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

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Abstract

Introduction: Oral 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=5-6/cohort) received either single (Part 1 - 5mg, 10mg, 25mg, 35mg) or multiple (Part 2 -10mg, 20mg, 35mg) doses of PUR1900 over 14d. In Part 3 stable, adult asthmatics received a single dose of 20mg PUR1900 or 200mg of oral itraconazole in a 2-period cross-over design. Itraconazole plasma and sputum concentrations were evaluated.

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 AE was the infrequent occurrence of mild cough. At steady-state, PUR1900 resulted in plasma exposure ($AUC_{0\text{-}24h}$) that was 106- to 400-fold lower across doses tested than reported for oral itraconazole. In asthmatics, PUR1900 achieved C_{max} sputum concentrations that were 70-fold higher and plasma $AUC_{0\text{-}24h}$ concentrations that were 66-fold lower than with oral itraconazole.

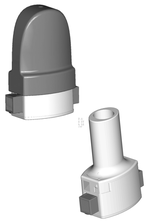
Conclusions: PUR1900 was safe and well-tolerated under the study conditions tested, and achieved significantly higher lung and lower plasma exposure compared to oral itraconazole, supporting the potential of PUR1900 to improve upon both the efficacy and safety profile observed with oral itraconazole in patients with ABPA.

ABPA and PUR1900

In asthma and cystic fibrosis patients, colonization of the airways by *Aspergillus* may cause allergic bronchopulmonary aspergillosis (ABPA), a Th2 hypersensitivity response that leads to local inflammation, reduced lung function and worsening of asthma symptoms[1]. Untreated ABPA may result in pulmonary fibrosis, respiratory failure and potentially death. Oral itraconazole therapy is used to reduce fungal burden and the inflammatory stimulus, however, poor safety, tolerability, and pharmacokinetics (PK) limit use[2].

PUR1900 is an inhaled dry powder formulation of itraconazole that is formulated using a proprietary dry powder platform iSPERSE[3]. PUR1900 enables efficient delivery of high itraconazole doses directly to the lung. We hypothesize that PUR1900 will result in high lung concentrations of itraconazole, while minimizing systemic exposure associated with adverse events and toxicity.

PUR1900 capsule-based dry powder inhaler



PUR1900 particles for inhalation

1. Moss, RB (2014) Eur Respir J 43:1487.; 2. Sermet-Gaudelus, et al. (2001) Antimicrob. Agents Chemother. 45(6):1937; 3. Sung JC, et. al. (2011) RDD Europe

Part 1: Single Ascending Dose Design and Safety

PUR1900 (5 mg) → PUR1900 (10 mg) → PUR1900 (25 mg) → PUR1900 (35 mg)

Part 1 was a single ascending dose (SAD) study in healthy volunteers (n=5-6/cohort). Safety, tolerability and PK were assessed following single doses of PUR1900 given by DPI in a fasted state. Subjects remained resident in the clinic until Day 2, and were discharged after completion of safety assessments at 24h post-dose. Provided there were no safety concerns, they were discharged from the unit and returned to the clinic on Days 3 and 5 for collection of PK samples and safety evaluations, and on Day 14 (± 2 days) for a follow-up visit. There was an interim review of safety and tolerability data before dose escalation to the next dose level.

	Part 1 (N=23)	
	Mean (SD)	Range (min-max)
Age (years)	35.3 (13.3)	19-60
Height (cm)	169.7 (9.52)	152-184
Weight (cm)	78.5 (14.1)	55.4-112
BMI (kg/m2)	27.2 (3.71)	20.9-34.8
Male:Female (n)	10:13	

Incidence of Treatment Emergent Adverse Events : Part 1 (SAD)

	5 mg (n=5)		10 mg (n=6)		25 mg (n=6)		35 mg (n=6)		Overall (n=23)	
	n (%)	Event	n (%)	Event	n (%)	Event	n (%)	Event	n (%)	Event
Subjects reporting TEAEs	2 (40)	3	2 (33.3)	8	5 (83.3)	11	4 (66.7)	4	13 (56.5)	26
Respiratory, thoracic and mediastinal disorders										
Cough	0	0	0	0	4 (66.7)	4	4 (66.7)	4	8 (34.8)	8
Epistaxis	0	0	1(16.7)	1	0	0	0	0	1 (4.3)	1
Musculoskeletal and connective disorders	2 (40)	3	0	0	1 (16.7)	2	0	0	3 (13)	5
Gastrointestinal disorders	0	0	1 (16.7)	1	1 (16.7)	1	0	0	2 (8.7)	2
Injury, poisoning, and procedural complications	0	0	1 (16.7)	2	1 (16.7)	1	0	0	2 (8.7)	3
Nervous system disorders	0	0	0	0	2 (33.3)	2	0	0	2 (8.7)	2
Skin and subcutaneous tissue disorders	0	0	1 (16.7)	1	1 (16.7)	1	0	0	2 (8.7)	2
Infections and infestations	0	0	1 (16.7)	3	0	0	0	0	1 (4.3)	3

Part 2: Multiple Ascending Dose Design and Safety

PUR1900 (10 mg) → PUR1900 (25 mg) → PUR1900 (35 mg)

Part 2 was a multiple ascending dose (MAD) study in healthy volunteers (n=6/cohort). Safety, tolerability and PK were assessed following once daily doses of PUR1900 for 14 days. Safety, tolerability and PK were evaluated at specified time points during the study, and a full PK profile was collected on Days 1 and 14. Subjects remained resident in the clinic until the morning of Day 15 (24 h after the last dose). Subjects were discharged after completion of safety assessments and returned to the clinic on Days 18 and 21 for collection of PK samples and safety evaluations, and on Day 28 (± 3 days) for a follow-up visit. There was an interim review of safety and tolerability data before dose escalation to the next dose level.

	Part 2 (N=18)	
	Mean (SD)	Range (min-max)
Age (years)	42.9 (13.7)	21-60
Height (cm)	171.7 (5.33)	159-178
Weight (cm)	80.8 (12.6)	64-102
BMI (kg/m2)	27.4 (3.83)	22.7-34.9
Male:Female (n)	14:4	

Incidence of Treatment Emergent Adverse Events : Part 2 (MAD)

	10 mg (n=6)		20 mg (n=6)		35 mg (n=6)		Overall (n=18)	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Subjects reporting TEAEs	2 (33.3)	4	5 (83.3)	19	5 (83.3)	13	12 (66.7)	36
Respiratory, thoracic and mediastinal disorders								
Cough	2 (33.3)	3	3 (50)	12	3 (50)	6	8 (44.4)	21
Epistaxis	0	0	1(16.7)	2	1 (16.7)	1	2 (11.1)	3
General disorders and administration site conditions	1 (16.7)	1	0	0	2 (33.3)	2	3 (16.7)	3
Nervous system disorders	0	0	1 (16.7)	1	2 (33.3)	3	3 (16.7)	4
Musculoskeletal and connective tissue disorders	0	0	1 (16.7)	1	1 (16.7)	1	2 (11.1)	2
Eye disorders	0	0	1 (16.7)	1	0	0	1 (5.6)	1
Renal and urinary disorders	0	0	1 (16.7)	1	0	0	1 (5.6)	1
Infections and infestations	0	0	1 (16.7)	1	0	0	1 (5.6)	1

Part 3: Single Dose Crossover Design and Safety

Oral ITRA (200 mg) / PUR1900 (20 mg) → Oral ITRA (200 mg) / PUR1900 (20 mg)

	Part 3 (N=17)	
	Mean (SD)	Range (min-max)
Age (years)	38.8 (11.1)	18-55
Height (cm)	173.2 (9.49)	154-187
Weight (cm)	82.1 (13.9)	59.5-107.7
BMI (kg/m2)	27.3 (3.01)	24.0-32.3
Male:Female (n)	10:7	

Part 3 was a 2-period, randomized, crossover study in adult subjects with mild-to-moderate stable asthma (n=17; GINA Steps 2 and 3). Safety, tolerability and PK of single doses of PUR1900 or oral itraconazole (Sporanox®) were assessed. Subjects were randomized to receive a single oral dose of 200mg itraconazole solution or a single 20mg inhaled dose of PUR1900 in Period 1. Each subject then received the alternative treatment in Period 2 after a minimum washout of 14 days. Induced sputum samples were collected following inhalation of hypertonic saline at specified timepoints after dosing. Subjects remained resident in the clinic until Day 2, and were discharged after completion of assessments up to 24h post-dose. Subjects returned to the clinic on Days 3 and 5 for collection of PK and induced sputum samples, and safety evaluations were completed. Subjects returned to the clinical unit no earlier than Day 12 in Period 1 and at least the day before dosing in Period 2 for collection of an induced sputum sample for drug concentration assessments. There was a follow-up visit on Day 14 (± 2 days) of Period 2.

Incidence of Treatment Emergent Adverse Events : Part 3

	Oral ITRA (n=17)		PUR1900 (n=16)	
	n (%)	Events	n (%)	Events
Subjects reporting TEAEs	6 (35.3)	7	11 (68.8)	16
Respiratory, thoracic and mediastinal disorders				
Cough	0	0	3 (18.8)	3
Chest discomfort	0	0	1 (6.3)	1
Wheezing	1 (5.9)	1	0	0
Nervous system disorders	2 (11.8)	2	4 (25)	5
Skin and subcutaneous tissue disorders	2 (11.8)	2	3 (18.8)	3
Immune system disorders	0	0	2 (12.5)	2
General disorders and administration site conditions	1 (5.9)	1	0	0
Investigations	0	0	1 (6.3)	1
Psychiatric disorders	1 (5.9)	1	0	0

Part 3: Single Dose Pharmacokinetics in Asthmatics

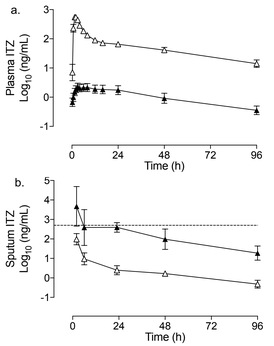
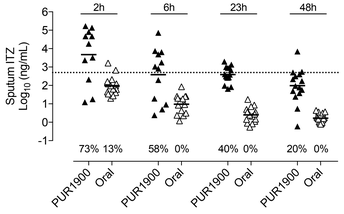


Figure 3 (left). Plasma and sputum pharmacokinetics of itraconazole. Geometric mean and 95%CI of itraconazole plasma levels (a) or sputum levels (b) were determined after single doses of PUR1900 or oral itraconazole. Data depict the concentrations for PUR1900 20mg (▲) or oral itraconazole 200mg (△).

Figure 4 (right). Sputum itraconazole concentrations for each subject over time. The dotted line indicates the MIC_{90} for *A. fumigatus*. The geometric mean is indicated by a line and the percentage of subjects above the MIC_{90} are shown.



Single dose plasma pharmacokinetics

	Itraconazole			Hydroxy-itraconazole		
	T_{max} (h)	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (h.ng/mL)	T_{max} (h)	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (h.ng/mL)
PUR1900	4	2.5 (58.5)	45.3 (64.0)	8	1.37 (64.9)	23.6 (73.3)
Oral ITRA	1.5	606 (37.6)	3660 (27.6)	3	581 (24.3)	8280 (18.8)

C_{max} and $AUC_{0\text{-}24h}$ data are geometric mean (%CV); t_{max} is median

- **Low itraconazole and hydroxy-itraconazole systemic exposure was observed following inhalation of PUR1900**
  - **Adjusted geometric mean $AUC_{0\text{-}t}$ 66-fold lower for itraconazole and 310-fold lower for hydroxy-itraconazole compared to 200 mg oral itraconazole**
- **Sputum itraconazole 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 maintain sputum levels greater than the *A. fumigatus* MIC_{90} for 24h**

Part 1: Single Dose Pharmacokinetics

Single dose itraconazole PK

	Itraconazole			
Dose (mg)	T_{max} (h)	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng.h/mL)	
5	6	0.873 (35.4)	15.9 (36.5)	
10	6	2.28 (26.8)	38.9 (43.1)	
25	3	3.90 (38.2)	64.9 (30.6)	
35	18	4.58 (48.4)	86.9 (42.6)	

C_{max} and $AUC_{0\text{-}24h}$ data are geometric mean (%CV); t_{max} is median

Single dose hydroxy-itraconazole PK

	Hydroxy-Itraconazole			
Dose (mg)	T_{max} (h)	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng.h/mL)	
5	6	0.416 (34.9)	7.18 (37.5)	
10	8	0.820 (46.4)	14.8 (53.1)	
25	9	3.06 (56.4)	31.2 (31.0)	
35	6	1.78 (77.9)	32.8 (81.6)	

C_{max} and $AUC_{0\text{-}24h}$ data are geometric mean (%CV); t_{max} is median

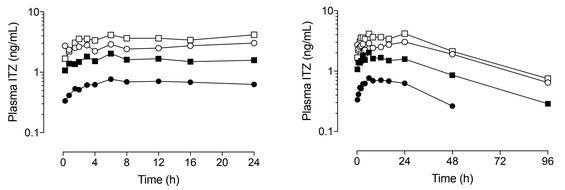


Figure 1. Single dose pharmacokinetics of PUR1900. Itraconazole plasma levels were determined after single doses of PUR1900 for up to 96h after dosing using an LC-MS/MS method with a LLOQ of 0.1ng/mL. Data depict geometric mean concentrations for PUR1900 5mg (●), PUR1900 10mg (■), PUR1900 25mg (○), and PUR1900 35mg (□).

- **PUR1900 is rapidly absorbed into the systemic circulation (quantifiable within 15 minutes)**
- **Itraconazole and hydroxy-itraconazole plasma exposure increased with increasing dose in a broadly dose proportional manner**
- **Sustained plasma exposure over 24h indicative of high and sustained lung exposure and supports once daily dosing**

Part 2: Multiple Dose Pharmacokinetics

Day 14 multiple dose pharmacokinetics

	Itraconazole			
Dose (mg)	T_{max} (h)	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng.h/mL)	AR
10	5	3.77 (34.2)	73.2 (35.1)	3.0
25	4	8.98 (37.9)	175 (32.7)	3.3
35	0.75	15.2 (49.3)	276 (62.2)	2.8
	Hydroxy-itraconazole			
Dose (mg)	T_{max} (h)	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng.h/mL)	AR
10	6	2.25 (25.3)	42.4 (26.1)	3.8
25	6	6.43 (54.7)	128 (56.1)	4.4
35	8	8.68 (91.0)	169 (116)	4.5

C_{max} and $AUC_{0\text{-}t}$ data are geometric mean (%CV); AR = accumulation ratio

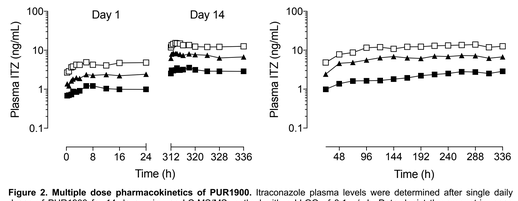


Figure 2. Multiple dose pharmacokinetics of PUR1900. Itraconazole plasma levels were determined after single daily doses of PUR1900 for 14 days using an LC-MS/MS method with a LLOQ of 0.1ng/mL. Data depict the geometric mean concentrations for PUR1900 10mg (■), PUR1900 25mg (○), and PUR1900 35mg (□).

- **Itraconazole and hydroxy-itraconazole plasma exposure increased with increasing dose in a broadly dose proportional manner**
- **Steady state systemic exposure appeared to be achieved within 14 days of dosing**
- **Sustained systemic exposure after multiple doses over 24 h post-dose indicative of high and sustained lung exposure and supports once daily dosing**
- **Mono-exponential elimination rate was consistent across single and multiple doses indicating that no dose-related lung accumulation or evidence of prolonged exposure following higher doses was observed**

Pharmacokinetic Conclusions

- Plasma exposure following inhalation of PUR1900 was generally similar between asthmatic subjects and healthy subjects
- Very low itraconazole and hydroxy-itraconazole systemic exposure was observed across all doses
  - 106- to 400-fold lower itraconazole exposure and 267- to 1000-fold lower hydroxy-itraconazole exposure after 14 days of PUR1900 relative to reported values for oral itraconazole solution
- Relative to oral dosing, PUR1900 achieved high and sustained itraconazole lung exposure and low systemic exposure
  - 40% of subjects achieved lung concentrations above the MIC_{90} after a single dose; with repeat dosing and similar accumulation as observed in healthy volunteers PUR1900 is expected to achieve consistent concentrations above the MIC_{90} for at least 24h

Safety Conclusions

Part 1 and 2:

- All study drug- AEs were characterized as mild, and no subject experienced an AE leading to withdrawal
- No clinically significant changes in any individual subject's ECG, vital signs, laboratory or spirometry data were observed
- PUR1900 appeared to be safe and well tolerated in normal healthy volunteers at doses up to 35 mg of inhaled PUR1900 over 14 days of administration

Part 3:

- All AEs considered as at least possibly related to study drug were characterized as mild, and no subject experienced serious or severe AEs, or an AE leading to withdrawal.
- No clinically significant changes in any individual subject's ECG, vital signs, laboratory data were observed.
  - One subject experienced a symptomatic reduction in FEV1 following PUR1900 at 0.5 and 1.5 h post dose that was associated with an ADR of "chest discomfort" and wheezing
- Single doses of PUR1900 20 mg and oral itraconazole 200 mg appeared to be safe and well tolerated in asthmatic subjects