

# EFFICACY AND TOLERABILITY OF MAP0004, FEATURING A NOVEL DELIVERY SYSTEM, IN TREATING ACUTE MIGRAINE

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## OBJECTIVE

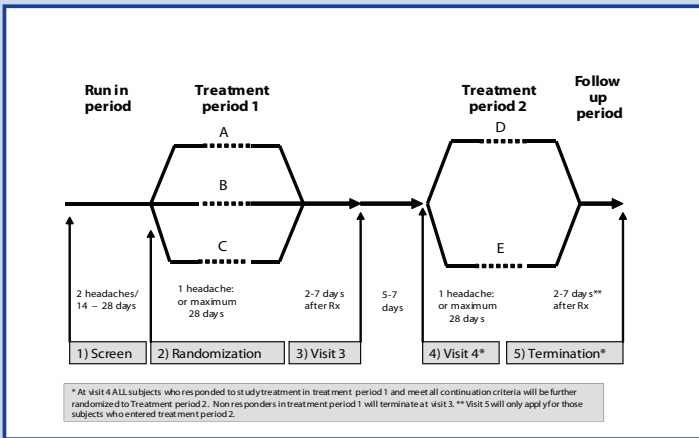
Individual migraine patient's treatment needs are often unmet by the current available therapies, including the seven triptans, due to inconsistency of response, high recurrence rates, slow onset of action and potential for medication overuse headaches (MOH). IV dihydroergotamine (DHE) provides rapid relief, low recurrence rates and no reported MOH. However, IV-DHE is difficult to administer. MAP0004 delivers inhaled DHE with similar T<sub>max</sub> and AUC as IV by a less invasive and more practical route of administration.

The objective of this study was to evaluate the efficacy and tolerability of 3 different doses of MAP0004, orally inhaled DHE administered at home by the Tempo<sup>®</sup> inhaler.

## STUDY DESIGN

This was a randomized, double-blind, parallel-group, placebo-controlled, 2-part study of 3 doses of MAP0004 in migraineurs, conducted at 9 sites in the United States (US). The study consisted of a total of 5 clinic visits.

Treatment Period	Group	Treatment		Delivery Method
		MAP0004	Placebo	
Treatment Period 1	A	2 actuations MAP0004 (~0.5mg total)	2 actuations placebo from 2 Tempo inhalers	Oral inhalation through Tempo inhaler
	B	4 actuations MAP0004 (~1.0mg total);	2 actuations from each of 2 Tempo inhalers	
	C	4 actuations placebo;	2 actuations from each of 2 Tempo inhalers	
Treatment Period 2	D	2 actuations MAP0004 (~0.25mg total);	both actuations from a single Tempo inhaler	Tempo inhaler
	E	2 actuations placebo;	both actuations from a single Tempo inhaler	



## RESULTS

In Treatment Period 1, the 3 treatment groups in the Intend-to-treat (ITT) population (i.e. all randomized subjects, N = 86) were comparable for baseline characteristics, mean % predicted FEV<sub>1</sub>, mean years of migraine, mean years of smoking, and current smoking status.

Overall, 82.6% of subjects were female. The mean age was 41.3 years (range 19 - 59 years). 88.4% were White; 1.2% were Hispanic or Latino. Mean % predicted FEV<sub>1</sub> was 100.9%; mean migraine history was 23 years. None (0%) were current smokers and 82.6% had never smoked.

The "As-Treated" populations (on whom efficacy and exploratory endpoint analyses were performed for Treatment Period 1) were similar to the ITT population. Demographic data and baseline characteristics were comparable between Treatment Period 1 and 2.

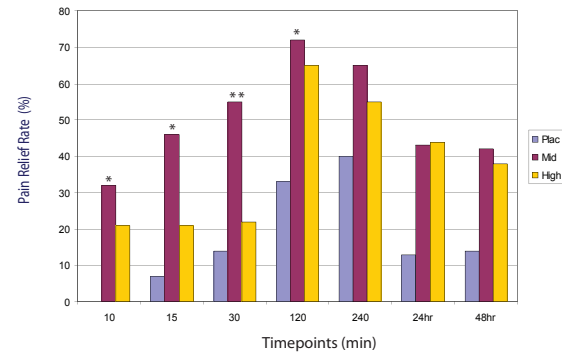
Eighty-six (86) subjects were randomized, with 69 in the "As-Treated" population in Period 1. The primary endpoint (pain relief at 2 hours) was greater for MAP0004 0.5mg and 1.0mg doses than for placebo, with therapeutic gains (TG) of 39% (p=0.019) and 32% (p=0.071), respectively (Table 1 and Figure 1). Similarly, for 10 minute pain relief TGs of 32% (p=0.019) and 22% (p=0.060), respectively, were achieved. Freedom from other symptoms (as shown in Tables 2, 3, and 4) was also noted. Pain relief was sustained over 24 hours [TG of 30% (p=0.066) for 0.5mg dose]. Period 2 randomized 35 subjects, treated 24 attacks with 0.25mg MAP0004 dose or placebo and reported a smaller TG.

Table 1: Efficacy Results: (As-Treated Population) – Period 1

	N (As Treated, # providing data)			Efficacy			Therapeutic Gain (TG)		P-value	
	0.5mg	1.0mg	Plac	0.5mg	1.0mg	Plac	0.5mg	1.0mg	0.5mg	1.0mg
Pain relief at 10 minutes	22	18	15	32%	22%	0%	32%	22%	0.019	0.060
Pain relief at 30 minutes	22	17	14	55%	24%	14%	41%	10%	0.022	0.523
Pain relief at 2 hours	25	20	15	72%	65%	33%	39%	32%	0.019	0.071
Sustained relief 2-24 hours	21	18	15	43%	44%	13%	30%	31%	0.066	0.060

## RESULTS continued

Figure 1: Efficacy Results: (As-Treated Population) – Period 1



\* p=0.019 \*\* p=0.022 vs. placebo

Tables 2, 3 & 4 Efficacy Results: Rates of Freedom from Phonophobia, Photophobia, and Nausea – Period 1

Phonophobia free %/ timepoints	Placebo	MAP0004 – 0.5mg (p vs placebo)	MAP0004 – 1.0mg (p vs placebo)
Baseline	13%	15%	16%
2 hours	33	44 (0.516)	33 (0.987)
4 hours	40	50 (0.548)	50 (0.575)
Sustained 24hrs	7	38 (0.037)	24 (0.184)

Photophobia free %/ timepoints	Placebo	MAP0004 – 0.5mg (p vs placebo)	MAP0004 – 1.0mg (p vs placebo)
Baseline	19%	4%	16%
2 hours	33	44 (0.516)	39 (0.757)
4 hours	33	54 (0.216)	39 (0.757)
Sustained 24hrs	13	38 (0.112)	29 (0.276)

Nausea free %/ timepoints	Placebo	MAP0004 – 0.5mg (p vs placebo)	MAP0004 – 1.0mg (p vs placebo)
Baseline	25%	42%	37%
2 hours	53	76 (0.143)	61 (0.642)
4 hours	40	73 (0.037)	56 (0.383)
Sustained 24hrs	20	48 (0.098)	53 (0.064)

MAP0004 was well tolerated, with no SAEs or severe AEs in either treatment period. Moderate or mild AEs were reported for few subjects in Period 1 (Table 5). Only dysgeusia (bitter/bad taste) was reported as treatment related (2 subjects on placebo, 0 on MAP0004 0.5mg, 6 on MAP0004 1.0mg – all in Period 1). No spirometry, vital sign, ECG, or laboratory changes of concern were noted in either treatment period.

Data from Treatment Period 2 did not demonstrate consistent differentiated benefit and is not presented here.

Table 5: Brief Summary of Treatment-emergent Adverse Events: Safety Population - Period 1

	Subjects (N = 68) Number (%)					
	Placebo (n = 13)		MAP0004 0.5 mg (n = 25)		MAP0004 1.0 mg (n = 30)	
Any AEa	2 (15.4)		3 (12.0)		8 (26.6)	
Withdrawals due to AE	0		0		1 (3.3)	
Subjects who had SAEs	0		0		0	
	Related	Not Related	Related	Not Related	Related	Not Related
Subjects with Any AE by Relationship and Severity	2 (15.4)	0	0	3 (12.0)	7 (23.3)	1 (3.3)
Mild	1 (7.7)	0	0	3 (12.0)	2 (6.7)	0
Moderate	1 (7.7)	0	0	0	5 (16.7)	0
Severe	0	0	0	0	0	0

## CONCLUSION

As shown in this study, MAP0004 was well tolerated and effective at delivering clinically significant, rapid, and sustained relief of pain and other symptoms for migraine sufferers.