Cover Page

Study PAH-001, NCT02587325

Protocol Including Statistical Analysis

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Protocol Title
A phase 1/1b clinical trial of ABI-009, an mTOR inhibitor, for patients with pulmonary arterial hypertension (PAH)

A phase 1/1b clinical trial of ABI-009, an mTOR inhibitor, for patients with pulmonary arterial hypertension (PAH)

INVESTIGATIONAL PRODUCT (IP):	**ABI-009**
PROTOCOL NUMBER:	**PAH-001**
VERSION HISTROY:	
Original:	**December 10, 2015**
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IND NUMBER:	**128090**
SPONSOR NAME/ ADDRESS:	Aadi Bioscience, Inc. 17383 Sunset Blvd., Suite A250 Pacific Palisades CA 90272

MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

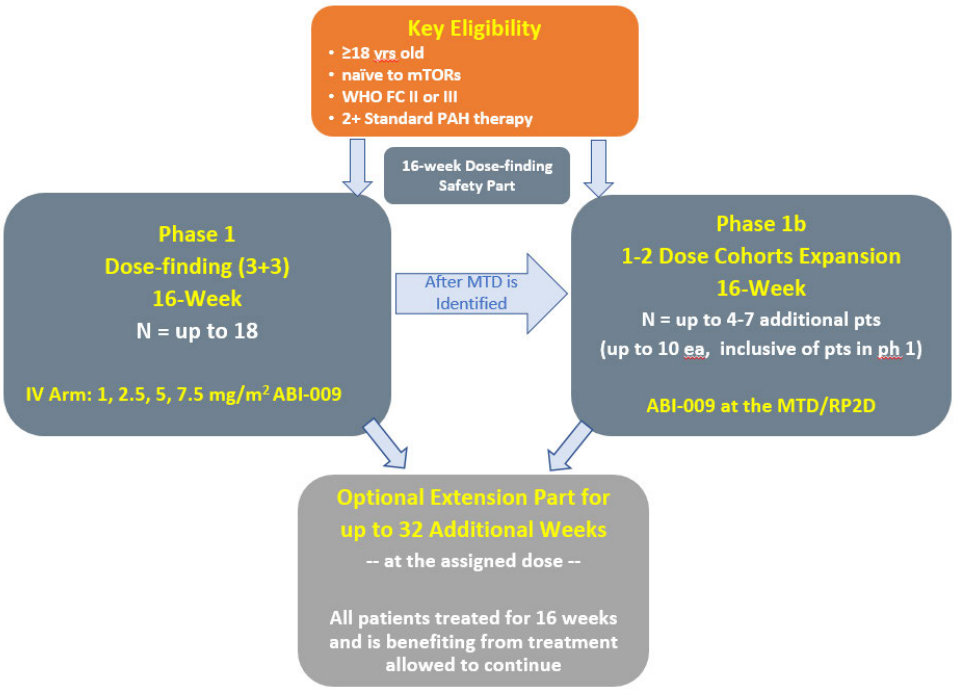
Aadi OFFICIAL SIGNATURE PAGE

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

PROTOCOL SYNOPSIS

Investigational Product (IP)	ABI-009, sirolimus albumin-bound nanoparticles for injectable suspension, *nab*-sirolimus, formerly *nab*-rapamycin
Study Title	A phase 1/1b dose-finding clinical trial evaluating the safety of ABI-009 as antiproliferative therapy for patients with pulmonary arterial hypertension (PAH)
Protocol Number	PAH-001
Phase	1
Indication	Intravenous (IV) ABI-009 as antiproliferative therapy for patients with pulmonary arterial hypertension (PAH). The patient population is adults with PAH (World Health Organization [WHO] Function Class II and III), a subset of patients known to have a poor prognosis and worse survival.
Study Objectives	**Objectives** This phase 1/1b study will involve dose escalation to determine the maximum tolerated dose (MTD) and safety of 16 weeks of therapy (Dose-finding Safety Part) followed optionally by up to 32 additional weeks of therapy (Extension Part) with ABI-009 IV in patients with PAH who are WHO Functional Class II or III despite best available background therapy. The MTD will be determined on the basis of the results from the safety evaluation. After the MTD is reached in phase 1, there will be up to 2 cohort expansions in phase 1b at the MTD and/or one alternate dose or schedule to determine the recommended phase 2 dose. The expanded cohorts will be such that up to 10 patients for each of the cohorts will be enrolled to obtain additional safety and efficacy data, inclusive of patients from phase 1. The recommended phase 2 dose, which may differ from the MTD, will be determined on the basis of results from safety, efficacy, pharmacologic and correlative studies in this phase 1/1b study. **Exploratory Objectives** • To evaluate pharmacokinetic information that may be correlated with safety and/or efficacy observations.
Study Endpoints	**Endpoints** **Primary Endpoints** • MTD, dose-limiting toxicities (DLT, defined in 7.2.1), and safety profile of 16 weeks of ABI-009 given IV.

	• Safety profile of the up to 48 weeks of treatment **Secondary Endpoints** The following will be measured before treatment at baseline and at week 17 (after 16 weeks of treatment in the Dose-finding Safety Part): • pulmonary vascular resistance (PVR) by right heart catheterization • pulmonary artery pressure (PAP) • pulmonary capillary wedge pressure (PCWP) • central venous pressure (CVP) The following will be measured at baseline, 5, 9, 13, and 17 weeks: • Doppler-echocardiographic assessments of right ventricular structure and function • 6-minute walk distance (6MWD) • WHO functional class • Pulmonary function test The following will be measured at every 8 weeks during the additional 32 weeks of the Extension Part (ie, at week E9, E17, E25, and E33): • 6MWD • WHO Functional Class • Pulmonary function test **Exploratory Endpoints** • Pharmacokinetic (PK) profile and trough level of sirolimus for weekly treatment during the 16 weeks of Dose-finding Safety Part and every other week treatment during the Extension Part • Measurement of brain naturetic peptide (BNP), C-reactive protein (CRP) and troponin levels, indicative of right ventricular strain, at baseline, 5, 9, 13, and 17 weeks, and for BNP, every 8 weeks in the optional Extension Part (E9, E17, E25, E33) • Change from baseline to week 17, and to weeks E17 and E33 in the Extension Part in 36-Item Short Form Health Survey (SF-36) physical functioning scale • Change from baseline to week 17, and to weeks E17 and E33 in the Extension Part in emPHasis10 questionnaire

STUDY DESIGN	This study is a prospective phase 1/1b, single arm, open-label, multi-institutional study to determine the MTD, safety, and preliminary efficacy of IV ABI-009 in patients with PAH. Patients who, in the opinion of the investigator and Safety Committee, tolerate ABI-009 well and achieve clinical benefit during the first 16-week treatment (Dose-finding Safety Part), and for whom there are no alternative therapies available, may opt to continue therapy for an additional 32 weeks at their assigned dose or lower, if permanently reduced (optional Extension Part). The Extension Part should start within 4 weeks after the last dose of the 16-week Dose-finding Safety Part. The study will be conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCPs). 
Sample Size	Phase 1: Up to 24 patients will be enrolled using the standard 3+3 dose escalation design in the dose-finding phase. Phase 1/b: Additional 4-7 patients will be enrolled in up to 2 expansion cohorts to obtain a total of 10 patients at each of the 2 dose levels (inclusive of patients from phase 1), the MTD and/or an alternate dose or schedule.
Study Population	Patients with PAH (WHO Functional Class II or III) in spite of 2 or more standard PAH therapies, assessed locally in each institution for enrollment.

Inclusion Criteria	1) Male or female age ≥18 years old with a current diagnosis of WHO Group 1 PAH including idiopathic pulmonary arterial hypertension (IPAH), heritable pulmonary arterial hypertension (HPAH), drug and toxin induced PAH, or PAH associated with connective tissue disease, or congenital heart defects (repaired greater than 1 year prior to Screening) 2) Must meet following hemodynamic definition prior to initiation of study drug a. Mean PAP of ≥25 mmHg b. PCWP or left ventricular end diastolic pressure (LVEDP) of ≤15 mm c. PVR >5 mmHg/L/min (Woods unit) 3) Functional class II or III according to the WHO set forth at the Dana Point Classification 2008 Meeting 4) On 2 or more specific standard PAH therapies (for ≥8 consecutive weeks and at stable dose for ≥4 consecutive weeks) unless documented inability to tolerate 2 standard therapies 5) Meet the following criteria determined by pulmonary function tests completed at screening: a. Forced expiratory volume in one second (FEV1) ≥55% of predicted normal b. FEV1: forced vital capacity (FVC) ratio ≥0.60 6) 6MWD ≥150 meters and ≤450 meters 7) Male or non-pregnant and non-breast feeding female: • Females of child-bearing potential must agree to use effective contraception without interruption from 28 days prior to starting IP 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 after the end of study treatment. A second form of birth control is required even if she has had a tubal ligation. • Male patients must practice abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study. A second form of birth control is required even if he has undergone a successful vasectomy. 8) Ability to provide written informed consent by the patient or legal guardian
Exclusion Criteria	1) History of heart disease including left ventricular ejection fraction (LVEF) ≤40% or clinically significant valvular constrictive or atherosclerotic heart disease (myocardial infarction, angina, cerebrovascular accident) 2) History of malignancy in 2 years prior to enrollment 3) Pulmonary hypertension (PH) belonging to groups 2 to 5 of the 2013 Nice classification

	4) Current or recent (<3 months) use of intravenous inotropic or vasopressor agents for the treatment of PAH 5) Recent (<2 months) PAH-related hospital admission 6) History of allergic reactions attributed to compounds of similar chemical or biologic composition including macrolide (eg, azithromycin, clarithromycin, dirithromycin, and erythromycin) and ketolide antibiotics 7) Uncontrolled diabetes mellitus as defined by HbA1c >8% despite adequate therapy 8) Uncontrolled hyperlipidemia (serum triglyceride ≥300 mg/dL) 9) Serum cholesterol ≥350 mg/dL 10) Surgery within 3 months of start date of study drug 11) Baseline cytopenias: a. Absolute Neutrophil Count ≤1.5 x 10^9/L b. Hemoglobin ≤9 g/dL c. Platelet count ≤100,000/mm^3 12) Baseline liver disease: ALT/AST, total bilirubin, alkaline phosphatase ≥1.5 x ULN 13) Creatinine clearance (Cockroft formula) ≤30 mL/min 14) Inability to attend scheduled clinic visits 15) Prior use of an mTOR inhibitor within previous 6 months from enrollment 16) Previous lung transplant 17) Known Human Immunodeficiency Virus (HIV) 18) Active Hepatitis B or Hepatitis C 19) Uncontrolled intercurrent illness that in the opinion of the investigator would limit compliance and tolerance to study requirements (eg, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, diabetes, uncontrolled hypertension, coronary artery disease, or psychiatric illness/social situations) 20) Concomitant enrollment in another investigational treatment protocol for PAH 21) Use of strong inhibitors and inducers of CYP3A4 within the 14 days prior to receiving the first dose of ABI-009. Additionally, use of any known CYP3A4 substrates with narrow therapeutic window (such as fentanyl, alfentanil, astemizole, cisapride, dihydroergotamine, pimozide, quinidine, terfanide) within the 14 days prior to receiving the first dose of ABI-009
Length of Study	The study is expected to take approximately 30 months from first patient enrolled to last patient follow-up, including approximately 18 months of enrollment period, up to 16 weeks of Dose-finding Safety Part (or until treatment is not tolerated), , followed by an optional Extension Part for up to 32 weeks, and at least 28 days follow-up after

	the last dose either in the Dose-finding Safety or Extension Part, whichever is later. The End of Study (EOS) defined as either the date of the last visit of the last patient to complete the study, or the date of receipt of the last data point from the last patient that is required for primary, secondary, and/or exploratory analysis, as pre-specified in the protocol. End of Treatment is defined as the date of the last dose of ABI-009. End of Treatment Visit is when efficacy and safety assessments and procedures are performed after the last treatment. • For a patient who does not complete the 16-week treatment, EOT Visit must occur within 4 weeks (±7 days) after the last dose of ABI-009. • For patients who complete the 16-week treatment, the final efficacy and safety assessments and procedures (EOT Visit) are performed at week 17. Follow-up period is the on-study time period for at least 28 days after the last treatment either in the Dose-finding Safety Part or optional Extension Part, whichever is later. All patients that discontinue study drug and have not withdrawn full consent to participate in the study will continue in the follow-up phase for survival and therapy. Follow up will continue up to 1 year, approximately every 12 weeks (±3 weeks), until withdrawal of consent, or the study closes, whichever is the earliest. This evaluation may be made by record review and/or telephone contact.
Study Treatments	This phase 1/1b study will have a 16-week Dose-finding Safety Part to identify recommended phase 2 dose and evaluate the safety and efficacy profile of weekly ABI-009 (via dose-finding and dose-expansion cohorts), followed by an optional 32-week Extension Part to obtain additional safety and efficacy data on longer term treatment with ABI-009. **16 weeks of Dose-finding Safety Part** In the dose-finding phase 1 portion of the study, 4 dose levels of ABI-009 will be tested in cohorts of 3 patients each (1, 2.5, 5, and 7.5 mg/m^2, see Table 1), using the 3+3 dose escalation design. There will be no intra-patient dose escalation allowed. Escalation to the next dose level with a new cohort of 3 patients will occur after no DLT was observed in the first treatment cycle of 4 weeks. If a DLT occurs in a cohort, additional 3 patients will be recruited to the cohort. If no further DLTs occur, then a new cohort of 3 patients at the next higher dose level can be enrolled. If 2/6 patients at dose level 1a experience a DLT, then that cohort will be closed to further enrollment and the study may be

terminated. If 2/6 patients at dose levels 2a, 3a, or 4a experience a DLT, then the previous dose level is considered the MTD.

It is estimated that a maximum of up to 24 patients will be required to achieve the MTD; however, MTD could be reached with as few as 9 patients. Patients will be allowed to dose reduce by one dose level for reasons of toxicity, with a maximum of 2 dose reductions allowed for a patient. At the lowest dose level, a dose reduction of 25% will be allowed.

Table 1: Doses of ABI-009 Given Weekly

Dose Level	1a	2a	3a	4a
ABI-009 Weekly Dose (mg/m^2)	1	2.5	5	7.5

Note: The original protocol (dated December 10, 2015) included dose levels 1 (10 mg/m^2), 2, (20 mg/m^2) and 3 (30 mg/m^2), and dose level -1 (5 mg/m^2).

After the MTD is reached, in phase 1b, there may be up to 2 cohort expansions at the MTD and/or one alternate dose or schedule to determine the recommended phase 2 dose.

Optional 32-week Extension Part

Patients who, in the opinion of the investigator and Safety Committee, tolerate ABI-009 well and achieve clinical benefit during the Dose-finding Safety Part, and for whom there are no alternative therapies available, may opt to continue therapy (optional Extension Part) for up to an additional 32 weeks at their assigned dose or lower, if permanently reduced. The optional Extension Part should start within 4 weeks after the last dose of the 16-week Dose-finding Safety Part.

Key Safety Assessments

Overview of Key Safety Assessments During Dose-finding Safety and Optional Extension Part

Physical exam including a complete set of vital signs and clinical laboratory monitoring will be conducted weekly on the day of drug infusion. Patients will be closely monitored for adverse events (AEs). Safety and tolerability will be monitored through continuous reporting of treatment-emergent and treatment-related AEs, AEs of special interest (identified based on previous experience in a similar population), laboratory abnormalities, and incidence of patients experiencing dose modifications, dose delay/dose not given, dose interruptions, and/or premature discontinuation of IP due to an AE. All AEs will be recorded by the investigator from the time the patient signs informed consent

	until 28 days after the last dose of IP and those serious adverse events (SAEs) made known to the investigator at any time thereafter that are suspected of being related to IP. Toxicities will be graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAEs) v4.1. Physical examination, vital sign, laboratory assessments (eg, serum chemistry, hematology) will be monitored. All SAEs (regardless of relationship to ABI-009) will be followed until resolution. Laboratory analysis will be performed as per study schedule.
Key Efficacy Assessments	**Overview of Key Efficacy Assessments During the 16-week Dose-finding Safety Part** The following will be measured before treatment at baseline and at 17 weeks (after 16 weeks of treatment in the Dose-finding Safety Part): • PVR by right heart catheterization • PAP • PCWP • CVP The following will be measured at baseline, 5, 9, 13, and 17 weeks: • Doppler-echocardiographic assessments of right ventricular structure and function • 6MWD • Pulmonary function test **Overview of Key Efficacy Assessments During the Optional Extension Part** The following will be measured every 8 weeks form the start of the Extension Part (ie, at week E9, E17, E25, and E33): • 6MWD • WHO Functional Class • Pulmonary function test
Statistical Considerations	The dose-escalation portion of this clinical study will enroll up to 24 patients. Dose escalation will follow the 3+3 rule to establish the MTD. Three planned dose levels are to be used (Table 1). The minimum number of patients required to establish the MTD is 9 patients. In case there is a dose limiting toxicity at each of the 4 dose levels, each cohort of 3 patients will be expanded to 6 patients, in which case a total of 24 patients will be treated.

	After the MTD is achieved, up to 2 cohorts (at the MTD and/or one alternate dose or schedule) will be expanded to enroll a total of 10 patients in each cohort to further evaluate safety and preliminary utility (potential for clinical efficacy) of ABI-009 in the treatment of PAH. **Safety Analyses:** The treated population will be the analysis population for all safety analyses. Adverse events will be coded using the Medical Dictionary for Medical Activities (MedDRA) and grouped by their system organ class and preferred term. Summary tables will include the number and percentage of patients with treatment-emergent and treatment-related AEs, AEs of special interest, SAEs, and incidence of patients experiencing dose modifications, dose delay/dose not given, dose interruptions, and/or premature discontinuation of IP due to an AE.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABI-009	nanoparticle albumin-bound sirolimus
AE	Adverse events
ALT/AST	alanine aminotransferase / aspartate aminotransferase
CBC	complete blood count
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CVP	central venous pressure
DLT	dose-limiting toxicity
EOS	End of study
EOT	end of treatment
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practices
HPAH	heritable pulmonary arterial hypertension
ICH	International Conference on Harmonisation
IPAH	idiopathic pulmonary arterial hypertension
LVEF	left ventricular ejection fraction
MTD	maximum tolerated dose
NCI	National Cancer Institute
PAH	pulmonary arterial hypertension
PAP	pulmonary artery pressure
PAVSCM	pulmonary artery vascular smooth muscle cell
PCWP	pulmonary capillary wedge pressure
PK	pharmacokinetic
PVR	pulmonary vascular resistance
SAE	serious adverse events
SF-36	36-Item Short Form Health Survey
ULN	upper limit of normal
WHO	World Health Organization
6MWD	6-minute walk distance

1. INTRODUCTION

1.1. Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a rare, debilitating and fatal disease for which there is currently no cure. The disease specifically affects the endothelium and smooth muscle of the pulmonary arteries, with cellular constriction and hyperproliferation leading to vascular remodeling, stiffening, and narrowing. The progressive increase in pulmonary vascular resistance (PVR) over time increases right ventricular afterload and leads to right ventricular dilation and failure. Progressive reduction in cardiac output from right ventricular failure leads to decreased exercise capacity and death [1]. The current FDA approved therapies for PAH target vascular factors that regulate vasodilation and vasoconstriction and include the prostacyclin analogues, endothelin-1 receptor antagonists, phoshodiesterase 5 (PDE-5) inhibitors and soluble guanylate cyclase (sGC) stimulators. These agents alone and in combination improve exercise capacity and delay the time to clinical worsening but do not significantly prolong survival [2, 3] or specifically address the underlying hyperproliferation of the endothelial and smooth muscle cells in the pulmonary arteries.

Recent human clinical trials using the antiproliferative agent imatinib (Novartis), suggests that new approaches targeting vascular endothelial and smooth muscle proliferation is an efficacious approach for patients with PAH [4]. While imatinib was effective in treating PAH, i.e., it significantly decreased PVR and increased 6-minute walking distance (6MWD) [4], the clinical development of imatinib was halted by the sponsor (Novartis) for high risk of severe toxicity, specifically, subdural hematoma. Therefore, there is a great need for new safer 'antiproliferative' agents to be evaluated in the treatment of PAH.

Recent *in vitro* studies [5, 6], animal models [6, 7], new translational data using human PAH patient samples [6] and a clinical case report [8] suggest strongly that rapamycin (sirolimus), an allosteric mammalian target of rapamycin (mTOR) inhibitor, can prevent and reverse PAH. mTOR signaling is hyperactivated in PAH, and inhibiting this pathway is a promising novel treatment approach. mTOR inhibition resulted in strong antiproliferative activity, particularly in vascular smooth muscle cells, which was demonstrated by Goncharov (2014) [6], Houssaini (2013) [9], and Kyrmskaya et al (2011) [5]. In addition, the suppression of mTOR has been described to affect the canonical hypoxia-inducible factor (HIF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and p27 cell cycle pathways, which are known to be central to PAH pathogenesis [5, 10, 11].

nab-Sirolimus (ABI-009, Aadi, Pacific Palisades, CA) is a novel albumin-bound nanoparticle form of sirolimus that has shown excellent antiproliferative activity in tumor xenograft models as well as a porcine restenosis model with strong evidence of vascular smooth muscle cell suppression and high accumulation in the lung. A recent phase 1 clinical trial in patients with solid tumors showed evidence of clinical activity, low toxicity, and favorable pharmacokinetic (PK) profile [12]. The safety profile of ABI-009, despite higher doses, compared very favorably to oral sirolimus and rapalogs in this patient population (historical comparison). In this application, we propose the clinical testing of

ABI-009, the long acting nanoparticle human albumin-bound formulation of sirolimus, as a novel targeted systemic therapy for PAH.

The significance of this study lies in addressing a debilitating disease with a new antiproliferative approach specifically targeting the disease biology.

Pulmonary arterial hypertension is classified into subgroups including idiopathic PAH (IPAH), familial, and PAH associated with other conditions (APAH). Idiopathic PAH accounts for at least 40% of PAH cases, 4% are familial type, and the remaining cases are APAH (>50%).

The number of patients with PAH in the US is estimated to be 30,000; however, PAH is widely recognized as a disease that is underdiagnosed [13]. Pulmonary arterial hypertension has an incidence of 2.4 cases per million people per year, and an estimated prevalence of between 15 to 50 cases per million people [14]. The prevalence of PAH in certain at-risk groups is substantially higher: in patients with systemic sclerosis it is 7% to 12% [15, 16]. PAH is considered a complex, multidisciplinary medical condition that, if left untreated, can be life threatening with 3-year survival after diagnosis at only about 50%. The mean age at diagnosis is 36 years, but PAH can affect people from 20 to 90 years old. Women are affected approximately twice as often as men.

Treatment for PAH and the Rationale for using ABI-009

The FDA has approved several drugs to date for the treatment of PAH, all of which are vasodilators and offer only symptomatic relief. The administration routes include oral, inhaled, subcutaneous (SC), and intravenous (IV). They belong to 4 classes based on the mechanism of action: Prostacyclin derivatives (epoprostenol, iloprost and treprostinil) are potent vasodilators; endothelin receptor antagonists (ERAs, eg. bosentan, macitentan and ambrisentan) block the binding of endothelin-1 to the receptor and inhibit the endothelin effects of vasoconstriction and smooth muscle growth; phosphodiesterase 5 (PDE-5) inhibitors (sildenafil and tadalafil) block the breakdown of cyclic guanosine monophosphate and enhance nitric oxide-mediated vasodilation; and soluble guanylate cyclase (sGC) stimulators (riociguat).

These current approved PAH therapeutics mainly function as vasodilators and do not address the endothelial and smooth muscle cell hyperproliferation aspect of the disease. Thus, an entire aspect of the biology of this disease has not been effectively explored. Importantly, current treatments provide largely symptomatic relief with temporary improvements in right heart function and exercise capacity; invariably PAH patients' disease progresses, even on combination therapy. The use of ABI-009 as a safe, efficacious and targeted anti-proliferative therapy represents a unique opportunity to help patients with debilitating PAH, already on maximal approved therapy, with the possibility of modifying the course of the disease. An effective treatment could have a large clinical impact on the lives of these patients.

Imatinib, a tyrosine kinase inhibitor targeting PDGF, Bcr/Abl and c-Kit, is the only antiproliferative drug that has been tested in PAH in late-stage clinical trials. In a phase 3 study, imatinib demonstrated efficacy, meeting the efficacy endpoints of improved 6MWD

and reduction in PVR, but an increase in unexpected rates of intracranial bleeding and high dropout rates due to AEs have led the sponsor (Novartis) to stop development of this drug [4]. These studies provide proof of principle that a vascular remodeling anti-proliferative agent can be efficacious in PAH patients, however, safety remains the key issue for such approaches.

This study will present a unique opportunity to develop a targeted molecular antiproliferative therapy for PAH. Recent evidence strongly suggests that the mTOR pathway is important in PAH development [5, 6], and sirolimus is efficacious in models of PAH [7, 8]. Systemic (IV) ABI-009, exhibits preferential lung uptake [17] with a favorable PK profile for PAH (unlike oral mTOR agents) and a favorable safety profile in a human phase 1 oncology trial [12].

1.2. ABI-009 Background

1.2.1. Rapamycin (Sirolimus) and Rapalogs

Sirolimus is a crystalline powder with the empirical formula C51H79NO13 and a molecular weight of 914.17. Sirolimus is a protein kinase inhibitor that is used for immunosuppression in transplant patients and is under investigation as a cancer treatment. Sirolimus inhibits the mammalian target of rapamycin (mTOR), a regulatory protein kinase in cancer that recognizes high stress levels, including depleted nutrient levels and states of hypoxia [18]. 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, stress, 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 [19]. 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. Sirolimus and its analogs (rapalogs) function as allosteric inhibitors of mTORC1 and are currently used in the treatment of advanced renal cell carcinoma and other tumors [20].

1.2.2. ABI-009 (*nab*-Sirolimus)

The nanoparticle albumin-bound sirolimus (*nab*-sirolimus, ABI-009) is freely dispersible in saline and is suitable for intravenous administration and have produced favorable safety profile and produced evidence of efficacy in patients with metastatic solid tumors [12].

The 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 [21]. This suggests that a *nab* formulation of sirolimus may also produce similar advantages over the standard sirolimus.

1.2.3. ABI-009, Albumin Mechanism of Transport and Selectivity for PAH Pathology

The *nab* technology utilizes albumin receptor-mediated (gp60) caveolar endothelial transcytosis to transport dugs to the subendothelium [22]. Indeed, we have seen in our laboratory that nab-drug transcytosis across the epithelial monolayer was dependent on albumin and caveolae formation [22]. Albumin is highly soluble, has long plasma half-life and broad binding affinity, and highly accumulated in disease sites such as tumors and during inflammation [23, 24], making it an ideal candidate for drug delivery. Consequently, the hyperproliferative and leaky vasculature in tumors resulted in increased albumin-based drug uptake for *nab*-drugs [25]. Increased gp60 expression and robust albumin uptake has been observed in rat lung tissues and wild-type mice endothelial cells of aorta relative to other tissues [26-28]. Mechanical stress as well as mediators such as cytokines and thrombin, a key player in the pathobiology of PAH, can mediate morphological changes in endothelial cells and widening of the intercellular junctions [29, 30]. PAH is associated with increased transendothelial permeability of macromolecules and lung edema, which contains high level albumin protein [24, 31]. It has been further observed that cells under stress, such as those in tumors and sites of inflammation, display significant higher albumin uptake than normal cells and degrade albumin for their nutrient and energy needs [23, 32, 33]. Accumulating evidence shows that PAVSM and endothelial cells in PAH share several analogous features with cancer cell stress response, such as increased proliferation and resistance to apoptosis [6, 34-37], association with metabolic glycolytic shift, deregulated mitochondrial function, and constitutive up-regulation of HIF1alpha [6, 36, 38]. Taken together, these results provide strong background that the hyperproliferative vascular lesions in PAH should result in enhanced uptake of albumin-bound sirolimus over oral sirolimus and that anti-proliferative strategies used in cancer are relevant to treat PAH.

1.2.3.1. Preclinical Studies with ABI-009

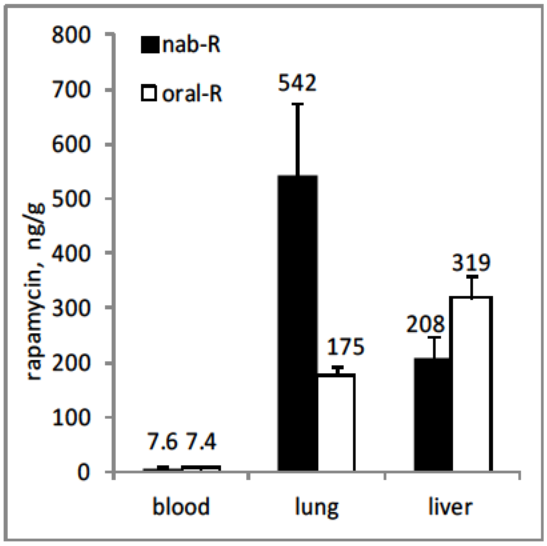
In preclinical studies, ABI-009 has shown an excellent safety and efficacy profile; it showed preferential accumulation in lungs; it reduced cell viability and decreased downstream signaling and showed excellent efficacy in various xenograft cancer models, including pancreatic, colorectal, multiple myeloma, and breast cancer [39-42]. Importantly, ABI-009 has also shown efficacy in models of proliferative vasculopathy of the peripheral artery, supporting its use for indications related to the therapeutic remodeling of vascular disease [43].

ABI-009 Preferential Uptake in Lungs compared to Oral Sirolimus in Rats

We compared whole blood PK and tissue distribution at 24 hrs after ABI-009 IV administration (dose 1 mg/kg) in rats (N=5) to oral sirolimus[44] (dose 1.6 mg/kg) in rats (N=5), to determine relative uptake into the lung (target organ for PAH) and liver (major excretion route for sirolimus). Blood and tissue levels were measured by LC/MS/MS or HPLC (Figure 1). Blood levels at 24 hrs were comparable. The calculated tissue extraction ratios (conc of rapa in tissue/conc of rapa in blood) in the lung were 72 and 24 respectively for ABI-009 and oral sirolimus indicating a 3-fold higher lung targeting for ABI-009. In contrast, the extraction ratios for the liver were 27 and 43 respectively for ABI-009 and

oral sirolimus, a 1.6-fold decrease for ABI-009 suggesting a lower rate of hepatic uptake due to the albumin bound formulation and supporting a longer persistence in the circulation. The roughly 2-fold higher levels in liver compared to lung for oral sirolimus are expected since hepatic metabolism is the major excretion pathway for oral sirolimus and confirms that there are no specific mechanisms to increase lung uptake for oral sirolimus. The 2.6-fold higher levels in lung compared to liver for ABI-009 support specific transport mechanisms of microvascular lung endothelial cells for albumin to increase lung uptake [28].

Figure 1: Sirolimus Levels (ng/g) in Blood, Lung and Liver of Rats at 24 hrs for ABI-009 and Oral Sirolimus (oral-R)



Actual values indicated (N=5 each group). ABI-009, levels in lung were significantly higher than in liver ($p<0.05$); ABI-009 lung levels were significantly higher than estimated Oral-R in lungs ($p<0.05$); ABI-009, liver levels were significantly lower than estimated Oral-R in liver ($p<0.05$). Paired Student's t-Test, used for all comparisons

ABI-009 in Porcine model of Peripheral Artery Restenosis – Biology Similar to PAH

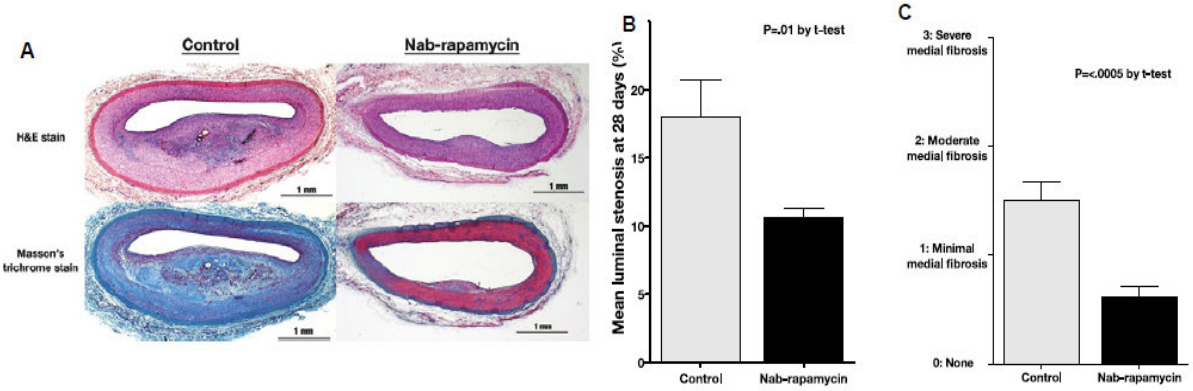
Restenosis after interventional procedures, such as angioplasty is known to occur due to hyper-proliferation of vascular smooth muscle and endothelial cells, similar to that seen in PAH. Recently Gasper et al (2013) demonstrated the antirestenotic effect of ABI-009 in a porcine restenosis model [43]. ABI-009 or control saline was administered into the adventitia of the femoral arteries after vessel injury [43]. Animals were sacrificed and vessels analyzed by histopathology at 28 days following the injury. Doses tested: 5, 50, or 500µg injected into both left and right femoral arteries of 2 animals. The femoral artery segments were analyzed for a primary endpoint of neointimal area as compared to media area, and for lack of toxicity. Secondary endpoints included reduction in tissue fibrosis, neovascularity, and endothelialization.

At 28 days, femoral arteries treated with the 500 µg dose of ABI-009 had the greatest effect, with a 41% reduction in luminal stenosis vs control, 18.2 ±16.6% vs 10.7 ±5.0% *P*

= 0.01. The 500 µg dose of ABI-009 also significantly reduced medial fibrosis by qualitative analysis, $P < 0.0001$ t-test, and media cell proliferation by Ki-67 staining, $P = 0.02$ t-test (Figure 2).

The observation suggests that a single ABI-009 dose has an antiproliferative effect on vascular endothelial and smooth muscle cells and suggests that ABI-009 may also be active in the treatment of PAH that shares similar hyper-proliferation characteristics.

Figure 2: Effect of ABI-009 on Injured Femoral Arteries

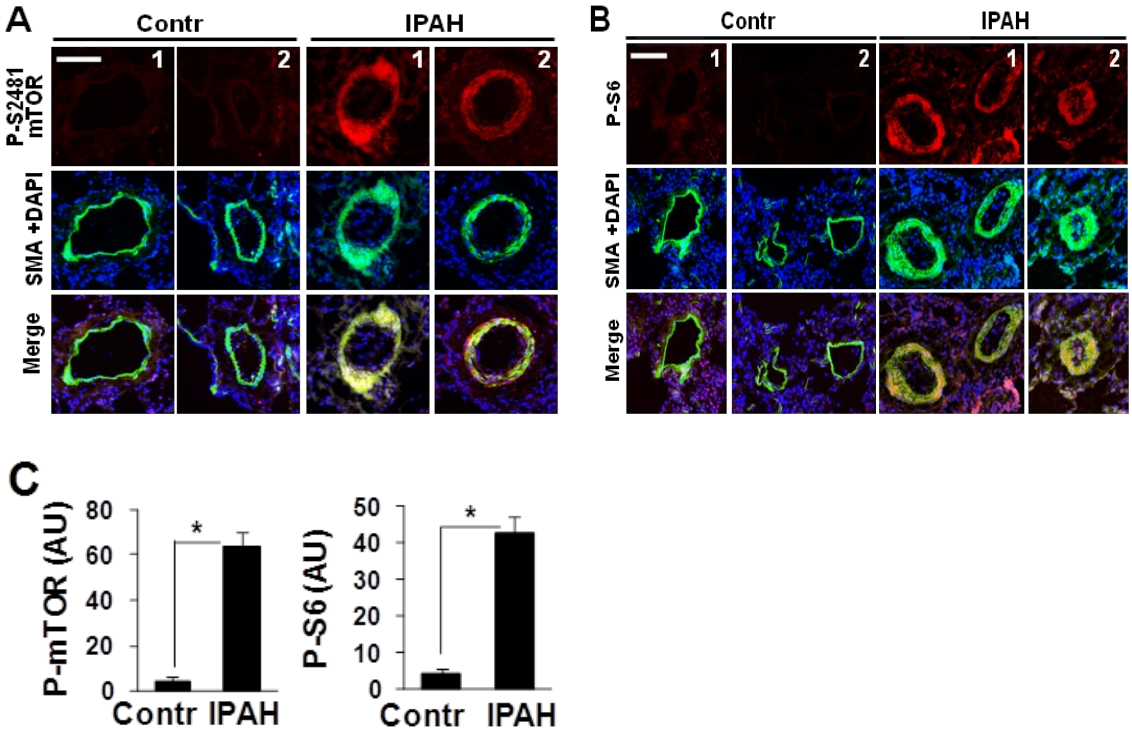


(A) Representative femoral artery sections 28 days after injury and periadventitial injection of control or 500 µg dose ABI-009. Both H&E and Masson's trichrome staining demonstrate less luminal stenosis or medial fibrosis in the ABI-009-treated femoral arteries. ABI-009 500 µg dose reduced artery lumen stenosis (B) and medial fibrosis (C) 28 days after double-injury [43].

1.2.3.2. Translational Studies in Human Idiopathic PAH (IPAH) Tissues

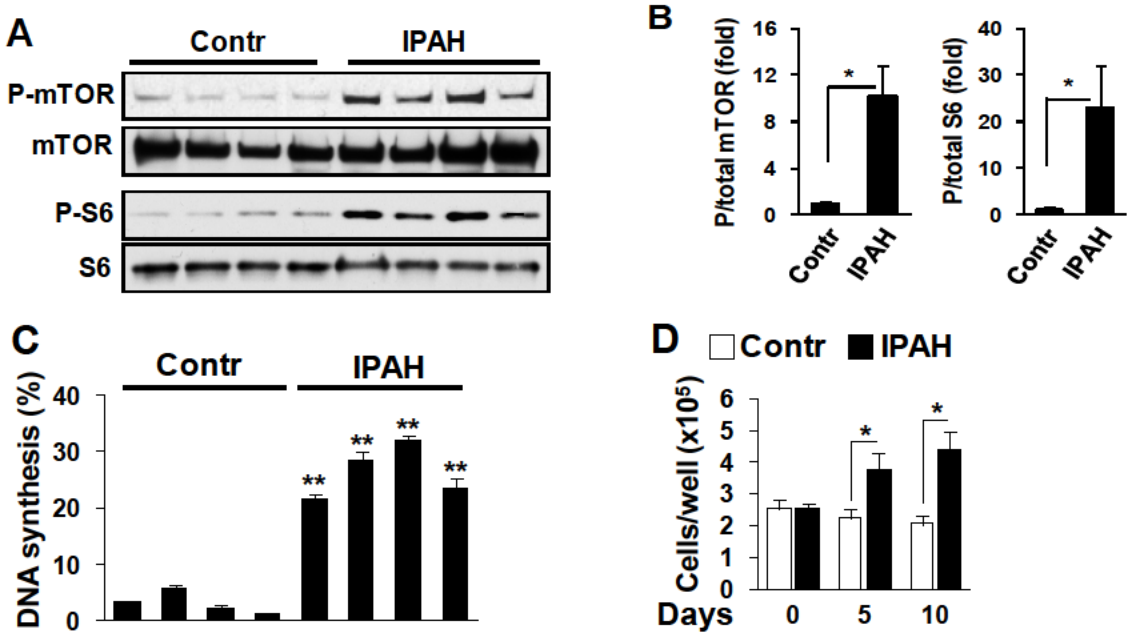
Goncharova et al. at University of Pittsburgh recently confirmed the importance of mTOR in human IPAH tissues. Immunohistochemical and immunoblot analyses revealed that mTOR signaling is markedly upregulated in small remodeled pulmonary arteries from human subjects with IPAH (Figure 3) [6]. Primary distal pulmonary artery vascular smooth muscle cells (PAVSMCs) from human subjects with IPAH have increased phosphorylation and activation of mTOR and its downstream effector S6 (S6) that is associated with increased proliferation and survival compared with normal controls (Figure 4) [6].

Figure 3: mTOR Signalling is Activated in Small Pulmonary Arteries from Lungs of Patients with IPAH



Dual immunohistochemical analysis of lung tissue specimens from 4 IPAH and 4 control (Contr) subjects with anti–P-S2481-mTOR, anti–P-S6 (red), and anti–smooth muscle actin (SMA) antibodies (green); DAPI staining (blue) was used to detect nuclei. **A,B** Images taken on a Nikon Eclipse 2000 microscope. Bar, 100 µm. **C**, Statistical analysis of phosphorylated (P) proteins in SMA-positive areas in small pulmonary arteries from IPAH and control lungs. Data are in arbitrary units (AU); 4 human subjects per group. P indicates phosphorylated. *P<0.01 by unpaired Student t test.

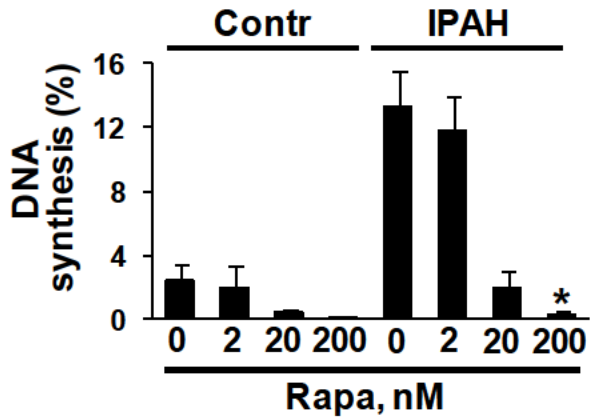
Figure 4: Human PAVSMCs from Lungs with IPAH have Activated mTOR Signaling and Increased Proliferation and Survival



A and **B**, Distal PAVSMCs from 4 non-diseased (Contr) and 4 IPAH human subjects were serum-deprived for 48h followed by immunoblot analysis to detect indicated proteins. Data represent fold changes in phosphorylated (P)/total protein ratios; P/total ratio for controls taken as 1-fold. Four subjects per group; *P<0.05 by unpaired Student t test. **C**, DNA synthesis analysis of serum-deprived for 48 hours PAVSMCs (bromodeoxyuridine incorporation) from 4 control and 4 IPAH human subjects; 3 measurements per subject; data from each subject presented as a separate bar. Data represent percentage of bromodeoxyuridine-positive cells per total number of cells. **P<0.001 vs controls by unpaired Student t test. **D**, Cell counts and viability of PAVSMCs from 4 IPAH and 4 control human subjects maintained in serum-free conditions. Data represent quantity of cells per well (**D**) and percentage of dead cells per total number of cells; *P<0.05 by unpaired Student t test.

Furthermore, sirolimus strongly inhibited the proliferation of IPAH PAVSMC at low nanomolar concentrations (Figure 5) [6].

Figure 5: Effects of Sirolimus on Proliferation Rates of IPAH and Non-diseased (Contr) PAVSMC



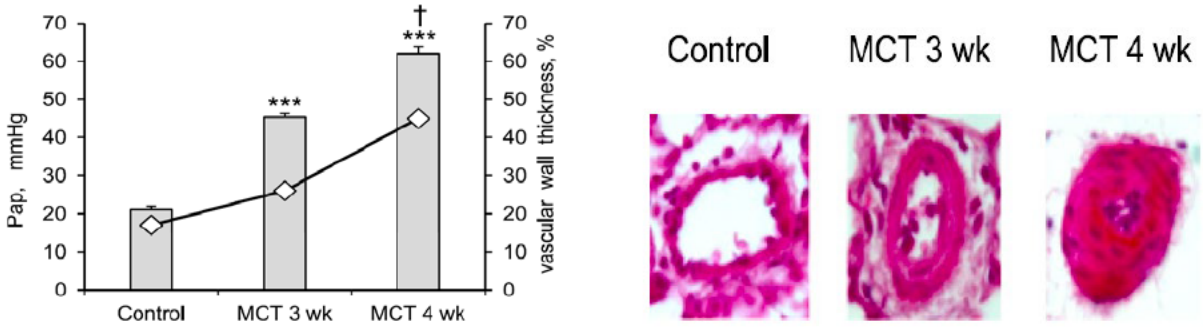
Serum-deprived for 48 h PAVSMC from 3 non-diseased (control) and three IPAH lungs were treated for 18 h with indicated concentrations of sirolimus or diluent and then subjected to DNA synthesis analysis (bromodeoxyuridine incorporation assay). Data represent percentage of bromodeoxyuridine -positive cells per total number of cells taken as 100%; 3 separate measurements were performed per each cell culture for each experimental condition. Data are means ± SE. *p < 0.05 for diluent- vs. sirolimus-treated IPAH PAVSMC (stratified independent t-test with corrections for multiple comparisons)

1.2.3.3. In Vivo Studies in a Rat Model of PAH

Houssaini et al (2013) compared sirolimus, fluoxetine and imatinib in rats with monocrotaline-induced pulmonary hypertension. The monocrotaline treated rats developed PAH (Figure 6) [9].

Figure 6: Development of Pulmonary Hypertension 3 and 4 weeks after Monocrotaline (MCT) Injection in Rats

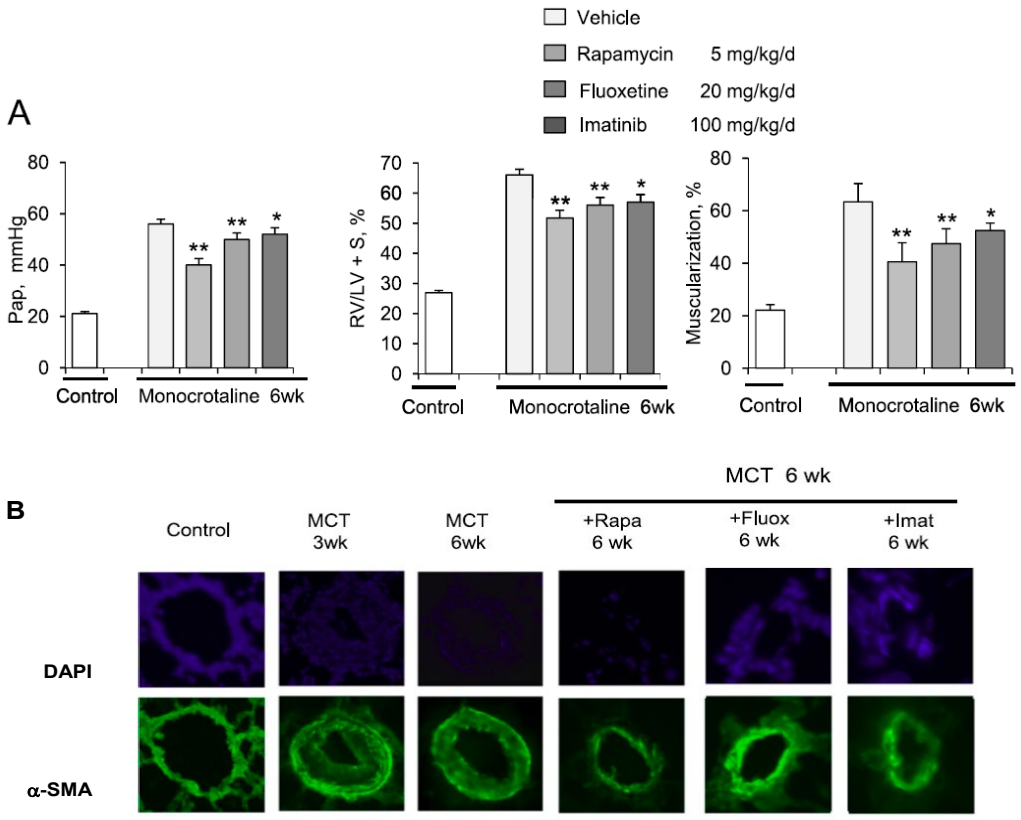
A **B**



A. the increases in mean pulmonary arterial pressure (Pap; bar graphs), and muscularization of distal pulmonary vessels, as assessed by pulmonary arterial wall thickness (diamonds); and **B.** representative photomicrographs of pulmonary vessels and pulmonary artery wall thickness from rats on Days 21 and 28 after MCT or saline (controls). ***p<0.001 compared with untreated control rats (Day 0); † p< 0.05

Sirolimus given preventively (Days 1–21) or curatively (Days 21–42, Figure 7A) inhibited monocrotaline-induced PAH to a greater extent than did imatinib or fluoxetine as indicated by changes in pulmonary artery pressure, right ventricular hypertrophy and percentage of partially muscularized and fully muscularized vessels. Representative photographs of immunofluorescence staining for α-SMA in control rats and MCT 6-week rats treated with sirolimus, fluoxetine, imatinib, or vehicle from Day 21 to Day 42 showed a reversal of PAH as indicated by reduced arterial wall thickness of the pulmonary arteries (Figure 7B). The authors concluded that sirolimus was more effective in prevention and reversal of PAH in a rat monocrotaline model than imatinib or fluoxetine [9].

Figure 7: Inhibition of MCT-induced Pulmonary Hypertension by Sirolimus



A. Pulmonary artery pressure (Pap), right ventricular hypertrophy index (RV/[LV +S] weights), and percentage of partially muscularized and fully muscularized vessels on Day 42 after saline (controls) or MCT administration combined with either sirolimus, fluoxetine, imatinib, or vehicle from Day 21 to Day 42 (n = 10 in each group). *p < 0.05, **p< 0.01 compared with values in control rats. **B.** Representative photographs of immunofluorescence staining for α-SMA in control rats and MCT 6-week rats treated with sirolimus, fluoxetine, imatinib, or vehicle from Day 21 to Day 42.

In a study of sirolimus in a chronic hypoxia mouse model of PAH, sirolimus prevented hypoxia-induced increase of proliferative activity within the pulmonary vasculature, blocked hypoxia-triggered media thickening of intrapulmonary vessels, attenuated hypoxia-induced right ventricular hypertrophy, reduced hypoxia-triggered hypertrophy of individual cardiomyocytes, and reversed hypoxia-induced pulmonary vascular remodeling [7].

1.2.3.4. Pilot Clinical Study in PAH Patients Treated with Everolimus

Seyfarth et al (2013) reported a pilot study with everolimus, an mTOR inhibitor, in 10 patients suffering from PAH (n = 8) or chronic thromboembolic PH (n = 2) with progressive disease despite therapy with at least 2 vasodilating drugs [45]. All patients were treated with everolimus at a dose of 0.75 mg orally twice daily for 2 days in addition to their prior medication. The dose was adjusted thereafter to achieve a target serum level of 5-8 ng/mL. The average daily dose was 2.1 mg (range 0.75-4.5 mg/day). Safety and tolerability were observed throughout the study. Pulmonary vascular resistance (PVR) and 6-minute walk distance (6MWD) were considered coprimary end points. In 2 patients, study medication was stopped prematurely because of an AE. One patient had acute bronchitis, and the other had right heart decompensation. The remaining 8 patients exhibited a significant 31% decrease in PVR (median [interquartile range], 1,012 [688–1,344] vs. 663 [546–860] dyn s cm–5; P = 0.018) and an increase in 6MWD (median [interquartile range], 236 [139–350] vs. 298 [207–450] m; P = 0.069) after 6 months of treatment with everolimus. This pilot study suggests that mTOR inhibition may be a suitable approach for the treatment of PAH.

1.2.3.5. Human Case Report in a PAH Patient Treated with Oral Sirolimus

Wessler et al (2010) reported the case of a 61-year-old woman who presented with a large pancreatic mass and metastasis to the liver and biopsies consistent with an islet cell tumor [8]. In 2007, this patient was diagnosed with PAH with no response to nitric oxide treatment. Despite inhaled iloprost, she remained in New York Heart Association (NYHA) class 3. In 2009, she was treated with oral sirolimus (1 mg bid) in the setting of progressive disease to the liver. After 8 weeks her liver metastasis responded to treatment and the patient reported markedly decreased effort dyspnea. She was now able to exercise by climbing flights of stairs (NYHA class 2). The patient continued treatment with sirolimus for 10 months and by early 2010, she was NYHA class 1, her pulmonary artery systolic pressure by echocardiogram was normal and her EKG findings of right-side heart strain had resolved. The authors concluded that the temporal association between sirolimus administration and the improvement in clinical, echocardiographic, and catheterization-documented pulmonary hypertension provides compelling evidence that sirolimus was effective in treating this patient's PAH. It should be noted that there was no discussion of any AEs related to oral sirolimus and that as a cancer patient, the type of acceptable toxicities would be different than in a PAH patient. The toxicities of oral sirolimus (1 mg bid ie, 2 mg daily) are described in the Rapamune prescribing information [46].

1.2.3.6. Clinical Studies with ABI-009

In a phase 1 dose escalation, tolerability and pharmacokinetics study conducted at MD Anderson Cancer Center (Protocol CA-401), ABI-009 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 [12]. Twenty-six patients were treated with 45, 56.25, 100, 125, 150 mg/m^2 ABI-009 per week for 3 weeks, followed by a week of rest (28-day cycle). ABI-009 administered intravenously. The maximum tolerated dose (MTD) was established at 100 mg/m^2.

Nineteen patients were evaluable for efficacy. One patient in the 45 mg/m^2 (95 mg actual sirolimus dose) cohort diagnosed with adenocarcinoma of the kidney and with bone and intrathoracic metastases had a confirmed PR. The target lesion of this patient was reduced by 35.1% and the duration of response lasted 183 days. Two (11%) patients (at doses 45 and 125 mg/m^2, with actual sirolimus doses of 88 mg and 193 mg, respectively) had an overall tumor evaluation of SD (confirmed): 1 patient with mesothelioma had SD for 365 days and 1 patient with a 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%) patients experienced at least 1 AE. The most common AEs were mucosal inflammation (10 patients, 38%), fatigue (7 patients, 27%), rash (6 patients, 23%), diarrhea (6 patients, 23%), and nausea (5 patients, 19%). Most of these AEs were grade 1/2 events, with only 3 grade 3 nonhematologic AEs (2 elevated AST and 1 dyspnea). Specifically, at the maximum-tolerated dose (MTD, 100 mg/m^2), all 7 patients experienced at least 1 AE of any grades, and the most common AEs were mucositis and fatigue (5 patients, 71% each). Four (15%) patients experienced at least 1 treatment-related SAE, including arrhythmia (grade 2) and mood alteration (grade 3) both in the 125 mg/m^2 cohort, vomiting (grade 3) in the 45 mg/m^2 cohort, and dyspnea (grade 3) in the 100 mg/m^2 cohort.

The most common hematologic AEs, for all cohorts and grades, were thrombocytopenia (58%), followed by hypokalemia (23%), anemia and hypophosphatemia (19% each), and neutropenia and hypertriglyceridemia (15% each). Most of these events were grade 1/2, and only 1 grade 4 hematologic event occurred (thrombocytopenia in the 150 mg/m^2 arm). At the MTD, the only hematologic AE was a grade 3 anemia.

For the present study in PAH patients, the starting dose will be 1 mg/m^2, which is 100-fold lower than the MTD obtained in the oncology phase 1 study. The original starting dose for this study was 10 mg/m^2. Four patients were treated at this dose. Two patients developed dose-limiting grade 2 rash, associated with persistent intolerable pruritus. One of the 2 patients with rash developed cellulitis of the abdominal wall, most likely as a result of infection introduced through the skin by scratching. Another patient developed grade 1 paresthesia, which was also dose-limiting. As a result of these DLTs, the starting dose was amended to 1 mg/m^2.

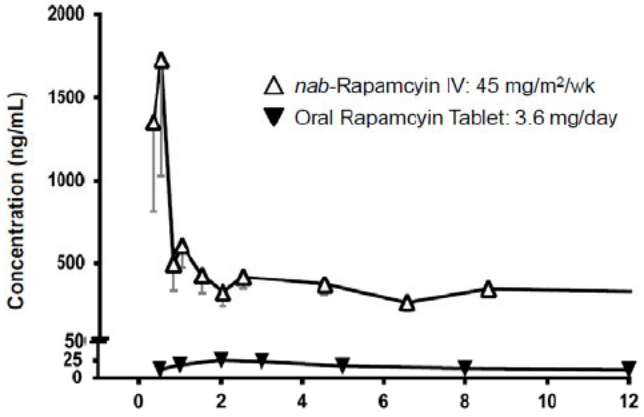
1.2.3.7. ABI-009 (*nab*-Sirolimus) Pharmacokinetics (PK) and Differentiation over Oral mTOR Inhibitors

Poor Oral Absorption and Variability: Oral sirolimus and oral everolimus are subject of poor and variable oral absorption that requires daily dosing and therapeutic dose monitoring via periodic blood level testing. Most often, therapeutic blood levels have to be maintained in the 5-20 ng/ml range through periodic testing of blood levels and adjustment of daily dosing. Additionally, the oral agents are poorly absorbed from the gut (<20% bioavailability) and cause GI toxicity not observed with ABI-009.

First pass advantage: IV administration of ABI-009 may provide a significant first pass PK advantage. Infusion from the peripheral vein directly into the right heart and pulmonary vasculature gives the highest possible nanoparticle concentration without excessive dilution directly into the pulmonary arterial tree for maximum local accumulation. Oral sirolimus and other oral rapalogs cannot achieve this due to first pass through liver from the GI tract – additionally the orally absorbed drug is subject immediately to first pass hepatic metabolism resulting in low blood levels without substantial peak levels.

High C_{max} and sustained blood levels (once/week): The PK profile of ABI-009 has high peak levels many folds higher than daily oral sirolimus provides added potential to drive the ABI-009 into PAH lesions. PK of IV ABI-009 was carefully studied in 26 patients over 168 hours (7 days) after administration and over a dose range of 45 – 150 mg/m^2 [12]. The peak concentration after administration (C_{max}) at 45 mg/m^2 (Figure 8) was 1776 ng/ml and plasma levels of sirolimus were maintained above 500 ng/ml for 1 hour and above 250 ng/ml for 2 hours at 45 mg/m^2.

Figure 8: Concentration vs Time Curves for ABI-009 and Oral Sirolimus Showing Dramatic Difference in Profile



Oral sirolimus PK from historical data [47]

The terminal half-life ranged between 40-91 hours. Since the C_{max} was fairly proportional to the dose, an estimation of expected C_{max} over doses relevant to the PAH study (10-45 mg/m^2) was determined. When compared to oral sirolimus (C_{max} 15.5 ng/mL at 5 mg dose [48], C_{max} of 37.9 ng/mL at 9 mg dose [49], C_{max} of 57.72 ng/mL at 60 mg dose) [50], and

an approved sirolimus prodrug temsirolimus (day 5 sirolimus C_{max} 133.9 ng/mL after 5 days of IV daily administration of temsirolimus at 19.1 mg/m^2 [51]), the C_{max} with ABI-009 was substantially higher. For continuous daily oral dosing of sirolimus at an average dose of 3.6 mg/day [47], the reported C_{max} was 25.3 ng/mL. Compared to oral sirolimus, the predicted C_{max} of ABI-009 at 1, 2.5, 5, and 7.5 mg/m^2, the proposed doses to be testing in the planned PAH study, respectively were up to 6, folds higher – with the potential advantage to obtaining higher lung concentrations with ABI-009 along with potentially lower toxicities compared to oral sirolimus.

1.2.3.8. Rationale for Starting Dose of ABI-009

The starting dose of 1 mg/m^2 for this study is selected based on the following considerations:

- Clinical safety of ABI-009 has been previously evaluated in a phase 1 oncology study, with the MTD established at 100 mg/m^2 of sirolimus (as *nab*-sirolimus or ABI-009) given weekly.
- The original starting dose for this study was 10 mg/m^2. Four patients were treated at this dose. Two patients developed dose-limiting grade 2 rash, associated with persistent intolerable pruritus. One of the 2 patients with rash developed cellulitis of the abdominal wall, most likely as a result of infection introduced through the skin by scratching. Another patient developed grade 1 paresthesia, which was also dose-limiting.
- The revised starting dose for this study is 1 mg/m^2 weekly, which is 10 folds lower than the initial starting dose.
- Rapammune (oral sirolimus) dosing used chronically for transplant patients (Rapamune PI) is >8x higher than the proposed starting dose of ABI-009 [46]. Rapamune is dosed at 2-5 mg/day, which is 14-35 mg/week. Starting dose of ABI-009 is 1 mg/m^2/wk, which is about 1.7 mg/week assuming a BSA of 1.7 m^2.
- Safety of everolimus in the PAH patients (Seyfarth 2013) was studied in 10 patients that received an average of 2.1 mg/day or 14.7 mg/wk for 24 weeks in addition to standard PAH therapy [45]. Everolimus was well tolerated in that study.
- Safety profiles of everolimus and Rapamune are similar. Everolimus dosing levels are similar to Rapamune dosing (Rapamune PI), with both being in the same range as the planned starting dose of ABI-009.
- Drug-drug interaction potential of ABI-009 with standard PAH drugs is low (see Section 9.3).
- Animal studies and clinical studies of ABI-009 have not shown any AEs that have not been previously described for mTOR inhibitors.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

This phase 1/1b study will involve dose escalation to determine the MTD and safety of 16 weeks of therapy (Dose-finding Safety Part) followed by up to 32 additional weeks of therapy (optional Extension Part) with ABI-009 IV in patients with PAH who are WHO Functional Class II or III despite best available background therapy. The MTD will be determined on the basis of the results from the safety evaluation.

After the MTD is reached in phase 1, there will be up to 2 cohort expansions in phase 1b, one at the MTD and/or one alternate dose or schedule, to determine the recommended phase 2 dose (RP2D). The expanded cohorts will be such that up to 10 patients for each of the cohorts will be enrolled to obtain additional safety and efficacy data. The RP2D, which may differ from the MTD, will be determined on the basis of results from safety, efficacy, pharmacologic and correlative studies in this phase 1/1b study.

The exploratory objective of the study is to evaluate pharmacokinetic information that may be correlated with safety and/or efficacy observations.

2.2. Primary Endpoints

- Dose finding phase: Establish the MTD, DLT, and safety of 16 weeks of ABI-009 given IV
- Safety profile of the up to 48 weeks of treatment

2.3. Secondary Endpoints

The following will be measured before treatment at baseline and at 17 weeks (after 16 weeks of treatment in the Dose-finding Safety Part):

- pulmonary vascular resistance (PVR) by right heart catheterization
- pulmonary artery pressure (PAP)
- pulmonary capillary wedge pressure (PCWP)
- central venous pressure (CVP)

The following will be measured at baseline, 5, 9, 13, and 17 weeks:

- Doppler-echocardiographic assessments of right ventricular structure and function
- 6-minute walk distance (6MWD)
- WHO functional class
- Pulmonary function test

The following will be measured every 8 weeks form the start of the Extension Part (ie, at week E9, E17, E25, and E33):

- 6MWD
- WHO Functional Class
- Pulmonary function test

2.4. Exploratory Endpoints

- Pharmacokinetic (PK) profile and trough level of sirolimus for weekly treatment during the 16 weeks of Dose-finding Safety Part and every other week treatment during the Extension Part
- Measurement of brain naturetic peptide (BNP), C-reactive protein (CRP) and troponin levels, indicative of right ventricular strain at baseline, 5, 9, 13, and 17 weeks, and for BNP, every 8 weeks in the optional Extension Part (E9, E17, E25, E33)
- Change from baseline at week 17, and to weeks E17 and E33 in the Extension Part in 36-Item Short Form Health Survey (SF-36) physical functioning scale
- Change from baseline at week 17, and to weeks E17 and E33 in the Extension Part in emPHasis10 questionnaire

3. OVERALL STUDY DESIGN

3.1. Study Design

This study is a dose-finding prospective phase 1/1b, single arm, open-label, multi-institutional study to determine the MTD, DLT, safety, and preliminary efficacy of 16 weeks of IV ABI-009 treatment in patients with PAH who are WHO Functional Class II or III despite best available background therapy.

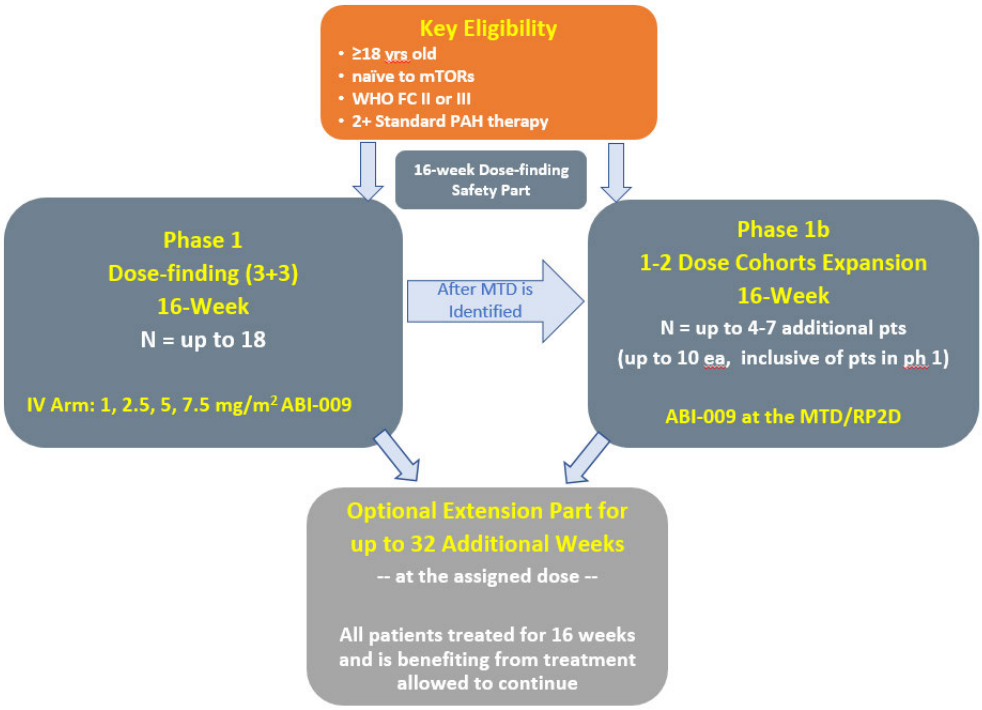
The study will be conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCPs).

In phase 1, up to 24 patients will be enrolled using the standard 3+3 dose escalation design in the dose-finding phase.

In phase 1b, an additional 4-7 patients in up to 2 expansion cohorts to obtain a total of up to10 patients at each of the 2 dose levels, MTD and/or an alternate dose or schedule. The MTD will be determined on the basis of the results from the safety evaluation. The RP2D, which may differ from the MTD, will be determined on the basis of results from safety, efficacy, and pharmacologic and correlative studies.

Patients who, in the opinion of the investigator and Safety Committee, tolerate ABI-009 well and achieve clinical benefit during the first **16-week Dose-finding Safety Part**, and for whom there are no alternative therapies available, may opt to continue therapy **(optional Extension Part) for up to an additional 32 weeks** at their assigned dose or lower, if permanently reduced. The optional Extension Part should start within 4 weeks after the last dose of the 16-week Dose-finding Safety Part.

Figure 9: Study Schema



3.2. Study Duration

The study was originally expected to take approximately 30 months from first patient enrolled to last patient follow-up, including approximately 18 months of enrollment period, up to 16 weeks of treatment (Dose-finding Safety Part) (or until treatment is tolerated), followed by an optional Extension Part for up to 32 additional weeks of ABI-009, and at least a 28 days follow-up after the last dose either in the Dose-finding Safety or Extension Part, whichever is later. With the addition of the 7.5 mg/m^2 dose cohort, it is anticipated that enrollment will take another 12 months for enrollment.

3.3. End of Study, End of Treatment, End of Treatment Visit, Follow-up Period

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

End of Treatment (EOT) is defined as the date of the last dose of ABI-009.

End of Treatment Visit is when safety and efficacy assessments and procedures are performed after the last treatment. For patients who complete the 16-week treatment, EOT visit occur at week 17 (±3 days). For a patient who does not complete the 16-week treatment, EOT Visit must occur within 4 weeks (±7 days) after the last dose of ABI-009.

Follow-up period is the on-study time period for at least 28 days after the last treatment either in the Dose-finding Safety Part or optional Extension Part, whichever is later. All patients that discontinue study drug and have not withdrawn full consent to participate in the study will continue in the follow-up phase for survival and therapy. Follow-up will continue up to 1 year approximately every 12 weeks (±3 weeks), or more frequently as needed, until withdrawal of consent, or the study closes, whichever is the earliest. This evaluation may be made by record review and/or telephone contact.

4. STUDY POPULATION

4.1. Number of Patients

In phase 1: Up to 24 patients will be enrolled using the standard 3+3 dose escalation design.
In phase 1b: Additional 4-7 patients in up to 2 expansion cohorts to obtain a total of up to 10 patients at each of the 2 dose levels, MTD and an alternate dose or schedule.

4.2. Inclusion Criteria

1) Male or female age ≥18 years old with a current diagnosis of WHO Group 1 PAH including idiopathic pulmonary arterial hypertension (IPAH), heritable pulmonary arterial hypertension (HPAH), drug and toxin induced PAH, or PAH associated with connective tissue disease, or congenital heart defects (repaired greater than 1 year prior to Screening)
2) Must meet following hemodynamic definition prior to initiation of study drug
   a. Mean PAP of ≥25 mmHg
   b. PCWP or left ventricular end diastolic pressure (LVEDP) of ≤15 mm
   c. PVR >5 mmHg/L/min (Woods unit)
3) Functional class II or III according to the WHO set forth at the Dana Point Classification 2008 Meeting
4) On 2 or more specific standard PAH therapies (for ≥8 consecutive weeks and at stable dose for ≥4 consecutive weeks) unless documented inability to tolerate 2 standard therapies
5) Meet the following criteria determined by pulmonary function tests completed at screening:
   a. Forced expiratory volume in one second (FEV1) ≥55% of predicted normal
   b. FEV1: forced vital capacity (FVC) ratio ≥0.60
6) 6MWD ≥150 meters and ≤450 meters
7) Male or non-pregnant and non-breast feeding female:
   - Females of child-bearing potential must agree to use effective contraception without interruption from 28 days prior to starting IP 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 after the end of study treatment. A second form of birth control is required even if she has had a tubal ligation.
   - Male patients must practice abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study. A second form of birth control is required even if he has undergone a successful vasectomy
8) Ability to provide written informed consent by the patient or legal guardian

4.3. Exclusion Criteria

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

1) History of heart disease including left ventricular ejection fraction (LVEF) ≤40% or clinically significant valvular constrictive or atherosclerotic heart disease (myocardial infarction, angina, cerebrovascular accident)
2) History of malignancy in 2 years prior to enrollment
3) Pulmonary hypertension (PH) belonging to groups 2 to 5 of the 2013 Nice classification
4) Current or recent (<3 months) use of intravenous inotropic or vasopressor agents for the treatment of PAH
5) Recent (<2 months) PAH-related hospital admission
6) History of allergic reactions attributed to compounds of similar chemical or biologic composition including macrolide (eg, azithromycin, clarithromycin, dirithromycin, and erythromycin) and ketolide antibiotics
7) Uncontrolled diabetes mellitus as defined by HbA1c >8% despite adequate therapy
8) Uncontrolled hyperlipidemia (serum triglyceride ≥300 mg/dL)
9) Serum cholesterol ≥350 mg/dL
10) Surgery within 3 months of start date of study drug
11) Baseline cytopenias:
    a. Absolute Neutrophil Count ≤1.5 x 10^9/L
    b. Hemoglobin ≤9 g/dL
    c. Platelet count ≤100,000/mm^3
12) Baseline liver disease: ALT/AST, total bilirubin, alkaline phosphatase ≥1.5 x ULN
13) Creatinine clearance (Cockroft formula) ≤30 mL/min
14) Inability to attend scheduled clinic visits
15) Prior use of an mTOR inhibitor within previous 6 months from enrollment
16) Previous lung transplant
17) Known Human Immunodefiiency Virus (HIV)
18) Active Hepatitis B or Hepatitis C
19) Uncontrolled intercurrent illness that in the opinion of the investigator would limit compliance and tolerance to study requirements (eg, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, diabetes, uncontrolled hypertension, coronary artery disease, or psychiatric illness/social situations)
20) Concomitant enrollment in another investigational treatment protocol for PAH
21) Use of strong inhibitors and inducers of CYP3A4 within the 14 days prior to receiving the first dose of ABI-009. Additionally, use of any known CYP3A4 substrates with narrow therapeutic window (such as fentanyl, alfentanil, astemizole, cisapride, dihydroergotamine, pimozide, quinidine, terfanide) within the 14 days prior to receiving the first dose of ABI-009

5. TABLE OF EVENTS

The schedule of assessments in Table 2 outlines the specific time points for study assessments.

Table 2: Schedule of Assessments

Visit Days	Pre-Treatment	Study Treatment Monitoring During Up to 16 Weeks of Dose-finding Safety Part																End of Treatment Visit [l]	Optional Extension Part [m]	Safety Follow-up [n]
Weeks on Intervention / Study Procedure [a]	Baseline Screening [b]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Week 17	Weekly, unless indicated	28 days after last dose, then Q12W
Informed Consent	x																			
Medical History/Demographics	x																			
I/E Criteria	x																			
Physical Exam	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Vital Signs, height, and weight [c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
BSA [d]		x																		
Pregnancy Test [e]	x																	x	E17, E33	
HIV and hepatitis tests	x																			
CBC/Differential/Chemistry	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	Every 2 weeks (E2-E32)	
NT Pro-BNP	x					x				x				x				x	E9, 17, 25, 33	
CRP	x					x				x				x				x		
Troponin	x					x				x				x				x		
Biomarker [f]	x																	x		
Fasting Lipids	x					x				x				x				x	Every 4 weeks (E5-E29)	
Sirolimus level – central assays [g]		x	x	x	x															
Sirolimus level – local assays [g]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		Every 2 weeks (E2-E32)	
Echocardiogram [h]	x					x				x				x				x		
6-minute walk distance	x					x				x				x				x	E9, 17, 25, 33	
WHO Function Class	x					x				x				x				x		
Pulmonary function test	x					x				x				x				x		
Right heart catheterization [i]	x																	x [i]		
ABI-009 administration [j]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	
Concomitant meds	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse event assessment [k]	Continuous, starting from signing of Informed Consent until 28 days after last dose of study drug																			
SF-36 and emPHasis10 QNR	x																	x	E17, E33	

[a] All visits are allowed to occur in a window of ±3 days unless otherwise specified.
[b] Baseline screening visit will be done within 28 days prior to study treatment Day 1.
[c] Height measurement is only required at screening.
[d] BSA will be calculated at week 1 and recalculated if the weight changes by >10%.
[e] Serum pregnancy test will be conducted at screening, urine pregnancy test will be conducted at week 17 or at the end of treatment visit.
[f] Blood sample will be taken and stored for biomarker testing for patients who consent.
[g] Sirolimus levels for central labs are done for patients in dose-finding phase of the study: week 1 predose, immediately after termination of infusion (end infusion), then 1, 2, and 4 hrs post infusion, and predose at weeks 2, 3, 4. Local labs for trough levels (predose) of sirolimus from week 2 and thereafter are done for all treated patients (in both Dose-finding Safety and Extension Part). An optional PK evaluation via local lab at weeks 1 and 3 (at 24, 48, and 72 hrs) are done for patients who consent in the Dose-finding Safety Part.
[h] Echocardiogram studies will follow the Echo Core Lab Manual and will be uploaded to central lab for analysis.
[i] RHC will be submitted to centralized core labs for analysis and is optional for patients who do not complete the 16-week treatment but opt to have RHC performed.
[j] ABI-009 must be administered after all study specific assessments are done in a visit.
[k] Continuous, starting from signing of Informed Consent until 28 days after last dose of study drug
[l] End of Treatment Visit for patients who do not complete the 16-week treatment must be within 4 weeks of last study treatment (±7 days).
[m] Optional Extension Part is for patients who tolerated ABI-009 well and showed clinical benefit during the Dose-finding Safety Part based on the opinion of the investigator and Safety Committee. This Extension Part should start within 4 weeks after the last dose of ABI-009 in the Dose-finding Safety Part. ABI-009 will be given at the originally assigned dose (or lower if reduced) for a maximum of 32 additional weeks, followed by an evaluation on week 33 for select assessments: urine pregnancy test, NT Pro-BNP, 6MWD, WHO functional class assessment, pulmonary function test, and SF-36 and emPHasis10 questionnaires. If treatment discontinues prior to week 32, the week 33 assessments should be done within 4 weeks of last treatment.
[n] Safety follow-up will continue for a minimum of 28 days then approximately every 12 weeks (±3 weeks) by phone call after the last treatment either in the Dose-finding Safety Part or optional Extension Part. Follow-up will continue up to 1 year approximately every 12 weeks (±3 weeks), or more frequently as needed, until withdrawal of consent, or the study closes, whichever is the earliest.

6. PROCEDURES

6.1. Screening Evaluations

This study will be conducted at approximately 5 sites in the US. Additional sites may be added.

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

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

Before patients may be entered into the study, the Sponsor requires a copy of the site's written IRB/IEC approval of the protocol, informed consent form, and all other patient information and/or recruitment material, if applicable. A signed and dated Institutional Review Board (IRB) approved informed consent form (latest approved version) must be obtained from each patient prior to performing any study-specific procedures. All patients or legally acceptable representatives must personally sign and date the consent form before commencement of study-specific procedures. Patients who lack capacity to understand protocol requirements will be excluded. Adverse Events are to be collected for a patient upon signing the informed consent until 28 days after last dose of study drug.

Screening evaluations will be performed for all patients to determine study eligibility. These evaluations must be completed within 28 days prior to enrollment. Any questions regarding patient eligibility should be directed to Aadi or other sponsor-nominated representatives or designees for approval.

The following procedures are to be completed during the **screening period**, after signed informed consent has been obtained, designated in the Schedule of Assessments, Table 2. The 6MWD test will be conducted following guidelines by American Thoracic Society [52].

- Informed consent
- Medical history, demographics
- Complete blood count with differential and chemistry panel
- Physical exams, vital signs, height, and weight
- Serum pregnancy test
- NT Pro-BNP
- CRP
- Troponin

- Biomarker test (optional)
- Fasting lipid test
- SF-36 and emPHasis10 questionnaire
- Echocardiogram
- 6MWD test
- WHO Functional Class
- Pulmonary function test
- Right heart catheterization
- Concomitant medication
- HIV test
- Hepatitis B surface antigen, hepatitis B and C antibody tests
- Adverse Events

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

All screening tests and procedures must be performed within 28 days of study day 1. Once eligibility is confirmed, a site representative will complete and fax a patient eligibility criteria worksheet to an Aadi representative. The Aadi representative will acknowledge receipt of the paperwork and confirm enrollment for that individual patient.

6.2. Dose-finding Safety Part (up to 16 weeks)

A patient is considered enrolled on study day 1 when the IP, ABI-009, is first administered. ABI-009 is to be administered after all other protocol-specified pre-dose assessments have been performed during each visit that it is required. ABI-009 will be administered weekly for 16 weeks. All weekly visits are allowed to occur in a window of ±3 days.

6.2.1. Every Week Assessments During the 16-week Dose-finding Safety Part

The following assessments will be performed every week:

- Physical exams, vital signs and weight
- Complete blood count with differential and chemistry panel
- Sirolimus PK
- Concomitant medications
- Adverse Events

Week 1 evaluations may be omitted if screening evaluations are performed within 72 hours. For complete analyte listing, refer to Table 3.

Table 3: Analyte Listing

Chemistry	Hematology	Other Labs
Sodium	WBC	Pregnancy test
Potassium	RBC	Sirolimus PK
Bicarbonate	Hemoglobin	HIV
Chloride	Hematocrit	HBV sAg
Total protein	MCV	HBV cAb
Albumin	MCH	HCV Ab
Calcium	MCHC	Total Cholesterol
Magnesium	RDW	HDL
Phosphorus	Platelets	LDL
Glucose	Differential:	Triglyceride
BUN	-Neutrophils	Biomarker development
Creatinine	-Lymphocytes	NT Pro-BNP
Total bilirubin	-Monocytes	CRP
Alkaline phosphatase	-Eosinophils	Troponin
AST (SGOT)	-Basophils	
ALT (SGPT)		
Amylase		
Lipase		

6.2.2. Every 4-Week Assessments During the 16-week Dose-finding Safety Part

The following assessments will be performed every 4 weeks at week 5, week 9, and week 13:

- NT Pro-BNP
- CRP
- Troponin
- Fasting lipids
- Echocardiogram
- 6MWD test
- WHO Functional Class
- Pulmonary function test

All efficacy measurements will occur prior to the administration of ABI-009 during the visit.

6.2.3. Efficacy Assessment During the 16-week Dose-finding Safety Part

Efficacy assessment will occur at baseline and at EOT Visit (to evaluate the utility (potential for clinical efficacy) of ABI-009 in the treatment of PAH as measured by a change in PVR and other hemodynamic parameters. Change from baseline in 6MWD (absolute difference in distance), echo cardiographic assessments and WHO functional class will be measured. Changes from baseline to week 17 in 36-Item Short Form Health Survey (SF-36) physical functioning scale and in emPHasis10 questionnaire will be measured as exploratory endpoints.

For efficacy assessment, all sites need to refer to standard instructions provided, including Right Heart Catherization (RHC), RHC Parameter Worksheet, Six Minute Walking Test (6MWT) Instruction, Borg dyspnea index (BDI), WHO Classification Worksheet, Echocardiogram Instruction, and Pulmonary Function Test Instruction. Echocardiogram and RHC assessments will be submitted to centralized core labs for analysis.

6.3. End of Treatment Visit Assessment

End of Treatment Visit assessment for a patient is when efficacy and safety assessments and procedures are performed after the last treatment in the 16-week Dose-finding Safety Part. For patients who complete the 16-week treatment, EOT assessments occur on week 17 (±3 days) and for patients who do not complete the 16-week treatment, EOT assessments must occur within 4 weeks (±7 days) after the last dose of ABI-009.

- Physical exams, vital signs, and weight
- Complete blood count with differential and chemistry panel
- Concomitant medications
- Adverse Events
- Urine pregnancy
- NT Pro-BNP
- CRP
- Troponin
- Biomarker analysis (optional)
- Fasting lipids
- Echocardiogram
- 6MWD test
- WHO Functional Class
- Pulmonary function test
- Right heart catheterization

- SF-36 and emPHasis10 questionnaire

For patients who fail to complete the 16-week treatment, RHC can be performed if patients opt to have the procedure. RHC results from these patients will be analyzed separately from those of patients who complete the 16-week treatment.

6.4. Pharmacokinetic Study

A PK study of sirolimus will be performed with limited PK sampling on all patients in the dose-finding portion of the study during the first 4 weeks of treatment, assessed via central lab:

- Blood samples will be obtained on day 1 (week 1) and will be taken immediately predose (before infusion), immediately after termination of infusion (end infusion), then at 1 hr, 2 hrs, and 4 hrs post infusion. Thereafter, blood samples will be taken every week immediately predose for the next 3 weeks (weeks 2, 3, and 4) to determine a trough level.

Additional PK samples for sirolimus analysis will be obtained for local lab assessment to help correlate AEs with blood levels during treatment:

- From all treated patient in the 16-week Dose finding Safety Part (including expansion cohort/s): Immediately predose starting at week 2 and continuing for the duration of the study
- From all treated patients in the up to 32 weeks of Extension Part: Immediately predose starting at week E2 and continuing every other week for the duration of the study
- Optional PK samples for consenting patients: During weeks 1 and 3 of the Dose-finding Safety Part at 24, 48, and 72 hours post infusion.

Note that T = 0 is defined as the start of infusion, ie, all sample collection times are relative to the start of infusion. The sample at the end of the infusion is collected immediately after the infusion is stopped. If the duration of infusion is changed, the sample should be collected immediately before termination of the infusion and the time noted.

Whole-blood samples will be collected in EDTA tubes for determination of sirolimus in a central laboratory.

Sample Handling for Central Lab:

- Collect approximately 4 mL blood into vacutainer tubes containing EDTA as the anticoagulant.
- Mix the whole blood gently but thoroughly in the tube immediately after collection.
- Split the sample into two tubes. One tube will be kept as a back-up sample.
- Ensure that both tubes are labeled identically.
- Store the blood samples deep frozen at a temperature between -20 and -80°C.
- The samples will be shipped to a designated laboratory.

Sample Labeling:

The following information should be on each sample:

- Protocol number
- Patient ID
- Nominal sample time point
- Collection clock time and date

A simple regression model will be applied to assess the relationship of the pharmacokinetic parameters with dose.

6.5. Samples for Optional Biomarker Analysis During the 16-week Dose-finding Safety Part

For consented patients enrolled in the expansion cohort, blood samples will be collected for blood outgrowth endothelial cell (BOECs) at baseline and EOT to correlate response to therapeutic intervention with ABI-009.

6.6. Assessments During the Optional Extension Part

For patients who tolerated ABI-009 well and showed clinical benefit during the Dose-finding Safety Part, based on the investigator and Safety Committee's judgement can continue treatment for up to an additional 32 weeks. All assessments must be done prior to dosing:

Every visit when ABI-009 is given (E1 through E32):

- Physical exams
- Vital signs and weight
- Concomitant medications

Every 2 visits when ABI-009 is given from E2 through E32:

- Complete blood count with differential and chemistry panel

SirolimusEvery 4 weeks when ABI-009 is given (E5 through E29):

- Lipids

Every 8 weeks (ie, at weeks E9, E17, E25, and E33):

- 6MWD test
- WHO Functional Class
- Pulmonary function test
- NT Pro-BNP

Every 16 weeks (ie, at weeks E17 and E33):

- SF-36 and emPHasis10 questionnaire

7. DESCRIPTION OF STUDY TREATMENTS

7.1. ABI-009 Dosage, Administration, and Schedule

The planned treatment period is 16 weeks, with ABI-009 given weekly. Patients, who based on the investigator and Safety Committee's assessment, tolerate ABI-009 and show clinical benefit during the 16-week Dose-finding Safety Part, and for whom there are no alternative therapies available, may opt to continue therapy in the optional Extension Part, with ABI-009 given weekly at the originally assigned dose (or lower, if permanently reduced) for up to 32 additional weeks. 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.

In the dose-finding portion of the study, 4 dose levels of ABI-009 will be tested in cohorts of 3 patients each (1, 2.5, 5, and 7.5 mg/m^2, see Table 1 and below), using the 3+3 dose escalation de-escalation design. There will be no intra-patient dose escalation allowed. Escalation to the next dose level with a new cohort of 3 patients will occur after no DLT was observed in the first treatment cycle of 4 weeks. If a DLT occurs in a cohort, additional 3 patients will be recruited to the cohort. If no further DLTs occur, then a new cohort of 3 patients at the next higher dose level can be enrolled. If 2/6 patients at dose level 1a experience a DLT, then that cohort will be closed to further enrollment and the study may be terminated. If 2/6 patients at dose levels 2a, 3a, or 4a experience a DLT, then the previous dose level is considered the MTD.

It is estimated that a maximum of up to 24 patients will be required to achieve the MTD; however, MTD could be reached with as few as 9 patients. Patients will be allowed to dose reduce by one dose level for reasons of toxicity, with a maximum of 2 dose reductions allowed for a patient. At the lowest dose level, a dose reduction of 25% will be allowed.

Dose Level	**1a**	**2a**	**3a**	**4a**
ABI-009 Weekly Dose (mg/m^2)	*1*	*2.5*	*5*	*7.5*

Note: The original protocol included dose levels 1 (10 mg/m^2), 2, (20 mg/m^2) and 3 (30 mg/m^2), and dose level -1 (5 mg/m^2).

7.2. Dose Modification and Stopping Rules

7.2.1. Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

If treatment cannot be administered on the planned visit date, ABI-009 may be administered ±3 days from the scheduled date. Prior to ABI-009 administration, patients must meet the following hematological requirements:

- ANC ≥1.5 x 10^9/L
- Platelet count ≥100 x 10^9/L

- Hemoglobin ≥9 g/dL

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

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

A DLT is defined as a study-drug -related grade ≥3 hematologic AE 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.

Dose reduction of ABI-009 to the next lower dose level should be considered as clinically indicated for patients who are receiving ABI-009 at above the lowest dose level. At the lowest dose level, a dose reduction of 25% will be allowed. Once a dose has been reduced, it must not be increased to the previous level. A maximum of 2 dose reductions are allowed for a patient in the entire duration of the study.

The maximum delay between a missed scheduled dose and the next one (whichever dose was missed) should not be longer than 14 days. Approval from the Medical Monitor is required to restart study treatment after ≥21 days of interruption.

8. STUDY DRUG MANAGEMENT

8.1. Description of ABI-009

8.1.1. ABI-009 Packaging, Labeling, and Storage

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

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

Temperature records for ABI-009 must be made available to Aadi or Sponsor nominated Contract Research Organization monitoring teams for verification of proper study drug storage.

8.2. ABI-009 Accountability, Disposal, and Compliance

Only completely unused study drug vials should be retained by the site until a representative from Aadi or Sponsor-nominated CRO 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.

The Investigator, or designee, shall record the dispensing of study drug to patients and any remaining study drug after dosing in a study drug accountability record. The study drug record will be made available to Aadi or authorized Aadi-designated 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 Aadi or their designee and a plan for resolution will be documented.

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

8.3. ABI-009 Reconstitution

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

ABI-009 will be reconstituted by appropriate study personnel following the Pharmacy Manual, and administered to the patient in the study site. The Investigator will calculate the BSA of the patient in order to determine the total amount of ABI-009 to be administered.

8.4. Receipt and Return of ABI-009

Upon receipt of the study drug supplies, the Investigator or designee will conduct an inventory and sign both copies of the study drug receipt and forward one copy to the address indicated on the form. One copy of the receipt and the packing slip must be retained in the Investigator's regulatory file records.

A representative from Aadi or his/her designee will inspect the study drug inventory, Drug Accountability Record form(s), and will arrange for the disposition of any remaining unused study drug. No study drug may be returned to Aadi without the representative from Aadi or other Aadi-designated personnel first inspecting the study drug inventory and accountability documentation.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

All concomitant treatments, including blood and blood products, must be reported on the eCRF. Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 9.2.

Concomitant therapies are to be collected from enrollment/randomization through the EOT Visit. Therapy name including indication, dose, frequency, route, start date and stop date will be recorded on each patient's eCRF(s).

9.1. 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 eCRF. 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 eCRF.

Patients 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, and 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.

9.2. 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 Aadi medical monitor 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 (patients with known HIV are ineligible for study participation).
- Herbal remedies (eg, St. John's wort) unless approval is granted by the medical monitor.
- Sirolimus is metabolized primarily by CYP3A4. Drugs that are strong inhibitors or inducers of CYP3A4 may only be used under special circumstances (eg, as a single use for a procedure) while treatment with study drug is interrupted. The list may be modified based on emerging data.
- Use of any known CYP3A4 substrates with narrow therapeutic window (such as fentanyl, alfentanil, astemizole, cisapride, dihydroergotamine, pimozide, quinidine,

terfanide) within the 14 days prior to receiving the first dose of ABI-009. Other medications may be allowed if there is agreement between the sponsor and investigator

- Use of strong inhibitors and inducers of CYP3A4 within the 14 days prior to receiving the first dose of ABI-009

9.3. Drug-Drug Interactions of ABI-009 and Standard PAH Medications

The potential for drug-drug interactions between ABI-009 and standard PAH medications is low. Sirolimus is a substrate for (i.e., it is metabolized by) both cytochrome P-450 3A4 (CYP3A4) and p-glycoprotein (P-gp). It is not an inducer or inhibitor of CYP3A4 or P-gp. Several of the standard PAH medications, eg, bosentan, sildenafil, ambrisentan, treprostinil etc are also metabolized primarily by CYP3A4. Since none of these medications are strong inducers or inhibitors of CYP3A4, they are used in together in combination for treatment of PAH. Therefore, addition of ABI-009 to standard PAH therapy is not expected to alter the PK of these drugs or cause adverse drug interactions. Nevertheless, in the planned clinical study the starting dose is 10X below the MTD determined in an oncology phase 1 study, giving a very wide safety margin for the patients. Additionally, safety will be closely monitored along with the PK of sirolimus in the PAH phase 1 study, and it may be possible to identify if any AE is related to drug interactions through analysis of sirolimus plasma levels.

10. STATISTICAL CONSIDERATIONS

10.1. Study Endpoints

Primary Endpoints:

MTD, DLTs, and toxicities and safety profile of 16 weeks, as well as safety profile of the up to 48 weeks of ABI-009 given IV, in patients with PAH who are WHO Functional Class II or III despite best available background therapy.

In the dose-finding portion of the study, 4 dose levels of ABI-009 will be tested in cohorts of 3 patients each (1, 2.5, 5, and 7.5 mg/m^2), using the 3+3 dose escalation design. There will be no intra-patient dose escalation allowed. Escalation to the next dose level with a new cohort of 3 patients will occur after no DLT was observed in the first treatment cycle of 4 weeks. If a DLT occurs in a cohort, additional 3 patients will be recruited to the cohort. If no further DLTs occur, then a new cohort of 3 patients at the next higher dose level can be enrolled. If 2/6 patients at dose level 1a experience a DLT, then that cohort will be closed to further enrollment and the study may be terminated. If 2/6 patients at dose levels 2a or 3a experience a DLT, then the previous dose level is considered the MTD.

The treated population will be the analysis population for all safety analyses. Adverse events will be coded using the Medical Dictionary for Medical Activities (MedDRA) and grouped by their system organ class and preferred term. Summary tables will include the number and percentage of treatment-emergent and treatment-related AEs, AEs of special interest, SAEs, and incidence of patients experiencing dose modifications, dose delay/dose not given, dose interruptions, and/or premature discontinuation of IP due to an AE.

An external Safety Monitoring Committee (SMC) will assess safety data periodically as needed.

Secondary Endpoint(s):

The following will be measurements will be summarized at baseline and at 17 weeks (after 16 weeks of treatment in the Dose-finding Safety Part):

- pulmonary vascular resistance (PVR) by right heart catheterization
- pulmonary artery pressure (PAP)
- pulmonary capillary wedge pressure (PCWP)
- central venous pressure (CVP)

The following will be measurements will be summarized at baseline, 5, 9, 13, and 17 weeks:

- Doppler-echocardiographic assessments of right ventricular structure and function
- 6-minute walk distance (6MWD)
- WHO functional class
- Pulmonary function test

The following will be measurements will be summarized every 8 weeks of the Extension Part (ie, at week E9, E17, E25, and E33):

- 6MWD
- WHO Functional Class
- Pulmonary function test

Exploratory Endpoint(s):

- Pharmacokinetic (PK) profile and trough level of sirolimus for weekly treatment during the 16 weeks of Dose-finding Safety Part and every other week treatment during the Extension Part
- Measurement of brain naturetic peptide (BNP), C-reactive protein (CRP) and troponin levels, indicative of right ventricular strain at baseline, 5, 9, 13, and 17 weeks and for BNP, every 8 weeks in the optional Extension Part (E9, E17, E25, E33)
- Change from baseline to week 17 and to weeks E17 and E33 in the Extension Part in 36-Item Short Form Health Survey (SF-36) physical functioning scale
- Change from baseline to week 17 and to weeks E17 and E33 in the Extension Part in emPHasis10 questionnaire

10.2. Sample Size Considerations

The dose-escalation portion of this clinical study will enroll up to 24 patients. Dose escalation will follow the 3+3 rule to establish the MTD. Three planned dose levels are to be used (Table 1). The minimum number of patients required to establish the MTD is 9 patients. In case there is a dose limiting toxicity at each of the 4 dose levels, each cohort of 3 patients will be expanded to 6 patients, in which case a total of 24 patients will be treated.

After the MTD is achieved, up to 2 cohorts (one including the MTD and one alternate dose or schedule) will be expanded to enroll a total of up to 10 patients in each cohort to further evaluate safety and preliminary utility (potential for clinical efficacy) of ABI-009 in the treatment of PAH.

10.3. Pharmacokinetic Analysis

Pharmacokinetic analysis will include all patients in the phase 1 dose escalation who received ABI-009 during the first 4 weeks (central analysis).

An additional (local) PK study will be conducted to obtain trough sirolimus levels throughout the study (both in the first 16-week Dose-finding Safety (weekly samples) and optional 32-week Extension Part (every-2-week samples) from all enrolled patients , as well as a more detailed sirolimus PK from weeks 1 and 3 from patients who consent. The whole blood concentration of sirolimus will be summarized by descriptive statistics as appropriate. A simple regression model will be applied to assess the relationship of the pharmacokinetic parameters with dose and pharmacodynamics and safety.

11. MONITORING, RECORDING AND REPORTING OF ADVERSE EVENTS

11.1. Toxicities of ABI-009

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

More details on the known precautions, warnings, and AEs of sirolimus and rapalogs are found in the Rapamune® and Torisel® Package Inserts [46, 53].

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a patient during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the patient's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a preexisting condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to the IP should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. Any sequela of an accidental or intentional overdose of the IP should be reported as an AE on the AE CRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself.

All patients will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the patient's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

All AEs will be recorded by the investigator from the time the patient signs informed consent until 28 days after the last dose of ABI-009 and those SAEs made known to the investigator at any time thereafter that are suspected of being related to IP. AEs and SAEs will be recorded on the AE page of the eCRF and in the patient's source documents. All SAEs must be reported to Aadi Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

The investigator's clinical judgment is used to determine whether a patient is to be removed from treatment due to an AE. The investigator is responsible for ensuring that all AEs observed by the investigator or reported by the patient that occur after the first dose of IP through the EOT Visit are reported using the applicable eCRF (eg, AE Summary CRF).

11.2. Evaluation of Adverse Events

The investigator must assign the following AE attributes:

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

The AE toxicity grading scale used will be the NCI CTCAE Version 4.03.

11.3. Serious Adverse Events

11.3.1. Definition of Serious Adverse Events

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

- fatal
- life-threatening (places the patient at immediate risk of death)
- requires 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 (eg, overnight stay).

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

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

11.3.2. Reporting Procedures for Serious Adverse Events

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 eCRF. All SAEs must be reported to Aadi Drug Safety within 24 hours of the investigator’s knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

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

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a patient died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Aadi 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 Drug Safety.

Where required by local legislation, the 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 investigator must keep copies of all SAE information on file including correspondence with Aadi and the IRB/EC.

11.4. Pregnancy and Breast Feeding Reporting

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

The investigator will follow the female patient until completion of the pregnancy, and must notify Aadi Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form. If a lactation case occurs while the female patient is taking protocol-required therapies, report the lactation case to Aadi 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.

12. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

12.1. Discontinuation from Investigational Product

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

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

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

12.2. Discontinuation from the Study

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

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

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

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

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

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

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

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

13. REGULATORY OBLIGATIONS

13.1. Informed Consent

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

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

The investigator is also responsible for asking the patient if the patient has a primary care physician and if the patient agrees to have his/her primary care physician informed of the patient's participation in the clinical study. If the patient agrees to such notification, the investigator is to inform the patient's primary care physician of the patient's participation in the clinical study. If the patient does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the patient's medical record.

The acquisition of informed consent and the patient's agreement or refusal of his/her notification of the primary care physician is to be documented in the patient's medical records, and the informed consent form to be signed and personally dated by the patient or a legally acceptable representative 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 patient or legally acceptable representative.

If a potential patient is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the patient and must allow for questions. Thereafter, both the patient and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

13.2. Institutional Review Board/Independent Ethics Committee

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

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

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

13.3. Patient Confidentiality

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

- Patients are to be identified by a unique patient identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRF demographics page, in addition to the unique patient identification number, include the age at time of enrollment.
- For SAEs reported to Aadi, patients are to be identified by their unique patient identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Aadi (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

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

13.4. Protocol Amendments

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

13.5. Termination of the Study

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

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

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

14.2. Data Management

Data will be collected via eCRF 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.

14.3. Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including patients not receiving protocol-required therapies) as stipulated in the protocol for each patient in the study. For patients who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 2), the investigator can search publicly available records (where permitted) to ascertain survival status.

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

14.4. Sample Storage and Destruction

Any blood, biomarker or pharmacokinetic sample collected according to the Schedule of Assessments (Table 2) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study patients. 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.

If informed consent is provided by the patient, Aadi can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the disease, the dose response and/or prediction of response to ABI-009, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the patient directly or to alter the treatment course, the results of biomarker, biomarker development, or other exploratory studies are not placed in the patient's medical record and are not to be made available to

the patient, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The patient retains the right to request that the sample material be destroyed by contacting the Investigator. Following the request from the patient, the investigator is to provide the sponsor with the required study and patient 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 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 patient through the Investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The patient has no commercial rights to such product and has no commercial rights to the data.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1. Study Monitoring

The Aadi representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, eCRFs and other pertinent data) provided that patient confidentiality is respected.

The Aadi representative is responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. Monitoring will include on-site visits with the investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, IP storage area, eCRFs, patient's source documents, and all other study documentation will be inspected/reviewed by the Aadi representative in accordance with the Study Monitoring Plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

15.2. 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's Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, and 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.

16. 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.

17. REFERENCES

1. Waxman AB, and Zamanian RT (2013). Pulmonary arterial hypertension: new insights into the optimal role of current and emerging prostacyclin therapies. *Am J Cardiol* **111**, 1A-16A.
2. Rich S (2009). The effects of vasodilators in pulmonary hypertension: pulmonary vascular or peripheral vascular? *Circulation. Heart failure* **2**, 145-150.
3. Macchia A, Marchioli R, Tognoni G, Scarano M, Marfisi R, Tavazzi L, and Rich S (2010). Systematic review of trials using vasodilators in pulmonary arterial hypertension: why a new approach is needed. *Am Heart J* **159**, 245-257.
4. Hoeper MM, Barst RJ, Bourge RC, Feldman J, Frost AE, Galie N, Gomez-Sanchez MA, Grimminger F, Grunig E, Hassoun PM*, et al.* (2013). Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: Results of the randomized IMPRES study. *Circulation* **127**, 1128-1138.
5. Krymskaya VP, Snow J, Cesarone G, Khavin I, Goncharov DA, Lim PN, Veasey SC, Ihida-Stansbury K, Jones PL, and Goncharova EA (2011). mTOR is required for pulmonary arterial vascular smooth muscle cell proliferation under chronic hypoxia. *FASEB J* **25**, 1922-1933.
6. Goncharov DA, Kudryashova TV, Ziai H, Ihida-Stansbury K, Delisser H, Krymskaya VP, Tuder RM, Kawut SM, and Goncharova EA (2014). Mammalian Target of Rapamycin Complex 2 (mTORC2) Coordinates Pulmonary Artery Smooth Muscle Cell Metabolism, Proliferation, and Survival in Pulmonary Arterial Hypertension. *Circulation* **129**, 864-874.
7. Paddenberg R, Stieger P, von Lilien AL, Faulhammer P, Goldenberg A, Tillmanns HH, Kummer W, and Braun-Dullaeus RC (2007). Rapamycin attenuates hypoxia-induced pulmonary vascular remodeling and right ventricular hypertrophy in mice. *Respir Res* **8**, 15.
8. Wessler JD, Steingart RM, Schwartz GK, Harvey BG, and Schaffer W (2010). Dramatic improvement in pulmonary hypertension with rapamycin. *Chest* **138**, 991-993.
9. Houssaini A, Abid S, Mouraret N, Wan F, Rideau D, Saker M, Marcos E, Tissot CM, Dubois-Rande JL, Amsellem V*, et al.* (2013). Rapamycin reverses pulmonary artery smooth muscle cell proliferation in pulmonary hypertension. *Am J Respir Cell Mol Biol* **48**, 568-577.
10. Cool CD, Groshong SD, Oakey J, and Voelkel NF (2005). Pulmonary hypertension: cellular and molecular mechanisms. *Chest* **128**, 565S-571S.
11. Wiederrecht GJ, Sabers CJ, Brunn GJ, Martin MM, Dumont FJ, and Abraham RT (1995). Mechanism of action of rapamycin: new insights into the regulation of G1-phase progression in eukaryotic cells. *Prog Cell Cycle Res* **1**, 53-71.
12. Gonzalez-Angulo AM, Meric-Bernstam F, Chawla S, Falchook G, Hong D, Akcakanat A, Chen H, Naing A, Fu S, Wheler J*, et al.* (2013). Weekly nab-Rapamycin in Patients with Advanced Nonhematologic Malignancies: Final Results of a Phase I Trial. *Clin Cancer Res* **19**, 5474-5484.
13. Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, Barst RJ, Benza RL, Liou TG, Turner M*, et al.* (2010). Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. *Chest* **137**, 376-387.

14. Peacock AJ, Murphy NF, McMurray JJ, Caballero L, and Stewart S (2007). An epidemiological study of pulmonary arterial hypertension. *Eur Respir J* **30**, 104-109.
15. Mukerjee D, St George D, Coleiro B, Knight C, Denton CP, Davar J, Black CM, and Coghlan JG (2003). Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. *Ann Rheum Dis* **62**, 1088-1093.
16. Hachulla E, Gressin V, Guillevin L, Carpentier P, Diot E, Sibilia J, Kahan A, Cabane J, Frances C, Launay D*, et al.* (2005). Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. *Arthritis Rheum* **52**, 3792-3800.
17. Abraxis BioScience (2003) Report PK-AB-1: Whole Blood Kinetics and Tissue Distribution of Rapamycin in Rats after Intravenous and Intratracheal Administration.
18. Yuan R, Kay A, Berg WJ, and Lebwohl D (2009). Targeting tumorigenesis: development and use of mTOR inhibitors in cancer therapy. *J Hematol Oncol* **2**, 45.
19. Corradetti MN, and Guan KL (2006). Upstream of the mammalian target of rapamycin: do all roads pass through mTOR? *Oncogene* **25**, 6347-6360.
20. Dowling RJ, Topisirovic I, Fonseca BD, and Sonenberg N (2010). Dissecting the role of mTOR: lessons from mTOR inhibitors. *Biochim Biophys Acta* **1804**, 433-439.
21. Gradishar WJ, Tjulandin S, Davidson N, Shaw H, Desai N, Bhar P, Hawkins M, and O'Shaughnessy J (2005). Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol* **23**, 7794-7803.
22. Desai N, Trieu V, Yao Z, Louie L, Ci S, Yang A, Tao C, De T, Beals B, Dykes D*, et al.* (2006). Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel. *Clin Cancer Res* **12**, 1317-1324.
23. Stehle G, Sinn H, Wunder A, Schrenk HH, Stewart JC, Hartung G, Maier-Borst W, and Heene DL (1997). Plasma protein (albumin) catabolism by the tumor itself--implications for tumor metabolism and the genesis of cachexia. *Crit Rev Oncol Hematol* **26**, 77-100.
24. Maniatis NA, Chernaya O, Shinin V, and Minshall RD (2012). Caveolins and lung function. *Adv Exp Med Biol* **729**, 157-179.
25. Maeda H (2001). The enhanced permeability and retention (EPR) effect in tumor vasculature: the key role of tumor-selective macromolecular drug targeting. *Adv Enzyme Regul* **41**, 189-207.
26. Lever MJ, and Jay MT (1990). Albumin and Cr-EDTA uptake by systemic arteries, veins, and pulmonary artery of rabbit. *Arteriosclerosis* **10**, 551-558.
27. Schubert W, Frank PG, Razani B, Park DS, Chow CW, and Lisanti MP (2001). Caveolae-deficient endothelial cells show defects in the uptake and transport of albumin in vivo. *J Biol Chem* **276**, 48619-48622.

28. Vogel SM, Minshall RD, Pilipovic M, Tiruppathi C, and Malik AB (2001). Albumin uptake and transcytosis in endothelial cells in vivo induced by albumin-binding protein. *Am J Physiol Lung Cell Mol Physiol* **281**, L1512-1522.
29. Bogatcheva NV, Garcia JG, and Verin AD (2002). Molecular mechanisms of thrombin-induced endothelial cell permeability. *Biochemistry. Biokhimiia* **67**, 75-84.
30. Budhiraja R, Tuder RM, and Hassoun PM (2004). Endothelial dysfunction in pulmonary hypertension. *Circulation* **109**, 159-165.
31. Hastings RH, Folkesson HG, and Matthay MA (2004). Mechanisms of alveolar protein clearance in the intact lung. *Am J Physiol Lung Cell Mol Physiol* **286**, L679-689.
32. Wunder A, Muller-Ladner U, Stelzer EH, Funk J, Neumann E, Stehle G, Pap T, Sinn H, Gay S, and Fiehn C (2003). Albumin-based drug delivery as novel therapeutic approach for rheumatoid arthritis. *J Immunol* **170**, 4793-4801.
33. Wang Z, Li J, Cho J, and Malik AB (2014). Prevention of vascular inflammation by nanoparticle targeting of adherent neutrophils. *Nat Nanotechnol* **9**, 204-210.
34. Eddahibi S, Humbert M, Fadel E, Raffestin B, Darmon M, Capron F, Simonneau G, Dartevelle P, Hamon M, and Adnot S (2001). Serotonin transporter overexpression is responsible for pulmonary artery smooth muscle hyperplasia in primary pulmonary hypertension. *J Clin Invest* **108**, 1141-1150.
35. Teichert-Kuliszewska K, Kutryk MJ, Kuliszewski MA, Karoubi G, Courtman DW, Zucco L, Granton J, and Stewart DJ (2006). Bone morphogenetic protein receptor-2 signaling promotes pulmonary arterial endothelial cell survival: implications for loss-of-function mutations in the pathogenesis of pulmonary hypertension. *Circ Res* **98**, 209-217.
36. Xu W, Koeck T, Lara AR, Neumann D, DiFilippo FP, Koo M, Janocha AJ, Masri FA, Arroliga AC, Jennings C*, et al.* (2007). Alterations of cellular bioenergetics in pulmonary artery endothelial cells. *Proc Natl Acad Sci U S A* **104**, 1342-1347.
37. Adnot S, and Eddahibi S (2007). Lessons from oncology to understand and treat pulmonary hypertension. *International journal of clinical practice. Supplement*, 19-25.
38. Tuder RM, Davis LA, and Graham BB (2012). Targeting energetic metabolism: a new frontier in the pathogenesis and treatment of pulmonary hypertension. *Am J Respir Crit Care Med* **185**, 260-266.
39. Cirstea D, Hideshima T, Rodig S, Santo L, Pozzi S, Vallet S, Ikeda H, Perrone G, Gorgun G, Patel K*, et al.* (2010). Dual inhibition of akt/mammalian target of rapamycin pathway by nanoparticle albumin-bound-rapamycin and perifosine induces antitumor activity in multiple myeloma. *Mol Cancer Ther* **9**, 963-975.
40. Trieu V, Ran S, Volk L, Stutzman A, D'Cruz O, and Desai N (2009) CNS safety, antitumor activity, and antiangiogenic activity of nab-rapamycin (ABI-009) [abstr 136], Denver, CO.
41. De T, Trieu V, Yim Z, Cordia J, Yang A, Beals B, Ci S, Louie L, and Desai N (2007) Nanoparticle albumin-bound (nab) rapamycin as an anticancer agent [abstr 4719], Los Angeles, CA.

42. Kennecke H, Rahman M, Yip S, Woods R, Schaeffer D, and Tai I (2011) Effect of nab-rapamycin versus rapamycin in colorectal cancer cell lines and associations with KRAS and PI3K mutations. J Clin Oncol Chicago, IL,, abstr e13532.
43. Gasper WJ, Jimenez CA, Walker J, Conte MS, Seward K, and Owens CD (2013). Adventitial Nab-Rapamycin Injection Reduces Porcine Femoral Artery Luminal Stenosis Induced by Balloon Angioplasty via Inhibition of Medial Proliferation and Adventitial Inflammation. *Circulation. Cardiovascular interventions*.
44. Napoli KL, Wang ME, Stepkowski SM, and Kahan BD (1997). Distribution of sirolimus in rat tissue. *Clinical biochemistry* **30**, 135-142.
45. Seyfarth HJ, Hammerschmidt S, Halank M, Neuhaus P, and Wirtz HR (2013). Everolimus in patients with severe pulmonary hypertension: a safety and efficacy pilot trial. *Pulmonary circulation* **3**, 632-638.
46. Wyeth Pharmaceuticals Inc. (2015) Rapamune® Package Insert, New York, NY.
47. Kelly PA, Napoli K, and Kahan BD (1999). Conversion from liquid to solid rapamycin formulations in stable renal allograft transplant recipients. *Biopharm Drug Dispos* **20**, 249-253.
48. Garrido-Laguna I, Tan AC, Uson M, Angenendt M, Ma WW, Villaroel MC, Zhao M, Rajeshkumar NV, Jimeno A, Donehower R*, et al.* (2010). Integrated preclinical and clinical development of mTOR inhibitors in pancreatic cancer. *Br J Cancer* **103**, 649-655.
49. Jimeno A, Rudek MA, Kulesza P, Ma WW, Wheelhouse J, Howard A, Khan Y, Zhao M, Jacene H, Messersmith WA*, et al.* (2008). Pharmacodynamic-guided modified continuous reassessment method-based, dose-finding study of rapamycin in adult patients with solid tumors. *J Clin Oncol* **26**, 4172-4179.
50. Cohen EE, Wu K, Hartford C, Kocherginsky M, Eaton KN, Zha Y, Nallari A, Maitland ML, Fox-Kay K, Moshier K*, et al.* (2012). Phase I studies of sirolimus alone or in combination with pharmacokinetic modulators in advanced cancer patients. *Clin Cancer Res* **18**, 4785-4793.
51. Hidalgo M, Buckner JC, Erlichman C, Pollack MS, Boni JP, Dukart G, Marshall B, Speicher L, Moore L, and Rowinsky EK (2006). A phase I and pharmacokinetic study of temsirolimus (CCI-779) administered intravenously daily for 5 days every 2 weeks to patients with advanced cancer. *Clin Cancer Res* **12**, 5755-5763.
52. Laboratories ATSCoPSfCPF (2002). ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* **166**, 111-117.
53. Wyeth Pharmaceuticals Inc. (2015) TORISEL® Package Insert, Philadelphia, PA.