Severe Pulmonary Arterial Hypertension Treated with ABI-009, *nab*-Sirolimus, an mTOR inhibitor

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Relevant Financial Relationship Disclosure Statement

Severe Pulmonary Arterial Hypertension Treated with ABI-009, nab-Sirolimus, an mTOR inhibitor

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I will discuss investigational use of the following drug: ABI-009 (*nab*-sirolimus)

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M. Simon, MD, M. Gomberg-Maitland, MD, R.J. Oudiz, MD, R. Machado, MD, and J.M. Elinoff, MD received research support from Aadi Bioscience

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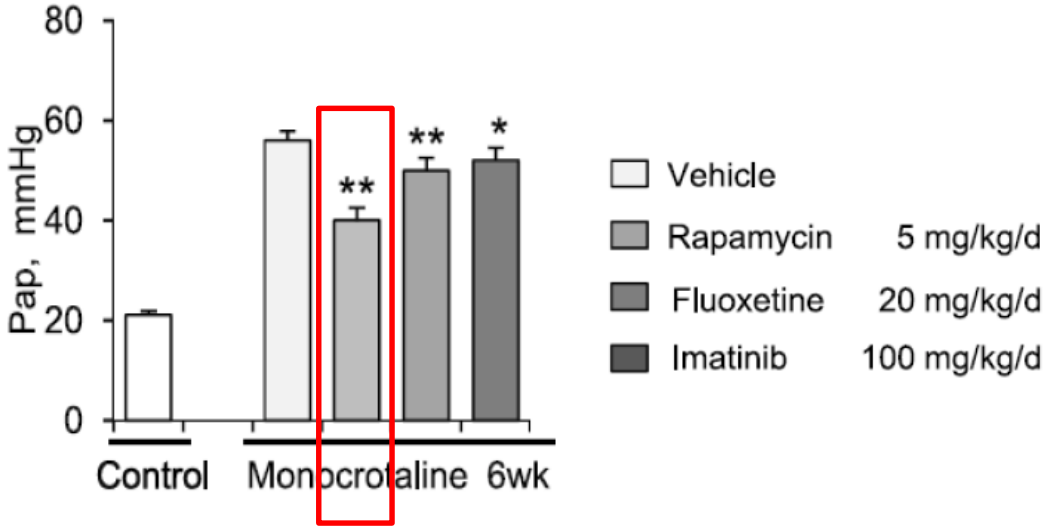
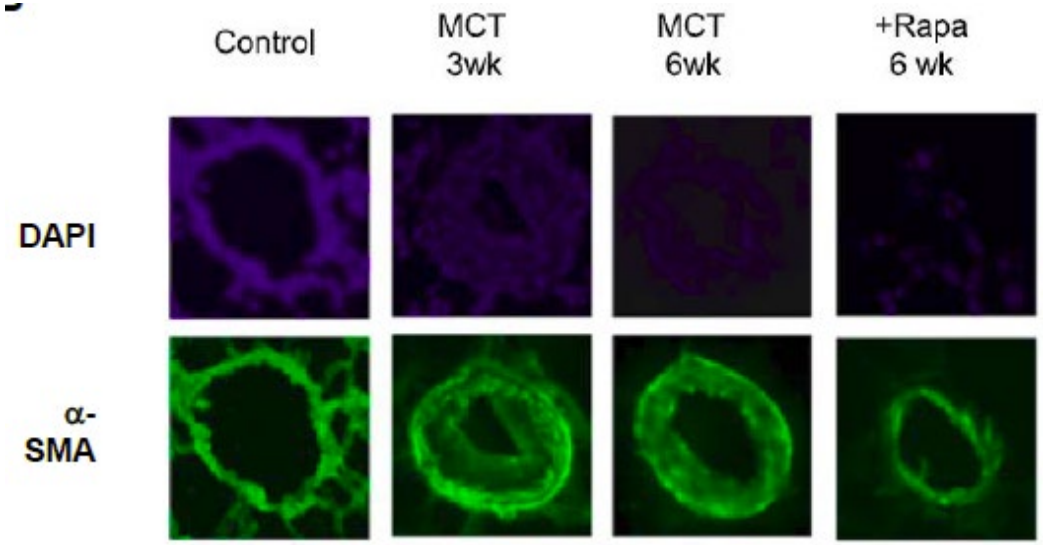
Severe Pulmonary Arterial Hypertension
Treated with ABI-009, *nab*-Sirolimus, an mTOR inhibitor
Phase 1/2 Clinical Trial Rationale

mTOR Pathway is activated in PAH

Sirolimus (mTOR inhibitor) is effective in reversing PAH in animal models

Monocrotaline (MCT) induced PAH in Rats : Rapamycin Treatment days 21-42





However, oral sirolimus doses required (5 mg/kg/d = 30 mg/m²/d) are too high and not clinically feasible

Houssaini et al., 2013. *Am J Respir Cell Mol Biol 48:568-77*
Goncharov et al., 2014 *Circulation*

Severe Pulmonary Arterial Hypertension
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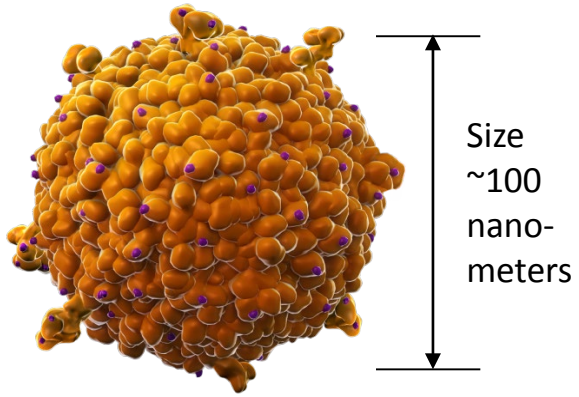
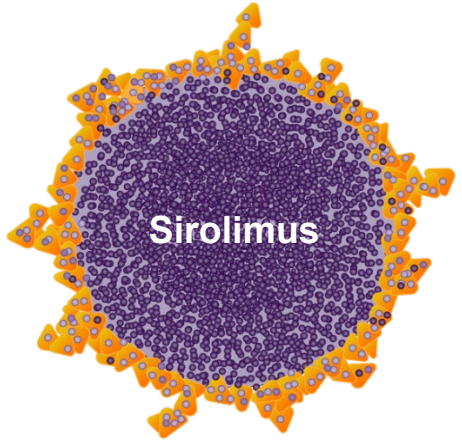
Phase 1/2 Clinical Trial Rationale

- ABI-009, is currently in clinical trials for various oncology and nononcology indications.
- ABI-009 achieves high lung tissue levels (3-fold higher vs oral rapalogs), long half-life, and can be combined with standard PAH therapies. [1,2]

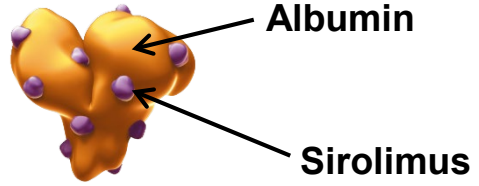
***nab*-Sirolimus Nanoparticle Schematic**



Cross Section



Albumin-bound Sirolimus



- The aim of this open-label, prospective, multicenter phase 1/2 clinical study is to investigate the safety and identify the optimal dose of ABI-009 added to standard PAH therapy in patients with severe PAH.

1. Napoli et al., Clinical Biochem 1997, 30:135-142
2. Hou et al., AACR 2019

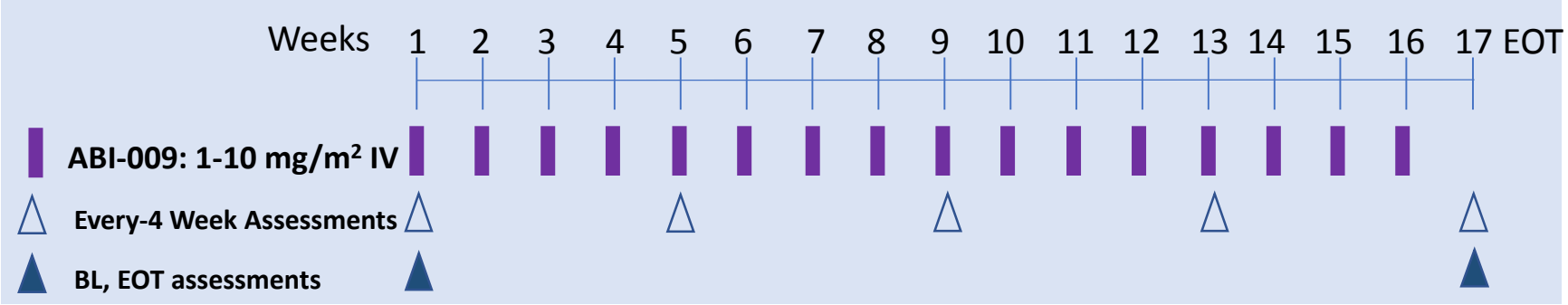
Severe Pulmonary Arterial Hypertension
Treated with ABI-009, *nab*-Sirolimus, an mTOR inhibitor
Phase 1/2 Clinical Trial Design

ClinicalTrials.gov: NCT02587325

Key Eligibility

- ≥ 18 years old
- No prior mTOR inhibitor
- WHO Functional Class III
- On ≥ 2 standard PAH therapies
- PVR ≥ 5 Woods units
- 6MWD 150-450 meters

Dose finding: 1, 2.5, 5, 10 mg/m² (3+3); escalation/de-escalation
ABI-009 IV once weekly for 16 weeks
N = up to 18 patients



- **Primary Endpoint**
  - MTD, DLT, and safety profile of 16 weeks of IV ABI-009

- **Key Secondary Endpoints (change from baseline to 17 wk)**
  - WHO functional class
  - 6-min walk distance
  - Pulmonary vascular resistance
  - Cardiac Output
  - NT-proBNP

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Preliminary Safety Results – 9 Treated Patients, as of Feb 22, 2019

Parameters	10 mg/m² n = 4	1 mg/m² n = 3	2.5 mg/m² n = 2
16-weeks completed	n = 3	n = 2	n = 0
Permanent Dose Reduction	• 2 patients reduced to 5 mg/m² (G2 rash, G1 paresthesia) • 1 pt discontinued at week 8 (G3 cellulitis, SAE)	None	None
Most common (≥2) Treatment-related AEs	**All Grade 1 and 2 toxicities:** • Headache • Diarrhea • Rash • Fatigue • Hypertriglyceridemia • Nausea • Thrombocytopenia	**Only G1 toxicities:** • Headache • Pain	None

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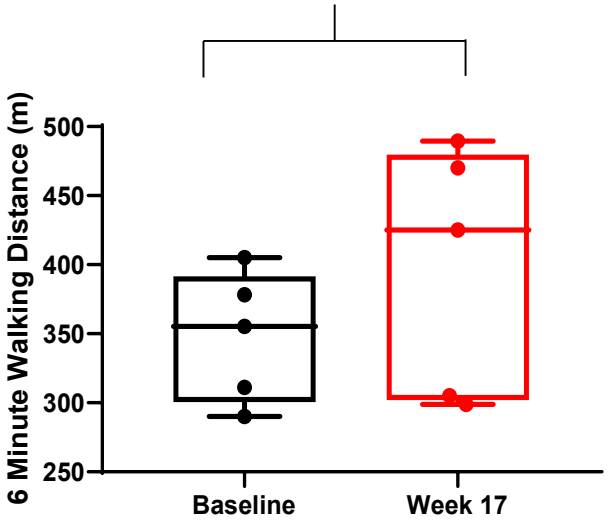
Preliminary Results for 5 patients completing the 16-week treatment: 3/5 patients improved from WHO FC III to FC II

6MWD

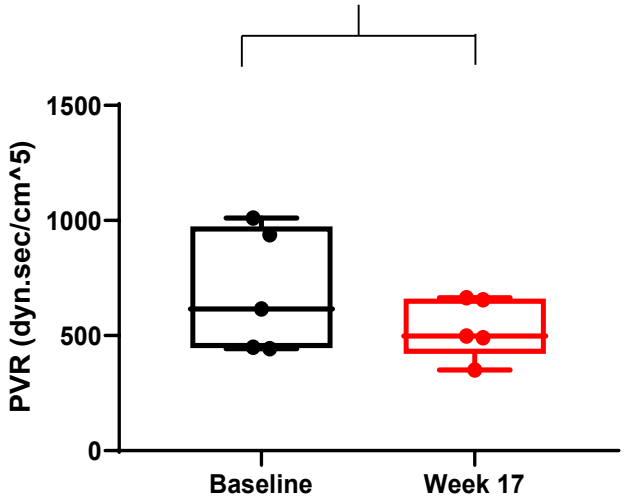
Δ (median) = +20%



- Median ↑ from 355 to 425 meters
- 2 pts improved >130 meters

PVR

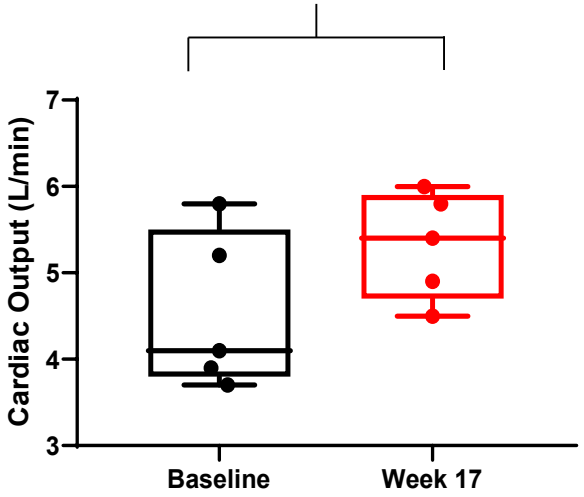
Δ (median) = -19%



- Median ↓ from 616 to 498 dyn.sec/cm^5
- 4/5 pts had improved PVR
- 2 pts ↓ ≥30%

Cardiac Output

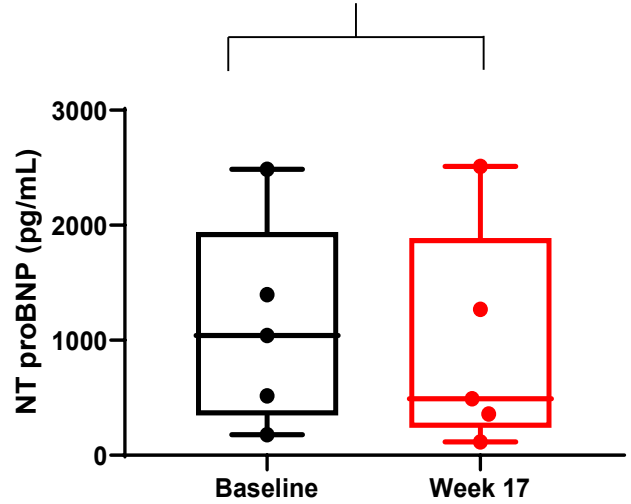
Δ (median) = +32%



- 3 pts had 38% to 62% ↑

NT-proBNP

Δ (median) = -53%



- Median ↓ from 1041 to 492 pg/mL
- 4/5 pts had decreased NT-proBNP

The whiskers represent min and max, the boxes span the interquartile range.

ABI-009, an mTOR Inhibitor, for Patients With Severe Pulmonary Arterial Hypertension

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