Pulmonary delivery of PUR1900 enables high lung exposure of Itraconazole relative to oral dosing

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Introduction

Pulmonary fungal infections in Cystic Fibrosis are likely underdiagnosed[1] and are a significant source of morbidity and mortality. Oral triazoles are the most commonly prescribed treatment, yet historically, oral bioavailability and achieved lung concentrations are variable and often subtherapeutic[2]. In addition, triazoles like itraconazole are metabolized in liver with an extensive list of drug-drug interactions (DDI), including with ivacaftor[3]. Pulmatrix have set out to develop an inhaled dry powder formulation of itraconazole, PUR1900. This formulation has the potential to allow for improved local delivery and efficacy, reduced variability in exposure and less likelihood of DDI events. PUR1900 is formulated using our proprietary particle engineered dry powder platform called iSPERSE (Figure 1). iSPERSE offers advantages over traditional technologies in enabling diverse classes of inhaled compounds with improved delivery efficiency to the lung. PUR1900 is engineered to have a small aerosol particle size for efficient pulmonary delivery and is intended to be delivered using a capsule based dry powder inhaler. PUR1900 formulations in development have mass median aerosol diameters (MMAD) of ~3mm and high fine particle doses (FPD; % of the nominal dose < 5mm), which should result in more than 50% of the nominal dose reaching the lungs with reduced throat deposition. Notably, the aerosol target range of PUR1900 is similar to that of *Aspergillus* conidia, which, in theory, should result in PUR1900 delivery to lung sites where aspergillus spores also deposit upon inhalation

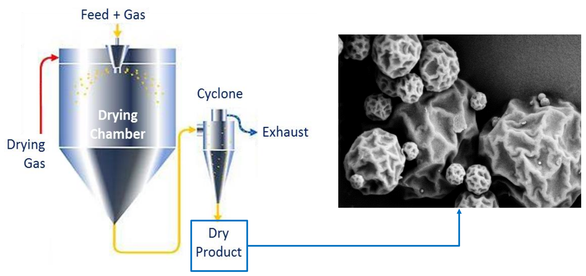


Figure 1. iSPERSE particle engineering. iSPERSE utilizes the combination of particle engineering by spray drying and novel excipient combinations to create homogenous particles for inhalation. Spray drying is a continuous, scalable process able to produce dry powders from solutions or suspensions. Atomized droplets of feedstock solutions are dried in a drying chamber and collected from the cyclone. The collected dry product is directly filled into a capsule or delivery device and does not require further blending. iSPERSE particles of different physicochemical properties and morphologies can be achieved through changes in process and excipient selection.

Aims

- To evaluate the systemic pharmacokinetics and lung concentrations of itraconazole when PUR1900 is delivered to the lungs of rats
- To compare systemic and lung exposure to itraconazole following inhalation dosing with PUR1900 with that following an oral dose of itraconazole (Sporanox® oral solution).

Methods

7-Day Rat Pharmacokinetic Study

Sprague-Dawley rats were dosed daily *via* nose-only inhalation exposure at a target delivered inhaled doses of 5 mg/kg/day PUR1900 for 7 consecutive days. Exposure was performed using a rotating brush aerosol generator and directed flow system as shown in Figure 2. An additional group of rats was dosed *via* oral gavage once daily with 5 mg/kg/day Sporanox® for 7 consecutive days

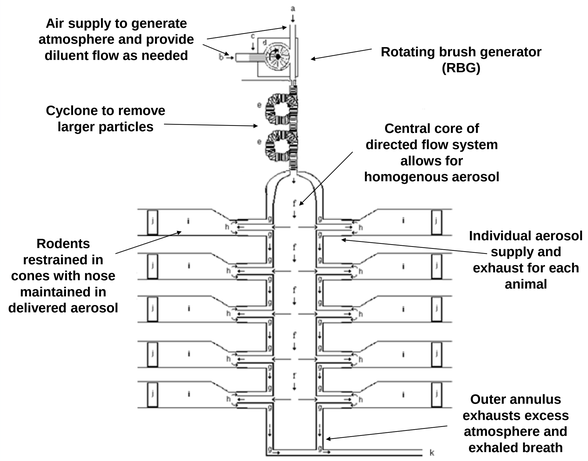


Figure 2. The inhalation exposure system This system consists of a rotating brush generator and diluent air supply system to generate the aerosol. The aerosol is delivered to the directed flow exposure system where each animal receives an individual aerosol from the central reservoir. Exhaled breath and excess aerosol are removed *via* the outer annulus to waste. Aerosol concentration and Mass Median Aerodynamic Diameter (MMAD) particle size samples are collected from one animal port at the breathing zone of the animals at several time points during the study.

Table 1. Group mean target and achieved aerosol concentration and inhaled and oral doses.

Group	Treatment	Target Aerosol Concentration (mg/L)	Achieved Aerosol Concentration (mg/L)	Target Delivered Dose (mg/kg/day)	Achieved Delivered Dose (mg/kg/day)
Inhaled	PUR1900	0.11	0.11	5	5.2
Oral	Sporanox®	NA	NA	5	5

Blood samples for determination of plasma concentrations of itraconazole and it's active metabolite, hydroxy-itraconazole, were collected from 3 rats/sex/group/time point on days 1 and 7 at pre-dose, immediately after the end of dosing (IAD - within 5 minutes) and 2, 4, 8 and 24 hours after dose. In addition, lung samples were collected for determination of peak and trough lung levels of itraconazole on Day 1 at IAD and 24 hours after dose and on Day 7 at 24 hours after the last dose.

Plasma and lung samples were analyzed by by LC-MS/MS. Pharmacokinetic analysis was performed with WinNonlin PhoenixTM software version 6.3 using individual animal data and non-compartmental analysis

Results

Itraconazole systemic exposure is lower after inhalation relative to oral dosing

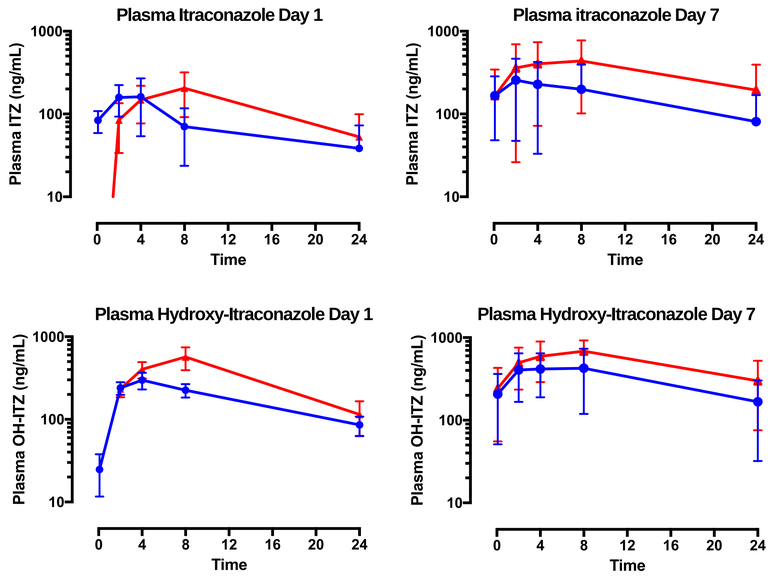


Figure 3. Systemic pharmacokinetic profile following oral and lung delivery.
A. Plasma profile for itraconazole on Day 1 after oral Sporanox® or inhaled PUR1900 at 5 mg/kg. Systemic exposure exhibited an earlier T_{max} after inhalation but overall exposure was higher following oral dose with the C_{max} values following inhalation exposure approximately 20% lower and the AUC_{0-24} values approximately 44% lower than following oral dose.

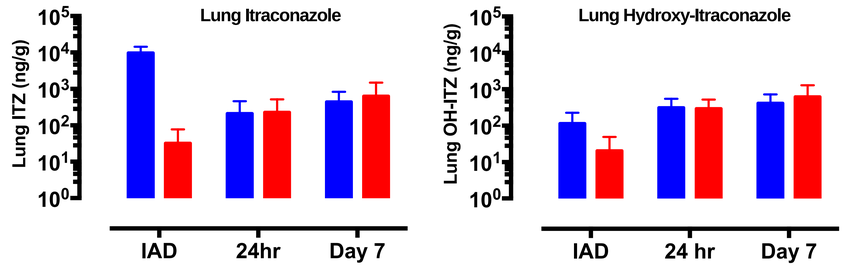
B. Plasma profile for itraconazole on Day 7 after oral or inhaled dose. A similar pattern of exposure to Day 1 was evident with exposure higher after oral dose relative to inhaled. Systemic accumulation was noted in females but not males.

C. Plasma profile for hydroxy-itraconazole on Day 1 after oral Sporanox® or inhaled PUR1900.

D. Plasma profile for hydroxy-itraconazole on Day 7 after oral or inhaled dose. A similar pattern of exposure to Day 1 and itraconazole Day 7 was evident with exposure higher after oral dose relative to inhaled. Systemic accumulation was again noted in females but not males

Itraconazole pulmonary exposure is higher after inhaled relative to oral dose

Figure 4. Pulmonary exposure profile following oral and lung delivery.
Pulmonary exposure for itraconazole (A) or hydroxy-itraconazole (B) following inhalation of PUR1900 or oral Sporanox®, immediately after dose, 24 hours after dose on Day 1 and 24 hours after the final dose on Day 7. Peak lung exposure *via* inhalation was approximately 300-fold higher than that after oral dose. Trough lung levels on Days 1 and 7 were similar with both oral and inhaled doses.



Target delivered dose level (mg/kg/day)	C_{max} (ng/mL)				AUC_{0-25} (ng.h/mL)			
	Day 1		Day 7		Day 1		Day 7	
	Males	Females	Males	Females	Males	Females	Males	Females
5 (PUR1900)	120	257	78.0	436	995	2880	721	7580
5 (Sporanox)	114	296	138	737	1580	4590	2020	14000

Table 2. Systemic pharmacokinetics of PUR1900 following lung and oral delivery. Drug concentrations were quantified in plasma samples following oral or pulmonary delivery of PUR1900 dry powder. Each data point represents the mean and SD (n=3). Data indicate a sex difference in exposure, with females showing higher systemic exposure relative to males after both inhaled and oral dose as well as a significantly greater propensity for accumulation. The sex difference appears to be rodent-specific.

Conclusions

- Inhaled PUR1900 provides substantially higher lung exposure and lower systemic exposure relative to oral dosing with an equivalent total dose of itraconazole (Sporanox®)
- Rats show sex differences in both systemic and lung exposure and accumulation, though these appear to be species specific
- PUR1900 shows promise as an inhaled therapy for treatment of pulmonary aspergillosis

References

1. Armstead J, Morris J, Denning DW (2014) Multi-Country Estimate of Different Manifestations of Aspergillosis in Cystic Fibrosis. PLoS ONE 9(6): e98502
2. Sermet-Gaudelus, *et al.* (2001) Sputum Itraconazole Concentrations in Cystic Fibrosis Patients. Antimicrob. Agents Chemother. 45(6):1937
3. Vertex Prescribing Information for Kaleydeco® http://pi.vrtx.com/files/uspi_ivacaftor.pdf
4. Sung JC, *et. al.* (2011) iSPERSE: Formulation and In Vitro Characterization of a Novel Dry Powder Drug Delivery Technology. RDD Europe