

SUSTAINED PAIN RELIEF IN MIGRAINE IS NOT NECESSARILY DEPENDENT ON THE PK OF A DRUG AND DOES NOT HAVE TO BE AT THE COST OF RAPID ONSET OF RELIEF

Shashidhar Kori and Stephen Shrewsbury

MAP Pharmaceuticals Inc., Mountain View, CA

BACKGROUND

The relationship between the efficacy of a given drug in treating an acute migraine and the corresponding pharmacokinetics has not been well studied. There are no correlations established between the T_{max} , C_{max} , and AUC of any drug and its efficacy as measured by the speed of onset, sustained pain response, and freedom from pain. But many physicians continue to believe that shorter acting triptans tend to have quicker onset of relief, but have higher rates of recurrence compared to slower absorbed triptans with longer half-life. This has led to attempts to prolong the half-life of acute migraine drugs by using techniques like transdermal diffusion. However, the sustained pain relief and pain free responses may be a function of how quickly and effectively the cascade of pathophysiological changes that lead to a full blown migraine were interrupted, rather than the actual half-life of any given drug. Here we present data that demonstrate the long-lasting relief provided by MAP0004, an inhaled DHE, in addition to its rapid onset of action. Present data demonstrates the long-lasting relief provided by MAP0004, an inhaled DHE, in addition to its rapid onset of action, as measured by 10 minute pain relief, 2-24 and 2-48 hour sustained pain relief and pain free rates, rescue medication use and time to use of rescue medication.

OBJECTIVE

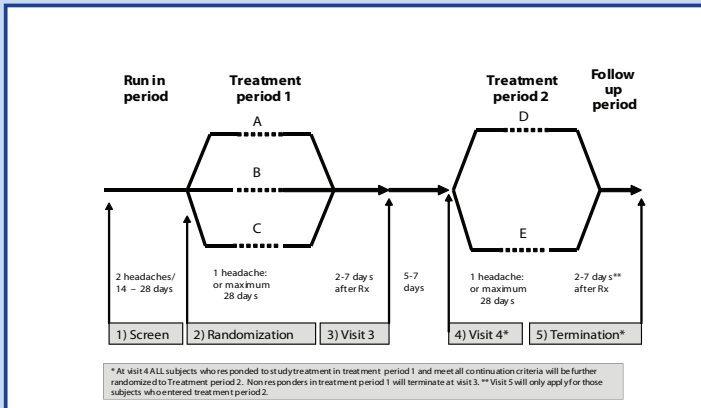
The objective of this study was to demonstrate rapid onset and sustained relief provided by MAP0004 delivered by the Tempo® inhaler during treatment of an acute migraine, as measured by 10-minute pain relief, 2-24 and 2-48 hour sustained pain relief and pain-free rates, rescue medication use, and time to use of rescue medication.

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



Treatment Period	Group	Actuations	Inhaler
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	
	E	2 actuations placebo; both actuations from a single Tempo inhaler	

RESULTS

Data from the 0.5mg systemic equivalent dose is presented here. The 1.0mg dose was not statistically different from the 0.5mg dose.

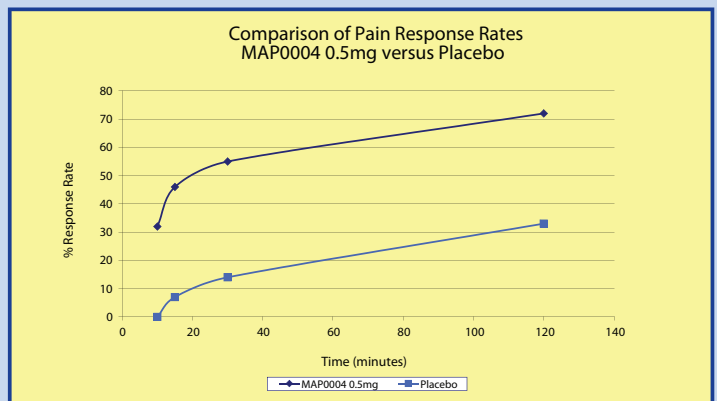
A total of 86 subjects were randomized. At 10 minutes, 32% of active patients and 0% of placebo patients reported pain relief ($p=0.039$). The rates for 2-24 and 2-48 hour sustained pain relief were 43% and 42% for MAP0004, respectively and 13% and 14% for placebo, respectively. The sustained pain-free rates for 2-24 and 2-48 hours were 38% and 37%, respectively, for MAP0004 and 7% and 7%, respectively, for placebo. Rescue medication use was 35% for MAP and 60% for placebo. Median time to rescue medication use was more than 48 hours for MAP and was 17.5 hours for placebo.

Data from Treatment Period 2 did not demonstrate consistent differentiated benefit.

RESULTS continued

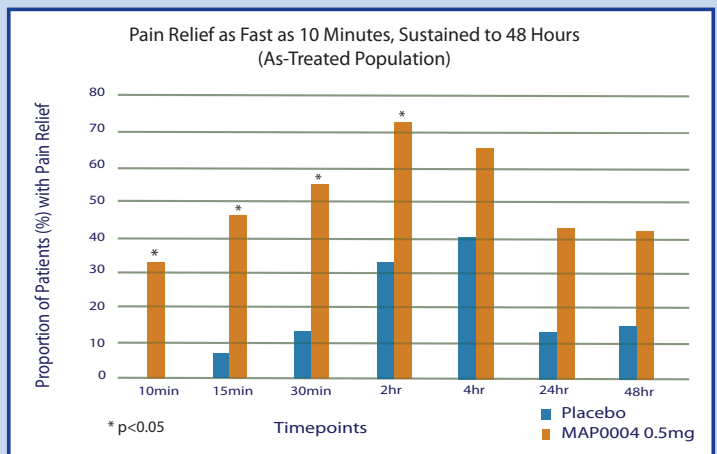
Migraine Pain Relief (As-Treated Population)

Pain Relief Timepoints	Placebo (n=16)	MAP0004 0.5mg (n=26)	P-value
10 minutes	0	32	(0.019)
15 minutes	7	46	(0.019)
30 minutes	14	55	(0.022)
60 minutes	43	64	(0.273)
2 hours (Primary)	33	72	(0.019)
Sustained 24 hours	13	43	(0.066)
Sustained 48 hours	14	42	(0.096)



DISCUSSION

Contrary to common belief, there has been no scientific documentation that sustained pain relief rates and low recurrence rates are functions of the half-life of an acute migraine treatment. Comparing the sustained response rates in patients treated with different formulations of the same drug, and hence the same half-life, suggests that formulations and routes of administration that result in rapid T_{max} also tend to have better sustained responses. This strongly suggests that the earlier the cascade of neurochemical changes is interrupted in the pathophysiology of migraine, the quicker and longer lasting the relief from migraine symptoms is likely to be.



CONCLUSION

As shown in this study, MAP0004 provided both rapid onset of pain relief and long lasting pain relief. Sustained pain relief may not be primarily dependent on the PK of a drug, but may also be related to early and effective interruption of the migraine cascade, and possibly extended receptor occupancy.