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RESEARCH SUBMISSIONS

Safety, tolerability, and pharmacokinetics of a single orally inhaled dose of PUR3100, a dry powder formulation of dihydroergotamine versus intravenous dihydroergotamine: A Phase 1 randomized, double-blind study in healthy adults

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Abstract

Background: Intravenous dihydroergotamine (DHE) has well-established efficacy for the acute treatment of migraine, but its use is limited by the need for in-hospital administration and the nausea/vomiting associated with a high maximum plasma concentration (C_{max}). Inhalation is an alternative to intravenous dosing. The surface area of the lung allows for rapid absorption of a self-administered dose.

Objective: This study evaluated the safety, tolerability, and systemic pharmacokinetics (PK) of a dry powder formulation (PUR3100) DHE when delivered via inhalation compared to intravenous delivery.

Methods: In this double-blind, double-dummy Phase 1 study, healthy volunteers ($N = 26$) were randomized (1:1:1:1) to one of four groups: orally inhaled placebo plus intravenous DHE 1.0 mg or orally inhaled PUR3100 (0.5, 1.0, or 1.5 mg) plus intravenous placebo. Blood samples were drawn pre-dose and at time points post-dose over 48 h. Standard PK and safety parameters were assessed and values for C_{max} and area under plasma concentration time curve (AUC) were used to assess comparative exposures of PUR3100 versus intravenous DHE.

Results: All doses of PUR3100 were associated with a lower incidence of nausea (21% vs. 86%), vomiting (0% vs. 29%), and headache (16% vs. 57%) compared to intravenous DHE. The PK profile of PUR3100 versus intravenous DHE was characterized by a similar mean time to C_{max} (5 vs. 5.5 min), with reduced AUC_{0-2h} (1120–4320 vs. 6340), and a lower C_{max} (3620–14,400 vs. 45,000). Compared to intravenous DHE 1.0 mg, the highest nominal PUR3100 dose (1.5 mg), which delivers a fine-particle dose of approximately 0.9 mg to the lungs, had a geometric mean ratio percentage

Abbreviations: (TE)AE, (treatment-emergent) adverse event; AUC, area under plasma concentration time curve; AUC_{0-2h}, AUC from time zero to 2 h post-dose; AUC_{0-inf}, AUC from time zero to infinity; AUC_{0-t}, AUC from time zero to time of the last quantifiable concentration; C_{max}, maximum plasma concentration; DHE, dihydroergotamine; FEV_1, forced expiratory volume in 1 s; 8-OH-DHE, 8-hydroxy-DHE; PK, pharmacokinetic; T_{max}, time to maximum plasma concentration.

(90% confidence interval [CI]) for C_{max} of 32% [17.2, 59.6] and AUC_{0-inf} of 93% (62.9, 138.5), the latter of which was not significantly different.

Conclusions: Inhaled PUR3100 is associated with rapid systemic PK within the therapeutic window and an improved safety profile relative to intravenous DHE.

Plain Language Summary: Intravenous dihydroergotamine (DHE) works for the acute treatment of migraine; however, it must be given in a hospital or clinic and has side-effects including nausea and vomiting. A dry powder formulation of DHE (PUR3100) delivered by oral inhalation had fewer side-effects than intravenous DHE in healthy volunteers. The pharmacokinetics (the amount of the study drug in blood) showed that inhaled PUR3100 was associated with rapid absorption of DHE into the blood within the desired range associated with pain relief.

KEYWORDS
acute migraine, dihydroergotamine, inhalation, pharmacokinetics, safety

INTRODUCTION

Migraine is a highly prevalent neurovascular disorder that affects >1 billion people worldwide and is associated with profound clinical, quality of life, economic, and social burdens.[1] There are numerous agents available for the prevention of migraine and for the treatment of acute attacks. Triptans are the most commonly used agents for acute treatment, and although these agents can be effective, the proportion of patients who achieve pain freedom or pain relief is variable.[2] The route and timing of administration is a major factor that influences response to triptans, as are clinical presentation, external triggers, and pharmacogenomics.[2] Gepants can also be effective for the acute treatment of migraine and are safe and tolerable; however, efficacy appears to be lower than for triptans.[3] Dihydroergotamine (DHE) has been shown to be effective in the relief of migraine, but due to low oral bioavailability, its use is limited to (i) parenteral dosing, requiring in-hospital use, or (ii) intranasal dosing, which has limited efficacy data supporting its use.

An important goal of acute migraine medications is rapid relief (i.e., within 30 min) with no/minimal adverse events (AEs) and no recurrence.[4,5] There are substantial differences regarding the onset of action between various agents, with differences influenced by route of administration and pharmacologic properties. Subcutaneous administration of sumatriptan appears to have the shortest onset (~10 min),[6] followed by rizatriptan oral disintegrating tablets, zolmitriptan nasal spray, and eletriptan (~30 min each),[7,8] oral sumatriptan, almotriptan, and zolmitriptan (~45–60 min),[7,8] and naratriptan and frovatriptan (up to 4 h).[7,9] In addition, recurrence of headaches with triptans is common (15%–40%), requiring repeat doses.[7]

Dihydroergotamine has long been used for the treatment of acute migraine and continues to be an option, including for the treatment of status migrainosus and cluster headache.[10] Systemic DHE has a rapid onset of action, a minimal risk of medication-overuse headache, high rates of sustained migraine relief, and is effective in patients who are triptan resistant;[10] however, the drug is associated with gastrointestinal and cardiovascular adverse effects and it has poor bioavailability, limiting it to non-oral routes of administration.[10] Intravenous DHE is limited by the need for in-hospital administration; intranasal DHE (Migranal®) is associated with variable absorption and poor bioavailability relative to the injectable administration (32%) and is associated with local irritation in the nose and throat, as well as disturbances in taste (dysgeusia).[11] A newer intranasal formulation of DHE (Trudhesa®) with an improved pharmacokinetic (PK) profile was approved in 2021, but the achievement of peak plasma concentrations is still somewhat delayed (30 min); it is also associated with local irritation and dysgeusia.[12,13] An orally inhaled formulation of DHE (MAP0004) demonstrated promising efficacy and safety results, but issues with manufacturing and the delivery system have prevented regulatory approval.[10] Moreover, an intranasal dry powder formulation (STS101) is currently in development and demonstrated numerical but not statistically significant differences versus placebo for co-primary endpoints in a Phase 3 trial.[14]

PUR3100 is an orally inhaled formulation of DHE, that uses the iSPERSE™ platform. iSPERSE is a novel, engineered inhaled dry powder delivery technology. PUR3100 is designed to be easily administered using a capsule-based passive dry powder inhalation device, distributed to the lung periphery, and rapidly absorbed into the systemic circulation. The purpose of the present study was to assess the safety, tolerability, and systemic PK of DHE when delivered via inhalation of PUR3100 and to compare that to the standard intravenous delivery of DHE.

METHODS

Study design

This was a Phase 1, randomized parallel-group, double-blind, double-dummy study performed in healthy adults that took place from July 8, 2022 (first participant randomized) to September 22, 2022 (last

participant's last visit). Participants who passed the screening and met eligibility criteria were randomized (1:1:1:1) to one of four dose groups: orally inhaled placebo plus intravenous DHE 1.0 mg or orally inhaled PUR3100 0.5, 1.0, or 1.5 mg plus intravenous placebo (Figure 1). The PUR3100 nominal clinical dose of 1.5 mg has an estimated delivered fine-particle dose (FPD) <5 μm of ~60%, thus, the 1.5 mg nominal dose would be expected to deliver ~0.9 mg of DHE to the lung.

A computer-generated block randomization scheme was created and provided to the unblinded pharmacy staff who were not involved in any other aspect of the study, including the administration of the drug. Randomization was carried out in blocks of four to ensure equal assignment of participants to each of the four treatment groups throughout enrollment. The unblinded pharmacist used the predetermined list to manually assign each participant a randomization number sequentially in the order that they were eligible for randomization during the screening process (i.e., at the Day 1 visit). Replacements were assigned to the same treatment group as the participant being replaced. Unblinded pharmacy staff prepared and distributed the assigned study drug for each participant to the blinded site personnel for administration. Each dosing kit for each participant contained three capsules of the study drug. PUR3100 and placebo capsules were of the same shape, size, and color to ensure that the blind was maintained. The number of capsules that contained PUR3100 corresponded to the dose being evaluated for a given group and the participant's treatment assignment. All participants inhaled the same number of capsules to maintain the blind. The sponsor, investigators, and study participants were blinded to dose group assignments.

The study was conducted in compliance with the ethical principles of the Declaration of Helsinki, the requirements of applicable local regulatory authorities, the US Food and Drug Administration Code of Federal Regulations, and in accordance with the International Council for Harmonization Guidelines for Good Clinical Practice. The protocol was approved by the Institutional Review Board/Independent Ethics Committee (The Alfred Hospital Ethics Committee, Melbourne, Australia) and all participants provided written informed consent prior to the initiation of any study procedures.

Participants

Healthy male or female adults aged 18–55 years with normal blood pressure and a body mass index between 18 and 35 kg/m^2 were eligible for inclusion. Female participants were required to have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to dosing. All participants were required to abstain from alcohol for 48 h prior to admission to the study site until completion of the 7-day follow-up visit and were required to consume no more than two to three cups of caffeine- and xanthine-containing beverages or food per day.

Exclusion criteria included a history of or suspected coronary artery disease, coronary vasospasm, peripheral vascular disease, other ischemic disease, cardiac disorder, or history of heart attack, stroke, hypertension, diabetes mellitus, liver/kidney disease, aortic aneurysm, chronic pulmonary disease, or recent sepsis or vascular surgery. Participants with a current active pulmonary disease (i.e., asthma, chronic obstructive pulmonary disease, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, interstitial lung disease), clinically significant abnormal laboratory values, prolonged QTc, impaired lung function, a history of drug/alcohol abuse, a positive drug/alcohol test at screening or Day −1, or a positive test for hepatitis B or C were also excluded.

Assessments and outcome variables

Blood samples to determine concentrations of DHE and its major active metabolite, 8-hydroxy-DHE (8-OH-DHE) were drawn at predose and at 5, 10, 15, and 30 min and 1, 2, 4, 8, 12, 24, and 48 h post-dose. Safety assessments included the documentation of AEs from the signing of the consent form through the safety follow-up visit on Day 7. The AEs were coded using the Medical Dictionary for Regulatory Activities version 25.0 and were assessed for severity and toxicity. Other safety assessments included clinical laboratory tests (hematology, clinical chemistry, coagulation, urinalysis), electrocardiograms, vital signs (e.g., systolic blood pressure, diastolic blood pressure, pulse), spirometry (forced expiratory volume in 1 s [FEV_1]), and physical examination.

Bioanalytical and PK methods

The analytical method used to determine plasma levels of DHE and 8-OH-DHE employed solid phase extraction for sample preparation followed by liquid chromatography with tandem mass spectrometry using electrospray ionization in positive ion, multiple reaction

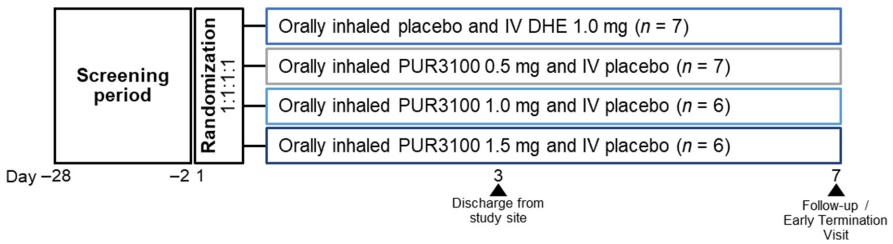

FIGURE 1 Study design. DHE, dihydroergotamine; IV, intravenous.

monitoring mode. The overall precision and bias for the quality control samples were within 15% at all levels, indicating that the method performed reliably during the analysis of study samples. The reproducibility of the validated analytical method when applied to incurred plasma samples was also within the required acceptance limits for the re-analysis of incurred samples stored at −80°C. Standard PK parameters were calculated using non-compartmental methods in Phoenix™ WinNonlin® (version 8.3.4.295, Certara USA, Inc.). The calculation of PK parameters was based on actual elapsed times (h) relative to dosing.

Statistical methods

A total of 24 healthy participants were planned for this study. The sample size of six participants per group was chosen to minimize exposure of PUR3100 to healthy adults while allowing an adequate assessment of safety and PK. The study was not powered for any formal hypothesis test, therefore any *p* value presented is descriptive. Missing data was not imputed unless it was needed to flag treatment-emergent AEs (TEAEs) or concomitant medications. Only participants who had sufficient PK sample collection to generate the key PK parameters (area under plasma concentration time curve from time zero to time of the last quantifiable concentration [AUC_{0-t}], AUC from time zero to infinity [AUC_{0-inf}], and maximum plasma concentration [C_{max}]) were included in the PK analysis. PK parameters and safety variables were summarized using descriptive statistics (e.g., mean, median, coefficient of variation, standard deviation, geometric mean, geometric mean coefficient of variation, minimum, and maximum). The comparative bioavailability of PUR3100 versus intravenous DHE was assessed using a linear mixed-effects model on the natural log-transformed values for C_{max}, AUC_{0-t}, and AUC_{0-inf}. The model included treatment as a fixed effect and the natural log-transformed values for each PK parameter as the dependent variable. The analysis was performed using the Statistical Analysis System (SAS©) using the Mixed Procedure. For each comparison, the differences in the least squares means between the three doses of PUR3100 and intravenous DHE and the corresponding 90% confidence intervals (CIs) were obtained from the model. The results were exponentiated to provide the test/reference ratios of geometric means and 90% CIs on a linear scale.

RESULTS

Participants

Of the 86 participants screened for the study, 60 failed the screening (Figure 2). The reasons for screening failure were primarily due to failure to meet inclusion/exclusion criteria ($n = 43$) and withdrawal by participants prior to randomization ($n = 13$). In all, 26 participants were randomized to treatment and included in the safety and PK analysis sets. Two participants had major protocol deviations related to missed PK assessments (post-dose PK samples at 5, 10, and 15 min were not collected due to AEs). Due to the insufficient PK sample collection, these two participants were replaced and excluded from the analysis of PK parameters. The addition of two replacement participants resulted in a total of 26 participants rather than the planned 24 participants. Demographic characteristics were generally similar among groups (Table 1); most participants were female (62%; 16/26) and White (69%; 18/26). The mean (range) age was 27.2 (18–49 years), and the mean body mass index was 23.7 kg/m^2.

Safety/tolerability

Overall, TEAEs were observed in 17/26 participants (65%), with 14/26 participants (54%) experiencing TEAEs that were considered related to study medication (Table 2). No deaths, serious AEs, or discontinuations due to AEs occurred in the study. TEAEs and treatment-related AEs were more frequent in participants treated with intravenous DHE than in any of the PUR3100 dose groups. The severity of TEAEs was greater in the intravenous DHE treatment group. Of the 19 TEAEs reported in six participants in the intravenous DHE group, 11 were mild, seven were moderate, and one was severe. In contrast, of the 22 TEAEs reported in 11 participants in the overall PUR3100 groups, 21 were mild and one was moderate.

The most frequently reported TEAEs were nausea, headache, dizziness, and vomiting (Table 2). Nausea and headache were more common in participants receiving intravenous DHE compared with any of the PUR3100 dose groups. Vomiting only occurred in participants in the intravenous DHE group. Mild respiratory AEs were reported in two participants (pharyngeal disorder [one in the intravenous DHE group] and productive cough [one in the PUR3100 0.5 mg group]). There were no reports of dysgeusia.

Most measured vital signs remained stable over time. Consistent with the vasoconstrictive effects of DHE, there were some transient changes in vital signs (blood pressure, pulse) during the study, but these changes remained within normal values and were not clinically meaningful. There were no clinically significant changes in hematology, clinical chemistry, or urinalysis parameters. There were also no abnormal or clinically significant physical examination findings, electrocardiogram results, or spirometry (FEV_1).

Pharmacokinetics

The plasma concentration time curves (4 and 24 h) for DHE in all four dose groups were characterized by an early peak followed by a rapid decline in DHE concentrations (Figure 3A,B). Maximum plasma concentrations for all dose groups were observed at the 5-min post-dose time point. DHE concentrations were highest for the intravenous DHE group during the first 15 min post-dose. For the PUR3100 1.5 mg dose group, from 30 min to 48 h post-dose, concentrations were slightly higher than in the intravenous DHE group.

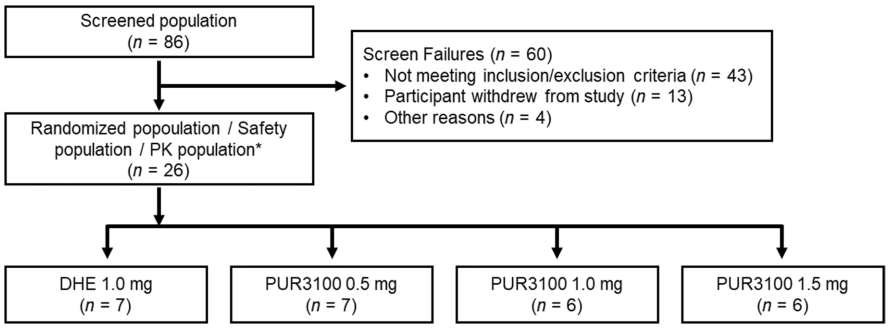

FIGURE 2 Enrollment and study flowchart. *Two participants had major protocol deviations related to missed PK assessments (post-dose PK samples at 5, 10, and 15 min were not collected due to adverse events). Due to insufficient PK sample collection, these 2 participants were replaced and excluded from analysis of PK parameters. The addition of 2 replacement participants resulted in a total of 26 participants rather than the planned 24 participants. DHE, dihydroergotamine; PK, pharmacokinetics.

TABLE 1 Participant demographics and baseline characteristics.

Variable	DHE 1.0 mg IV (*n* = 7)	PUR3100 0.5 mg (*n* = 7)	PUR3100 1.0 mg (*n* = 6)	PUR3100 1.5 mg (*n* = 6)	PUR3100 Overall (*n* = 19)	Overall (*N* = 26)
Age, years						
Mean (SD)	27.3 (8.3)	25.6 (6.5)	28.3 (5.9)	27.8 (10.9)	27.2 (7.6)	27.2 (7.7)
Range	18–43	19–34	19–37	21–49	19–49	18–49
Female, *n* (%)	4 (57)	4 (57)	3 (50)	5 (83)	12 (63)	16 (62)
Ethnicity, *n* (%)						
Not Hispanic or Latino	7 (100)	6 (86)	5 (83)	5 (83)	16 (84)	23 (89)
Race, *n* (%)						
White	4 (57)	5 (71)	3 (50)	6 (100)	14 (74)	18 (69)
Asian	3 (43)	1 (14)	2 (33)	0	3 (16)	6 (23)
Other	0	0	1 (17)	0	1 (5)	1 (4)
Multiple races	0	1 (14)	0	0	1 (5)	1 (4)
Height, cm, mean (SD)	171.9 (12.3)	172.0 (9.9)	169.7 (11.9)	165.3 (8.1)	169.2 (9.9)	169.9 (10.4)
Weight, kg, mean (SD)	73.3 (19.8)	66.9 (10.3)	72.5 (18.6)	62.3 (9.2)	67.2 (13.1)	68.8 (15.0)
BMI, kg/m^2, mean (SD)	24.6 (5.2)	22.6 (2.9)	24.8 (3.3)	22.8 (3.3)	23.3 (3.2)	23.7 (3.7)

Abbreviations: BMI, body mass index; DHE, dihydroergotamine; IV, intravenous; SD, standard deviation.

Derived PK parameters for DHE for the four dose groups are summarized in Table 3. The mean C_{max} was higher in the intravenous DHE group (45,000 pg/mL) than in any of the PUR3100 groups (3620 pg/mL, 5190 pg/mL, and 14,400 pg/mL for the PUR3100 0.5, 1.0, and 1.5 mg groups, respectively). Overall DHE exposure, as measured by AUC_{0-inf}, was generally similar between the intravenous DHE 1.0 mg group (10,900 h•pg/mL) and the PUR3100 1.5 mg group (10,200 h•pg/mL). Systemic exposure following inhaled PUR3100 was slightly greater than dose proportional with a three-fold increase in dose (i.e., from 0.5 to 1.5 mg), resulting in a 3.7- to 4.0-fold increase in geometric mean C_{max} and AUC values of DHE. Clearance (range 92–243 L/h) was rapid for all dose groups. For the first 2 h, AUC_{0-2h} was ~60% of the AUC_{0-inf} for the 1.0 mg intravenous dose and ~40% of the AUC_{0-inf} for each of the PUR3100 doses. The elimination half-life ($t_{1/2}$) values were similar for all dose groups, ranging from 10.9 to 14.9 h.

There were statistically significant differences between intravenous DHE and the PUR3100 0.5 and 1.0 mg dose groups when comparing C_{max}, AUC_{0-t}, and AUC_{0-inf} (Table 4). The C_{max} geometric mean ratio percentages (90% CI) for each dosing group versus intravenous DHE were 8 (4.3, 15.0), 12 (6.2, 21.5), and 32 (17.2, 59.6), for PUR3100 0.5, 1.0, and 1.5 mg, respectively. The calculated geometric mean ratio was 93% for AUC_{0-inf} for PUR3100 1.5 mg relative to intravenous DHE 1.0 mg; therefore, the total exposure from PUR3100 1.5 mg is 7–8% lower than after intravenous administration.

The PK profile of the active metabolite (8-OH-DHE) generally followed a similar pattern to that seen for DHE in all treatment groups, except that exposure to 8-OH-DHE was much lower compared to DHE, with average C_{max}, AUC_{0-2h}, and AUC_{0-t} values of 8-OH-DHE compared to DHE ranging from 1% to 3%, 3–9%, and 8–14%, respectively, across PUR3100 doses. Peak concentrations of 8-OH-DHE were slightly delayed relative to the parent compound, with C_{max}

TABLE 2 Adverse events.

Variable	DHE 1.0 mg IV (*n* = 7)	PUR3100 0.5 mg (*n* = 7)	PUR3100 1.0 mg (*n* = 6)	PUR3100 1.5 mg (*n* = 6)	PUR3100 Overall (*n* = 19)	Overall (*N* = 26)
Any TEAE, *n* (%)	6 (86)	3 (43)	4 (67)	4 (67)	11 (58)	17 (65)
TEAE related to study drug, *n* (%)	6 (86)	2 (29)	2 (33)	4 (67)	8 (42)	14 (54)
SAEs	0	0	0	0	0	0
TEAE leading to early withdrawal	0	0	0	0	0	0
TEAEs, *n* (%)						
Headache	4 (57)	1 (14)	1 (17)	1 (17)	3 (16)	7 (27)
Dizziness	2 (29)	0	0	2 (33)	2 (11)	4 (15)
Nausea	6 (86)	1 (14)	1 (17)	2 (33)	4 (21)	10 (39)
Vomiting	2 (29)	0	0	0	0	2 (8)
Asthenia	0	0	1 (17)	0	1 (5)	1 (4)
Chest discomfort	1 (14)	0	0	0	0	1 (4)
Fatigue	0	0	1 (17)	0	1 (5)	1 (4)
Feeling hot	0	1 (14)	0	0	1 (5)	1 (4)
Suprapubic pain	1 (14)	0	0	0	0	1 (4)
Oral herpes	0	0	1 (17)	0	1 (5)	1 (4)
Urinary tract infection staphylococcal	0	1 (14)	0	0	1 (5)	1 (4)
Pharyngeal disorder	1 (14)	0	0	0	0	1 (4)
Productive cough	0	1 (14)	0	0	1 (5)	1 (4)
Vitreous floaters	0	1 (14)	0	0	1 (5)	1 (4)
Procedural nausea	0	1 (14)	0	0	1 (5)	1 (4)
Anxiety	1 (14)	0	0	0	0	1 (4)

Abbreviations: DHE, dihydroergotamine; IV, intravenous; TEAE, treatment-emergent adverse event; SAE, serious adverse event.

concentrations occurring between 10 and 15 min post-dose. Similar to the parent compound, mean C_{max} values for 8-OH-DHE were highest in the intravenous DHE group, with values increasing in a generally dose-dependent manner for the PUR3100 dose groups. Systemic exposure of 8-OH-DHE is unlikely to contribute to either the efficacy or safety of the drug.

DISCUSSION

Although intravenous DHE has well-established efficacy for the acute treatment of migraine, its use is hampered by gastrointestinal side-effects and a requirement of in-hospital administration.[10] Previous DHE formulations have included intramuscular, subcutaneous, and rectal administration. An oral inhalation formulation may be a more tolerable or convenient route of administration, also allowing for self-administration.

The DHE drug development process is challenging as it has a relatively narrow therapeutic window. Intranasal formulations of DHE have improved the safety and tolerability profile; however, the onset of action is slower with lower efficacy rates than intravenous DHE. Based on the reported efficacy of intranasal and inhaled DHE, the minimum C_{max} of DHE required to achieve efficacy appears to be ~1000 pg/mL.[12] All doses of PUR3100 were associated with mean C_{max} above the 1000 pg/mL threshold. At the upper end of the therapeutic window, a pooled analysis of data from the development of MAP0004 indicated that nausea was observed in 50% of patients with a DHE C_{max} exceeding 13,400 pg/mL, but in fewer than 2% of patients with a DHE C_{max} under 5000 pg/mL.[10] The mean C_{max} of PUR3100 ranged from 3620 to 14,400 pg/mL. Assuming the C_{max} is related to initial therapeutic potential, the ability of PUR3100 to achieve a higher C_{max} relative to intranasal formulations may offer higher efficacy rates while maintaining an improved safety profile relative to the intravenous formulation.

Intravenous DHE generally results in a C_{max} far more than that needed for both efficacy and clinical benefit, whereas the commercially available intranasal formulations generally achieve a C_{max} only slightly above the minimum effective level. The goal for this study was to achieve plasma concentrations with PUR3100 that would allow examination of the entire reported therapeutic window,[12] to determine the dose with highest C_{max}—and hence the best likelihood of achieving efficacy—while minimizing as much as possible the unwanted side-effect profile.

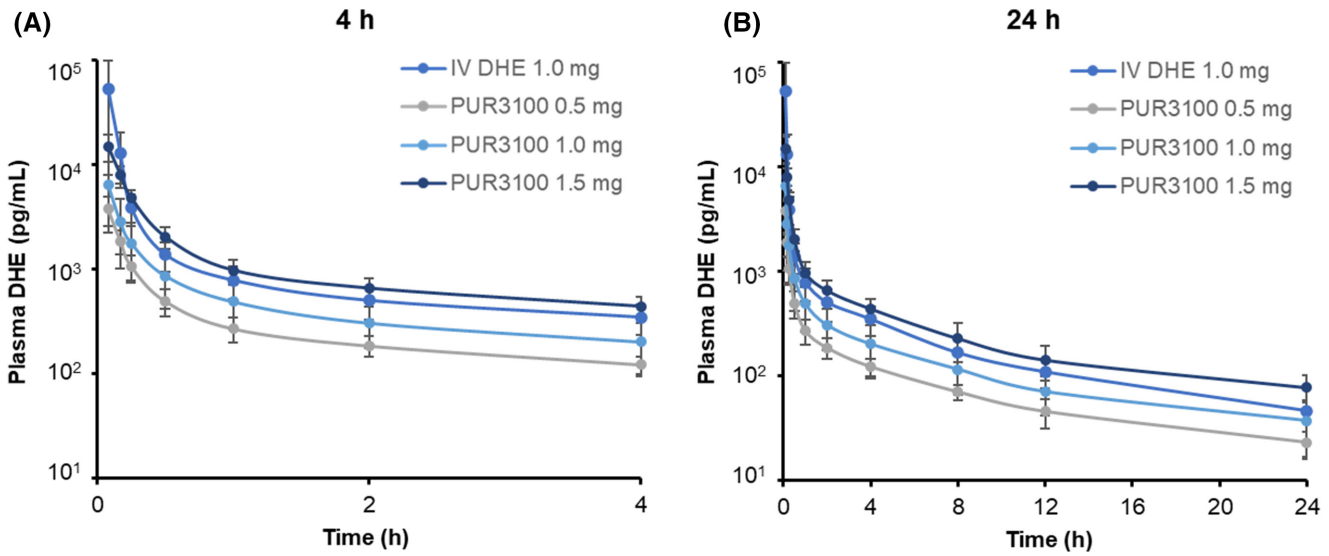

FIGURE 3 Mean plasma DHE concentration-time profiles for IV DHE and PUR3100 over 4 (A) and 24 h (B). DHE concentration (mean ± standard deviation) presented on a log10 scale by nominal timepoint. DHE, dihydroergotamine; IV, intravenous.

TABLE 3 Dihydroergotamine pharmacokinetics parameters (mean [CV%], unless otherwise specified).

Variable	DHE 1.0 mg IV ($n=6$)[a]	PUR3100 0.5 mg ($n=6$)[a]	PUR3100 1.0 mg ($n=6$)	PUR3100 1.5 mg ($n=6$)
T_{max}, h[b]	0.0917 (36.3)	0.083 (0.00)	0.083 (0.00)	0.083 (28.8)
C_{max}, pg/mL[c]	45,000 (103)	3620 (32.6)	5190 (93.5)	14,400 (32.8)
AUC_{0-t}, h•pg/mL[c]	10,500 (39.0)	2530 (25.9)	3780 (70.9)	9630 (26.1)
AUC_{0-2h}, h•pg/mL[c]	6340 (53.9)	1120 (21.3)	1640 (74.5)	4320 (23.5)
AUC_{0-inf}, h•pg/mL[c]	10,900 (37.5)	2770 (27.2)	4110 (65.7)	10,200 (26.1)
AUC_{extrap}, %[d]	3.25 (50)	8.39 (26)	7.30 (50)	5.09 (36)
CL or CL/F×, L/h[d]	91.7 (37.5)	181 (27.2)	243 (65.7)	147 (26.1)
V_z or V_z/F×, L[d]	1810 (51.0)	2610 (27.9)	3910 (49.3)	3140 (30.8)
λ_z, 1/h[d]	0.0515 (19.8)	0.0746 (39.2)	0.0639 (24.8)	0.0472 (12.8)
$t_{1/2}$, h[d]	13.9 (19.3)	10.9 (47.0)	11.4 (25.6)	14.9 (12.0)
T_{last}, h[d]	48.0 (0.184)	32.0 (38.7)	36.1 (36.1)	48.0 (0.075)
C_{last}, pg/mL[c]	18.0 (13.7)	16.1 (40.5)	18.7 (33.4)	24.3 (41.3)

Abbreviations: AUC, area under the concentration time curve; AUC_{0-2h}, AUC from time zero to 2 h post-dose; AUC_{0-inf}, AUC from time zero to infinity; AUC_{0-t}, AUC from time zero to time of the last quantifiable concentration; AUC_{extrap}, percentage of the AUC from time zero to infinity based on extrapolation; CL, plasma clearance; CL/F apparent total plasma clearance; C_{last}, last quantifiable concentration; C_{max}, maximum plasma concentration; CV%, coefficient of variation; DHE, dihydroergotamine; IV, intravenous; PK, pharmacokinetics; $t_{1/2}$, apparent terminal half-life; T_{last}, time of last quantifiable concentration; T_{max}, time to maximum concentration; V_z, volume of distribution; V_z/F, apparent volume of distribution; λ_z, terminal elimination rate constant.

[a]One participant excluded due to insufficient PK concentration data.

[b]Median.

[c]Geometric means.

[d]Arithmetic means.

In this study, more study drug-related TEAEs occurred in participants in the intravenous DHE 1.0 mg group (six of seven [86%]) than in any of the PUR3100 groups (1.5 mg, four of six [67%]; 1.0 mg, two of six [33%]; and 0.5 mg, two of seven [29%]), with nausea and headache being more common in participants receiving intravenous DHE compared with any of the PUR3100 dose groups. Moreover, vomiting only occurred in participants in the intravenous DHE group. Therefore, the side-effect profile of the three doses (0.5, 1.0, and 1.5 mg) of PUR3100 following inhalation compares favorably to that of intravenous DHE in healthy participants.

Overall, the time course and patterns of DHE plasma concentrations associated with inhaled PUR3100 were similar to those seen with intravenous DHE, with both formulations having a short time to maximum plasma concentrations (5 min) and a rapid subsequent

TABLE 4 Statistical comparison of natural log-transformed systemic exposure of dihydroergotamine from inhaled PUR3100 versus intravenous dihydroergotamine 1.0 mg.

Comparison	Dependent variable	LS mean PUR3100	LS mean IV DHE 1.0 mg	Geometric mean PUR3100	Geometric mean IV DHE 1.0 mg	Geometric mean ratio % (90% CI)	*p*	CV%
PUR3100 0.5 mg vs. IV DHE 1.0 mg	C_{max}	8.2	10.7	3620	45,000	8 (4.3, 15.0)	<0.001	69.0
	AUC_{0-t}	7.8	9.3	2530	10,500	24 (16.0, 36.3)	<0.001	43.0
	AUC_{0-inf}	7.9	9.3	2770	10,900	25 (17.1, 37.7)	<0.001	41.2
PUR3100 1.0 mg vs. IV DHE 1.0 mg	C_{max}	8.6	10.7	5190	45,000	12 (6.2, 21.5)	<0.001	69.0
	AUC_{0-t}	8.2	9.3	3780	10,500	36 (23.8, 54.2)	<0.001	43.0
	AUC_{0-inf}	8.3	9.3	4110	10,900	38 (25.4, 55.9)	<0.001	41.2
PUR3100 1.5 mg vs. IV DHE 1.0 mg	C_{max}	9.6	10.7	14,400	45,000	32 (17.2, 59.6)	0.005	69.0
	AUC_{0-t}	9.2	9.3	9630	10,500	92 (60.8, 138.1)	0.717	43.0
	AUC_{0-inf}	9.2	9.3	10,200	10,900	93 (62.9, 138.5)	0.767	41.2

Note: Results are from a linear mixed effects model on the natural log-transformed values for C_{max}, AUC_{0-t}, and AUC_{0-inf}, including treatment as a fixed effect. For each comparison, the least squares means were obtained from the model; these results were exponentiated to provide the Test (PUR3100)/Reference (DHE) ratios of geometric means and the 90% CIs on a linear scale. *p* values presented are for the difference in LS mean estimates between the Test (PUR3100) and Reference (DHE) for each comparison.

Abbreviations: AUC_{0-inf}, AUC from time zero to infinity, calculated as: $AUC_{0-inf} = AUC_{0-t} + C_{last}/\lambda_z$, where C_{last} is the last quantifiable concentration and λ_z is the terminal elimination rate constant; AUC_{0-t}, area under the concentration-time curve from time-zero to the time of the last quantifiable concentration, calculated using the linear up/log down trapezoidal method; CI, confidence interval; C_{max}, maximum plasma concentration; CV%, coefficient of variation, DHE, dihydroergotamine; IV, intravenous; LS, least squares.

decline in plasma concentrations. Given the relatively slow onset of action of DHE, it is postulated that a PK profile that results in rapid achievement of a therapeutic concentration is likely to result in early onset of pain relief and pain freedom observed with intravenous dosing.[15] Due to the relatively rapid metabolism of DHE, the short time to peak concentration with intravenous DHE or inhaled PUR3100 is associated with rapid clearance. However, DHE has been shown to have prolonged efficacy that persists beyond the PK exposure period.[15]

The primary difference between the inhaled and intravenous formulations was a lower peak exposure to DHE with PUR3100 relative to intravenous DHE. For example, the highest dose of PUR3100 (1.5 mg) had a 68% lower C_{max} (based on the geometric mean ratio) compared to intravenous DHE 1.0 mg while achieving similar total exposure. Primary differences in PK between the PUR3100 inhaled and that reported in the literature for nasal formulations are a faster time to maximum plasma concentration (T_{max}) and higher C_{max}. The T_{max} of PUR3100 (5 min) is substantially shorter than Trudhesa® (30 min) and Migranal® (47 min).[12,13] The C_{max} for all PUR3100 doses were higher than either Trudhesa® (1301 pg/mL) or Migranal® (300 pg/mL).[12] These observations may reflect the greater surface area of the lung relative to the nasal mucosa. The shorter T_{max} and higher C_{max} values achievable with PUR3100, coupled with the relatively low incidence of AEs, indicate that advancement into patients with acute episodic migraine is appropriate.

In assessing the comparative bioavailability of PUR3100 relative to intravenous DHE, the bioavailability of the PUR3100 1.5 mg dose appears to be similar. The PUR3100 1.5 mg dose group was expected to deliver 0.9 mg DHE to the lung, based on a delivered fine-particle dose of <5 μm estimated to be ~60%. The PUR3100 1.5 mg dose group achieved a similar AUC_{0-inf} relative to intravenous DHE 1.0 mg (geometric mean ratio of 93%), indicating high bioavailability of inhaled DHE. Based on the lower C_{max} and AUC_{0-2h} with inhaled PUR3100, these data suggest a similar total exposure with inhaled PUR3100 relative to intravenous DHE at equivalent delivered doses. It is proposed that inhalation of PUR3100 results in slower entry of DHE from the lung to the systemic circulation relative to intravenous DHE, sufficient to achieve a lower C_{max} while still achieving a rapid T_{max}.

The PK profile of PUR3100 likely explains the improved safety and tolerability of PUR3100 relative to intravenous DHE. In the present study, a lower proportion of participants receiving PUR3100 experienced AEs than did participants receiving intravenous DHE, and the events tended to be less severe. There was substantially less nausea and vomiting, and fewer headaches with each of the PUR3100 dose groups compared with those receiving intravenous DHE. There were also no treatment-related discontinuations in any of the PUR3100 dose groups. Intranasal formulations of DHE can be associated with nasopharyngitis, rhinitis, nasal discomfort, sinusitis, and taste abnormalities.[11,13] In the present study, there was one reported respiratory AE (cough) and no reports of dysgeusia in the PUR3100 groups. Moreover, there were no clinically meaningful effects on respiratory function as measured by FEV_1.

In conclusion, this study established that inhaled PUR3100 in doses of 0.5, 1.0, and 1.5 mg is safe and well tolerated with fewer AEs, particularly vomiting, than intravenous DHE. Relative to intravenous DHE, PUR3100 is characterized by good bioavailability and a similar rapid achievement of therapeutic DHE concentrations but with reduced C_{max} and AUC_{0-2h} values. The data suggest that total DHE exposure with inhaled PUR3100 1.5 mg is similar to that of intravenous DHE 1.0 mg but with a slower entry from the lungs to the systemic circulation, sufficient to achieve a lower C_{max} while still achieving a rapid T_{max} within 5 min of dosing. Lower doses of PUR3100 have similar T_{max} values and peak exposures in the therapeutic window. These findings, while in a smaller population, inform the dose selection for evaluation in a future clinical study.

AUTHOR CONTRIBUTIONS

Susan Bodie: Data curation; writing – original draft; writing – review and editing. **Aidan K. Curran:** Conceptualization; data curation; visualization; writing – original draft; writing – review and editing. **Aaron C. Gonzalez-Nelson:** Resources; writing – original draft; writing – review and editing. **Jason M. Perry:** Supervision; writing – original draft; writing – review and editing. **Debora C. Manning:** Formal analysis; writing – original draft; writing – review and editing. **Margaret M. Wasilewski:** Data curation; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Susan Bodie, **Aaron C. Gonzalez-Nelson**, **Jason M. Perry**, and **Margaret M. Wasilewski** are employees of Pulmatrix Inc. (Bedford, MA, USA). **Aidan K. Curran** was an employee of Pulmatrix Inc. at the time of the study. **Debora C. Manning** is an employee of Veristat, a company that received funding from Pulmatrix Inc. for time spent analyzing this research.

CLINICAL TRIALS REGISTRATION NUMBER

This trial is registered with ClinicalTrials.gov (NCT05351086).

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