

RAPID AND SUSTAINED CLINICAL EFFICACY AND SAFETY OF INHALED DIHYDROERGOTAMINE MESYLATE VIA A NOVEL INHALER (TEMPO™ INHALER)

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ABSTRACT

Objective: This adult migraineurs study (MAP0004-CL-P201) compared efficacy and safety of inhaled dihydroergotamine mesylate delivered by the Tempo™ inhaler (MAP0004) with placebo.

Methods: Randomized, double blind, placebo-controlled, two period study, across 9 U.S. headache centers.

Results: 86 subjects randomized, 69 in “As Treated” population in period 1. The primary endpoint (pain relief at 2 hours) was greater for MAP0004 0.5mg and 1.0mg than for placebo (Therapeutic Gains (TG) of 39% (p=0.019) and 32% (p=0.071) (Table 1)), and 10 minute pain relief TG of 32% (p=0.039) and 25% (p=0.086). Pain relief was sustained over 24 hours (TG of 30% (p=0.066) for 0.5mg dose). Period 2 randomized 35 subjects and treated 24 attacks with 0.25mg MAP0004 or placebo and reported a smaller TG. MAP0004 was well tolerated (No SAEs or severe AEs in either period). Moderate or mild AEs were reported for few subjects in period 1. Only dysgeusia (bitter/bad taste) reported as treatment related (2 subjects on placebo, 6 on MAP0004 1.0mg – all in period 1). No spirometry, vital sign, ECG, or laboratory changes of concern were noted in either period.

Conclusions: MAP0004 is well tolerated and effective at delivering clinically significant, rapid, and sustained relief of pain and other symptoms for migraine sufferers.

OBJECTIVES

The primary objective of this study was to evaluate the efficacy and tolerability of 3 different doses of orally inhaled dihydroergotamine (DHE) administered by the Tempo breath-synchronized, plume-controlled inhaler (hereafter: MAP0004) in migraineurs.

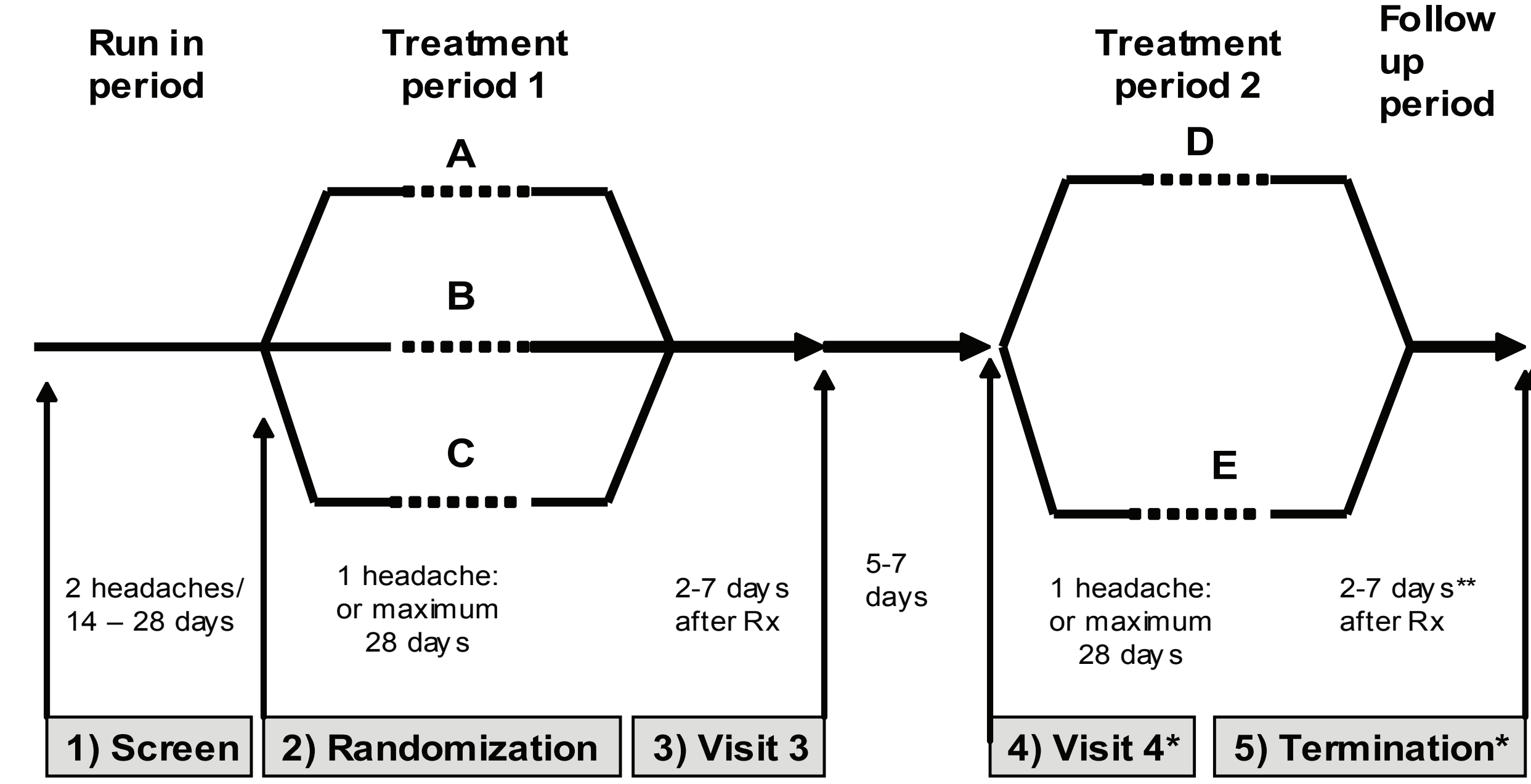
The secondary objective was to characterize the tolerability of MAP0004 for at home administration in treating acute migraine (MAP0004-CL-P201).

METHODS

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:

- Visit 1: Screening visit
- Visit 2: Randomization to Treatment Period 1 (14 to 28 days after Visit 1)
- Visit 3: Safety assessments and determination of response to study treatment in Treatment Period 1 (2 to 7 days after first qualifying migraine in Treatment Period 1 or no more than 28 days after Visit 2)
- Visit 4: Randomization to Treatment Period 2 for those who had responded to study treatment in Treatment Period 1 (5 to 7 days after Visit 3)
- Visit 5: Termination visit (2 to 7 days after first qualifying migraine in Treatment Period 2 or no more than 28 days after Visit 4)

STUDY DESIGN



* At visit 4 ALL subjects who responded to study treatment in treatment period 1 and meet all continuation criteria will be further randomized to Treatment period 2. Non responders in treatment period 1 will terminate at visit 3.
** Visit 5 will only apply for those subjects who entered treatment period 2.

Treatment Period	Group	Actuations	Inhaler
Treatment Period 1	A	2 actuations MAP0004 (~0.5mg total) + 2 actuations placebo from 2 Tempo inhalers	Oral inhalation via 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	

Major Inclusion Criteria

- Nonsmoking, M/F, 18 - 60 yrs; F contracepting/sterile (or postmenopausal for ≥ 12 months)
- Documented h/o migraine (+/- aura) excluding hemiplegic or basilar migraine) for ≥ 12 months, + h/o 2 - 8 attacks/month in previous 6 months
- h/o allodynic migraine (and nonallodynic) allowed
- FEV₁ ≥ 80% predicted normal; Normal 12-lead ECG and rhythm strip

Major Exclusion Criteria

- h/o proven or suspected CAD, heart attack, coronary vasospasm, PVD or other ischemic diseases or cardiac disorder
- h/o stroke, diabetes, liver or kidney disease, aortic aneurysm or recent (within 3 months) sepsis or vascular surgery
- h/o clinically significant pulmonary disease active within the previous 12 months
- ≥ intermediate or higher risk for cardiac disease, having ≥ 2 of the following major risk factors:
 - Cigarette smoking
 - Hypertension (SBP > 140 or DBP > 90) or on anti-HT Rx
 - Hyperlipidemia—high LDL cholesterol ≥ 159mg/dL or low HDL cholesterol ≤ 40mg/dL (or on anticholesterol treatment)
 - Family history of premature CAD (< 55 years of age in male first-degree relatives or < 65 years of age in female first-degree relatives)
 - Age (men ≥ 45 years)
- Use of triptans or ergot-based drugs between Visit 2 or 4 and 24 hours after the onset of a qualifying migraine and administration of blinded study treatment

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 FEV₁, mean years of migraine, mean years of smoking, and current smoking status.

Overall, 82.6% 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 FEV₁ was 100.9%; mean migraine history was 23 yrs. 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.

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) (Table 1 and Figure 1). Similarly, 10 minute pain relief TG of 32% (p=0.019) and 22% (p=0.060) were achieved. Freedom from other symptoms was also noted (Tables 2, 3 & 4). 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.

	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 min	22	18	15	32%	22%	0%	32%	22%	0.019	0.060
Pain relief at 30 min	22	17	14	55%	24%	14%	41%	10%	0.022	0.523
Pain relief at 2 hrs	25	20	15	72%	65%	33%	39%	32%	0.019	0.071
Sustained relief 2-24 hrs	21	18	15	43%	44%	13%	30%	31%	0.066	0.060
Total migraine relief* at 2 hrs	25	20	15	44%	35%	13%	31%	22%	0.051	0.153

* Total Migraine Relief = Pain reduced to mild or none. All other symptoms reduced to none.

Table 1. Efficacy results: (As Treated population) – Period 1

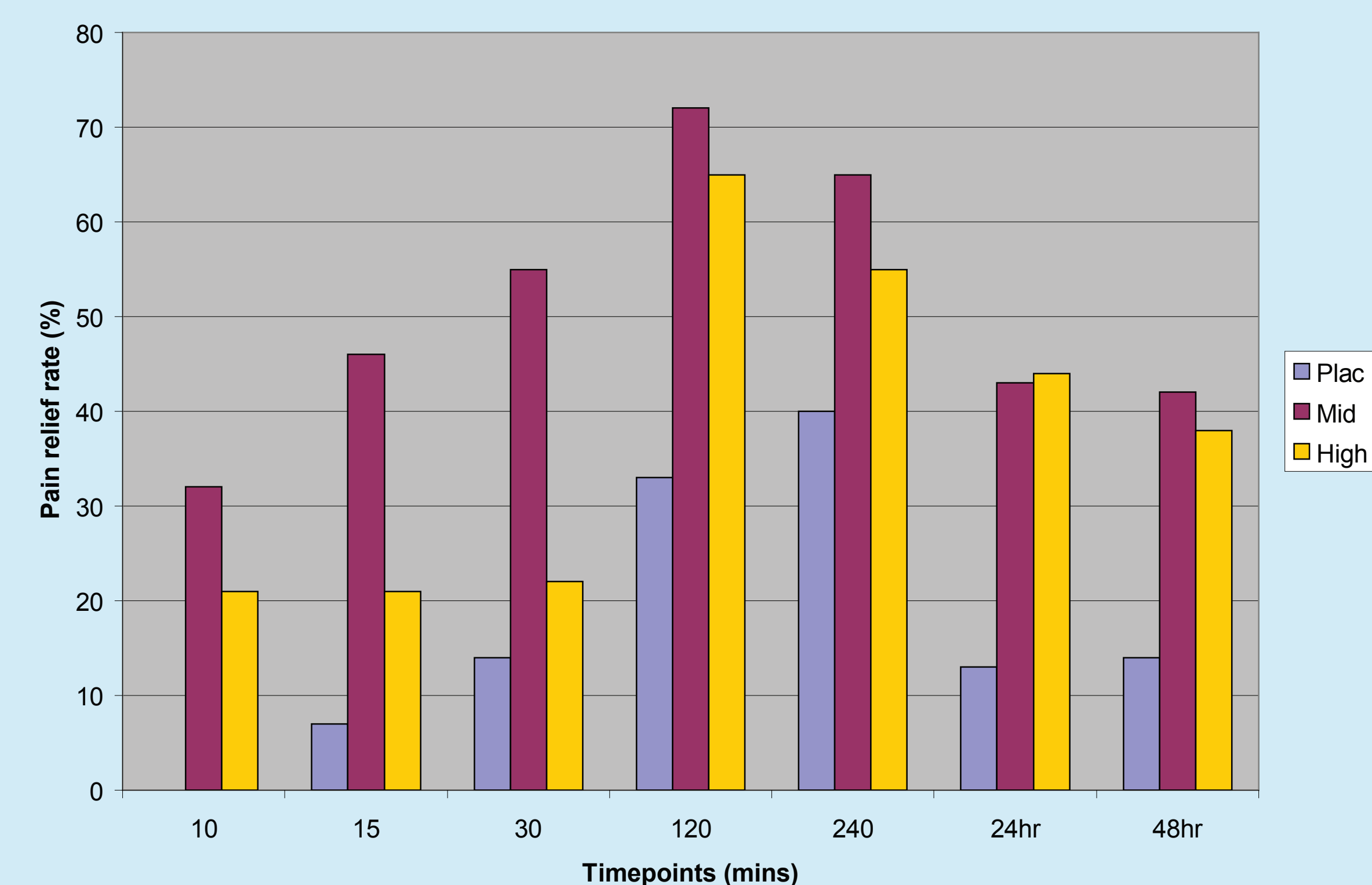


Figure 1. Efficacy results: (As Treated population) – Period 1

RESULTS continued

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)

Tables 2, 3 & 4. Efficacy results: rates of phonophobia, photophobia, and nausea freedom – Period 1

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) reported as treatment related (2 subjects on placebo, 6 on MAP0004 1.0mg – all in Period 1). No spirometry, vital sign, ECG, or laboratory changes of concern were noted in either period.

	Number (%) Subjects (N = 68)					
	Placebo (n = 13)		MAP0004 0.5 mg (n = 25)		MAP0004 1.0 mg (n = 30)	
Any AE ^a	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

Table 5. Brief summary of treatment-emergent adverse events: Safety population – Period 1

CONCLUSION

MAP0004 is well tolerated and is effective at delivering clinically significant, rapid, and sustained relief of pain and other symptoms for migraine sufferers. Further studies with MAP0004, including initiation of a Phase 3 program, are planned.