A Phase 1 Study to Assess Safety, Tolerability, and Pharmacokinetics of PUR3100, a Novel Dry Powder Formulation of DHE for Oral Inhalation, in Healthy Adults

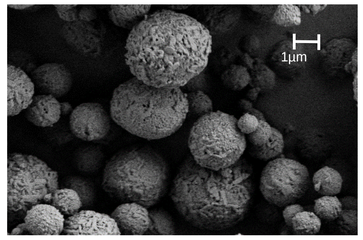
MM Wasilewski, S Bodie, AC Gonzalez Nelson, RG Clayton and AK Curran
Pulmatrix, Inc., Lexington, Massachusetts, USA

Introduction

PUR3100 is a dry powder formulation of dihydroergotamine mesylate (DHE) for oral inhalation, being developed by Pulmatrix, Inc., for the acute treatment of migraine headaches with or without aura. PUR3100 is comprised of DHE as the active ingredient and delivered to the lungs via a capsule-based passive dry powder inhaler (DPI), which utilizes the subject's own inhalation energy to deliver and disperse the formulated powder.

PUR3100 Dry Powder Inhaler

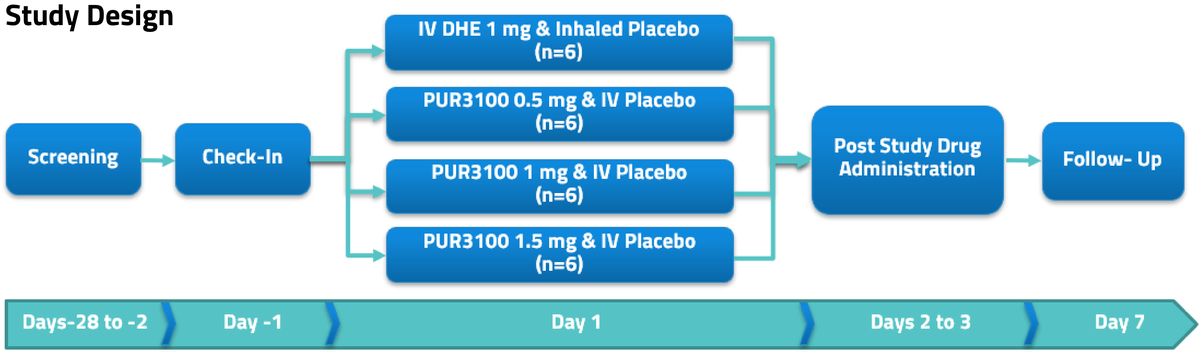
PUR3100 iSPERSE Engineered Particles



Each capsule of PUR3100 was filled with iSPERSE powder which is comprised of DHE mesylate, with mannitol, L-leucine, and sodium chloride as excipients.

Methodology

Study Design



This was a randomized, parallel group, double-blind, double dummy study in healthy adults.

Safety assessments included adverse events, spirometry, hematology, clinical chemistry, coagulation, urinalysis, vital signs, electrocardiogram and physical examination.

Blood for pharmacokinetic (PK) assessment was collected through 48 hours after dose.

Objectives

- To determine the safety and tolerability of single doses of inhaled PUR3100 in healthy adult subjects
- To characterize the systemic PK of single doses of inhaled PUR3100
- To explore the comparative PK of inhaled PUR3100 versus IV DHE

Results

A total of 26 subjects, with an age range of 18 to 49 years, were randomized to receive study drug and all randomized subjects were included in the PK and Safety Populations.

Safety and Tolerability

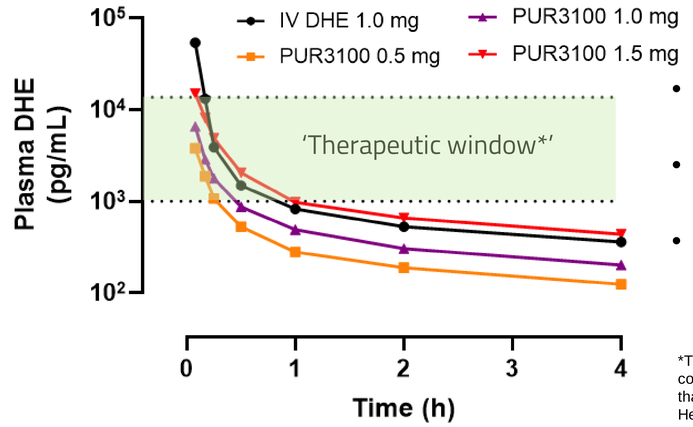
- PUR3100 was generally well tolerated with fewer TEAEs in PUR3100-treated groups than in the IV DHE-treated group.
- There were no deaths, SAEs, or AEs leading to study withdrawal.

Treatment Related TEAEs Reported in ≥2 Subjects

Preferred Term, n (%)	IV DHE 1 mg (N=7)	PUR3100 0.5 mg (N=7)	PUR3100 1.0 mg (N=6)	PUR3100 1.5 mg (N=6)
Nausea	6 (85.7)	2 (28.6)*	1 (16.7)	2 (33.3)
Headache	4 (57.1)	2 (28.6)**	1 (16.7)	1 (16.7)
Dizziness	2 (28.6)	0	0	2 (33.3)
Vomiting	2 (28.6)	0	0	0

* Includes one subject with preferred term=procedural nausea
**Includes one subject with preferred term=tension headache

PUR3100 Pharmacokinetics



- T_{max} was at the first time point (5 min) for all PUR3100 doses
- All three doses achieved 'therapeutic' exposure levels (>1000 pg/mL)
- C_{max} was within the desired exposure window, with similar T_{max} and dose-normalized AUC relative to IV DHE

*Therapeutic Window defined as the exposure between the lowest systemic concentration required for efficacy and the concentration above which more than 50% of patients experience nausea. Silberstein, S. D., et al., Headache J Head Face Pain 60, 40–57 (2019).

Inhaled PUR3100 was safe, well tolerated and rapidly absorbed.

These data support further development of PUR3100 for the treatment of acute migraine.

PUR3100 Phase 1 Study Results: Demographics

	IV DHE 1.0 mg (N=7)	PUR3100 0.5 mg (N=7)	PUR3100 1.0 mg (N=6)	PUR3100 1.5 mg (N=6)
Mean age, years (SD)	27.3 (8.34)	25.6 (6.53)	28.3 (5.85)	27.8 (10.87)
Sex, n (%)				
Male	3 (42.9)	3 (42.9)	3 (50.0)	1 (16.7)
Female	4 (57.1)	4 (57.1)	3 (50.0)	5 (83.3)
Race, n (%)				
White (Caucasian)	4 (57.1)	5 (71.4)	3 (50.0)	6 (100)
Asian	3 (42.9)	1 (14.3)	2 (33.3)	0
Other	0	0	1 (16.7)	0
Multiple Race	0	1 (14.3)	0	0
Mean BMI, kg/m² (SD)	24.6 (5.19)	22.6 (2.92)	24.8 (3.32)	22.8 (3.33)

Source: Table 14.1.2

PUR3100 Phase 1 Study Results: Overall Summary of TEAEs

	IV DHE 1.0 mg (N=7) n (%)	PUR3100 0.5 mg (N=7) n (%)	PUR3100 1.0 mg (N=6) n (%)	PUR3100 1.5 mg (N=6) n (%)
Any TEAE	6 (85.7)	3 (42.9)	4 (66.7)	4 (66.7)
TEAEs related to study drug	6 (85.7)	2 (28.6)	2 (33.3)	4 (66.7)
TEAEs by Maximum Severity				
Mild	1 (14.3)	3 (42.9)	4 (66.7)	3 (50.0)
Moderate	4 (57.1)	0	0	1 (16.7)
Severe	1 (14.3)	0	0	0
Serious TEAEs	0	0	0	0
TEAE leading to early withdrawal	0	0	0	0

Abbreviations: n = number of subjects with adverse event; TEAE = Treatment emergent adverse event

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Source: Table 14.3.1.1

PUR3100 Phase 1 Study Results: Treatment Related TEAEs Reported in at Least Two Subjects

- Nausea and headache were observed in each treatment group with higher incidence in IV DHE group

Preferred Term	IV DHE 1 mg (N=7) n (%)	PUR3100 0.5 mg (N=7) n (%)	PUR3100 1 mg (N=6) n (%)	PUR3100 1.5 mg (N=6) n (%)
Nausea	6 (85.7)	2 (28.6)*	1 (16.7)	2 (33.3)
Headache	4 (57.1)	2 (28.6)**	1 (16.7)	1 (16.7)
Dizziness	2 (28.6)	0	0	2 (33.3)
Vomiting	2 (28.6)	0	0	0

* Includes one subject with preferred term=procedural nausea
** Includes one subject with preferred term=tension headache

- 2 subjects reported mild respiratory TEAEs in the upper airway that resolved without treatment: 1 subject with mild pharyngeal disorder in IV DHE 1 mg group and 1 subject with mild productive cough in the PUR3100 0.5 mg group

- No dysgeusia was reported

Source: Table 14.3.1.3

PUR3100 Phase 1 Study Results: Treatment Related Nausea and Vomiting TEAEs by Subject

Treatment Group	Subject ID	Preferred Term	TEAE onset# (minutes)	TEAE duration	Severity Grade	Ondansetron administered
IV DHE 1.0 mg	01-011	Nausea	4	2h 51m	moderate	Y
	01-018	Nausea	30	0h 25m	moderate	Y
		Vomiting	47	0h 0m	mild	Y
	01-023	Nausea	5	13h 24m	moderate	Y
	01-041	Nausea	12	1h 38m	moderate	Y
		Vomiting	15	13h 54m	moderate	Y
	01-060	Nausea	6	0h 20m	moderate	Y
	01-068	Nausea	7	0h 33m	mild	Y
PUR3100 0.5 mg	01-058	Nausea*	9	0h 15m	mild	Y
	01-070	Nausea	67	1h 48m	mild	Y
PUR3100 1.0 mg	01-020	Nausea	3	1h 47m	mild	N
PUR3100 1.5 mg	01-001	Nausea	37	1h 14m	moderate	Y
	01-065	Nausea	6	1h 42m	mild	Y

#Onset time = AE onset date/Time-Study Drug Administration Date/Start Time of most recent dose (inhalation or IV)
*Preferred term = procedural nausea

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Source: Listing 16.2.7.1

PUR3100 Phase 1 Study Results: PUR3100 and IV DHE Pharmacokinetic Parameters

- PUR3100 kinetics show rapid T_{max} and C_{max} in target therapeutic window

Formulation	Nominal Dose (mg)	Estimated Delivered Dose (FPD < 5 µm)* (mg)	Geo. Mean C_{max} (pg/mL)	Median T_{max} (min)	Geo. Mean AUC_{0-48h} (pg.h/mL)	Mean $T_{1/2}$ (h)
IV DHE	1.0	1.0	45,000	5.5	10,500	13.9
PUR3100	1.5	0.9	14,400	5	9,630	14.9
PUR3100	1.0	0.6	5,190	5	3,780	11.4
PUR3100	0.5	0.3	3,620	5	2,530	10.9

*Delivered dose is the estimated fine particle dose < 5 µm - ~ 60% of the nominal inhalation dose delivered to the lung

Source:Tables 14.4.3.1, 14.4.3.2, 14.4.3.3, 14.4.3.4