

Systemic Pharmacokinetics of DHE When Delivered Via the Lung to Asthmatics by the Tempo® Inhaler

Stephen Shrewsbury¹, Shashidhar Kori¹, David Miller², Andrew Pedinoff³, Steven Weinstein⁴

¹MAP Pharmaceuticals Inc., Mountain View, CA ²Northeast Medical Research, Dartmouth, MA ³Princeton Center for Clinical Research, Skillman, NJ ⁴Allergy Asthma Specialists, Huntington Beach, CA

INTRODUCTION

Dihydroergotamine mesylate (DHE) is widely recognized as effective for the treatment of acute migraine and has been used for decades by various routes of administration. However, an optimal route of administration is not currently available. Intravenous (IV) DHE requires administration in the emergency room or doctor's office. Subcutaneous or intramuscular administration is limited by a delayed onset and erratic absorption from injection sites. Additionally, patients are reluctant to self-administer by injection. Intranasal administration of DHE is inconvenient and limited by inconsistent delivery of a therapeutic dose.

MAP0004, orally inhaled DHE delivered by the Tempo® inhaler, is being developed for the potential rapid and long lasting treatment of migraine. This innovative (non-nasal and non-injectable) delivery method provides a pharmacokinetic (PK) profile similar to that of IV DHE, but with improved tolerability.

MAP0004 has been shown to be well tolerated both in healthy subjects and migraineurs. Clinical trials in patients with acute migraine are ongoing. The present study was undertaken to evaluate the safety and tolerability of MAP0004 in a population of asthmatic adults because asthma and migraine often occur as co-morbid conditions. In addition, the study sought to confirm that the pharmacokinetics of MAP0004 delivered by inhalation to subjects with pre-existing lung disease, such as asthma, were comparable to those observed in healthy volunteers.

METHODS

This was a Phase 2, double-blind, randomized, placebo-controlled, 2-arm, 3-period, incomplete block crossover study conducted at three clinical centers in the United States. Male and female subjects 18 - 50 years old were eligible to participate in this study if they had a diagnosis of asthma with or without specific asthma treatment.

The asthma diagnosis was confirmed by spirometry, unless spirometry had been performed and documented within the previous 12 months. At baseline, subjects had to have a forced expiratory volume in 1 second (FEV₁) ≥60% of predicted normal and demonstrated FEV₁ reversibility of ≥15% within 15-20 minutes after inhalation of a short acting beta₂-agonist, in accordance with the NIH EPR-2 Asthma Guidelines. Subjects were maintained on their current asthma medications during the study, but no new medications were added. Subjects were prohibited from taking any medication that might interfere with the pharmacokinetic (PK) results of the study. All bronchodilators were withheld before each observed dosing: long acting bronchodilators for at least 12 hours and short acting bronchodilators for at least 4 hours.

The study design is presented in Table 1. At Visit 1, after informed consent was obtained, potential subjects were screened. Subjects who met the eligibility criteria and agreed to enroll in the study (n=19) returned 1-7 days later for Visit 2. At this visit, subjects were randomized in a 2:1 ratio to either 2.0 mg nominal dose (1.0 mg systemic equivalent) of MAP0004 or placebo and received, under supervision, their first dose of study drug from the inhaler. (*Note: Delivery is two inhalations.) Subjects received subsequent doses of study drug at Visits 3 and 4 (7 ±1 day and 14 ±1 day, respectively after the initial dose) and returned for Visit 5, the follow up visit, 2-4 days after Visit 4 (15-19 days after the first dose of study drug).

Blood samples were collected at Visit 2 within 30 minutes before dosing and at 5, 10, 15, 30, and 60 minutes and at 2, 4, 24, and 36 hours after the first actuation to determine MAP0004 plasma concentrations for each patient in each treatment arm. Quantitative liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used to determine plasma levels of MAP0004. The method was linear over the standard concentration range of 10 to 5000 pg · mL⁻¹ of MAP0004, and the coefficient of variation did not exceed 5.3%.

Replicate analyses of intra- and inter-batch MAP0004 quality control samples showed accuracy of 94.6% - 105.5% and assay imprecision ≤11.5%. Mean (±SD) MAP0004 recovery from human plasma was 85.0% (2.1%). PK parameters measured for MAP0004 included maximal plasma concentration (C_{max}), area under the plasma concentration from 0 to 36 hours post-dose (AUC₀₋₃₆), area under the plasma concentration from 0 to infinity (AUC_{0-∞}), time at which maximal plasma concentration was observed (t_{max}), and elimination half life (t_{1/2}).

METHODS continued

Safety and tolerability were evaluated from reports of adverse events, changes in pulmonary function measured by spirometry (FEV₁, FEV_{1-25%}, FVC, and % predicted values), clinical laboratory values including immunoglobulin E (IgE), vital signs, and ECG. The safety measures of primary interest were the change from baseline in FEV₁ after each dose and any increase in IgE after two sequential doses of MAP0004.

Table 1. Study Design

Sequence Group	Dose 1 (Visit 2)	Dose 2 (Visit 3)	Dose 3 (Visit 4)	N (19)
A	Placebo	MAP0004	MAP0004	6
B	MAP0004	Placebo	MAP0004	7
C	MAP0004	MAP0004	Placebo	6

RESULTS & DISCUSSION

Table 2. Baseline Demographics and Clinical Characteristics

	Sequence A (n=6)	Sequence B (n=7)	Sequence C (n=6)	All Subjects (N=19)
Male: female	3:3	2:5	2:4	7:12
Mean (SD) age (years)	28.2 (11.3)	35.4 (12.0)	24.3 (5.1)	29.6 (10.7)
Range	18 - 48	22 - 50	21 - 33	18 - 50
Mean (SD) weight (lb)	153.8 (38.2)	165.0 (34.8)	148.0 (17.9)	156.1 (30.8)
Smoking history, n(%)	1 (16.7)	1 (14.3)	0	2 (10.5)
Mean (SD) FEV ₁ (L)	2.6 (0.7)	2.4 (0.6)	2.9 (0.5)	2.6 (0.6)
Range (L)	2.2 - 3.9	1.7 - 3.2	2.3 - 3.5	1.7 - 3.9
Mean (SD) FVC (L)	3.6 (0.9)	3.2 (0.8)	3.8 (0.5)	3.5 (0.8)
Mean (SD) FEV _{1-25%}	2.0 (0.9)	2.0 (0.9)	2.6 (0.9)	2.2 (0.9)
Mean (SD) % Predicted FEV ₁ (L)	73.2 (8.2)	74.0 (6.4)	80.0 (16.2)	75.6 (10.7)
Range (%)	63.0 - 83.0	69.0 - 87.0	66.0 - 111.0	63.0 - 111.0
Mean (SD) % Predicted FVC (L)	84.0 (5.5)	82.1 (4.5)	88.3 (14.3)	84.7 (8.9)

- Male to female ratio of 7:12
- Mean age of 29.6
- Symmetric distribution across all the sequence groups

Table 3. Pharmacokinetic Parameters for MAP0004

PK Parameter	MAP0004 at Visit 2 (n=8)
Mean (SD) AUC _{0-∞} (pg·h/mL)	7897.0 (4186.1)
Geometric mean (SE)	6753.6 (1.3)
Range	2157.5 - 14954.2
Mean (SD) AUC ₀₋₃₆ (pg·h/mL)	8584.3 (4237.5)
Geometric mean (SE)	7482.9 (1.2)
Range	2290.2 - 15704.8
Mean (SD) t _{max} (minutes)	9.6 (3.0)
Geometric mean (SE)	9.0 (68.4)
Range	4.2 - 13.8
Mean (SD) C _{max} (pg/mL)	4097.4 (3507.8)
Geometric mean (SE)	3173.6 (1.3)
Range	855.2 - 12289.7
Mean (SD) Half-life (h)	9.80 (3.10)

- T_{max} of 9.6 minutes
- Geometric mean C_{max} of 3174 pg/mL

RESULTS & DISCUSSION continued

Table 4. Treatment Emergent Adverse Events that Occurred in at Least 10% of Subjects

	Number (%) of Subjects		
	Placebo (n=18)	MAP0004 1st Dose (n=19)	MAP0004 2nd Dose (n=17)
Number reporting ≥1 event	5 (27.8)	8 (42.1)	6 (35.3)
Nausea	1 (5.6)	4 (21.1)	1 (5.9)
Vomiting	1 (5.6)	2 (10.5)	2 (11.8)
Dysgeusia	0	2 (10.5)	1 (5.9)
Headache	0	2 (10.5)	2 (11.8)
Total number of events	6	19	8
Treatment related	3 (50.0)	14 (73.7)	7 (87.5)
Caused discontinuation	1 (5.6)	0	0

- No Serious Adverse Events
- No significant AEs
- No discontinuation due to AEs

Table 5. FEV₁ % Change from Measured Baseline Following Dosing

Time from dosing	Placebo (n=18)	First Dose MAP0004 (n=19)	Second Dose MAP0004 (n=17)
15 minutes	0.3	-0.9	-1.1
30 minutes	1.1	-1.2	0.2
60 minutes	2.4	0.4	-0.5
4 hours	1.8	1.5	0.4
Range	-2.2 to +4.2	-3.8 to +4.4	-4.6 to +4.5

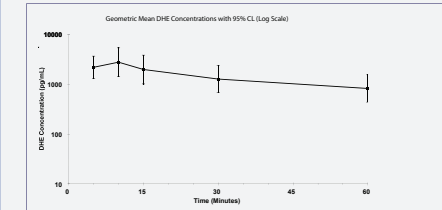
- No significant change from baseline in FEV₁

Table 6. Mean Serum IgE Concentrations at Baseline and After Treatment with MAP0004

	Mean (SD) IgE (IU/L)		
	Sequence A	Sequence B	Sequence C
Screening	229.8 (181.0) (n=6)	403.7 (287.6) (n=7)	302.8 (318.3) (n=6)
Visit 2 (pre-dose)	187.8 (176.9) (n=4)	307.1 (220.7) (n=4)	366.4 (418.8) (n=5)
Visit 3 (pre-dose)	246.8 (212.8) (n=6)	301.4 (216.1) (n=6)	325.8 (387.0) (n=6)
Visit 4 (pre-dose)	234.6 (185.7) (n=5)	264.9 (203.8) (n=6)	292.0 (328.1) (n=6)
Termination	227.3 (182.2) (n=6)	367.6 (280.4) (n=7)	300.8 (342.3) (n=6)

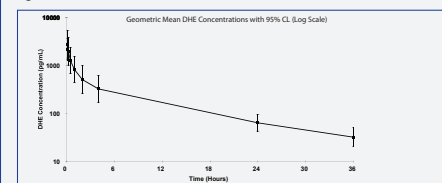
- No significant change from baseline in IgE concentration

Figure 1. Plasma DHE Concentrations Versus Time (First Hour)



- Mean T_{max} was 9.6 minutes, indicating a rapid absorption of MAP0004
- Geometric mean C_{max} of 3174 pg/mL

Figure 2. Plasma DHE Concentrations Versus Time (to 36 Hours)



- Demonstrates a biphasic decline in plasma concentration
- Terminal phase predominant after 4 hours
- Terminal phase geometric t_{1/2} of 9.5 hours

CONCLUSION

In this study, inhalation of MAP0004 was well tolerated and the reported adverse events in asthmatics were similar to those of placebo. Inhalation of MAP0004 with the Tempo inhaler resulted in rapid absorption of MAP0004 with a mean T_{max} of 9.6 minutes. Even though a non-asthmatic, healthy volunteer group was not included in this study, comparing the results from this study to a previous study by Shrewsbury and colleagues indicates that MAP0004 PK profiles are similar in asthmatic and non-asthmatic subjects. The presence of chronic lung disease had no appreciable effect on the pharmacokinetics of MAP0004 after administration of a single 2.0 mg nominal dose, the systemic equivalent to the standard approved 1.0 mg IV treatment for patients with acute migraine. Ongoing clinical trials are being conducted to confirm the efficacy, safety, and tolerability of MAP0004 in patients with acute migraine.

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