A PHASE 1/1B STUDY OF AN INHALED FORMULATION OF ITRACONAZOLE IN HEALTHY VOLUNTEERS AND ASTHMATICS


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Abstract

Inhalation: Itraconazole has variable pharmacokinetics and risks of significant adverse events (AEs) associated with high plasma exposure. A dry powder inhalation formulation of itraconazole (PUR1900) is being developed to treat Allergic Bronchopulmonary Aspergillosis (ABPA). This study was conducted to evaluate safety, tolerability and pharmacokinetics of PUR1900 in healthy volunteers and asthmatics.

Methods: The study was a 3-part, multi-center, open-label study. Healthy volunteers (n=45/68/group) received either single (Part 1: 5 – 10 mg, 20 mg, 30 mg) or multiple (Part 2: 5 mg, 10 mg, 25 mg) doses of PUR1900 over 14d. In Part 3, stable, asthmatic received a single dose of 20mg PUR1900 or 200mg of oral itraconazole in a 2-period, cross-over design. Results: All study drug-related AEs were mild, and no moderate, severe or serious study drug-related AEs were reported. The most common drug-related AEs were cough (10 mg: 4/28, 10 mg: 3/28, 20 mg: 1/28, 30 mg: 1/28). The most frequent occurrence of mild cough at steady state was 1/28. ITZ resulted in plasma AUC(max) that was 10x to 400x lower across across all groups compared to the oral formulation supporting once daily dosing. Mean ITZ concentrations that were 70 fold higher and plasma AUC(max) concentrations that were 66 fold lower than with oral itraconazole. Conclusions: PUR1900 was safe and well-tolerated under the study conditions tested, and achieved significantly higher lung and lower plasma exposure compared to oral itraconazole, supporting the potential of PUR1900 to improve upon both the efficacy and safety profile observed with oral itraconazole in patients with ABPA.

PART 1

Part 1: Single Ascending Dose Design and Safety

Part 1 was a single ascending dose (SAD) study in healthy volunteers conducted to determine the pharmacokinetics, safety and tolerability of single doses of PUR1900 at 5 – 10 mg, 20 mg, 30 mg, and 50 mg. Subjects were randomized to receive a single dose of PUR1900 5, 10, 20, 30, or 50 mg and returned to the clinic at Day 5 for safety assessment. There were no safety concerns with any dose level. Mean plasma ITZ levels were the highest at the 10 mg dose.

Part 1: Multiple Dose Design and Safety

Part 2 was a multiple ascending dose (MAD) study in healthy subjects at steady state conducted to determine the pharmacokinetics, safety and tolerability of multiple doses of PUR1900 at 5 mg, 10 mg, 25 mg, and 50 mg. Subjects were randomized to receive multiple doses of PUR1900 at 5 mg, 7.5 mg, 10 mg, and 12.5 mg at Days 1 and 14. There were no safety concerns with any dose level, except for cough related to the study drug. Plasma ITZ levels were the highest at the 50 mg dose.

PART 2

Part 3: Single Dose Crossover Design and Safety

Part 3 was a 2-period, randomized, crossover study in adult subjects with moderate to severe ABPA (n=17). Safety, tolerability and PK of single-dose PUR1900 (5 mg) were assessed. Subjects were randomized to receive a single oral dose of 20mg itraconazole solution or a single inhaled dose of PUR1900 (5 mg) at Day 1. Subjects returned to the clinic at Day 3 for follow-up. Plasma ITZ samples were collected following inhalation of hydroxy itraconazole at specific timepoints of 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours. Subjects returned to the clinic at Day 7 for completion of the single dose and PK testing. Plasma ITZ samples were tested for concentrations of therapeutic and AUC(0-24) with changes in safety and tolerability.

PATIENTS AND METHODS

In a 2-center, open-label, single-center study, eligible patients with moderate to severe ABPA (n=17) were randomized to receive a single oral dose of 20mg itraconazole solution or a single inhaled dose of PUR1900 (5 mg) at Day 1. Subjects returned to the clinic at Day 3 for follow-up. Plasma ITZ samples were collected following inhalation of hydroxy itraconazole at specific timepoints of 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours. Subjects returned to the clinic at Day 7 for completion of the single dose and PK testing. Plasma ITZ samples were tested for concentrations of therapeutic and AUC(0-24) with changes in safety and tolerability.

Part 3: Single Dose Pharmacokinetics in Asthmatics

PUR1900 was found to be well tolerated and highly efficacious in asthmatic subjects. This is the first study to report plasma ITZ concentrations following inhalation of hydroxy itraconazole in asthmatics. In asthmatics, lower plasma ITZ concentrations were observed with a median reduction of up to 3-fold lower for hydroxy itraconazole compared to the oral formulation. geometric mean peak sputum itraconazole exposure was 70-fold higher compared to 200 mg oral itraconazole dose 40% of subjects mean sputum levels greater than the 4 A respiratory MIC, 24h.

Safety

All study drug AEs were mild, and no subject experienced an AE leading to withdrawal. No clinically significant changes in any laboratory parameters were observed. One subject experiencing a symptomatic reduction in FEV1 following PUR1900 at 0.5 and 1.5 post-dose that was associated with an AEs.

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PART 3

Part 3: Single Dose Pharmacokinetics in Asthmatics

Low plasma ITZ and hydroxy-itraconazole systemic exposure was observed following inhalation of PUR1900. Advantages geometric mean AUC(0-24h) of hydroxy-itraconazole compared to 20mg mg oral itraconazole. Sputum ITZ levels were higher with PUR1900 compared to oral itraconazole and maintained over 24h. geometric mean peak sputum itraconazole exposure was 70-fold higher compared to 200 mg oral itraconazole dose 40% of subjects mean sputum levels greater than the 4 A respiratory MIC, 24h.