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ABI-009, *nab*-Sirolimus, an mTOR Inhibitor with High Lung Accumulation in Preclinical Models: Initial Results from an Ongoing Phase I/II Safety and Preliminary Efficacy Study in Severe PAH

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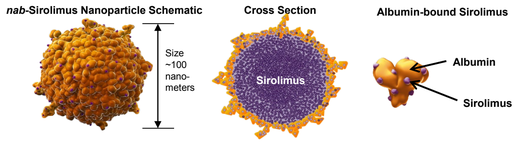
INTRODUCTION

- Pulmonary arterial hypertension (PAH) is a rare, debilitating and fatal disease for which there is currently no cure.
- PAH is characterized by remodeling of the small arteries in the lung, which increases resistance to blood flow.
- Activation of the mTOR pathway has been implicated in PAH
  - Preclinical studies have shown that an mTOR inhibitor can reverse or control the disease, including the remodeling of the small arteries in PAH. [1]
  - Anecdotal clinical data supports the investigation of an mTOR inhibitor to treat PAH. [2, 3]
- ABI-009 is a novel formulation of albumin-bound sirolimus nanoparticles (*nab*-sirolimus) and has produced encouraging results in oncology at doses up to 100 mg/m^2 given intravenously (NCT00635284). [4]
- Herein, we report the preclinical data on lung uptake of ABI-009 and the preliminary results from a phase I/II clinical trial of safety/efficacy in PAH.



METHODS– Biodistribution Studies

- Preclinical Study A: n = 3 rats / time-group received a single dose of ABI-009 IV at 1.7 mg/kg (10 mg/m^2). Whole blood, brain, lungs, liver, heart, and pancreas were collected at the following time points: 2, 8, 24, 72, and 120 hrs to analyze sirolimus levels by LC/MS/MS.
- Preclinical Study B: n = 5 rats / group: compared sirolimus levels in blood, lung, and liver at 24 hrs after 1mg/kg ABI-009 vs 1.6 mg/kg/d oral sirolimus from published data. [5]

METHODS – Clinical Study Design

Key Eligibility
- ≥ 18 years old
- No prior mTOR inhibitor
- WHO Functional Class III
- On ≥ 2 standard PAH therapies

Dose finding: 1, 2.5, 5, 10 mg/m^2 (3+3) ABI-009 IV weekly for 16 weeks
N = up to 18 patients

Cohort expansion
ABI-009 at the MTD and/or an alternate dose/schedule
N = up to 8-10 patients per dose/schedule

Optional Extension Phase
Weekly up to 32 additional weeks at the assigned dose

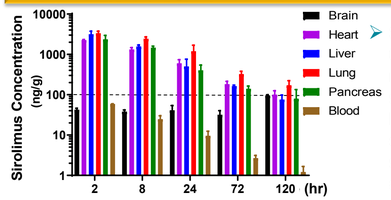
Primary Endpoint During Dose-finding and Cohort Expansion
- MTD, dose limiting toxicity (DLT), and safety profile of 16 weeks of IV ABI-009

Secondary Endpoints: Safety and Exploratory Efficacy
- **Changes in hemodynamics from baseline to EOT (baseline and week 17):** pulmonary vascular resistance (PVR), cardiac output (CO), pulmonary artery pressure, pulmonary capillary wedge pressure, and right atrial pressure

Key Exploratory Endpoints
- Changes in PAH biomarkers: NT-proBNP
- Changes in EmPHasis10 questionnaire

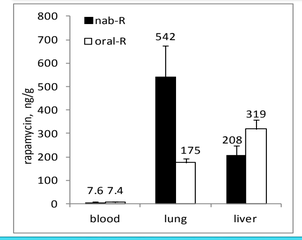
RESULTS - Biodistribution

Preclinical Study A



- Single infusion of ABI-009 IV at 1.7 mg/kg (10 mg/m^2 human dose) shows high distribution in lung tissue maintained over 5 days, >100 ng/g, supporting weekly administration in humans.
- The tissue exposure (AUC) was significantly higher in the lung vs other tissues over 5 days ($P < 0.0001$, ANOVA). Sirolimus lung concentrations (from ABI-009 infusion) were 3358, 2436, 1190, 322, and 171 ng/g at 2, 8, 24, 72, and 120 hrs and lung/blood ratios were 57, 98, 125, 121, and 140, respectively.

Preclinical Study B

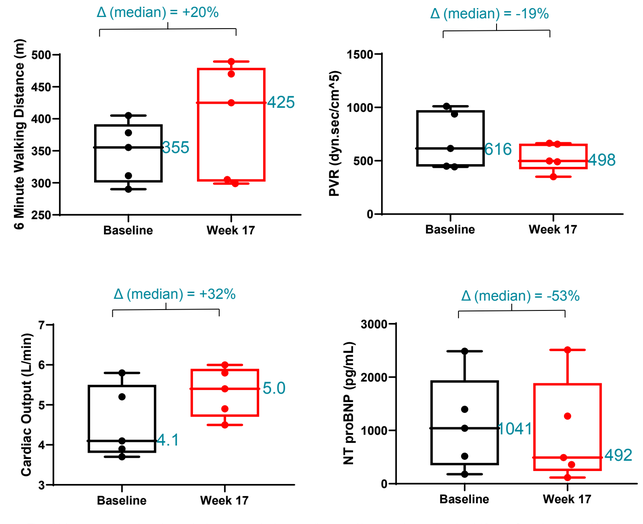


- ABI-009 sirolimus levels in the lung were approx. 3 fold higher compared to oral sirolimus ($p<0.05$). [5]
- In contrast, oral sirolimus levels were higher in liver suggesting no preferential lung accumulation.

RESULTS - Preliminary Clinical

- As of 2/22/2019, 9 patients received treatment with ABI-009: 4 at 10 mg/m^2, 3 at 1 mg/m^2, and 2 at 2.5 mg/m^2; 5 have completed 16 weeks of therapy

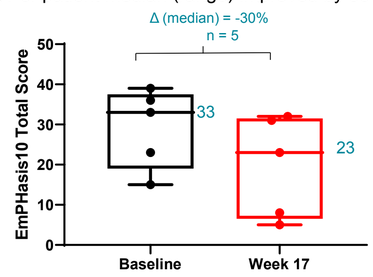
Results for the first 5 patients completing the 16-week treatment



The whiskers represent min and max, the boxes span the interquartile range. Note, 1 patient at dose level 10 mg/m^2 was in a car accident that resulted in a fractured foot during course of therapy and while most parameters improved, 6MWD did not. PVR, pulmonary vascular resistance

EmPHasis10 Questionnaire

- The total score for 5 patients improved from 146 at baseline to 99 at week 17; Per patient median (range) improved by 30%.



Safety (9 treated patients)
- **10 mg/m^2 cohort:**
  - **4 patients received ABI-009; 3/4 completed 16 weeks of treatment**:
    - 1 patient discontinued early at week 8 (cellulitis)
    - 1 patient had no safety concerns
    - 2 patients were dose reduced to 5 mg/m^2 due to rash (week 5) or paresthesia (week 7) and had no further safety concerns
    - The dosing scheme was then reduced to 1, 2.5, and 5 mg/m^2
- **1 mg/m^2 cohort:**
  - **3 patients received ABI-009; 2/3 patients completed 16-weeks of treatment** without significant safety concerns; 1 pt ongoing
- **2.5 mg/m^2 cohort:**
  - **2 patients received ABI-009** and are currently on treatment
- The most common AEs (all grade 1 and 2) have been diarrhea (4 patients), thrombocytopenia, rash, and fatigue (2 patients for each). These AEs occurred at the 10 mg/m^2 dose level and were manageable.

Efficacy (5 efficacy evaluable patients – completed 16 weeks of therapy; Figures). Baseline to Week 17:
- **WHO FC**: 3/5 patients improved from WHO FC III to FC II.
- **6MWD:** 3/5 patients showed 16%-47% increase; 2/5 patients improved >130 m.
- **PVR:** 4/5 patients had reduction in PVR; 2 pts ↓ ≥30%
- **Cardiac Output:** 3 patients at the 10 mg/m^2 dose level had a 38% to 62% increase in cardiac output.
- **NT-proBNP:** 4/5 patients had a decrease in their NT-proBNP levels.
- **Forced vital capacity** measured during pulmonary function test.

CONCLUSIONS

- Preferential delivery of ABI-009 (albumin-bound sirolimus nanoparticles) into the lung compared with oral sirolimus in animal models supports clinical studies in PAH.
- The 10 mg/m^2 dose was not tolerated in PAH. Dosing was reduced to 1, 2.5, and 5 mg/m^2 which is ongoing and without SAE's to date in the 1 and 2.5 mg/m^2 cohorts.
- Functional and hemodynamic measures, and EmPHasis10 QOL results support the ongoing investigation of ABI-009 in patients with severe PAH.

DISCLOSURES

ABI-009 is an investigational agent. The presented clinical trial is supported by Aadi Bioscience; Dr. Simon received research support from Aadi Bioscience.

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