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Patients With Severe Pulmonary Arterial Hypertension Treated With ABI-009, *nab*-Sirolimus, an mTOR Inhibitor: Interim Results From a Phase 1 Clinical Trial

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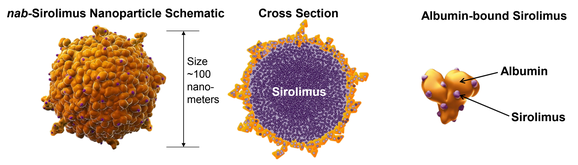
INTRODUCTION

- 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 pressure and the resistance to blood flow through the lungs.
- Activation of the mTOR pathway has been implicated in the development and progression of PAH
  - Preclinical studies have shown that an mTOR inhibitor can reverse or control the disease, including the remodeling in the small arteries PAH. [1]
  - Anecdotal clinical data supports the investigation of an mTOR inhibitor to treat PAH. [2, 3]
- ABI-009 is a novel albumin-bound sirolimus nanoparticle (*nab*-sirolimus) and has produced encouraging results in oncology at doses up to 100 mg/m^2 given intravenously (NCT00635284). [4]
- ABI-009 can achieve high lung tissue levels (3-fold higher than with oral mTOR agents) and can be combined with standard therapy in PAH. [5, 6]



- The aim of this open-label, prospective, multicenter phase 1 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.

Patient Disposition

- As of Feb 22, 2019, 9 patients have received treatment with ABI-009, IV: 4 at 10 mg/m^2, 3 at 1 mg/m^2, and 2 at 2.5 mg/m^2.
  - 5 patients have completed 16 weeks of ABI-009 treatment; 1 patient discontinued early at week 8 (cellulitis)
  - 3 patients are currently on active treatment and have not completed 16 weeks of therapy (1 at 1 mg/m^2 and 2 at 2.5 mg/m^2).

REFERENCES

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2. Wessler et al., Chest 2010, 138:991-993.
3. Seyfarth et al., Pulmonary Circulation 2013, 3: 632-638.
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5. Napoli et al., Clinical Biochem 1997, 30:135-142.
6. Aadi, Data on file

METHODS

ClinicalTrials.gov:NCT02587325

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

Treatment Schema

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

→ Cohort expansion after dose finding
ABI-009 at maximum tolerated dose (MTD) and an alternate dose/schedule
N = up to 8-10 patients per dose/schedule

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

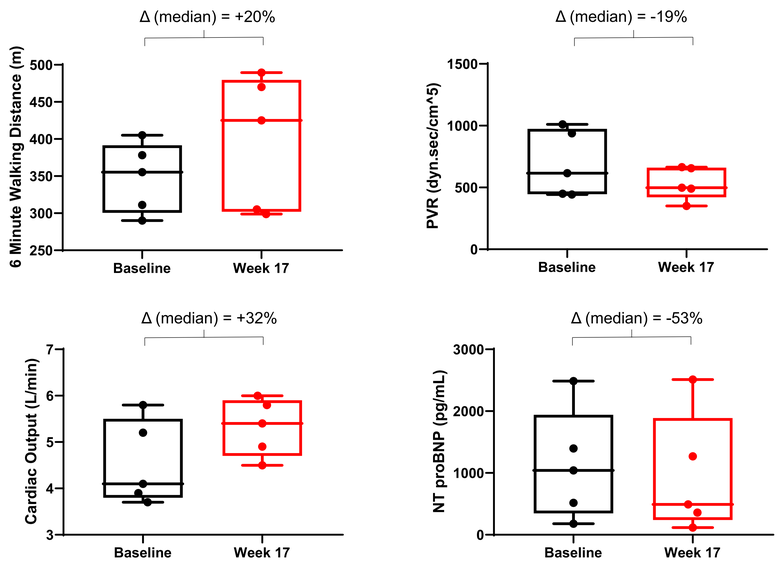
Primary Endpoint
- MTD, dose limiting toxicity (DLT), and safety profile of 16 weeks of IV ABI-009
- Safety profile of the up to 48 weeks of treatment

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
- Changes at every-4-week assessments (baseline and weeks 5, 9, 13, and 17): doppler-echocardiography of right ventricular structure/function, 6-min walk distance (6MWD), WHO FC, pulmonary function testing
- The following will be measured at every 8 weeks of the Extension Phase (additional 32 weeks): 6MWD, WHO FC and pulmonary function testing

Tertiary Safety and Exploratory Endpoints
- PK and trough levels of sirolimus for weekly treatment in patients with PAH
- Changes in PAH biomarkers: N-terminal pro-brain natriuretic peptide (NTproBNP), C-reactive protein, troponin
- Changes in quality of life (emPHasis-10 questionnaire
- Optional blood biomarkers for mTOR, correlative assessment with PAH biomarkers, clinical efficacy/safety

PRELIMINARY RESULTS

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



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

Safety (9 treated patients)
- 4 patients received ABI-009 at 10 mg/m^2 (original starting dose), 3 of which completed 16 weeks of treatment:
  - 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 completed therapy at 5 mg/m^2 without further safety concerns
  - 1 patient discontinued treatment at week 8 due to cellulitis.
- The dosing schema was subsequently modified to escalate dosing from 1 mg/m^2, followed by 2.5 and 5 mg/m^2 if there were no safety concerns at each step.
- 2 patients completed the 16-week ABI-009 protocol at 1 mg/m^2 without significant safety concerns and 1 patient at this dose level is ongoing at week 15 without safety concerns. The 2.5 mg/m^2 dose cohort is now enrolling with 2 patients currently on treatment.
- The most common adverse events (all grade 1 and 2) have been diarrhea (4 patients), thrombocytopenia, rash, and fatigue (2 patients for each). These adverse events occurred at the 10 mg/m^2 dose level and were managed with dose modifications and standard of care.

Exploratory efficacy (5 efficacy evaluable patients – completed 16 weeks of therapy; Figures)
- WHO FC: 3/5 patients improved from WHO FC III to FC II.
- 6MWD: 3/5 patients showed 16%-47% increase; 2 patients improved >130 meters.
- PVR: 4/5 patients had reduction in PVR; median ↓19% from 616 to 498 dyn.sec/cm^5 (2 pts ↓ ≥30%)
- Cardiac Output: 3 patients at the 10 mg/m^2 dose level had a 38% to 62% increase in cardiac output.
- Forced vital capacity measured during pulmonary function test: median ↑ 10%
- NT-proBNP: 4/5 patients had a decrease in their NT-proBNP levels; median ↓ 53% (1041 to 492 pg/mL).

CONCLUSIONS

- Sixteen weeks of ABI-009 treatment combined with standard PAH therapy was safe and the dose finding phase is ongoing.
- Interim safety and efficacy results, including functional and hemodynamic measures support the ongoing investigation of ABI-009 in patients with severe PAH.

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