy

	Exploratory • To study the correlation of clinical outcomes with Next Generation Sequencing and Immunohistochemical analyses of tumor biomarkers, including baseline secreted protein acidic and rich in cysteine (SPARC) expression. • To assess baseline tumoral immune parameters, including PD-1, PD-L1, mutational burden, and infiltrating lymphocytes, in correlation with clinical outcomes.
STUDY ENDPOINTS	**Endpoints in Phase 1** **Primary Endpoint** • Dose-limiting-toxicities (DLTs), used to estimate the maximum-tolerated dose (MTD) of nab-Sirolimus in combination with pazopanib, where the MTD is defined as the highest dose where ≤1 of 6 (or 0 of 3) subjects experience a DLT, thus a target DLT rate of roughly 17%. **Secondary Endpoint** • Adverse Events profile (based on National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v5.0) of all subjects and each dose cohort **Endpoints in Phase 2 – data both from Phase 1 and 2** **Primary Endpoint** • Progression-free survival (PFS) rate at 3 months, based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 **Secondary Endpoint** • Adverse Events profile (based on NCI CTCAE v5.0) • Median PFS, PFS rate at 6 months, based on RECIST v1.1 • Median overall survival (OS), OS at 12 months • Objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 • Disease control rate (DCR), defined as complete response (CR) plus partial response (PR) plus stable disease (SD) ≥18 weeks, based on RECIST v1.1 • Duration of response **Exploratory endpoints**

	• Optional pre-treatment tumor tissue collection (fresh or archival) for biomarker analysis: 1. Correlation of genetic profiling and tissue biomarker analysis with clinical benefit 2. Correlation of baseline secreted protein acidic and rich in cysteine (SPARC) expression with clinical benefit 3. Correlation of baseline immune parameters with clinical benefit
STUDY DESIGN	This is an open label, dose-finding, single-arm, prospective phase 1/2 study to identify the RP2D of nab-Sirolimus given IV on either Day 1 and Day 8 (qw2/3), or Day 1 only of a 21-day cycle (qw1/3), plus daily oral pazopanib in subjects with advanced nonadipocytic STS. The study will be conducted in compliance with International Conference on Harmonization (ICH) Good Clinical Practices (GCPs). **Dose-finding Phase 1 Portion of the Study:** Dose levels of nab-Sirolimus will be tested in cohorts of 3 subjects each using the 3+3 dose-finding design. A summary of dose levels and cohorts are provided in Table 1 and Table 2. **Phase 2 Portion of the Study:** This will be conducted using Simon's two-stage design. Subjects enrolled in the phase 1 study at the RP2D cohort will be included for response and safety evaluation in phase 2.
STUDY DRUG ADMINISTRATION	Subjects will receive nab-Sirolimus by IV infusion over a minimum of 30 (+10) minutes at 100, 75, 60, 45, 30, 20, or 15 mg/m^2 either Days 1 and 8 in a 21-day cycle or on Day 1 only in a 21-day cycle. Pazopanib will be given per standard of care guidelines, daily. Pazopanib dosing may be initiated at 400, or 800 mg once daily by mouth, without food (at least 1 hour before or 2 hours after a meal). Pazopanib starting dose must remain consistent within a dose-finding cohort. Subjects will continue therapy until unequivocal clinical disease progression, unacceptable toxicity, until in the opinion of the investigator the subject is no longer benefiting from therapy, or at the subject's discretion.

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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
CI	confidence interval
CNS	central nervous system
CR	complete response
CT	computed tomography
DLT	dose-limiting toxicity
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	Immunohistochemistry
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 rapamycin
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	Progression-free survival
PK	pharmacokinetics
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

Abbreviation or Term	Definition/Explanation
Study Day 1	First day that protocol-specified IP is administered to the subject.
End of Treatment	The date of the last dose of ABI-009 or pazopanib, whichever is later for an individual subject.
End of Treatment Visit	For a subject 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 or pazopanib, whichever is later.
30 Day Follow-Up Visit	For a subject is when safety assessments and procedures are performed after the End of Treatment visit. The 30-Day Follow-Up visit should occur 30 days (+/- 7 days) after the last dose of ABI-009 or pazopanib, whichever is later.
End of Study	Either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary, and/or exploratory analysis, as pre-specified in the protocol.
Follow-up Period	The on-study time period after the 30-Day Follow-Up Visit. All subjects 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) from the 30-Day Follow-Up Visit, 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.
Primary Analysis	For this study will occur after all subjects have either completed the study or completed 12 months of treatment. Subjects 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 subjects with measurable tumor per RECIST v1.1 at baseline who received at least 2 doses of ABI-009 and had a follow-up CT / MRI (modified treated population).

Full Analysis Set	All enrolled subjects who receive at least 1 dose of ABI-009 (treated population).
Per-protocol Analysis Set	All enrolled subjects who do not have any prospectively defined protocol violations.
Progression-free survival	The time from the first dose date to the first observation of a disease progression or death due to any cause.
Overall survival	The time from the first dose date to the date of death due to any cause.
Overall response rate	The proportion of subjects who achieve a confirmed partial response or complete response per RECIST v1.1. 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.

1. INTRODUCTION

1.1. Soft Tissue Sarcomas

Soft tissue sarcoma (STS) is a relatively rare and histologically diverse neoplasm of mesenchymal origin, occurring with an incidence of about 1% of all adult cancers, and includes >70 histologic subtypes.[1-3] For localized resectable disease, surgical resection is the standard of care, and for unresectable sarcomas, radiation therapy is offered. However, recurrence rate is high (~50%) and treatment options for metastatic/relapsed STS are limited to anthracycline-based chemotherapy (i.e., doxorubicin), administered alone or in combination with alkylating agents (ifosfamide and/or dacarbazine).[4-6] However, drug resistance and toxicities often limit benefits of chemotherapy used to treat metastatic sarcomas.

Recently, in 2015, 2 therapeutics were approved by the United States Food and Drug Administration (US FDA) for STS, pazopanib (Votrient®, Novartis Pharma) and trabectedin (Yondelis®, Janssen Biotech, Inc.). Pazopanib is a multiple tyrosine kinase inhibitor (TKI), which hinders growth factor-mediated signal transduction pathways involved in tumor angiogenesis, and was approved for nonadipocytic STSs refractory to chemotherapy.[7-9] Trabectedin, a natural alkaloid which interferes with gene transcription and DNA repair, was approved for liposarcoma and leiomyosarcoma.[10,11] Although the new therapeutic options offer improvement of the course of disease in specific subtypes of STSs, the prognosis of advanced disease has remained uniformly poor, with an estimated median survival of only 8 to 13 months,[12-14] and more efficacious therapeutics options are needed.

1.1.1 mTOR Inhibition in Soft Tissue Sarcoma

Aberrant signaling of the mammalian target of rapamycin (mTOR) pathway is common in sarcomas and other malignancies. A multicenter, open-label, single-arm, phase 2 trial with oral ridaforolimus, an mTOR inhibitor, showed evidence of activity in sarcomas.[15] A total of 212 heavily pretreated subjects were treated in 4 separate histologic cohorts of STS; 61 subjects (28.8%) achieved disease control rate (DCR, defined as subjects who achieved complete response (CR) or partial response (PR) or stable disease (SD) for ≥16 weeks). Median progression-free survival (PFS) was 15.3 weeks; median overall survival (OS) was 40 weeks, which compared favorably to historical metrics. The confirmed overall response rate (ORR) was 1.9%, with 4 subjects achieving confirmed PR (2 with osteosarcoma, 1 with spindle cell sarcoma, and 1 with undifferentiated pleomorphic sarcoma [formerly malignant fibrous histiocytoma]). Related adverse events (AEs) were generally mild or moderate and consisted primarily of stomatitis, mucosal inflammation, mouth ulceration, rash, and fatigue, all typical of the rapalogs.

Based on promising results from phase 2, a large randomized placebo-controlled phase 3 trial (N = 711) evaluated ridaforolimus to assess disease control in advanced sarcomas after benefit from prior chemotherapy.[16] Subjects with metastatic soft tissue or bone sarcomas who achieved objective response or SD with prior chemotherapy were randomly assigned to receive ridaforolimus 40 mg or placebo once per day for 5 days every week. Ridaforolimus treatment led to a modest, although significant, improvement in PFS per independent review compared with placebo (hazard ratio [HR], 0.72; $P < 0.001$; median PFS, 17.7 v 14.6 weeks). Ridaforolimus induced a mean 1.3% decrease in target lesion size vs a 10.3% increase with placebo ($P < 0.001$).

Median OS with ridaforolimus was modest: 90.6 weeks versus 85.3 weeks with placebo (HR, 0.93; *P* = 0.46). Adverse events were more common with ridaforolimus than with placebo and were as expected with mTOR inhibition, including stomatitis, infections, fatigue, thrombocytopenia, noninfectious pneumonitis, hyperglycemia, and rash. Grade 3 AEs were 64% vs 26% for ridaforolimus vs placebo, respectively. While there was no associated survival benefit, the trial provided proof of principle that mTOR inhibition could demonstrate clinical activity in STS.

Other mTOR inhibitors, including sirolimus and everolimus, have also been tested in clinical trials for advanced STS as single-agents or as part of a combination regimen, producing modest improvement. While rapamycin and analogs (rapalogs) are promising therapeutics for the treatment of sarcomas, they have low water solubility (hydrophobic), limiting their bioavailability. Oral agents, such as rapamycin, everolimus, or ridaforolimus are primarily eliminated via hepatic clearance, which result in negligible drug levels in most organs, limiting their therapeutic potential. Temsirolimus, a prodrug of rapamycin requiring conversion by CYP3A, has higher water solubility than the oral agents but still require solvents (polysorbate 80, polyethylene glycol, and dehydrated alcohol) for the injectable formulation. Solvents reduce drug efficacy due to micellar sequestration and thus, improved formulations are needed that are both solvent-free and allow high bioavailability in order to unleash the full potential of mTOR inhibitors.

A novel mTOR inhibitor ABI-009 (albumin-bound rapamycin nanoparticles, *nab*-rapamycin) is solvent-free and has relatively high bioavailability, and is a promising new therapeutic for sarcoma.

1.2. Nab-Sirolimus Background

1.2.1. Rapamycin and Rapalogs

Rapamycin is a protein kinase inhibitor that is approved for immunosuppression in renal transplant subjects and is under investigation as a cancer treatment. Rapamycin inhibits mTOR, a regulatory protein kinase in cancer that recognizes high stress levels, including depleted nutrient levels and states of hypoxia.[17] mTOR is a serine/threonine-specific protein kinase, downstream of the phosphatidylinositol 3-kinase (PI3K)/Akt (protein kinase B) pathway, and a key regulator of cell survival, proliferation, and metabolism. Additionally, mTOR is involved in regulating angiogenesis by controlling endothelial and smooth muscle cell proliferation via the hypoxia-inducible factor-1α and vascular endothelial growth factor (VEGF).[18] Consistent with its role in cell proliferation, the mTOR pathway is frequently overactivated in a number of human malignancies, and is thus considered to be an attractive target for anti-cancer therapy. Rapamycin 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.[19]

Although rapamycin (sirolimus) is an efficacious mTOR inhibitor, it has poor solubility, low oral bioavailability, and produce dose-limiting toxicities (DLTs), including mucositis and stomatitis.[17,20] Marketed rapamycin analogs are temsirolimus and everolimus. Temsirolimus, a prodrug of rapamycin, is approved for the treatment of kidney cancer. Everolimus is approved for pediatric and adult subjects with subependymal giant cell astrocytoma, for advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane, progressive

neuroendocrine tumors of pancreatic origin (PNETs), subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis and advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.[21-25]

Oral rapamycin 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.[26-28] The most frequently occurring grade 3 or 4 AEs were hyperglycemia (17%), hypophosphatemia (13%), anemia (9%), and hypertriglyceridemia (6%).[29] These side effects lead to the discontinuation of the treatment in 60% of subjects in some studies.

1.2.2. Nab-Sirolimus (ABI-009, *nab*-Rapamycin)

The novel nanoparticle albumin-bound rapamycin (nab-Sirolimus, *nab*-rapamycin, ABI-009) is freely dispersible in saline and is suitable for intravenous (IV) administration, and has produced both a favorable safety profile and evidence of efficacy in subjects with metastatic solid tumors.[30]

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 compared with the conventional paclitaxel formulation.[31] This suggests that the *nab* formulation of rapamycin may also produce similar advantages over the standard rapamycin.

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.[32,33] Albumin circulating in the bloodstream can interact with gp60 to initiate caveolae-mediated transcytosis to reach tumor cells.[34,35] Indeed, *nab*-paclitaxel transcytosis across the epithelial monolayer was dependent on caveolae formation.[36] 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.[36]

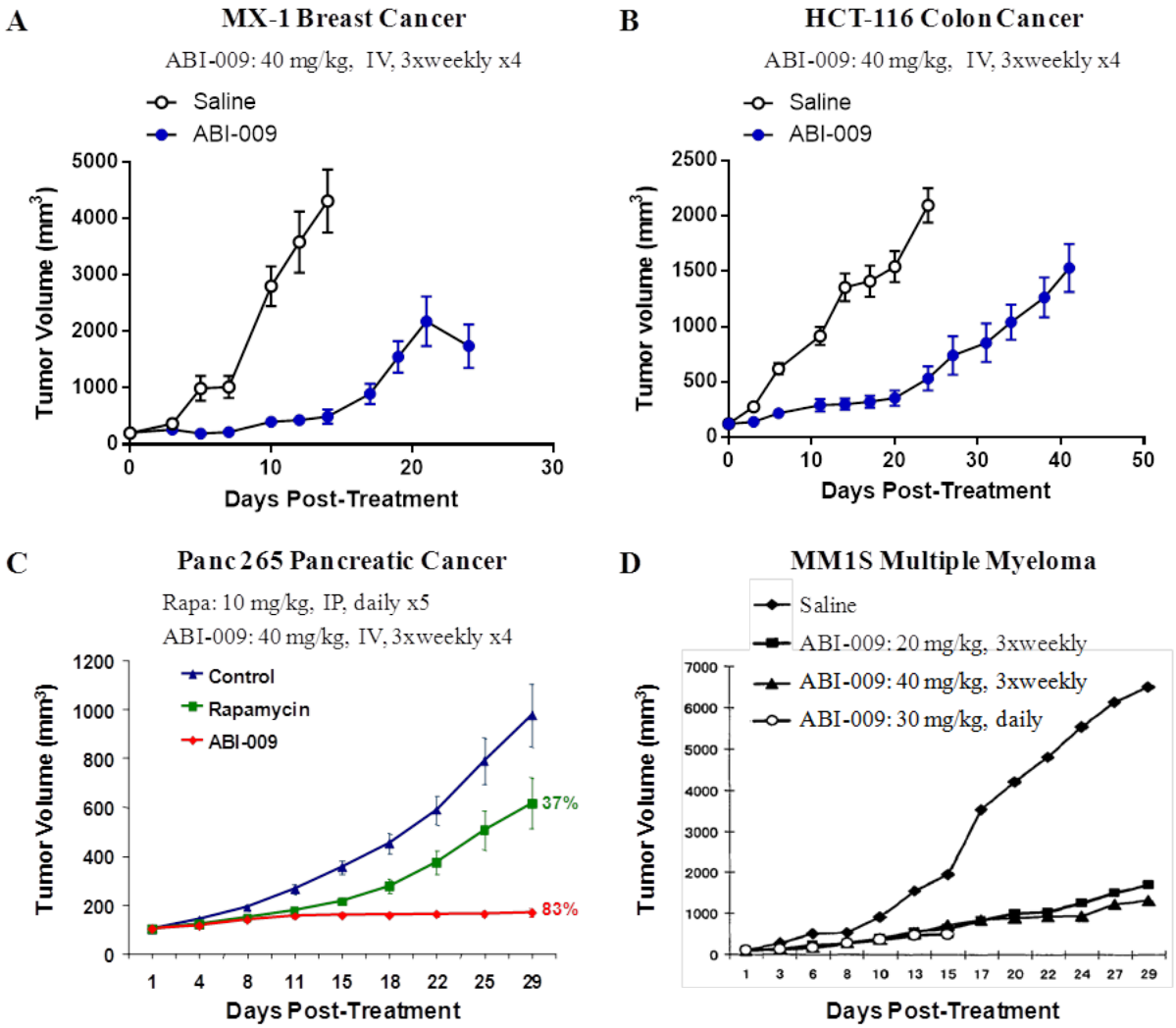
Additionally, a study previously published by our group examined the prognostic implications of expression of the Serum Protein Acidic and Rich in Cysteine (SPARC) in sarcomas.[37] We found that elevated SPARC expression, found in about 50% of a random selection of cases, was associated with a particularly adverse prognosis, as compared to those with low expression. SPARC has been hypothesized as a potential receptor of nanoparticle-albumin encapsulated drug preparations, making nab-Sirolimus a promising targeted mTOR for the treatment of STSs.

1.2.3. Preclinical Studies with nab-Sirolimus

Preclinical primary pharmacology studies in vivo demonstrated significant antitumor activity of nab-Sirolimus as a single agent administered intravenously at 40 mg/kg, 3 times weekly for 4 weeks, across different tumor xenograft models in nude mice (see Figure 1 below), including breast, colorectal, multiple myeloma, and pancreatic cancer.[38-42] This dose level correlates to approximately 360 mg/m^2/week in human. These findings are consistent with published information on rapamycin as an mTOR inhibitor and the role of mTOR in tumor growth.[43] In

addition, recent preclinical study has demonstrated that combination of nab-Sirolimus with the Akt inhibitor perifosine induced synergistic antitumor activity and prolonged survival compared with either agent alone in multiple myeloma.[41]

Figure 1: Antitumor Activity of nab-Sirolimus in Tumor Xenografts



Preclinical pharmacokinetic (PK) studies in rats showed that IV nab-Sirolimus exhibited linear PK with respect to dose and large volume of distribution (Vz), due to efficient tissue extraction of rapamycin from the central blood compartment.[40] Shortly after dosing, tissue rapamycin level was 3-5 folds higher than that of blood, indicating efficient extraction. The terminal half-life of nab-Sirolimus 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 rapamycin literature,[44] 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 nab-Sirolimus were evaluated in a series of preclinical studies. In a Good Laboratory Practice (GLP) repeat-dose toxicity study in male and female rats, nab-Sirolimus 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 nab-Sirolimus showed no new or unexpected toxicity compared to what is already known for rapamycin and other rapalogs.[45-47] Refer to the Investigator's Brochure for details on preclinical studies.

1.2.4. Clinical Studies with nab-Sirolimus

In a phase 1 dose-finding, tolerability, and PK study conducted at MD Anderson Cancer Center (Protocol CA401, NCT00635284), nab-Sirolimus was well tolerated with evidence of responses and SD in various solid tumors including renal cell carcinoma and bladder cancer, both of which typically express mTOR.[30] Twenty-six subjects were treated with 45, 56.25, 100, 125, or 150 mg/m^2 nab-Sirolimus per week for 3 weeks, followed by a week of rest (28-day cycle, q3/4w). ABI-009 was administered IV. The maximum tolerated dose (MTD) was established at 100 mg/m^2.

Nineteen subjects were evaluable for efficacy. One subject in the 45 mg/m^2 (95 mg actual rapamycin dose) cohort diagnosed with adenocarcinoma of the kidney and with bone and intrathoracic metastases had a confirmed PR. The target lesion of this subject was reduced by 35.1% and the duration of response (DOR) lasted 183 days. Two (11%) subjects (at doses 45 and 125 mg/m^2, with actual rapamycin doses of 88 mg and 193 mg, respectively) had an overall tumor evaluation of SD (confirmed): 1 subject with mesothelioma had SD for 365 days and 1 subject with a neuroendocrine tumor 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%) subjects experienced at least 1 treatment-related AE (TRAE). The most common nonhematological TRAEs were mucosal inflammation (10 subjects, 38%), fatigue (7 subjects, 27%), rash (6 subjects, 23%), diarrhea (6 subjects, 23%), and nausea (5 subjects, 19%). Specifically, at the MTD of 100 mg/m^2, all 7 subjects experienced at least 1 TRAE of any grades, and the most common AEs were thrombocytopenia, mucositis and fatigue (5 subjects, 71% each). A total of 7 subjects (27%) in the CA401 study had treatment-related infections, including candidiasis, oral candidiasis, cellulitis, folliculitis, and urinary tract infection. All these events were grade 1 or 2. Four (15%) subjects experienced at least 1 treatment-related serious AE (SAE), including cardiac arrhythmia (grade 2), failure to thrive (grade 3), 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 TRAEs, for all cohorts and grades, were thrombocytopenia (58%), followed by hypokalemia (23%), anemia and hypophosphatemia (19% each), and neutropenia (15%). 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 subjects (62%) had treatment-related AEs (TRAEs) requiring a week dose delay.

Currently, there are several ongoing trials investigating the safety and efficacy of single-agent *nab*-Sirolimus in various disease areas, including a basket trial in subjects with pathogenic inactivating *TSC1* or *TSC2* alterations (NCT05103358). The particularly safe toxicity profile of nab-Sirolimus allows this mTOR inhibitor to be combinable with other therapeutics and a trial in subjects with advanced STS is complete and evaluating the combination of nab-Sirolimus and nivolumab (NCT03190174). Refer to the Investigator's Brochure for details on clinical studies.

1.3. Pazopanib in Soft Tissue Sarcoma

Angiogenesis has been explored as a potential target for the treatment of STS.[48] A variety of multi-targeted TKIs with prominent anti-angiogenic activity (aa-TKI's) have been studied, including pazopanib, with evidence of clinically significant activity.

Pazopanib was initially approved for the treatment of advanced renal carcinoma and more recently, based on a phase 3 randomized trial, as salvage therapy in subjects with advanced, nonadipocytic STS.[8] In that registrational placebo-controlled, randomized phase 3 study, pazopanib demonstrated improved PFS vs placebo in pretreated subjects (median 4.6 vs 1.6 months; HR=0.31; $P < 0.0001$).[8] Overall survival was not significantly improved and the ORR was relatively low (6% pazopanib vs 0% placebo). The most common AEs were fatigue (65% vs 49%), diarrhea (58% vs 16%), nausea (54% vs 28%), weight loss (48% vs 20%), and hypertension (41% vs 7%) in the pazopanib vs placebo arms, respectively. Although approved for management of STS, the activity of pazopanib monotherapy is admittedly modest, with considerable toxicity profile.

A meta-analysis showed evidence that aa-TKIs, including pazopanib, demonstrated improved median PFS and ORR vs placebo for the treatment of sarcomas; however, there was no difference in the median PFS, median OS, and ORR of pazopanib vs other aa-TKIs.[49] Similar to the registrational phase 3 study, the meta-analysis also failed to show improvement in median OS for aa-TKIs compared with placebo.

The identification of sarcoma subtypes with particular sensitivity to aa-TKI, along with appropriate combination therapies to increase the overall activity in STSs remains an unmet need.

1.4. Rationale for Combination of nab-Sirolimus with Pazopanib for Nonadipocytic Soft Tissue Sarcoma

The feasibility to combine an mTOR inhibitor (everolimus) with an aa-TKI (vandetanib) had been demonstrated in a phase 1 study in subjects with bone and STSs (N = 21).[50] Median PFS and OS were 4.5 and 13.9 months, respectively. Two subjects (9.5%) had a CR. These results favorable compared with the results from the meta-analysis, in which aa-TKIs produced 3.2 and 11.8 months of median PFS and OS, respectively, and 5% ORR.[49] These results provided proof-of-concept for the potential to improve efficacy outcomes for subjects with STS with the combination of an aa-TKI and an mTOR inhibitor.

Based on the promising results from the phase 1 study with everolimus combined with vandetanib,[50] the acceptable toxicity profile of single agent nab-Sirolimus along with evidence of antitumor activity in various solid tumors,[30] it is plausible that nab-Sirolimus with an aa-TKI may potentially offer clinical benefits for subjects with STS. Based on a phase 3 study, PALETTE,[8] pazopanib is now a standard of care for subjects with advanced nonadipocytic STS. Here, we propose a phase 1/2 assessment of the safety and antitumor activity of the combination of nab-Sirolimus with pazopanib for subjects with advanced nonadipocytic STSs. Given non-overlapping toxicity profiles, we hypothesize that combining the 2 drugs will be feasible.

1.5. Rationale for Starting Dose Selection and Schedule of nab-Sirolimus and Pazopanib

The established MTD of single-agent nab-Sirolimus for subjects with advanced solid tumors is 100mg/m^2. In the initial cohorts of nab-Sirolimus with pazopanib, the planned starting dose of 60 mg/m^2 ABI-009 [given IV weekly for 2 weeks with a week of rest (q2/3w)] gave a 40% safety margin over the established MTD of 100 mg/m^2 for subjects with advanced solid tumors adipocytic. This dose, assuming a BSA of 1.7, is 102 mg/week (or 68 mg/week on average in a 3-week cycle), which is within or above the therapeutic range for rapalogs:

- Rapamune (oral rapamycin) dosing used chronically for transplant subjects is similar to the proposed starting dose of nab-Sirolimus.[46] Rapamune is dosed at 2-5 mg/day, which is 14-35 mg/week. Safety profiles of everolimus and Rapamune are similar. Everolimus dosing levels[47] are similar to Rapamune dosing, with both being in the same range as the planned starting dose of ABI-009.
- Using the PK data from the phase 1 study[30], linear modeling of rapamycin blood concentration predicts that 1 week after 10 and 20 mg/m^2 nab-Sirolimus IV administration, therapeutic trough rapamycin levels are still maintained (7.11 and 14.22 ng/mL, respectively, Aadi data on file). Thus, potential dose reduction from the starting dose of 60 mg/m^2 should still result in therapeutic levels.
- Nab-Sirolimus has shown similar safety profile to other rapalogs, even at a higher dose of 100 mg/m^2, with no new or unexpected toxicity had been observed. In particular, mucositis/stomatitis that were observed with other mTOR inhibitors has not been dose-limiting with nab-Sirolimus.

The q2/3w schedule allowed 2 additional drug holidays in 6 months than the q3/4w schedule studied in the first-in-human study for nab-Sirolimus (CA401, NCT00635284), allowing more time for recovery from potential AEs and is more convenient for subjects.

A recommended phase 2 dose (RP2D) could not be established in the initial dosing cohorts in this present study, after treating 13 subjects. DLTs were observed in all dose cohorts, with the most prominent DLT being thrombocytopenia. Despite DLT, subjects have been able to tolerate therapy after dose adjustment (dose reductions and delays): only 3 of the first 13 subjects enrolled discontinued therapy due to adverse events. Two patients experienced grade 3 and 4 thrombocytopenia after a single dose of nab-Sirolimus and missed Cycle 1 Day 8, subsequently recovered from the event, and were able to resume therapy. Additionally, 10/13 (77%) patients experienced myelosuppression during the first cycle, 6 of them had a delay of the next planned cycle, D1. Together missed Day 8 doses and dose delays of Day 1 occurred in nearly all patients (12/13, 92%) at some point during the treatment course, resulting in 3-week gap between dosing, which allowed resolution of AEs and continuous therapy. These results lead to the conclusion that administration of the combination may be feasible but require optimization of the q2/3w schedule; and therefore, a new cohort set will explore a q1/3w schedule, i.e. nab-Sirolimus dosing on Day 1 of a 3-week cycle.

Assessment of clinical activity of this combination in STS is a secondary objective. Two of the 13 subjects enrolled in the initial phase I assessment experienced objective partial responses, in

spite of the dose modifications described above. The objective evidence of clinical activity further justifies continued efforts to identify a RP2D.

For further dose-finding studies, nab-Sirolimus will be administered at a starting dose of 30 mg/m^2 every three weeks. Dose escalation will be in steps, either down to 20 or 15 mg/m^2, or incrementally increasing to 45, 60, 75 and 100 mg/m^2 administered on day 1 of a 21-day cycle. This dose range, assuming a BSA of 1.7, yields dose intensity in the range of 8.5-56 mg/wk. While lower than expected in the initially planned dosing schema with q2/3w dosing, this range of dose intensity closely approximates that anticipated with rapalogs. In this study, pazopanib will be given as standard of care. The starting dose was 800 mg orally once daily without food (at least 1 hr. before or 2 hrs. after a meal), and is reduced to 400 mg orally once daily.[52] In our initial experience combining nab-Sirolimus with pazopanib, thrombocytopenia emerged as an apparent dose limiting toxicity when pazopanib was administered the daily dose of 800 mg recommended by the package insert.[52] Thrombocytopenia can be observed with both agents. We noted with several subject that dose reductions of pazopanib to either 400 or 600 mg daily allowed administration of nab-Sirolimus. Of the 2 doses, 400 mg of pazopanib daily appeared to be consistently compatible with nab-Sirolimus, whereas subjects receiving 600 mg daily have required additional dose reductions to 400 mg daily. In our further investigation of this combination, we propose continuing our investigations at a dose of 400 mg of pazopanib daily.

Selection of 400 mg of pazopanib as the starting dose for investigation is reasonable. The package insert for pazopanib recommends that "initial dose reduction should be 400 mg, and additional dose decrease, or increase should be in 200 mg steps based on individual tolerability." In addition, a subgroup analysis of subjects from the original pazopanib registration trial for soft-tissue sarcomas has recently been published.[53] Dose reductions and dose interruptions were reported in 32% (77/240) and 42% (101/240) of those available for analysis. Thus, changes to planned study treatment were frequent due to toxicity from pazopanib. Critically, neither dose reductions nor dose interruptions of pazopanib were associated with inferior progression free survival in the Intent-to-Treat population. Specifically, the authors addressed dosing at 400 and 600 mg daily. Within the study population, those receiving "…a daily dose between 400 and 600 mg had higher…[median Progression-Free Survival] then subjects receiving a daily dose between 600 and 800 mg or a daily dose of less than 400 mg…."[53]. While the longer progression-free survival among those receiving lower doses of pazopanib likely reflects some element of selection bias, the key point is that the lower doses were not associated with worsened progression-free survival, the primary endpoint of the study. Thus, it is reasonable to use a starting dose of 400 mg of pazopanib as we continue to investigate the combination with nab-Sirolimus.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Objectives in Phase 1

Primary

- To identify the recommended phase 2 dose (RP2D) of nab-Sirolimus given IV plus daily oral pazopanib, for subjects with nonadipocytic STS

Secondary

- To evaluate the safety profile of the nab-Sirolimus plus pazopanib combination therapy in advanced nonadipocytic STS

Objectives in Phase 2

Primary

- To evaluate the efficacy of the combination of ABI-009 and pazopanib at the RP2D.

Secondary

- To evaluate the safety profile and to further evaluate the efficacy of nab-Sirolimus plus pazopanib combination therapy

Exploratory

- To study the correlation of clinical outcomes with Next Generation Sequencing and Immunohistochemical analyses of tumor biomarkers, including baseline secreted protein acidic and rich in cysteine (SPARC) expression.
- To assess baseline tumoral immune parameters, including PD-1, PD-L1, mutational burden, and infiltrating lymphocytes, in correlation with clinical outcomes.

2.2. Endpoints

Endpoints in Phase 1

Primary Endpoint

- Dose-limiting-toxicities, as defined in Section 6.4

Secondary Endpoints

- Adverse Events profile (based on National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v5.0) of all subjects and each dose cohort

Endpoints in Phase 2 – Data from both phase 1 and 2

Primary Endpoint

- Progression-free survival rate at 3 months, based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Secondary Endpoint

- Adverse Events profile (based on NCI CTCAE v5.0)

- Median PFS, PFS rate at 6 months, based on RECIST v1.1
- Median OS, OS at 12 months
- Objective response rate based on RECIST v1.1
- Disease control rate, defined as CR plus PR plus SD ≥18 weeks, based on RECIST v1.1
- Duration of response

Exploratory endpoints

- Optional pre-treatment tumor tissue collection (fresh or archival) for biomarker analysis:
  - Correlation of genetic profiling and tissue biomarker analysis with clinical benefit
  - Correlation of baseline SPARC expression with clinical benefit
  - Correlation of baseline immune parameters with clinical benefit

2.3. Study Design

This is an open label, dose-finding, single-arm, prospective phase 1/2 study to identify the RP2D of nab-Sirolimus given IV on either Day 1 and Day 8, or Day 1 only of a 21-day cycle (q2/3w), plus daily oral pazopanib in subjects with advanced nonadipocytic STS. The target DLT rate is ≤20%.

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

Dose-finding Phase 1 Portion of the Study:

Dose levels of nab-Sirolimus will be tested in cohorts of 3 subjects each using the 3+3 dose-finding design. Potential doses of nab-Sirolimus are contained below in Table 1 and Table 2. All cohorts in Table 1 are considered completed. As of this amendment, new enrollments will follow the cohort schedule in Table 2.

Table 1. Day 1 and Day 8 Dosing Levels (Closed/Completed Cohorts)

Dose Levels (Day 1 and Day 8 Dosing)	Protocol Version Added	Planned Starting Dose of ABI-009 in mg/m2	Planned Starting Dose of Pazopanib in mg
-2	1.0	30	800
-1	1.0	45	800
0	1.0	**60**	**800**
1	1.0	75	800
2	1.0	100	800
0B	**3.0**	**60**	**400**
1B	3.0	75	400
2B	3.0	100	400
-1B	3.0	45	400
-2B	3.0	30	400

Table 2 - Day 1 Only Dosing Levels (Amendment 3, Version 4.0 and Later Only)

Dose Levels (Day 1 Only Dosing)	Planned Starting Dose of ABI-009 in mg/m^2	Planned Starting Dose of Pazopanib in mg
-2C	15	400
-1C	20	400
0C	**30**	**400**
1C	45	400
2C	60	400
3C	75	400
4C	100	400

After enrollment of the first 3 dose cohorts (0, -1, and -2) an RP2D had not yet been identified. DLTs were observed in all three of these enrolled cohorts. A total of 16 subjects were consented resulting in 13 enrollments and 3 screen failures. DLTs were observed at all dose levels. A summary of DLTs observed in Cohorts 0, -1, and -2 are provided below in Table 3. Of the 13 subjects enrolled, 11 subjects had nab-Sirolimus and/or pazopanib dose reduced, and three subjects discontinued due to toxicity.

Table 3 - Summary of DLT (Combined Cohorts 0, -1, -2)

Dose Limiting Toxicity	Occurrences
Platelet Count Decrease	8
WBC/Neutrophil Count Decrease	3
Lipase Increase	2
Proteinuria	1
Urinary Tract Infection	1
Mucositis, Oral	1
Alanine Aminotransferase Increase	1

Starting dose of pazopanib must remain consistent within each cohort but may be adjusted during treatment as needed due to toxicity. Protocol Amendment 3 added the option for additional cohorts, and modified the dosing schedule from Day 1/8 to Day 1 only of a 21-day cycle as summarized in Table 1 and Table 2. The starting dose began at 30 mg/m^2 of nab-Sirolimus on Day 1 and pazopanib at 400 mg daily (Cohort 0C). Starting with Amendment 3, the dose finding portion of the study was re-initiated, enrolling 3 subjects at 30 mg/m^2 of nab-Sirolimus and 400 mg of pazopanib with Day 1 dosing only. Cohort 0C and subsequent cohorts followed the same dose-finding and DLT rules outlined below.

The dose levels of nab-Sirolimus will be tested in cohorts of 3 subjects each using the 3+3 dose-finding design. The starting doses for each cohort and potential escalation or de-escalation are

summarized in Table 1 and Table 2. If no DLT is observed during the first 2 cycles at the starting dose in the first 3 subjects, the next dose cohort would enroll subjects at the next highest dose level. If no DLT is observed at the first 3 subjects at the higher dose level, the next dose cohort would continue to escalate to the next highest dose level, up to a maximum of 100 mg/m^2. If 1 DLT is observed any dose cohorts in the first 3 subjects, then the cohort will expand, and an additional 3 subjects will be enrolled at that dose level. The first three subjects in a given cohort must complete the DLT window prior to expanding to include the additional 3 subjects. If ≤1 of 6 subjects experience a DLT at the starting dose or higher, enrollment would continue to the next higher dose level.

If ≥2 subjects experience a DLT at dose level higher than the starting dose, enrollment will be discontinued for that dose cohort and the previous dose level would be declared the MTD. If ≥2 subjects experience a DLT at the starting dose of a given cohort, further enrollment at that dose level will be discontinued and nab-Sirolimus will be reduced to the next planned dose level, to a lower limit dose level of 15 mg/m^2. The MTD of nab-Sirolimus combined with pazopanib is the highest nab-Sirolimus dose level at which ≤1 of 6 (or 0 out of 3) subjects experienced a DLT, thus a target DLT rate of roughly 17%. RP2D is identified based of the totality of safety and efficacy data.

Phase 2 Portion of the Study:

This will be conducted using a Simon's two-stage design. Subjects enrolled in the phase 1 study at the RP2D cohort will be included for response and safety evaluation in phase 2.

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

The study is expected to take approximately 36 months from first subject enrolled to last subject follow-up, including approximately 30 months of enrollment period, an estimated 6 months of treatment (or until treatment is no longer tolerated).

End of Treatment (EOT) for a subject is defined as the date of the last dose of nab-Sirolimus or pazopanib, whichever is later. Single agent continuation of nab-Sirolimus is permitted. If a subject must discontinue nab-Sirolimus treatment, they will be discontinued from the study. End of Treatment Visit for a subject is when safety assessments and procedures are performed after the last treatment of nab-Sirolimus or pazopanib, whichever is later (+/- 3 days).

The 30-Day Follow-Up Visit for a subject is defined as the date when safety assessments and procedures are performed after the End of Treatment visit. The 30-Day Follow-Up visit should occur 30 days (+/- 7 days) after the last dose of nab-Sirolimus or pazopanib, whichever is later.

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

Follow-up period is the on-study time period after the 30-Day Follow-Up Visit. All subjects 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 from the 30-Day Follow-Up Visit (±3 weeks), 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.

3. STUDY POPULATION

3.1. Number of Subjects

Phase 1: up to 49 subjects to identify the MTD, but the MTD may be reached with as few as 22 subjects. Subjects who discontinue from the study prior to completing the DLT assessment window for reasons other than toxicity will be replaced at the same dose level.

Phase 2: In the first stage, at least 23 subjects would be enrolled, including the 3-6 subjects from phase 1 at the RP2D. If at least 11 were progression-free at the 3 months evaluation, then additional subjects would be enrolled to a total of 39 subjects in the Phase 2.

3.2. Inclusion Criteria

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

1. Subjects, ≥18 years old, must have a histologically confirmed diagnosis of nonadipocytic STS that is either metastatic or locally advanced and for which curative therapy is not available, surgery is not a recommended option, and pazopanib treatment is indicated.
2. Subjects must have one or more measurable target lesions by RECIST v1.1, assessed via CT scan or MRI.
3. Clinical or radiological progression or failure due to toxicity on at least 1 prior regimen of systemic treatment for advanced disease. Subjects may not have received more than 4 prior lines of systemic therapy (no more than 2 prior therapies may be combination cytotoxic therapies). Neo-adjuvant/adjuvant/maintenance treatments are not included for this criterion.
4. Last dose of prior therapy must have been completed a minimum of 14 days prior to start of protocol therapy. All ongoing toxicities related to prior therapy must be resolved or grade 1 (except alopecia).
    a. NOTE: Toxicities from prior therapy that have resolved with sequalae (e.g. hypothyroidism) and are asymptomatic or well-controlled are not exclusionary.
5. Subjects must have adequate organ function and blood chemistry and blood count parameters:
    a. Total bilirubin ≤ upper limit of normal (ULN) mg/dL (Subjects with known Gilbert's Syndrome and a Total Bilirubin ≤ 3 mg/dl are permitted to enroll to Phase 2/expansion phase only with sponsor-investigator approval)
    b. AST ≤2.5 x ULN and ALT ≤2.5x ULN
    c. Serum creatinine ≤1.5 x ULN (If serum creatinine is >1.5 mg/dL, calculated creatinine clearance >50 mL/min using the Cockcroft-Gault formula may be included)
    d. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L;
    e. Platelet count ≥100,000/mm^3 (100 × 10^9/L);
    f. Hemoglobin ≥9 g/dL
    g. Serum triglyceride ≤300 mg/dL; serum cholesterol ≤350 mg/dL.

6. Baseline cardiac left ventricular ejection fraction (LVEF) within institutional limits of normal (by echocardiogram or MUGA study).
7. Baseline electrocardiogram with QTc <480 millisecond (Bazett's).
8. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
9. Male or non-pregnant and non-breast feeding female:
    a. Females of child-bearing potential must agree to use highly effective contraception without interruption from initiation of therapy and while on study medication 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 at the end of study treatment. A highly effective method of contraception is defined as one that results in a low failure rate (that is, <1% per year), when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices, sexual abstinence, or a vasectomized partner (Appendix 1).
    b. Male subjects 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 (Appendix 1).
10. Life expectancy of >3 months, as determined by the investigator.
11. Ability to understand and sign informed consent.
12. Willingness and ability to comply with scheduled visits, laboratory tests, and other study procedures.

3.3. Exclusion Criteria

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

1. Soft tissue sarcomas with biology or defined treatments for which pazopanib is not indicated, including adipocytic STS, gastrointestinal stromal tumors (GIST), or Kaposi's sarcoma.
2. Previously received an mTOR inhibitor or angiogenesis inhibitor.
3. Known active uncontrolled or symptomatic central nervous system (CNS) metastases. A subject with controlled and asymptomatic CNS metastases may participate in this study. As such, the subject 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. Subjects with hemoptysis, central nervous system hemorrhage, or gastrointestinal hemorrhage within the last 6 months prior to treatment are excluded due to pazopanib-associated risk of bleeding.
5. Subjects with severe hepatic impairment and active gastrointestinal bleeding.

6. Uncontrolled serious medical or psychiatric illness.
7. Subjects with a currently active second malignancy other than non-melanoma skin cancers, carcinoma in situ of the cervix, resected incidental prostate cancer, or other adequately treated carcinoma-in-situ are ineligible. Subjects are not considered to have a currently active malignancy if they have completed therapy and are free of disease for ≥1 year).
8. 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).
9. No clinically significant gastrointestinal abnormalities including malabsorption syndrome, major resection of the stomach or small bowel that could affect the absorption of study drug, active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, or other gastrointestinal conditions with increased risk of perforation, history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment.
10. Uncontrolled diabetes mellitus as defined by HbA1c >8% despite adequate therapy.
11. Subjects with unstable coronary artery disease, myocardial infarction, or an arterial thromboembolic event during preceding 6 months.
12. Subjects with history of interstitial lung disease and/or pneumonitis, or pulmonary hypertension.
13. Use of strong inhibitors and inducers of CYP3A4 within the 14 days prior to receiving the first dose of nab-Sirolimus. Additionally, use of any known CYP3A4 substrates with narrow therapeutic window (such as fentanyl, alfentanil, astemizole, cisapride, dihydroergotamine, pimozide, quinidine, terfenadine) within the 14 days prior to receiving the first dose of nab-Sirolimus.
14. Active Hepatitis B or Hepatitis C infection.
15. Systemic immunosuppression, including HIV positive status with or without AIDS.
16. Subjects with history of intestinal perforations, fistula, hemorrhages and/or hemoptysis ≤ 6 months prior to first study treatment
17. Subjects with hypercholesterolemia receiving ongoing treatment with simvastatin.
18. Subjects who have had major surgery within 28 days of planned initiation of protocol therapy, or subjects who have/have had wound dehiscence, or other open wounds (including diabetic or infectious wounds) with active wound complications.
19. Subjects with prior history of severe hypersensitivity (Grade 3 or higher) to any known drug excipients, including anaphylaxis to human serum albumin.
20. Subjects with uncontrolled hypertension, defined as an average SBP ≥140 mmHg or an average DBP ≥90 mmHg despite best supportive care measures.

4. TABLE OF EVENTS

The schedule of assessments in Table 4 and Table 5 outline the specific time points for study assessments.

Table 4. Schedule of Assessments (Day 1 and Day 8 Dosing – Subjects enrolled under Amendment 2, v3.0 or earlier)

Assessments [a]	**Baseline Screening** [b]	**Treatment Phase** 21-day (3-week) Cycles Days			**End of Treatment (EOT) Visit** [d]	**30 Day Follow-Up Visit** (+/-7 days)	**Follow-up** Q12W after last visit till study closes or withdrawal of consent – via phone call
		1	8	15 [c]			
Informed Consent	x						
Medical History/Demographics	x						
I/E Criteria	x						
HIV, HBV sAg, HBV cAb, HCV Ab	x						
Urinalysis	x	x			x		
TSH, T3, T4 [e]	x						
Optional Biomarker [f]	x						
Pregnancy Test [g]	x				x	x	
LVEF (echocardiogram or MUGA)	x					x	
12-lead electrocardiogram [h]	x	x [h]					
Physical Exam	x	x	x	x	x	x	
Vital Signs, height, and weight [i]	x	x	x	x	x	x	
Prior / Concomitant Medications and Procedures	x	x	x	x	x	x	
CBC/Differential	x	x	x	x	x	x	
Chemistry Panel	x	x	x	x	x	x	
Lipid Panel [h]	x [h]	x [h]					
Rapamycin level [j]		x [j]	x [j]	x [j]			
ECOG performance status	x	x	x	x	x	x	
CT [k]	x	Every 6 weeks for the first year, then every 12 weeks					
nab-Sirolimus infusion [l]		x	x				
Pazopanib [m]		Daily					
Adverse Event Assessment		Continuous from time of consent to 30 days after last study drug					
Survival Assessment							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. Baseline scans should be completed within 28 days of C1D1, as close to C1D1 as possible.

[c] Day 15 visit is only in Cycle 1 and 2. Cycle 3+ does not have a Day 15 visit.

[d] End of Treatment-phase (EOT) Visit should be within ±3 days of last study treatment.

[e] Thyroid function test to be repeated as needed, based on investigator's opinion.

[f] Subjects who consent for pre-treatment tissue collection for biomarker analysis: either fresh-frozen or formalin-fixed paraffin-embedded (FFPE) tumor blocks or unstained slides (min 10). Fresh tissue collection may only be obtained if clinically feasible and without undue risk to the subject.

[g] For all female subjects of childbearing potential (see Inclusion 5), a serum pregnancy test will be done at screening. A serum or 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 and 30-Day Follow-Up (if applicable). Pregnancy tests conducted after screening will be recorded in the source documentation only.

[h] Single tracing ECG and lipids evaluations are every even cycle (C2, C4, C6, etc.). Only lipid panel at baseline is required to be fasting lipid.

[i] Height is measured only at C1D1. BSA is calculated ONLY on C1D1; to be recalculated only if the weight changes by > 10% in subsequent cycles, at which point the recalculated weight will become the new baseline. Vitals signs to include respiration rate, temperature, systolic/diastolic blood pressure, and pulse. Vital signs to be collected Pre-Dose (within 15 minutes prior to start of infusion) and Post-Dose (+10 minutes from end of infusion).

[j] Rapamycin levels are done locally and for all subjects in Phase 1 at Cycle 1 D8 prior to infusion (within 15 minutes prior to infusion) and on D15 (any time) to assess trough levels as well as in Cycle 2, D1 and D8 prior to infusion and on Day 15 (anytime).

[k] Baseline scans should be done within 4 weeks of C1D1, preferably as close to first treatment as possible. Every 6 weeks from C1D1 (±1 week) for the first year, then every 12 weeks (+/- 1 week) until disease progression or last treatment, regardless of missed or out of window doses. End of Treatment Visit CT/MRI should be performed only for those subjects that discontinue treatment for a reason other than disease progression. All responses must be confirmed by an additional CT scan after 6 weeks. MRI may be used if CT is contra-indicated for a subject. The same mode of imaging at screening must be used consistently throughout the study.

[l] Nab-Sirolimus must be administered after all study specific assessments are done in a visit. Pazopanib dosing is daily and oral and may be dosed anytime in relation to ABI-009 administration. Nursing supervision or documentation of pazopanib dosing on days where nab-Sirolimus is administered is not needed. See Section 6.2 for pazopanib dosing, schedule, and administration. Vital signs to be collected Pre-Dose (within 15 minutes prior to start of infusion) and Post-Dose (+10 minutes from end of infusion). There is a 60-minute observation window post end of infusion for Cycle 1. If a subject completes Cycle 1 with no infusion related reactions, the observation period may be omitted for Cycle 2 and onwards. If at any time the subject experiences an infusion related reaction, the 60-minute post-dose observation period will be reinstated.

[m] Subjects will complete daily drug diary when receiving pazopanib, to be reviewed on Day 1 of each cycle.

Table 5. Schedule of Assessments (Day 1 Only Dosing – Subjects Enrolled under Amendment 3, v 4.0 or later, or Subjects who swap to a D1 only dosing schedule)

Assessments [a]	**Baseline Screening** [b]	**Treatment Phase** 21-day (3-week) Cycles Days			**End of Treatment (EOT) Visit** [d]	**30 Day Follow-Up Visit** (+/-7 days)	**Follow-up** Q12W after last visit till study closes or withdrawal of consent – via phone call
		1	8	15 [c]			
Informed Consent	x						
Medical History/Demographics	x						
I/E Criteria	x						
HIV, HBV sAg, HBV cAb, HCV Ab	x						
Urinalysis	x	x			x		
TSH, T3, T4 [e]	x						
Optional Biomarker [f]	x						
Pregnancy Test [g]	x				x	x	
LVEF (echocardiogram or MUGA)	x					x	
12-lead electrocardiogram [h]	x	x [h]					
Physical Exam	x	x	X	x	x	x	
Vital Signs, height, and weight [i]	x	x	X	x	x	x	
Prior / Concomitant Medications and Procedures	x	x	X	x	x	x	
CBC/Differential	x	x	X	x	x	x	
Chemistry Panel	x	x	X	x	x	x	
Lipid Panel [h]	x [h]	x [h]					
Rapamycin level [j]		x [j]	x [j]	x [j]			
ECOG performance status	x	x	X	x	x	x	
CT [k]	x	Every 6 weeks for the first year, then every 12 weeks					
Nab-Sirolimus infusion [l]		x					
Pazopanib [m]		Daily					
Adverse Event Assessment		Continuous from time of consent to 30 days after last study drug					
Survival Assessment							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. Baseline scans should be completed within 28 days of C1D1, as close to C1D1 as possible.

[c] Day 15 visit is only in Cycle 1 and 2. Cycle 3+ does not have a Day 15 visit.

[d] End of Treatment-phase (EOT) Visit should be within ±3 days of last study treatment.

[e] Thyroid function test to be repeated as needed, based on investigator's opinion.

[f] Subjects who consent for pre-treatment tissue collection for biomarker analysis: either fresh-frozen or formalin-fixed paraffin-embedded (FFPE) tumor blocks or unstained slides (min 10). Fresh tissue collection may only be obtained if clinically feasible and without undue risk to the subject.

[g] For all female subjects of childbearing potential (see Inclusion 5), a serum pregnancy test will be done at screening. A serum or 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 and 30-Day Follow-Up (if applicable). Pregnancy tests conducted after screening will be recorded in the source documentation only.

[h] Single tracing ECG and lipids evaluations are every even cycle (C2, C4, C6, etc.). Only lipid panel at baseline is required to be fasting lipid.

[i] Height is measured only at C1D1. BSA is calculated ONLY on C1D1; to be recalculated only if the weight changes by > 10% in subsequent cycles, at which point the recalculated weight will become the new baseline. Vitals signs to include respiration rate, temperature, systolic/diastolic blood pressure, and pulse. Vital signs to be collected Pre-Dose (within 15 minutes prior to start of infusion) and Post-Dose (+10 minutes from end of infusion).

[j] Rapamycin levels are done locally and for all subjects in Phase 1 at Cycle 1 Day 1 Post-Dose (within +10 minutes from end of infusion), Cycle 1 Day 1 – 24-hour Post-Dose (optional, +/- 2 hours),), Cycle 1 Day 8 and Day 15 anytime, as well as in Cycle 2 Day 1 Pre-Dose (within 15 minutes prior to infusion) and on Cycle 2 Day 8 and Day 15 (anytime).

[k] Baseline scans should be done within 4 weeks of C1D1, preferably as close to first treatment as possible. Every 6 weeks from C1D1 (±1 week) for the first year, then every 12 weeks (+/- 1 week) until disease progression or last treatment, regardless of missed or out of window doses. End of Treatment Visit CT/MRI should be performed only for those subjects that discontinue treatment for a reason other than disease progression. All responses must be confirmed by an additional CT scan after 6 weeks. MRI may be used if CT is contra-indicated for a subject. The same mode of imaging at screening must be used consistently throughout the study.

[l] Nab-Sirolimus must be administered after all study specific assessments are done in a visit. Pazopanib dosing is daily and oral and may be dosed anytime in relation to ABI-009 administration. Nursing supervision or documentation of pazopanib dosing on days where nab-Sirolimus is administered is not needed. See Section 6.2 for pazopanib dosing, schedule, and administration. Vital signs to be collected Pre-Dose (within 15 minutes prior to start of infusion) and Post-Dose (+10 minutes from end of infusion). There is a 60-minute observation window post end of infusion for Cycle 1. If a subject completes Cycle 1 with no infusion related reactions, the observation period may be omitted for Cycle 2 and onwards. If at any time the subject experiences an infusion related reaction, the 60-minute post-dose observation period will be reinstated.

[m] Subjects will complete daily drug diary when receiving pazopanib, to be reviewed on Day 1 of each cycle

5. PROCEDURES

5.1. Screening Evaluations

This study will be conducted at the University of Washington, Seattle, USA; other centers may be considered to join. Each subject who enters into the screening period for the study receives a unique subject identification number before any study-related procedures are performed. The subject identification number will be assigned. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

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

Before subjects may be entered into the study, the Sponsor-Investigator requires a copy of the written IRB/IEC approval of the protocol, informed consent form, and all other subject 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 subject prior to performing any study-specific procedures. All subjects must personally sign and date the consent form before commencement of study-specific procedures.

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be obtained ≤28 days prior to enrollment. Baseline imaging should be obtained as close to initiation of protocol therapy as possible. Any questions regarding subject eligibility should be directed to the Sponsor-Investigator 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 found in Table 4 and Table 5.

- Demographics (if allowed by local regulations, date of birth, sex, race, and ethnicity)
- Physical examination (including medical/cancer history, ECOG performance status assessment, weight)
- Prior/concomitant medications and procedures evaluation to include all medications taken ≤28 days prior to date of informed consent
- Vital signs (temperature, sys/dias blood pressure, respiration rate, and pulse)
- ECG
- Left ventricular ejection fraction (LVEF, by echocardiogram or MUGA)
- Local Laboratory Assessments: chemistry, complete blood count (CBC with differential, platelet count, urinalysis, pregnancy test (women of child-bearing potential, includes tubal ligations), thyroid panel (TSH, T3, T4), HIV, hepatitis B surface antigen, hepatitis B core antibody (HBV cAb), hepatitis C antibody, lipids
- CT or MRI, must be done within 28 days of C1D1, but preferably should be done as close to the day of enrollment as possible

- Optional: Subjects who consent for pre-treatment tissue collection for biomarker analysis shall provide either fresh-frozen or formalin-fixed paraffin-embedded (FFPE) tumor blocks or unstained slides (min 10). Fresh tissue collection may only be obtained if clinically feasible and without undue risk to the subject.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria and an enrollment packet has been completed. The investigator is to document this decision and date, in the subject's medical record and in/on the electronic case report form (eCRF).

5.2. Treatment Period

A subject is considered enrolled on study day 1 when the IP, nab-Sirolimus, is first administered. Nab-Sirolimus is to be administered after all other protocol-specified pre-dose assessments have been performed during each visit that it is required. Subjects will continue therapy until disease progression, unacceptable AEs, or withdrawal of consent.

5.2.1. Day 1 Assessment

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

- Physical examination
- Weight assessment
- Height assessment (only in C1)
- Concomitant medication and procedures evaluation
- Vital signs (temperature, sys/dias blood pressure, respiration rate, and pulse)
- ECOG performance status
- CBC with differential
- Clinical chemistry panel
- ECG and lipid panel (every even visit, i.e. C2, C4, etc.)
- Urinalysis
- Adverse Event assessment
- Rapamycin levels (only in Phase 1, C1 and C2)
- 60-minute observation window post end of infusion for Cycle 1. If a subject completes Cycle 1 with no infusion related reactions, the observation period may be omitted for Cycle 2 and onwards. If at any time the subject experiences an infusion related reaction, the 60-minute post-dose observation period will be reinstated.

All Day 1 evaluations for Cycle 1 may be omitted if screening evaluations are performed within 72 hours of Cycle 1 Day 1. All Day 1 laboratory assessments and physical examination for Cycle 2+ may be performed up to 72 hours prior to planned treatment.

5.2.2. Day 8 Assessment

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

- Physical examination
- Weight assessment
- Vital signs (temperature, sys/dias blood pressure, respiration rate, and pulse)
- Concomitant medication and procedures evaluation
- CBC with differential
- Clinical chemistry panel
- Adverse Event assessment
- Rapamycin levels (only in Phase 1, C1 and C2)

For subjects receiving treatment on Day 8, all Day 8 laboratory assessments and physical examination may be performed up to 72 hours prior to planned treatment.

5.2.3. Day 15 Assessment

The following assessments will be performed on Day 15 of Cycle 1 and 2 only.

- Physical examination
- Weight assessment
- Vital signs (temperature, sys/dias blood pressure, respiration rate, and pulse)
- Concomitant medication and procedures evaluation
- CBC with differential
- Clinical chemistry panel
- Adverse Event assessment
- Rapamycin levels (only Phase 1)

Table 6. Analyte Listing

Chemistry	Hematology	Urinalysis	Other Labs
Sodium	WBC	Specific gravity	Pregnancy test
Potassium	RBC	pH	HIV
Bicarbonate	Hemoglobin	Blood	HBV sAg
Chloride	Hematocrit	Protein	HBV cAb
Total protein	MCV	Glucose	HCV Ab
Albumin	MCH	Ketones	Total Cholesterol
Calcium	MCHC	Microscopic	HDL
Magnesium	RDW		LDL
Phosphorus	Platelets		Triglyceride
Glucose	Differential:		TSH, T3, T4
BUN	-Neutrophils		Rapamycin
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 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/MRI scans to be performed at the following frequency:

- ≤4 weeks prior to C1D1 (as close to C1D1 as possible) (screening)
- Followed by every 6 weeks from C1D1 (± 1 week) for the first year; then every 12 weeks (± 1 week) until disease progression or unacceptable toxicity. End of Treatment Visit CT/MRI should be performed only for those subjects 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 for clinical management of subjects on study will be assessed at the local site. If an initial observation of objective response (CR or PR) is made, a confirmation scan should be done at 6 weeks after initial observation.

5.3. End of Treatment Visit Assessment

The EOT Visit is a safety follow-up visit that is to be performed after the last dose of nab-Sirolimus or pazopanib, whichever is later (±3 days). 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 in Table 4 and Table 5.

- Physical examination (including ECOG Performance Status assessment, weight)
- Vital signs (e.g., blood pressure, pulse, respiration rate, temperature)
- Concomitant medication and procedures evaluation
- Adverse Event assessment
- Laboratory assessments: chemistry, CBC with differential, platelet count, pregnancy test (women of child-bearing potential, includes tubal ligations), urinalysis
- Imaging Assessment: CT/MRI is to be performed at the end of study visit only for those subjects that discontinue treatment for a reason other than disease progression per RECIST v1.1

5.4. 30-Day Follow Up Visit

Active subject participation is complete after the 30-Day Follow-Up Visit. The 30-Day Follow-Up Visit is a safety follow-up visit that is to be performed 30 days after the last dose of protocol therapy (±7 days). All efforts should be made to conduct this visit. If it is not possible to conduct the 30-Day Follow-Up Visit, documentation of efforts to complete the visit should be provided.

The following procedures will be completed at the 30-Day Follow-Up Visit as designated in the Schedule of Assessments in Table 4 and Table 5.

- Physical examination (including ECOG Performance Status assessment, weight)
- Vital signs (e.g., blood pressure, pulse, respiration rate, temperature)
- Concomitant medication and procedures evaluation
- Adverse Event assessment
- Laboratory assessments: chemistry, CBC with differential, platelet count, pregnancy test (women of child-bearing potential, includes tubal ligations)
- Left ventricular ejection fraction (LVEF, by echocardiogram or MUGA)

5.5. Rapamycin Trough levels

Assays for rapamycin will be performed on subjects in the dose-finding (phase 1) portion of the study, who received nab-Sirolimus during C1 and C2, to determine trough levels, assessed via local lab. The rapamycin sampling schedule is outlined below, based on dosing schedule.

- **Q2/3W Dosing:**
    - Cycle 1:

- C1D8: Prior to treatment (within 15 minutes pre-infusion)
- C1D15: Day 15 collection any time

- Cycle 2:
  - C2D1: prior to treatment (within 15 minutes pre-infusion)
  - C2D8: prior to treatment (within 15 minutes pre-infusion)
  - C2D15: Day 15 collection any time

- **Q1/3W Dosing:**
  - Cycle 1:
    - C1D1: End of infusion (within +10 minutes of EOI) and Optional 24-hour post dose (Day 2, +/- 2 hours),
    - C1D8: Day 8 collection any time
    - C1D15: Day 15 collection any time
  - Cycle 2:
    - C2D1: prior to treatment (within 15 minutes pre-infusion)
    - C2D8: Day 8 collection any time
    - C2D15: Day 15 collection any time

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

Post-treatment survival time and any subsequent anticancer therapy information status will be monitored approximately every 12 weeks (±3 weeks) from 30-Day Follow Up 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. Nab-Sirolimus

6.1.1. Nab-Sirolimus/Pazopanib Dosage, Administration, and Schedule

Treatment with nab-Sirolimus combined with pazopanib will continue until disease progression, unacceptable toxicity, or withdrawal of consent. 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.

Table 7 - Day 1 and Day 8 Dosing Levels (Closed – Enrolled under Am2, v3.0 or earlier)

Dose Levels (Day 1 and Day 8 Dosing)	Planned Starting Dose of nab-Sirolimus in mg/m2	Planned Starting Dose of Pazopanib in mg
-2	30	800
-1	45	800
0	60	800
1	75	800
2	100	800
0B	60	400
1B	75	400
2B	100	400
-1B	45	400
-2B	30	400

Table 8 - Day 1 Only Dosing Levels

Dose Levels (Day 1 Only Dosing)	Planned Starting Dose of nab-Sirolimus in mg/m^2	Planned Starting Dose of Pazopanib in mg
-2C	15	400
-1C	20	400
0C	**30**	**400**
1C	45	400
2C	60	400
3C	75	400
4C	100	400

6.1.2. Nab-Sirolimus Dose Modification and Stopping Rules

If treatment cannot be administered on the planned visit date, nab-Sirolimus may be administered ±3 days from the scheduled date. Prior to nab-Sirolimus administration, subjects must meet the following hematological requirements for dosing on every dosing day:

- ANC ≥1.5 x 10^9/L
- Platelet count ≥100 x 10^9/L
- Hemoglobin ≥9.0 g/dL

The treatment may be held (delayed) up to 21 days due to toxicity. Treatment may also be interrupted for situations other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 21 days of the scheduled interruption, unless otherwise discussed with the Sponsor-Investigator. The reason for interruption should be documented in the subject's study record.

If the dose held or missed was to be Day 1 of the next cycle, the next cycle will not be considered to start until the day the first dose is actually administered to the subject.

If the subject is dosing on a q2/3w schedule, if the dose held or missed was to be Day 8, that week becomes the week of rest. Next dose becomes Day 1 of a new cycle. The cycle with the missed Day 8 dose would become 14 days long versus the normal 21-day cycle. If the cycle with the missed Day 8 dose is Cycle 1 or Cycle 2, the Day 15 visit would also be omitted. If the subject is dosing on a q1/3w schedule, a cycle is not considered to have begun until the subject receives the Day 1 dose. If the subject misses a Day 8 or Day 15 visit, the cycle continues without interruption and the visits are recorded as missed. The following cycle is considered to have begun when the subject receives their next dose.

In the event of clinically significant AE in any part of the study, treatment may be held, 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 21 days of stopping therapy, then treatment may be restarted.

Dose reduction of nab-Sirolimus to the next lower dose level should be considered as clinically indicated for subjects who are receiving nab-Sirolimus at above the lowest dose level. In phase 1, once a dose has been reduced, it may not be increased to the previous level. In phase 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 re-escalated to the previous dose level.

The maximum delay between a missed scheduled dose and the next one (whichever dose was missed) should not be longer than 21 days. If a dose delay over 21 days is required, Sponsor-Investigator Approval is required, otherwise the subject should be discontinued. If Sponsor-Investigator approval is granted, a secondary approval is required to restart study treatment after ≥21 days of interruption. If the toxicity does not resolve to at least grade 1 in less than 21 days, withdrawal from the treatment with the IP is recommended. However, if the investigator and

Sponsor-Investigator agree that further treatment would benefit the subject, treatment can continue with at least 1 dose level dose reduction. Adjustments to the dosing schedule may be made, at investigator discretion, according to Section 6.3.

Table 9. Dose Modification Algorithms for Adverse Events Possibly Related to ABI-009 (See also Table 10 and Table 11)

System/Organ	Adverse Event	CTCAE Grade v5.0	Dose modification Algorithm
Mucosa [a]	Stomatitis, mucosal inflammation	Grade 2 or 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.
		Grade 4	Permanently discontinue ABI-009.
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	Hyperlipemia (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		

		Grade ≥3	Hold ABI-009 until grade 2 or less, restart 1 dose level lower.
	Hypokalemia	Grade 2	Withhold treatment until Grade ≤1, restart at the same dose level. If recurs, restart 1 dose level lower.
		Grade ≥3	Withhold treatment until Grade ≤1, restart at 1 dose level lower. If recurs, permanently discontinue ABI-009.
Respiratory events	Pneumonitis, bronchiolitis obliterans, and/or organizing pneumonia, Interstitial Lung Disease	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 discontinue ABI-009. 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. Subjects will be withdrawn from the study if they fail to recover to ≤ grade 1 within 3 weeks. For grade 4 noninfectious pneumonitis, discontinue ABI-009.
Infections and infestations	Infections	Grade 3	Withhold treatment until resolved, then restart at 1 dose level lower. If recurs, permanently discontinue ABI-009.
		Grade 4	Withhold treatment until resolved. Restart at 1 dose level lower,. If recurs, or permanently discontinue ABI-009.
General Disorders	Hemorrhage	Grade 2 or 3	Withhold treatment until Grade ≤1, then resume at 1 dose level lower. If recurs, permanently discontinue ABI-009.

		Grade 4	Permanently discontinue ABI-009.
Other Adverse Reactions	Other Adverse Reactions	Grade 3	Withhold treatment until Grade ≤1, then restart at the same dose level. If recurs, restart at 1 dose level lower.
		Grade 4	Permanently discontinue ABI-009.

[a] Subjects who develop or at risk for stomatitis, a steroid mouthwash (10 mL dexamethasone 0.1 mg/mL oral solution four times daily) could be considered.

6.1.3. Nab-Sirolimus Hepatotoxicity Stopping Rules

Subjects with abnormal hepatic laboratory values (i.e., ALP, AST, ALT, total bilirubin TBL) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis may meet the criteria for withholding or permanent discontinuation of nab-Sirolimus as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

6.1.3.1. Criteria for Permanent Discontinuation of nab-Sirolimus Due to Potential Hepatotoxicity

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

- Total bilirubin >2 x 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 total bilirubin values include, but are not limited to:
  - Hepatobiliary tract disease
  - Viral hepatitis (e.g., 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 (e.g., Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (e.g., 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 (e.g., rhabdomyolysis, hemolysis)

6.1.3.2. Criteria for Conditional Withholding of nab-Sirolimus Due to Potential Hepatotoxicity

For subjects 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 subjects with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of nab-Sirolimus:

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

AST or ALT elevation
>8 x ULN at any time >5 x ULN but <8 x ULN for ≥2 weeks >5 x ULN but <8 x ULN and unable to adhere to enhanced monitoring schedule ≥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: Total bilirubin >3 x ULN at any time
- OR: Alk Phos >8 x ULN at any time

Nab-Sirolimus should be withheld pending investigation into alternative causes of DILI. Re-challenge 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.

6.2. Pazopanib

6.2.1. Dose Levels for Pazopanib

Pazopanib starting dose may be at either 400 or 800 mg daily. Pazopanib decrease should be in 200-mg steps,[52] for pazopanib-related AEs that require dose reductions (Section 6.2.2). Pazopanib dosing may not be reduced below 200 mg daily. Subjects requiring a dose reduction below 200 mg daily should discontinue pazopanib therapy. Pazopanib dosing may not be increased above 800 mg daily. Dose modification algorithms for specific toxicities are detailed below in Section 6.2.2. For all other Grade 3 or 4 non-hematologic toxicities (except alopecia, nausea, or vomiting) that are at least in part attributable to the study drug, the dose should be held until the toxicity resolves to ≤ Grade 1. Treatment should then be resumed at a reduction of one dose level. For recurrent grade 3 or 4 toxicity, the study drug should again be held until the toxicity resolves to ≤ Grade 1 and then reintroduced at another dose level reduction. If the toxicity has abated with reduction of the dose and dose re-escalation is considered safe by the investigator, the study drug dose can then be increased step-wise back to the pre-event dose (in 200 mg increments, after monitoring for 14 days at each dose level to ensure that toxicity did not recur or worsen).

Pazopanib is absorbed orally, with median time to achieve peak concentrations of 2 to 4 hours after the dose. If a dose is missed, it should not be taken if it is less than 12 hours until next dose. For pazopanib dose reduction and stopping rules, please refer to Table 10 and Table 11.

6.2.2. Pazopanib Dose Modification and Stopping Rules

Pazopanib is dosed continuously. Modifications to pazopanib dosing should follow the table below. Additional dose reductions may be made outside of the defined parameters below, at

investigator discretion. Dose levels may not be re-escalated outside of the defined guidelines. All dose reductions or re-escalations must be made in 200 mg increments, unless otherwise specified.

Table 10. Dose Modification Algorithms for Adverse Events Possibly Related to Pazopanib (See also Table 9 and Table 11)

System/Organ	Adverse Event	CTCAE Grade v5.0	Dose modification Algorithm
Skin/Mucosa	Palmar-plantar Erythrodysesthesia Syndrome	Grade 2	Hold pazopanib until resolved to ≤ grade 1, then resume with one dose level reduced. If recurrent, consider further dose reduction or discontinuation.
		Grade 3	Permanently discontinue pazopanib.
Lab Abnormalities	Proteinuria	UPC Ratio ≥ 2.0 and < 3.0 or urine protein ≥ 2.0 g/24 hours and < 3.0	Hold pazopanib until proteinuria resolves to UPC < 2.0 or urine protein < 2.0 g/24 hours, then resume pazopanib at current dose level.
		For UPC Ratio ≥ 3.0 and < 4.0 or urine protein ≥ 3.0 g/24 hours and < 4.0	Hold pazopanib until proteinuria resolves to UPC < 2.0 or urine protein <2.0 g/24 hours. Once resolved, resume pazopanib with one dose level reduced.
		For UPC Ratio ≥ 4.0 or Nephrotic Syndrome	Discontinue pazopanib.
	Hyperthyroidism / Hypothyroidism	Grade 3 or Grade 4	Discontinue pazopanib.
	Elevated Creatinine	Grade 2	Delay pazopanib until toxicity resolves to Grade 1 or better, then resume pazopanib with one dose level reduction.
		Grade 3-4	Discontinue pazopanib.

Cardiac Toxicity	Hypertension	Grade 3 (Systolic ≥ 160, Diastolic ≥ 100)	Hold pazopanib until grade ≤ 2, then resume pazopanib at 1 dose level reduction. HOWEVER, if the subject requires hospitalization for management of symptomatic systolic BP > 180 or diastolic BP > 110, permanently discontinue pazopanib.
		Grade 4	Permanently discontinue pazopanib.
	Venous Thrombosis	Grade 2-3, requiring anticoagulation	Delay pazopanib. If the planned duration of full dose anticoagulation is ≤ 2 weeks, omit pazopanib until anticoagulation is completed, then resume pazopanib at same dose. If the planned duration of full dose anticoagulation is > 2 weeks, pazopanib may be restarted at same dose during anticoagulation if all of the following are met: - The subject must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin or be on a stable dose of LMWH prior to restarting pazopanib. - The subject must not have any pathological condition that carries a high risk of bleeding. - The subject must not have had any hemorrhagic events while on study.
		Grade 4	Permanently discontinue pazopanib.
		Recurrent / Worsening Thrombosis	If venous thromboembolic events worsen or reoccur after resumption of pazopanib, permanently discontinue pazopanib.
	Arterial Thromboembolic Events	Any Grade	Discontinue pazopanib.
	ECG QTc Interval Prolonged (Bazett's)	Grade 3	Delay pazopanib until ≤ grade 1, then resume pazopanib with one dose level reduction.

		Grade 4	Discontinue pazopanib.
Other	CNS or Pulmonary Hemorrhage	Grade 2 or Greater	Permanently discontinue pazopanib.
	Non-CNS, Non-Pulmonary bleeding	Grade 2	Delay pazopanib until ≤ grade 1, then resume with one dose level reduction.
		Grade 3 or 4	Permanently discontinue pazopanib.
	Fistula, perforations, bowel obstruction, or wound dehiscence	Any Grade	For any grade perforation of any organ, GI leak, or any fistula, discontinue pazopanib. For any grade bowel obstruction requiring medical intervention, delay pazopanib until obstruction resolves completely, and then resume pazopanib at the previous dose. For obstruction requiring surgery delay pazopanib until full recovery from surgery, then resume pazopanib at the previous dose. For wound dehiscence requiring medical or surgical intervention discontinue pazopanib.
	Hemolytic Uremic Syndrome / Thrombotic Thrombocytopenic Purpura	Any Grade	For any grade of hemolytic uremic syndrome (thrombotic microangiopathy) or thrombotic thrombocytopenic purpura, discontinue pazopanib.
	Other Non-Hematologic Grade 3 or 4 Toxicity	Grade 3 or 4	For other grade 3 or 4 non-hematologic toxicity not described above, (excluding nausea, vomiting, and diarrhea; unless refractory to anti-emetics and/or antidiarrheals) and considered at least possibly related to treatment, delay pazopanib treatment until toxicity improves to ≤ grade 1, then resume treatment with one dose level reduction.

6.3. Dosing Schedules (D1 vs D1/D8)

Nab-Sirolimus may be dosed on either Day 1 or Day 1/Day 8 of a 21-day cycle, based on which cohort a subject is assigned to. Subjects initially assigned to Day 1/Day 8 dosing may switch to a Day 1 only dosing schedule at investigator discretion, after completion of at least two full cycles of treatment.

Subjects initially enrolled on a Day 1 only schedule may not switch the dosing schedule. Once a subject has switched a dosing schedule, this change is considered permanent and they may not switch back.

6.4. Dose Limiting Toxicity

Dose-limiting toxicities will be assessed in the first 2 cycles (2, 3-week cycles).

A DLT is defined as any Grade 3 or greater AE, at least possibly related to either or both nab-Sirolimus and pazopanib. Only toxicities with a clearly identified and documented alternative explanation may be deemed non-DLT. Dose-limiting toxicities include any death not clearly due to underlying disease or extraneous causes, or persistent intolerable nonhematologic AE of any grade that requires dose reduction or permanent discontinuation of the study-drug, in the opinion of the investigator.

The following adverse events may be excluded from being considered a DLT:

- Grade 3 nausea/vomiting or diarrhea for less than 72 hours, with adequate antiemetic and other supportive care;
- Grade 3 fatigue for less than 1 week;
- Grade 3 or higher electrolyte abnormality that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions.
- Lab abnormalities that have no clinical sequelae (e.g. febrile neutropenia from low ANC, bleeding from thrombocytopenia, etc.) and resolve to grade 1 or better within 7 days will not be considered a DLT.

Nab-Sirolimus dose modification guidelines are outlined in Table 9 and Table 11 for clinically significant toxicities that are deemed related to nab-Sirolimus.

6.5. Dose Modification Algorithms for Adverse Events Possibly Related to nab-Sirolimus and Pazopanib

Table 11 - Dose Modification Algorithms for Overlapping Adverse Events Possibly Related to nab-Sirolimus and Pazopanib (See also Table 9 and Table 10)

System/Organ	Adverse Event	CTCAE Grade v5.0	Dose Modification Algorithm
Hematologic toxicity	Thrombocytopenia, Anemia	Grade 2	**Nab-Sirolimus:** Nab-Sirolimus can be administered if meeting the following hematological requirements: platelets >100 × 10^9/L and hemoglobin ≥8 g/dL. **Pazopanib:** No changes to pazopanib dosing.
		Grade 3-4	**nab-Sirolimus:** Hold nab-Sirolimus immediately for the remainder of that cycle. Repeat blood collection within 3 days. Nab-Sirolimus can resume once meeting following requirements: platelet count >100 × 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. **Pazopanib:** Delay pazopanib until platelets ≤ grade 1, resume pazopanib with one dose level reduction.
	Neutropenia, Febrile or Afebrile	Grade 3	**nab-Sirolimus:** Hold nab-Sirolimus. Repeat blood collection within 3 days. Nab-Sirolimus can resume once meeting following requirements: absolute ANC ≥1.5×10^9/L. For 2nd and subsequent events, drug will be restarted at a reduced dose; G-CSF may be given as deemed indicated. **Pazopanib:** Delay pazopanib until ≤ grade 2, and then resume pazopanib at the current dose level.
		Grade 4	**Nab-Sirolimus:** Hold nab-Sirolimus. Repeat blood collection within 3 days. Nab-Sirolimus can resume once meeting following requirements: absolute ANC ≥1.5×10^9/L. For 2nd and subsequent events, drug will be restarted at a reduced dose; G-CSF may be given as deemed indicated. **Pazopanib:** Delay pazopanib until ≤ grade 2, then resume pazopanib with one dose level reduction.

Hepatic Toxicity	Hepatic Failure	Grade 3	**Nab-Sirolimus:** See Section 6.1.3.1and 6.1.3.2. Subjects with ALT/AST > 3 x ULN, or Total Bilirubin > 3 x ULN, or Alk Phos > 8 x ULN are recommended for withholding of nab-Sirolimus. **Pazopanib:** Discontinue pazopanib.
	ALT, AST, **or** Bilirubin Elevation	Grade 2	**Nab-Sirolimus:** See Section 6.1.3.1 and 6.1.3.2. Subjects with ALT/AST > 3 x ULN, or Total Bilirubin > 3 x ULN, or Alk Phos > 8 x ULN are recommended for withholding of nab-Sirolimus. **Pazopanib:** Continue pazopanib, but monitor weekly until ALT, AST, and bilirubin return to ≤ grade 1.
		Grade 3-4	**Nab-Sirolimus:** See Section 6.1.3.1and 6.1.3.2. Subjects with ALT/AST > 3 x ULN, or Total Bilirubin > 3 x ULN, or Alk Phos > 8 x ULN are recommended for withholding of nab-Sirolimus. **Pazopanib:** Delay pazopanib until improved to ≤ grade 1. Restart treatment with one dose level reduction of pazopanib.
	ALT/AST **and** Bilirubin (Grade 2 or greater ALT/AST elevation with concurrent Grade 2 or greater bilirubin elevation)	Grade 2+	**Nab-Sirolimus:** Discontinue nab-Sirolimus. **Pazopanib:** Discontinue pazopanib.
Other Adverse Reactions	Other Adverse Reactions	Grade 3	Withhold treatment until Grade ≤1, then restart at the same dose level. If recurs, restart at 1 dose level lower.

		Grade 4	Permanently discontinue nab-Sirolimus.

6.6. Overdose

6.6.1. Nab-Sirolimus

On a per dose basis, an overdose is defined as 10% over the protocol-specified dose of nab-Sirolimus or pazopanib assigned to a given subject, 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 (+10 minutes) for each infusion.

6.6.2. Pazopanib

No MTD was reached in the dose escalation study of pazopanib administered as a single agent at repeated doses of up to 2000 mg/day (Study VEG10003). Systemic exposure to pazopanib at steady-state appeared to plateau at doses greater than 800 mg once daily. Increases in the daily pazopanib dose above 800 mg in the fasted state resulted in a small or no increase in mean systemic exposure to pazopanib.

7. STUDY DRUG MANAGEMENT

7.1. Description of Study Drugs

7.1.1. Nab-Sirolimus Packaging, Labeling, and Storage

Nab-Sirolimus will be supplied Aadi Bioscience in single-use vials as lyophilized product. Each single-use 50-mL vial will contain 100 mg rapamycin 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 nab-Sirolimus should be stored in a refrigerator (2°-8°C; 36°-46°F) in original cartons to protect from light. Reconstituted nab-Sirolimus 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 nab-Sirolimus and reconstituted nab-Sirolimus should be stored in an area free of environmental extremes and must be accessible only to study personnel.

Temperature records for nab-Sirolimus must be made available to Aadi Bioscience or Sponsor-Investigator approved monitoring teams for verification of proper study drug storage.

7.2. Nab-Sirolimus and Pazopanib Accountability, Disposal, and Compliance

7.2.1. Nab-Sirolimus

For nab-Sirolimus, only completely unused study drug vials should be retained by the site until a representative from Aadi Bioscience or Sponsor-Investigator approved study monitor 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 nab-Sirolimus the Sponsor-Investigator, or designee, shall record the dispensing of study drug to subjects and any remaining study drug after dosing in a study drug accountability record. The study drug record will be made available to monitoring 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 the Sponsor-Investigator and Aadi Bioscience or their designee and a plan for resolution will be documented.

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

7.2.2. Pazopanib

Pazopanib is managed as a prescribed medication and administered as standard of care, according to institutional practices.

Accurate recording of all pazopanib administration will be made in the appropriate section of the subject's CRF and source documents. Subjects will complete a daily drug diary recording time of self-administration of pazopanib dosing. This diary will be reviewed at Day 1 of each cycle. Pharmacy accountability and dispensation records will not be maintained for pazopanib.

7.3. Nab-Sirolimus Reconstitution and Use

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

Nab-Sirolimus will be reconstituted by appropriate study personnel following the Pharmacy Manual and administered to the subject at the study site. The investigator or qualified designee will calculate the BSA of the subject in order to determine the total amount of nab-Sirolimus to be administered.

7.4. Receipt and Return of nab-Sirolimus

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 28 days prior to signing of informed consent through the 30-Day Follow Up Visit. Therapy name including indication, dose, frequency, route, start date and stop date will be recorded on each subject's CRF(s).

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.

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheas, and analgesics, and other care as deemed appropriate, in accordance with their institutional guidelines. WBC 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.

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 Sponsor-Investigator can approve such use.

The following medications or non-drug therapies are prohibited:

- Other anti-cancer therapy while on treatment in this study.
- Antiretroviral drugs (subjects with known HIV are ineligible for study participation).
- Herbal remedies (e.g., St. John's wort) unless approval is granted by the Sponsor-Investigator.
- Rapamycin is metabolized primarily by CYP3A4. Drugs that are strong inhibitors or inducers of CYP3A4 may only be used under special circumstances (e.g., 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)

within the 14 days prior to receiving the first dose of ABI-009. Other medications may be allowed with approval of the Sponsor-Investigator.

- 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

Endpoints in Phase 1

Primary Endpoint

- DLT, as defined in Section 6.4.

Secondary Endpoint

- Adverse Events profile (based on NCI CTCAE v5.0) of all subjects and each dose cohort

Endpoints in Phase 2 – Data from both phase 1 and 2

Primary Endpoint

- Progression-free survival (PFS) rate at 3 months, based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Secondary Endpoints

- Adverse Events profile (based on NCI CTCAE v5.0)
- Median PFS, PFS rate at 6 months, based on RECIST v1.1
- Median OS, OS at 12 months
- Objective response rate (ORR) based on RECIST v1.1
- Disease control rate, defined as CR plus PR plus SD ≥18 weeks, based on RECIST v1.1
- Duration of response

Exploratory endpoints

- Correlation of baseline immune parameters with clinical benefit
- Correlation of genetic profiling and optional tissue biomarker analysis with clinical benefit
- Correlation of baseline SPARC expression with clinical benefit

9.2. Safety Analysis

The safety analysis set includes all treated subjects.

Safety and tolerability will be monitored through continuous reporting of treatment emergent and TRAEs, AEs of special interest, laboratory abnormalities, and incidence of subjects 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 subject signs informed consent until 30 days after the last dose of protocol therapy. Adverse events will be graded by NCI CTCAE v5.0.

Physical examination, vital signs, laboratory assessments (e.g., serum chemistry, hematology), and ECOG performance status will be monitored and reviewed per institutional standards. 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

Subjects will be evaluated for ORR, DCR, or progressive disease (PD) by CT imaging. Contrast enhanced MRI can also be used if CT is contra-indicated, as long as the same modality is used throughout the study. Baseline scan results can be accepted from outside institutions but must be done within 4 weeks of starting therapy and must include (as clinically indicated), chest abdominal, and pelvic CT or MRI. The first response assessment by CT or MRI scans documenting target lesions will be done 6 weeks after C1D1 and should be repeated every 6 weeks for the first year, then every 12 weeks thereafter until the end of treatment. If an initial observation of objective response (CR or PR) is made, a confirmation scan should be done at 6 weeks after initial observation. Scans should continue on schedule regardless of delays in nab-Sirolimus dosing.

The efficacy endpoints of ORR (CR + PR), DCR (CR, PR, and SD ≥18 weeks), and PFS will be determined by a local radiologic assessment using RECIST v1.1. After the 30-Day Follow Up Visit, subjects will be followed for survival every 12 weeks (±3 weeks), or more frequently as needed, until death, withdrawal of consent, or the study closes, whichever is the earliest.

The number and percentage of subjects achieving response ORR, DCR, or progressed will be summarized.

Median PFS and OS will be summarized using Kaplan-Meier (KM) analysis. Analysis of other efficacy endpoints, PFS rate at 3 and 6 months, and OS rate at 12 months will be assessed via descriptive statistics, for the number of subjects is expected to be small.

Response duration usually will be measured from the time of initial response until documented tumor progression.

9.4. Exploratory Analysis

Presence/level of expression of immune parameters, gene profiling, and SPARC will be analyzed and their relationship to clinical responsiveness will be explored.

9.5. Sample Size Considerations

Phase 1: Up to 49 subjects to identify the MTD, but the MTD may be reach with as few as 22 subjects. Subjects who discontinue from the study prior to completing the DLT assessment window for reasons other than toxicity will be replaced at the same dose level.

Phase 2: For sample size determination, we assume the following:

1. For aa-TKI/pazopanib monotherapy in nonadipocytic STS, the baseline anticipated PFS rate at 3 months is approximately 50%[49].

2. An increase by the combination therapy of the PFS rate at 3 months to 70% would be considered clinically meaningful.

3. This is an exploratory phase 1/2 study. Thus, type I (false positive) errors are less worrisome than type II (false negative). We therefore set alpha=0.1 for rejection of null hypothesis. Beta is set at 0.1 (90% power), again, to minimize type II errors.

4. We are using a Simon's two-stage study design for the phase 2 efficacy evaluation.

In the first stage, at least 23 subjects would be enrolled, including the 3-6 subjects from phase 1 at the RP2D. If at least 11 were progression-free at the 3 months evaluation, then additional subjects would be enrolled to a total of 39 subjects in Phase 2. If at least 23 were progression-free at 3 months, then this would provide preliminary data to indicate that the combination was active and worthy of further evaluation in this clinical setting.

Subjects who fail to become evaluable for the secondary endpoint with a follow-up CT/MRI will be replaced.

To assess the primary endpoint, we elected to use a Simon's minimax design[52]. This was selected to be most conservative in evaluable subjects needed to answer the primary hypothesis. In this case, a total of 39 evaluable subjects will be required in the phase II component of the study, if it extends through both stages.

This type of design has greater statistical power than a single-arm design. For example, a single arm trial enrolling the same number of subjects (n=39) would only have a statistical power of 82%, versus 90% for the proposed design. Alternatively, it would require 50 evaluable subjects in a single-arm design to achieve the desired 90% power.

9.6. Primary Analysis

Primary analysis for this study will occur after all subjects have either completed the study or completed 12 months of treatment. Subjects 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 Nab-Sirolimus

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

More details on the known precautions, warnings, and AEs of rapamycin and rapalogs are found in the Rapamune® and Torisel® Package Inserts.[45,46]

10.2. Toxicities of Pazopanib

Per the Prescribing information, the most common AEs in subjects with advanced STS (greater than or equal to 20%) are fatigue, diarrhea, nausea, decreased weight, hypertension, decreased appetite, hair color changes, vomiting, tumor pain, dysgeusia, headache, musculoskeletal pain, myalgia, gastrointestinal pain, and dyspnea.[52]

10.3. 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
- Action taken

The AE toxicity grading scale used will be the NCI CTCAE Version 5.0.

10.4. Serious Adverse Events

10.4.1. 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 subject at immediate risk of death)
- requires in-patient 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 (e.g., 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 (e.g., 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 subject's medical record.

10.4.2. Reporting Procedures for Serious Adverse Events

All SAEs that are drug-related and unexpected must be reported by the Sponsor-Investigator to their IRB in writing, and to the FDA within 15 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 within 24 hours of the Sponsor-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 Sponsor-Investigator or treating 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 30 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 subject 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 Sponsor-Investigator is responsible for informing the IRB/EC of the SAE and providing them with all relevant initial and follow-up information about the event. The Sponsor-Investigator must keep copies of all SAE information on file including correspondence with Aadi Bioscience and the IRB/EC.

10.5. Pregnancy and Breastfeeding Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject 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 subject 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 the female subject consents to allow the study team to follow the pregnancy to completion or termination.

If a lactation case occurs while the female subject 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 subject 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 subject 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 subject 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 subject withdraws from treatment.

Subjects 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. Decision to Withdraw or Terminate Subject's Participation Prior to Study Completion

The Sponsor-Investigator can decide to withdraw a subject(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.

Subjects may be eligible for continued treatment with Aadi Bioscience's Investigational Product 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

The Informed Consent Document must be reviewed and approved by the Sponsor-Investigator, Aadi Biosciences, and the IRB prior to use. Updates to the informed consent document are to be communicated to Aadi Bioscience prior to submitting for IRB review and approval. For research participants who do not speak and/or read English, a short-form consent should be used. The short form is used to document that the elements of informed consent were orally presented to the research participant by a qualified interpreter. Both the short form and a written summary, which may also be the IRB-approved English-language informed consent document, must be submitted filed in the subject chart.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject 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 acquisition of informed consent is to be documented in the subject's medical records, and the informed consent form to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. 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 subject.

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

12.2. Institutional Review Board/Independent Ethics Committee

A copy of the protocol, informed consent form, other written subject 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 subjects into the study and shipment of Aadi Bioscience IP.

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

The Sponsor-Investigator is responsible for obtaining annual IRB approval [IRBs only]/renewal [IRBs and IECs] throughout the duration of the study. Copies of the Sponsor-Investigator's reports and the IRB continuance of approval must be sent to Aadi Bioscience.

12.3. Subject Confidentiality

The Sponsor-Investigator must ensure that the subject's confidentiality is maintained for documents submitted to Aadi Bioscience.

- Subjects are to be identified by a unique subject 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 subject identification number, include the age at time of enrollment.
- For SAEs reported to Aadi Bioscience, subjects are to be identified by their unique subject 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 (e.g., 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 Sponsor-Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review the subject'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 subject to permit such individuals to have access to his/her study-related records, including personal information.

12.4. Protocol Amendments

If Sponsor-Investigator amends the protocol, agreement from Aadi Bioscience must be obtained. The IRB must be informed of all amendments and give approval. The Sponsor-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 Sponsor-Investigator reserve the right to terminate the Sponsor-Investigator's participation in the study according to the study contract. The Sponsor-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 Sponsor-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. Responsibilities for Data Collection

The Sponsor-Investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (in Table 3, 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.

13.4. Sample Storage and Destruction

Any blood or tumor sample collected can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be no less than single coded prior to being shipped from the site for analysis, or storage. Tracking of samples will be independent of the subject's identification number for the study. Results are stored in a secure database to ensure confidentiality.

Results from this analysis are to be documented and maintained but are not necessarily reported as part of this study.

The records should be retained by the Sponsor-Investigator according to ICH, local regulations, or as specified in the Clinical Trial Agreement, whichever is longer; but at a minimum, all study documentation must be retained for 2 years after the last marketing application approval in an

ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of nab-Sirolimus.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the Sponsor-Investigator. Following the request from the subject, the Sponsor-Investigator is to provide the sponsor with the required study and subject number so that any remaining blood or tumor samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed.

The Sponsor-Investigator is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject, at the end of the storage period, or as appropriate (e.g., the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.

14. QUALITY CONTROL AND QUALITY ASSURANCE

14.1. Study Monitoring

Institutional support of trial monitoring will be in accordance with the FHCC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCC Clinical Research Support (CRS) coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCC Scientific Review Committee (SRC) and the FHCC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating subjects. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

14.2. Audits and Inspections

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Aadi Bioscience's Inspection of site facilities (e.g., pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

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.

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17. APPENDIX 1 - WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

17.1. Definitions

17.1.1. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
      Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
    - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes.

17.2. Contraception Guidance for Females of Childbearing Potential

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 3 months after last treatment. Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are User Dependent
Failure rate of < 1% per year when used consistently and correctly.[a]

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
    - oral
    - intravaginal
    - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
    - oral
    - injectable

Highly Effective Methods That are User Independent

- Implantable progestogen-only hormonal contraception associated with inhibition of

Ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in related to the duration of the study and the preferred and usual lifestyle of the participant.
    - It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests as specified in study calendar.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Less Than Highly Effective Contraceptive Methods That are User Dependent

Failure rate of > 1% per year when used consistently and correctly.
- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously.
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action

Unacceptable Methods of Contraception
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicide only
- Lactation amenorrhea method (LAM)

17.3. Contraception Guidance for Males of Childbearing Potential

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.

- Male participants are required to use a condom for study duration and until the end of relevant systemic exposure defined as 3 months after last systemic dose.

- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 3 months after last systemic dose.

- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 3 months after last systemic dose.

- Refrain from donating sperm for the duration of the study treatment and for 3 months after last systemic dose.

- Male participants may experience testicular side effects, such as reduced sperm production rates, reduced sperm concentrations, decreased epididymal weights, atrophy and degeneration of the testes with aspermia (no sperm production), hypospermia (low or reduced sperm production), and cellular changes in the epididymis (a tube within the testes that transports sperm).