PHASE 1 SAFETY AND TOLERABILITY STUDY OF IMB-1018972, A NOVEL ORAL MODULATOR OF MYOCARDIAL SUBSTRATE UTILIZATION DESIGNED TO IMPROVE CARDIAC METABOLIC EFFICIENCY AND BIOENERGETICS

P. Chamberlin[1], L. Barrett[1], N. Buckley[1], G. Mooney[1], L. Tremain[1], J. Van De Wetering[2], T. Van Iersel[2], J. Patel[1]

(1) Imbria Pharmaceuticals, Boston, United States of America (2) PRA Health Sciences, Groningen, Netherlands

BACKGROUND

- The heart has the highest energy demands (ATP/g tissue) of any organ to meet the demands of continual mechanical work and maintain ionic homeostasis
- Under normoxic conditions, the majority of ATP generated is derived from mitochondrial oxidative phosphorylation following metabolism of carbon substrates, principally fatty acids (FA) and glucose.
- Cardiac metabolic remodeling and energetic impairment are hallmarks of many inherited and acquired heart muscle disorders and may promote dysfunction.
- IMB-1018972 is a novel investigational mitotrope designed to partially shift myocardial substrate utilization in favor of glucose oxidation by reducing FA oxidation through direct competitive inhibition of 3-ketoacyl CoA thiolase.
- The metabolism of carbohydrate generates more ATP per unit oxygen consumption, thereby increasing myocardial metabolic efficiency.
- In preclinical models, the pharmacokinetic (PK) profile of IMB-1018972 following oral administration was characterized by a rapid appearance of IMB-1028814, the primary circulating metabolite.
- Preclinical efficacy of IMB-1018972 has been demonstrated in murine models of cardiac pressure overload, post-myocardial infarction heart failure and ex vivo global ischemia-reperfusion injury.

OBJECTIVES

- **Primary**: To determine the safety and tolerability of single and multiple oral doses of IMB-1018972 in immediate and modified release formulations, in healthy adult subjects.
- **Secondary**: To evaluate the PK characteristics of IMB-1018972 following single-and multiple-dose regimens, including with food.

METHODS

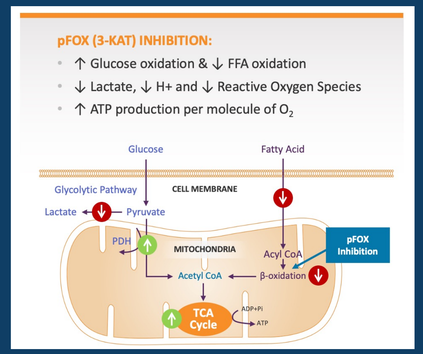
- First-in-human, phase 1, randomized, double-blind, placebo-controlled study.
- Part 1 evaluated IMB-1018972 in single ascending doses of 50, 150 (fed/fast), and 400 mg of an immediate-release (IR) formulation, N=6/2 active/placebo and a single dose of 35 mg trimetazidine MR as comparator, N=8 (**Figure 1**).
- Part 2 evaluated IMB-1018972 in multiple doses of 50 and 150 mg given twice daily (BID) for 14 days, N=9/3 active/placebo.
- Part 3 evaluated IMB-1018972 with 4 or 8 hour modified release (MR) profiles:
  - Single doses of 50 or 200 mg, given fed or fasted, N=12 active
  - Multiple doses of 200 mg 8-hour MR formulation given BID for 5 days, N=12 active
- Serial blood and urine samples were collected and analyzed for IMB-1018972, IMB-1028814, and trimetazidine with validated assays for PK analyses.
- Safety assessments included adverse event (AE) reporting, physical exam, clinical laboratories, 12-lead ECG and telemetry collection.

RESULTS

- 88 healthy adult subjects participated in the study comprised of: 66 receiving IMB-1018972; 14 receiving placebo; 8 receiving trimetazidine.
- For IMB-1018972 this consisted of:
  - 24 subjects received single doses (IR) of 50 to 400 mg
  - 18 subjects received 50 to 150mg (IR) BID for 14 days
  - 12 subjects received single doses of 50 and 200 mg (MR)
  - 12 subjects received multiple doses of 200 mg (MR) BID for 5 days

IMB-1018972 (IMB-101) is a novel, investigational cardiac mitotrope under development for the treatment of cardiovascular disease

IMB-101 acts as a partial fatty acid oxidation (pFOX) inhibitor to increase pyruvate dehydrogenase (PDH) activity and enhance carbohydrate oxidation



IMB-101 is a pro-drug of three active metabolites

IMB-101 is well tolerated and exhibits predictable PK characteristics in a phase 1 healthy volunteer study

IMB-101 is currently being investigated in 3 phase 2, proof-of-concept studies in patients with hypertrophic cardiomyopathy, stable angina and type 2 diabetes

For more information, scan the QR code, go to *www.imbria.com* or email *pc@imbria.com*

ACC.21

imbria PHARMACEUTICALS

Pharmacokinetics

- Following single and multiple oral doses, IMB-1018972 was rapidly absorbed into the systemic circulation; IMB-1018972 was not detected in plasma in doses below 400 mg except after 150 mg BID multiple dose for ≤30 mins.
- IMB-1028814 and trimetazidine were the predominant circulating moieties. Combining all cohorts, median times to maximum concentration (T_{max}) for IMB-1028814 and trimetazidine ranged from 0.5 to 5.0 hours and 1.5 to 8.0 hours, respectively.
- IMB-1028814 and trimetazidine concentrations declined rapidly after T_{max}. Combining all cohorts, geometric mean half-life ($t_{1/2}$) for IMB-1028814 and trimetazidine ranged from 2.5 to 4.5 hours and 6.5 to 9.5 hours, respectively.
- IMB-1028814 and trimetazidine peak plasma concentrations (Cmax) and area-under the concentration (AUC)-time curves increased in an approximately dose-proportional manner following single and multiple dose administrations.
- The sum of the molar concentrations of IMB-1018972 and trimetazidine, for C_{max} and AUC, had lower coefficients of variation percentage (CV%) than either moiety alone.
- No evidence for an effect of food was observed on the AUC of IMB-1028814 or trimetazidine after a 200 mg MR dose, C_{max} of IMB-1028814 was approximately 42% higher than in the fasted state.
- After 5 days of dosing with 200 mg MR IMB-1018972 BID, minimal accumulation of IMB-1028814 (R_{ac} of 1.22) and moderate accumulation of trimetazidine (R_{ac} of 2.28) were observed. Steady state plasma levels were reached by day 5.
- After a single oral dose of IMB-1018972 over the range of 50 to 400 mg, between 3.9% and 5.7% of the dose was excreted as IMB-10288214 and 23.1% and 32.5% as trimetazidine in the urine.

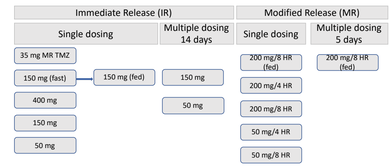
Safety

- Orally administered IMB-1018972 was well tolerated at all doses and formulations evaluated. Most AEs were mild in severity and transient.
- One SAE of influenza-like illness (not related) led to withdrawal
- One subject withdrew due to a moderate ALT (but not AST) increase.
- IMB-1018972 had no impact on hemodynamics or ECG indices (including QTc) and exhibited no adverse trends on clinical laboratory measures.

CONCLUSIONS

IMB-1018972 given as single or multiple oral doses of IR/MR formulations was well tolerated and exhibited predictable PK. Three phase 2 studies will examine the safety and pharmacodynamic effects of IMB-1018972 as a cardiac mitotrope in patients with hypertrophic cardiomyopathy, stable angina and type 2 diabetes commencing in early 2021.

FIG. 1 - STUDY DESIGN



The study design was made in accordance with the principles of formulation design space (McDermott & Scholes, *Ther Deliv* 2015) .

FIG. 2 - SINGLE ASCENDING DOSE PK

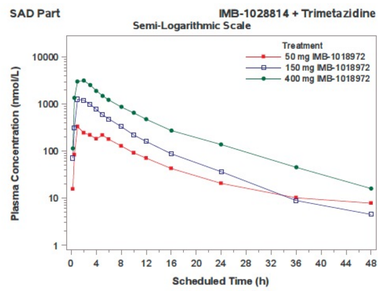


FIG. 3 - MULTIPLE ASCENDING DOSE PK

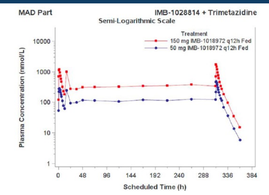
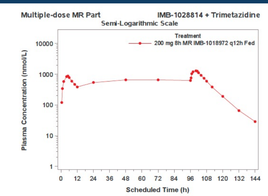


FIG. 4 - MR FORMULATION PK



DISCLOSURE INFORMATION

Author Disclosure. PC, LB, NB, GM, LT, and JP are employees/shareholders of Imbria. JdvW and TvI are employees of PRA Health Sciences.