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Randomized controlled trial of an oral CGRP receptor antagonist, MK-0974, in acute treatment of migraine

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ABSTRACT

Objective: To determine an effective and tolerable dose of a novel oral calcitonin gene-related peptide (CGRP) receptor antagonist, MK-0974, for the acute treatment of migraine.

Methods: Randomized, double-blind, parallel-group, clinical trial with a two-stage, adaptive, dose-ranging design. Patients were allocated to treat a moderate or severe migraine attack with MK-0974 (25, 50, 100, 200, 300, 400, or 600 mg), rizatriptan 10 mg, or placebo taken orally. The primary endpoint was pain relief (reduction to mild or none) 2 hours after dosing. Secondary endpoints included pain freedom at 2 hours and sustained pain relief at 24 hours. A prespecified, blinded, automated interim analysis was used to discontinue randomization to less effective doses.

Results: Per the adaptive study design, the four lowest MK-0974 groups (25, 50, 100, 200 mg) were discontinued due to insufficient efficacy. For the remaining treatment groups, the estimated pain relief proportions at 2 hours were 300 mg (n = 38) 68.1%, 400 mg (n = 45) 48.2%, 600 mg (n = 40) 67.5%, rizatriptan 10 mg (n = 34) 69.5%, and placebo (n = 115) 46.3%. The prespecified primary efficacy hypothesis test, which compared the average 2-hour pain relief response proportion of the combined 300, 400, and 600 mg MK-0974 groups to placebo, was significant ($P = 0.015$). A generally similar efficacy pattern was seen for other endpoints. MK-0974 was generally well tolerated and there did not appear to be an increase in adverse events with increasing dose.

Conclusions: The novel, orally administered calcitonin gene-related peptide (CGRP) receptor antagonist, MK-0974, was effective and generally well tolerated for the acute treatment of migraine. ***Neurology***® ▪▪▪

GLOSSARY

APT = all patients treated; **CGRP** = calcitonin gene-related peptide; **NSAID** = nonsteroidal anti-inflammatory drug.

Migraine is a common disease and a leading cause of disability.[1,2] In the United States, work loss due to migraine is estimated to cost $13 billion.[3] Currently, 5-$HT_{1B/1D}$ receptor agonists (triptans) represent the gold standard of acute treatment. However, some patients do not respond optimally to triptans and many only partially respond.[4,5] Furthermore, because of potential vasoconstrictive properties, triptans are contraindicated in patients with significant underlying cardiovascular disease, and are not recommended in those with risk factors for cardiovascular disease.[6] There remains a need for treatment of migraineurs with cardiovascular risk/disease, and those not optimally treated with current therapies.

Calcitonin gene-related peptide (CGRP) is a neuropeptide that may play a key role in

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the pathophysiology of migraine.[7-9] CGRP is increased during migraine and the activity of the triptans may be partly attributable to inhibition of CGRP release via an action on 5-HT_{1D} receptors.[10-13] Since CGRP receptor antagonists lack direct vasoconstrictor activity, this approach may offer advantages over triptans, where cardiovascular liabilities are a perceived risk. The hypothesis that CGRP receptor antagonism would produce pain relief in migraine without cardiovascular effects was supported in a study using an IV formulation of the CGRP receptor antagonist olcegepant.[14]

Because most migraine treatments are administered on an outpatient basis it is important to develop CGRP receptor antagonists which can be taken orally. The objective of our study was to perform an initial evaluation of the clinical profile of a novel, oral CGRP receptor antagonist, MK-0974, in the acute treatment of migraine.

METHODS

Patients. Patients were eligible for the study if they were 20 to 65 years of age, in good physical health, and had 1 to 6 moderate or severe migraine attacks per month with or without aura, as defined by International Headache Society criteria,[1] in the 2 months prior to the screening visit. Patients taking migraine prevention medication were allowed to enter the study provided that the prescribed daily dose had not changed during the 3 months prior to screening. The study was approved by the appropriate ethical review committee for each site and each patient provided written informed consent.

Study design. This was a randomized, double-blind (with in-house blinding), placebo- and active-controlled, parallel-group, outpatient study to evaluate the efficacy and tolerability of MK-0974 in patients with an acute migraine attack. MK-0974 is a novel, orally bioavailable, potent, selective competitive antagonist of the human CGRP receptor. The formulation used in this study had a t_{max} of approximately 1 to 2 hours and a $t_{½}$ of approximately 5 to 8 hours. The study was conducted at 20 sites in the United States between December 2005 and May 2006. Patients were allocated to one of the following treatment groups: MK-0974 25, 50, 100, 200, 300, 400, or 600 mg, rizatriptan 10 mg, or placebo. MK-0974 was supplied as a liquid-filled soft gel capsule formulation (with matching placebo for those patients assigned to the corresponding placebo group) and rizatriptan was supplied as a tablet formulation (with matching placebo for those patients assigned to the corresponding placebo group). MK-0974 was supplied in dose strengths of 25 mg, 100 mg, and 300 mg, requiring patients in some dose groups to take two capsules (e.g., patients assigned to MK-0974 200 mg took 2 100-mg capsules, and patients assigned to the corresponding placebo group took 2 visually identical capsules which contained placebo). Approximately one-third of all patients were randomized to placebo. A two-stage adaptive design was employed to facilitate optimal dose selection for further studies and to minimize patient exposure to non-efficacious doses. During Stage 1, patients were allocated to one of the seven MK-0974 dose levels (n = approximately 16 patients per group) or matching placebo (n = 56), or to rizatriptan 10 mg (n = 16) or matching placebo (n = 8). Once approximately 192 patients were randomized, an interim efficacy analysis was automatically executed in order to select the doses to be continued in Stage 2 (see Statistical Analysis). The rizatriptan and the highest three MK-0974 doses (300, 400, and 600 mg) with their corresponding placebo groups were prespecified to continue into Stage 2. Patients had the same chance of receiving placebo (one out of three) in both Stage 1 and Stage 2.

Computer simulation of study design. Computer simulation was used to determine the optimal number of patients and adaptive design strategy. The goal for the simulation was to determine the study design that would make most efficient use of approximately 300 to 400 patients across seven dose levels, a placebo group, and an active control group, to determine up to two doses for evaluation in further studies. For the simulation, the placebo 2-hour pain relief (reduction of pain to mild or none) response rate was assumed to be 30%. Since the expected efficacy gain of an effective dose was at least 25%, the highest dose response rate was assumed to be 55%. Various scenarios of the dose response curves were tested in the simulation. The simulation results showed that by using a novel adaptive contrast test statistic the adaptive design had a statistical power of at least 85% while preserving the overall false positive rate at 5%. In comparison, a traditional balanced design with a same number of evaluable patients in the MK-074 groups could have a statistical power as low as 60% in the situation where most low doses are ineffective.

Procedure. Patients who met all the study entry criteria were enrolled and provided with study drug (MK-0974, rizatriptan, or placebo) to be taken on an outpatient basis as soon as they experienced a moderate or severe migraine headache. A blinded optional second dose (active treatment or placebo) was provided in a separate bottle for patients still experiencing a moderate or severe headache at 2 hours following initial treatment. Treatment assignment for the optional second dose corresponded to a crossover of the patient's initial allocation: patients who initially received blinded placebo were provided with a blinded active optional second dose (dose level was prespecified at time of initial randomization) and patients who received a blinded active treatment as their first dose were provided with blinded placebo as an optional second dose. Rescue medication of any type, with the proviso that triptan use was restricted to rizatriptan, was allowed for non-responding headache and headache recurrence beginning 4 hours after initial treatment. Personnel at each study site used a central interactive voice recognition system to allocate eligible patients to treatment.

During the 48 hours following the initial dose of study medication, patients recorded subjective assessments of pain severity and other measures at specified time intervals on a migraine diary. Patients also recorded information about any adverse events (spontaneous reporting; not in response to a checklist). Patients returned to the study site within ap-

proximately 7 days after treatment to allow review of the diary, assessment of medication compliance, and tolerability and safety monitoring.

Efficacy measurements. Headache severity was recorded using a four-grade scale (no pain, mild pain, moderate pain, severe pain) at baseline (0 hours—time of taking study medication) and 0.5, 1, 1.5, 2, 3, 4, and 24 hours postdose. Presence or absence of associated symptoms (nausea, vomiting, photophobia, or phonophobia) and rating of functional disability (4-grade scale—normal, mildly impaired, severely impaired, requires bedrest) were recorded at the same time points as headache severity ratings. For those patients who had pain relief (reduction of pain to mild or none) or were pain free (no pain) at 2 hours, presence or absence of headache worsening within 48 hours was recorded. Use of rescue medication within 48 hours was also recorded for all patients. The present analyses focused on data up to 24 hours.

Tolerability and safety measurements. Tolerability and safety was assessed via spontaneous adverse experience reports and via routine pre and post study physical and laboratory examinations, including ECGs.

Statistical analysis. The biostatistical analysis was performed by X. Fan and C. Assaid from Merck Research Laboratories.

The all patients treated (APT) population was the primary population for assessing efficacy. The APT population for efficacy included all patients who had a baseline headache severity score and at least one headache severity score after taking at least one dose of the double-blind therapy. Patients were counted in the treatment group to which they were randomized. A supportive per-protocol analysis, in which patients who were considered to have major deviations from the protocol according to prespecified criteria were excluded, was also performed. Since only a small number of patients were classified as protocol violators, and this analysis yielded similar results to the APT analysis, the per-protocol results are not presented.

The primary hypothesis was that at least one MK-0974 dose would be superior to placebo in the treatment of migraine, as measured by the proportion of patients reporting pain relief from moderate to severe migraine headache to mild or none at 2 hours postdose. Other efficacy variables were the proportion of patients reporting pain freedom (no pain) at 2 hours, sustained pain relief at 24 hours postdose (defined as those with pain relief at 2 hours, no recurrence of moderate or severe headache from 2 to 24 hours, and no use of the optional second dose or additional migraine rescue medication from 2 to 24 hours), sustained pain freedom at 24 hours postdose (defined as those with pain freedom at 2 hours, no return of mild, moderate, or severe headache from 2 to 24 hours, and no use of the optional second dose or additional migraine rescue medication from 2 to 24 hours), associated symptoms at 2 hours postdose, functional disability at 2 hours postdose, use of optional second dose at 2 hours postdose, and use of rescue medication by 4 hours postdose.

The APT analysis imputed missing headache severity values, functional disability rating, and the presence of associated symptoms at 1, 1.5, or 2 hours after treatment by carrying forward the latest preceding value provided this value was obtained after treatment (LOCF method). However, no imputations were made to missing values at baseline or at 0.5 hour postdose. The analyses of response proportions were performed using a generalized linear model including terms for treatment, geographic region within the United States (northeast, south/west/southwest, midwest), and baseline headache severity (moderate or severe) using the APT approach. Comparisons between active treatment groups and placebo were made by the appropriate contrasts from the model. A linear contrast was tested for the primary and secondary efficacy hypotheses which compared the response proportions between the MK-0974 groups and placebo. The model was a generalized linear model with binary responses and identity link between the parameter and the true response rate. The average of the MK-0974 treatment groups that were a part of the Stage 2 randomization were compared to placebo. In addition, pairwise comparisons between these individual dose groups and placebo were also conducted in the context of the primary efficacy model. The study was not powered to detect differences between individual doses of MK-0974 or between MK-0974 doses and rizatriptan. Significance was set at $\alpha = 0.05$ for all treatment comparisons.

A prespecified, blinded, interim efficacy analysis was automatically generated once approximately 192 patients had been randomized in order to select the doses to be continued in Stage 2. The intention was to identify the lowest dose with ≥70% conditional probability of being nominally significant at the end of the trial (at $\alpha = 0.05$) based on a comparison of each MK-0974 dose with the total placebo group available at the time of the interim analysis. The MK-0974 groups (active and matching placebo) with dose levels at least as high as the identified dose level (if any) were to continue into Stage 2 and those lower dose groups (active and matching placebo) were to be dropped. Regardless of the identified dose, the three highest MK-0974 dose groups (300, 400, and 600 mg) were prespecified to continue into Stage 2. The transition to Stage 2 was also dependent on collection of primary efficacy results from a sufficient number of patients. A minimum of 11 evaluable patients in the active identified MK-0974 dose was required to complete the interim analysis.

All patients who were randomized and treated with study drug were included in the safety assessment. Patients were counted according to the active treatment they actually received or the placebo if no active dose was taken. All adverse experiences reported up to 14 days following the treatment were included in the tolerability analysis.

RESULTS

Patient accounting and demographics. Patient disposition is summarized in table 1. Of the 420 patients enrolled, 330 took the initial dose of study medication, and 154 also took the optional second dose. In a small number of cases (n = 15), the patient took an incorrect number of capsules or tablets, or doses from the wrong bottle; as noted in Methods, patients were counted according to the treatment they were randomized to for the efficacy analyses, and according to the treatment they actually received for the safety analyses. One patient in the MK-0974 300 mg group was excluded from the APT efficacy analysis due to missing baseline data.

The demographic characteristics of the patients taking treatment are summarized in table 2.

Table 1 CONSORT study flow chart

	Placebo	MK-0974, 25 mg*	MK-0974, 50 mg*	MK-0974, 100 mg*	MK-0974, 200 mg*	MK-0974, 300 mg	MK-0974, 400 mg	MK-0974, 600 mg	Rizatriptan, 10 mg
Randomized	147	16	18	17	16	54	54	53	45
Treated	115	14	15	16	12	39	45	40	34
Initial dose only	46	4	9	5	8	29	29	27	19
Initial and optional second dose	69	10	6	11	4	10	16	13	15
Not treated	32	2	3	1	4	15	9	13	11
Did not have migraine	4	0	0	0	1	3	2	1	4
Had migraine but did not treat	4	2	1	1	0	0	1	1	1
Protocol deviation	1	0	0	0	1	0	1	1	0
Lost to follow-up	3	0	0	0	2	2	1	2	0
Withdrew consent	2	0	0	0	0	0	1	1	0
Clinical trial terminated at site	10	0	0	0	0	7	1	6	2
Discontinued for other reason	8	0	2	0	0	3	2	0	4
Included in efficacy analysis	115	14	15	16	12	38	45	40	34
Excluded from efficacy analysis	0	0	0	0	0	1†	0	0	0

Values are numbers of patients.
*MK-0974 doses of 25 to 200 mg were discontinued per the prespecified interim efficacy analysis.
†Reason for exclusion was no baseline data.

The mean age of patients treated was approximately 41 years and approximately 88% were women. Most patients had previously used a triptan, a nonsteroidal anti-inflammatory drug, or both, to treat their migraine attacks. The treatment groups had generally similar demographic profiles, allowing for the small sample sizes in some of the groups (table 2).

The characteristics of the treated migraine attacks at baseline are summarized in table 3. Most treated headaches were not preceded by aura, and were associated with some level of functional disability. The treated headaches showed generally similar characteristics between the treatment groups, allowing for the small sample sizes in some of the groups (table 1).

Efficacy. Efficacy outcomes for all studied doses are summarized in table 4. Based on the adaptive study design, MK-0974 doses of 20 to 200 mg

Table 2 Patient demographics

	Placebo (n = 115)	MK-0974, 25 mg (n = 14)*	MK-0974, 50 mg (n = 15)*	MK-0974, 100 mg (n = 16)*	MK-0974, 200 mg (n = 12)*	MK-0974, 300 mg (n = 39)	MK-0974, 400 mg (n = 45)	MK-0974, 600 mg (n = 40)	Rizatriptan, 10 mg (n = 34)
Mean age, y	42.2	43.0	41.5	40.9	34.3	40.5	40.1	44.5	40.2
Gender									
Women	90.4	78.6	93.3	87.5	75.0	87.2	93.3	90.0	82.4
Men	9.6	21.4	6.7	12.5	25.0	12.8	6.7	10.0	17.6
Race									
White	80.0	71.4	73.3	68.8	50.0	74.4	75.6	95.0	82.4
Other	20.0	28.6	26.7	31.2	50.0	25.6	24.4	5.0	17.6
Usual migraine treatment									
None	2.6	0	0	0	0	0	0	2.5	2.9
NSAID	34.8	42.9	33.3	25.0	58.3	20.5	46.7	25.0	23.5
Triptan	30.4	42.9	40.0	43.8	0	41.0	37.8	45.0	47.1
NSAID and triptan	20.9	7.1	20.0	18.8	16.7	17.9	4.4	12.5	11.8
Other	11.3	7.1	6.7	12.5	25.0	20.5	11.1	15.0	14.7

Values are % of patients (except for age, where the mean is given).
*MK-0974 doses of 25 to 200 mg were discontinued per the prespecified interim efficacy analysis.
NSAID = nonsteroidal anti-inflammatory drug.

Table 3 Baseline characteristics of the treated migraine attack

	Placebo (n = 115)	MK-0974, 25 mg (n = 14)*	MK-0974, 50 mg (n = 15)*	MK-0974, 100 mg (n = 16)*	MK-0974, 200 mg (n = 12)*	MK-0974, 300 mg (n = 38)	MK-0974, 400 mg (n = 45)	MK-0974, 600 mg (n = 40)	Rizatriptan, 10 mg (n =34)
Aura									
Without	87.8	57.1	66.7	93.8	66.7	71.8	77.8	77.5	76.5
With	11.3	42.9	33.3	6.3	33.3	25.6	22.2	22.5	23.5
Headache									
Moderate	70.4	78.6	60.0	93.8	50.0	66.7	75.6	75.0	79.4
Severe	29.6	21.4	40.0	6.3	50.0	30.8	24.4	25.0	20.6
Associated symptoms									
Photophobia	89.5	100.0	86.7	68.8	83.3	84.2	84.1	80.0	82.4
Phonophobia	84.1	85.7	100.0	81.3	83.3	81.6	68.2	82.5	88.2
Nausea	55.0	42.9	42.9	62.5	50.0	44.7	52.3	41.0	55.9
Vomiting	4.5	0	7.1	0	0	2.6	4.5	7.9	5.9
Functional disability									
Normal	4.3	7.1	0	6.3	0	10.5	9.1	7.5	0
Mildly impaired	68.7	64.3	53.3	87.5	58.3	55.3	61.4	70.0	73.5
Severely impaired	17.4	28.6	33.3	6.3	25.0	28.9	20.5	17.5	23.5
Requiring bedrest	9.6	0	13.3	0	16.7	5.3	9.1	5.0	2.9

Values are % of patients. Patients with missing data for baseline migraine characteristics are not listed in the table.
*MK-0974 doses of 25 to 200 mg were discontinued per the prespecified interim efficacy analysis.

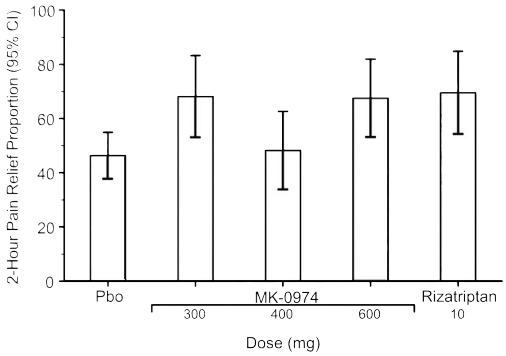
Table 4 Summary of efficacy of treatment on migraine symptoms and use of additional medication

Outcome measure	Placebo (n = 115)	MK-0974, 25 mg (n = 14)*	MK-0974, 50 mg (n = 15)*	MK-0974, 100 mg (n = 16)*	MK-0974, 200 mg (n = 12)*	MK-0974, 300 mg (n = 38)	MK-0974, 400 mg (n = 45)	MK-0974, 600 mg (n = 40)	Rizatriptan, 10 mg (n = 34)
Headache									
Pain relief at 2 h	46.3	35.6	63.7	44.0	48.6	68.1†	48.2	67.5†	69.5†
Pain free at 2 h	14.3	20.8	45.8†	16.6	15.7	45.2§	24.3	32.1†	33.4†
Sustained pain relief at 24 h	23.5	7.7	60.0‡	18.8	27.3	52.6‡	37.8	52.5‡	35.3
Sustained pain free at 24 h	11.0	9.3	46.3‡	17.0	7.3	39.6§	22.0	32.0†	18.4
Associated symptoms at 2 h¶									
Photophobia	61.3	81.5†	45.2	48.7	54.7	46.0	57.6	36.1‡	47.0
Phonophobia	56.9	70.6	39.1	68.8	55.5	30.1‡	51.5	39.6	46.5
Nausea	34.9	37.3	31.6	34.5	21.3	22.0	38.1	17.8†	17.2†
Vomiting	0.9	0	7.1†	0	0	2.6	2.2	2.5	0
Functional disability at 2 h¶‖									
Normal	26.1	28.6	53.3†	18.8	41.7	55.3‡	35.6	47.5†	41.2
Mildly impaired	48.7	28.6	20.0	62.5	33.3	31.6	33.3	30.0	41.2
Severely impaired	13.0	28.6	6.7	12.5	8.3	10.5	20.0	10.0	11.8
Requiring bedrest	12.2	14.3	20.0	6.3	16.7	2.6	11.1	12.5	5.9
Additional medication									
Optional 2nd dose at 2 h	59.5	73.2	39.3	75.3	32.4	25.5§	35.4‡	31.8‡	43.4
Rescue by 4 h	61.4	73.2	39.9	74.7	32.7†	28.2§	40.1†	34.2‡	45.8

Values are % of patients.
*MK-0974 doses of 25 to 200 mg were discontinued per the prespecified interim efficacy analysis.
†$p < 0.05$, ‡$p < 0.01$, §$p < 0.001$ for the active vs placebo pairwise comparison.
¶Comparisons were adjusted for baseline headache severity.
‖Analysis was based on the percentages of the normal rating.

The estimated responses and corresponding CIs adjust for baseline headache severity and study region.

Figure 1 Proportion of migraineurs with pain relief at 2 hours and associated 95% CIs

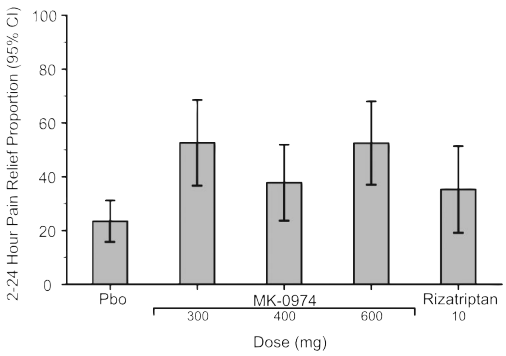


were dropped after Stage 1 following the interim analysis since none of the doses up to 200 mg achieved ≥70% conditional probability of being nominally significant at the end of the trial. Hence the final sample sizes for those dose groups were smaller than for the top three MK-0974 dose groups to which patients continued to be allocated in Stage 2. On the primary endpoint of pain relief at 2 hours, the overall treatment effect, defined as the average of the 300 mg, 400 mg, and 600 mg MK-0974 doses, demonstrated significance vs placebo ($p = 0.015$). This was also true for the pairwise comparisons of 300 mg ($p = 0.014$) and 600 mg ($p = 0.013$) vs placebo (figure 1). Rizatriptan was also effective vs placebo ($p = 0.010$; figure 1). The treatment-by-baseline severity and treatment-by-region interactions were not significant ($p > 0.10$), indicating that the 2-hour pain relief treatment effects were generally consistent across differing levels of baseline headache severity and across different geographic regions.

A similar pattern of results was found for the other measures including pain freedom at 2 hours (overall treatment effect $p < 0.001$), 24 hour sustained pain relief (overall treatment effect $p < 0.001$), 24 hour sustained pain freedom (overall treatment effect $p < 0.001$), associated symptoms of photophobia and phonophobia at 2 hours (photophobia, overall treatment effect $p = 0.020$; phonophobia, overall treatment effect $p = 0.008$), functional disability at 2 hours (overall treatment effect $p = 0.002$), use of optional second dose at 2 hours (overall treatment effect $p < 0.001$), and use of rescue medication by 4 hours (overall treatment effect $p < 0.001$).

MK-0974 doses of 300 to 600 mg appeared to be numerically more effective than the active control, rizatriptan 10 mg, on measures relating to sustained pain relief and sustained pain freedom from 2 to 24 hours (figure 2; table 4).

Figure 2 Proportion of migraineurs with sustained pain relief at 24 hours and associated 95% CIs



The estimated responses and corresponding CIs adjust for the baseline headache severity and study region.

Tolerability and safety. Clinical adverse events within 14 days after dosing are summarized in table 5. Single doses of 25 to 600 mg MK-0974 were generally well-tolerated in the acute treatment of migraine. The incidence of patients reporting adverse experiences and those considered drug-related by the investigator (while blinded to treatment assignment) appeared comparable between active treatment groups and placebo and there did not appear to be evidence of an increase in adverse experiences with increasing dose. The most common adverse experiences during the 14-day follow up period were as follows: MK-0974 300 mg to 600 mg—nausea, dizziness, and somnolence; rizatriptan—fatigue, nausea, and somnolence; placebo—nausea and dizziness. Only one serious adverse experience (appendicitis) was reported during the study and occurred in a patient who received placebo treatment.

The separate analysis of clinical adverse experience results within 2 hours of the initial dose is shown in table 6. This analysis also demonstrated a similar incidence of patients reporting adverse experiences and drug-related adverse experiences among MK-0974 300 mg to 600 mg doses and rizatriptan, with a slightly higher incidence for the active arms when compared to placebo. For clinical adverse experiences within 2 hours of initial dose, the most common adverse experiences were as follows: MK-0974 300 mg to 600 mg—nausea, dizziness, and somnolence; rizatriptan—asthenia, paraesthesia, and facial hypoesthesia; placebo—nausea, dizziness, and somnolence.

Laboratory abnormalities during the study were uncommon and no clinically relevant differences were seen between treatment and placebo groups. Other assessments including the percentage of patients who exceeded predefined levels of change on laboratory parameters, vital sign measurements, ECG measurements, and physical ex-

Table 5 Summary of number (%) of patients reporting clinical adverse experiences (AEs) within 14 days postdose

	Placebo (n = 47)	MK-0974, 25 mg (n = 17)*	MK-0974, 50 mg (n = 19)*	MK-0974, 100 mg (n = 27)*	MK-0974, 200 mg (n = 18)*	MK-0974, 300 mg (n = 51)	MK-0974, 400 mg (n = 52)	MK-0974, 600 mg (n = 49)	Rizatriptan, 10 mg (n = 50)
Any AEs	17 (36.2)	4 (23.5)	9 (47.4)	4 (14.8)	6 (33.3)	18 (35.3)	19 (36.5)	20 (40.8)	21 (42.0)
Any drug-related AEs†	11 (23.4)	2 (11.8)	7 (36.8)	2 (7.4)	5 (27.8)	13 (25.5)	14 (26.9)	12 (24.5)	14 (28.0)
Specific AEs occurring in >1 patient per treatment group									
Dry mouth	1 (2.1)	1 (5.9)	0	1 (3.7)	0	2 (3.9)	2 (3.8)	1 (2.0)	1 (2.0)
Nausea	6 (12.8)	0	0	1 (3.7)	0	3 (5.9)	4 (7.7)	5 (10.2)	1 (2.0)
Fatigue	0	1 (5.9)	3 (15.8)	1 (3.7)	0	0	1 (1.9)	1 (2.0)	2 (4.0)
Dizziness	2 (4.3)	0	2 (10.5)	0	2 (11.1)	3 (5.9)	1 (1.9)	4 (8.2)	1 (2.0)
Somnolence	0	0	1 (5.3)	1 (3.7)	2 (11.1)	2 (3.9)	1 (1.9)	4 (8.2)	2 (4.0)
Paraesthesia	0	0	1 (5.3)	0	0	0	0	1 (2.0)	2 (4.0)

The population in each treatment group was calculated based on the number of patients who received active therapy. For example, if a patient received placebo for the first dose and decided to take the optional second dose, he or she was not counted as a placebo patient because the second dose was active therapy. Instead such a patient was counted in the applicable active treatment group.
*MK-0974 doses of 25 to 200 mg were discontinued per the prespecified interim efficacy analysis.
†Rated as possibly, probably, or definitely drug-related by the investigator, while blinded to treatment assignment.

aminations indicated no clinically meaningful differences between treatment groups.

DISCUSSION We found that the orally administered CGRP receptor antagonist MK-0974 was effective in treating moderate or severe migraine attacks on the primary endpoint of pain relief at 2 hours. The effects of MK-0974 on the primary endpoint were mirrored on the other endpoints of pain freedom, improvement of associated symptoms and functional disability, and use of additional medication. In most cases, the effective MK-0974 doses appeared at least comparable to rizatriptan and in some instances appeared to be numerically superior, particularly with regard to measures of 2-hour pain freedom, 24-hour sustained pain freedom, and 24-hour sustained pain relief. However, the study was not powered to detect differences between active treatments. The sample size for rizatriptan was relatively small which may explain why significant differences vs placebo were only observed for 2-hour pain relief, 2-hour pain free, and the 2-hour nausea measures. Previous analyses based on larger datasets have demonstrated clear advantages for rizatriptan vs placebo on most of the outcome measures used in this trial.[15]

These findings support and extend the previous proof-of-concept findings with the IV administered CGRP receptor antagonist, olcegepant.[14] Like MK-0974 in the current study, olcegepant also exhibited good 24-hour sustained pain freedom. Whether CGRP receptor antagonists as a class will have sustained efficacy better than triptans requires larger comparative studies. In general, an oral formulation of a drug offers cru-

Table 6 Summary of number (%) of patients reporting clinical adverse experiences (AEs) within 2 hours postdose

	Placebo (n = 115)	MK-0974, 25 mg (n = 14)*	MK-0974, 50 mg (n = 14)*	MK-0974, 100 mg (n = 21)*	MK-0974, 200 mg (n = 11)*	MK-0974, 300 mg (n = 41)	MK-0974, 400 mg (n = 41)	MK-0974, 600 mg (n = 39)	Rizatriptan, 10 mg (n = 34)
Any AEs	17 (14.8)	2 (14.3)	4 (28.6)	1 (4.8)	2 (18.2)	9 (22.0)	8 (19.5)	10 (25.6)	12 (35.3)
Any drug-related AEs†	15 (13.0)	2 (14.3)	2 (14.3)	1 (4.8)	2 (18.2)	8 (19.5)	8 (19.5)	9 (23.1)	9 (26.5)
Specific AEs occurring in >1 patient per treatment group									
Nausea	1 (0.9)	0	0	1 (4.8)	0	2 (4.9)	3 (7.3)	5 (12.8)	1 (2.9)
Asthenia	0	0	0	0	0	0	0	0	2 (5.9)
Dizziness	4 (3.5)	0	0	0	1 (9.1)	1 (2.4)	0	2 (5.1)	1 (2.9)
Paraesthesia	0	0	1 (7.1)	0	0	0	0	0	2 (5.9)
Somnolence	2 (1.7)	0	1 (7.1)	0	1 (9.1)	1 (2.4)	1 (2.4)	2 (5.1)	0
Facial hypoesthesia	0	0	0	0	0	0	0	0	2 (5.9)

*MK-0974 doses of 25 to 200 mg were discontinued per the prespecified interim efficacy analysis.
†Rated as possibly, probably, or definitely drug-related by the investigator, while blinded to treatment assignment.

cial advantages over an IV formulation in terms of access, patient preference, healthcare costs, and therapeutic safety margin. In the field of migraine therapy, where most medication is self-administered by patients, the availability of an oral formulation is particularly important. The development of a CGRP receptor antagonist which can be taken orally therefore represents a key advance in migraine therapy.

Our study provided helpful information to guide dose selection for future clinical trials while maximizing patient exposure to effective doses of experimental treatment. After the interim efficacy analysis, the four lowest MK-0974 groups (25, 50, 100, and 200 mg) were discontinued due to insufficient efficacy and, per the prespecified algorithm, the three highest dose groups (300, 400, and 600 mg) were continued in the second stage. The prespecified test of the primary hypothesis, which compared the average 2-hour pain relief response proportion of the 300, 400, and 600 mg MK-0974 groups to that of the placebo group, was significant. The pairwise 2-hour pain relief treatment comparisons were also significant in the MK-0974 300 mg and 600 mg groups. Doses below 300 mg were ineffective on the primary endpoint of 2-hour pain relief. This was also true for the other endpoints (2-hour pain freedom, sustained 24-hour pain relief, and sustained 24-hour pain freedom), except that the differences between the 50 mg group and the placebo were nominally significant. However, the sample size was very small in the 50 mg group ($n = 15$), and the 25 mg, 100 mg, and 200 mg groups showed similar results to placebo on all endpoints. Therefore, we suspect that the observed differences between the 50 mg group and placebo were most likely due to random chance arising from the small sample size and the large number of pairwise comparisons.

In agreement with the previous findings using olcegepant,[14] we found that MK-0974 was generally well-tolerated for the acute treatment of migraine. The incidence of patients reporting adverse experiences within 14 days appeared comparable between active treatment groups and placebo and there did not appear to be evidence of an increase in adverse experiences with increasing MK-0974 dose. Clinical adverse experience results within 2 hours of the initial dose demonstrated a comparable incidence of adverse experiences and drug-related adverse experiences among MK-0974 300 mg to 600 mg doses and rizatriptan, and a slightly higher incidence for the active arms when compared to placebo. The most common adverse experiences for MK-0974 300 mg to 600 mg were nausea, dizziness, and somnolence. A generally similar pattern of adverse events was found when comparing those occurring within 2 hours after dosing vs those occurring within 14 days after dosing. Laboratory abnormalities were uncommon and no significant differences were seen between treatment and placebo groups. Likewise, no clinically meaningful differences were observed on physical examinations, vital signs, or ECGs, although these were assessed up to 7 days after patients took treatment. Thus, MK-0974 appeared to be generally well tolerated in our study, although the study sample size, extent of evaluations, and duration of treatment were too limited to draw any definitive safety conclusions. Additional larger studies are necessary to more fully characterize the clinical profile of MK-0974 and establish the appropriate clinical dose or doses.

APPENDIX

Clinical trial registry information: ClinicalTrials.gov identifier NCT00246337. The following investigators participated in the study: Gary Berman, MD, Clinical Research Institute, Plymouth, MN; Stanley Block, MD, Kentucky Pediatric Research, Inc., Bardstown, KY; Teresa Coats, MD, Benchmark Research, Austin, TX; Naomi De Sola Pool, MD, Research Testing Laboratories Inc., Great Neck, NY; Joel Eade, MD, Internal Medicine Research Assoc., Inc., Campbellsville, KY; Victor Elinoff, MD, Regional Clinical Research, Inc., Endwell, NY; Arthur Elkind, MD, Elkind Headache Center, Mt. Vernon, NY; Stephen Kayota, MD, Tidewater Integrated Medical Research, Virginia Beach, VA; Lisa Mannix, MD, Clinexcel Research, West Chester, OH; Nabih Ramadan, MD, Rosalind Franklin University of Medicine and Science, North Chicago, IL; Alan Rapoport, MD, New England Center Headache, Stamford, CT; George J. Rederich, MD, South Bay Neurology Research, Redondo Beach, CA; Joel Saper, MD, Michigan Head Pain Neurological Institute, Ann Arbor, MI; William Seger, MD, Benchmark Research, Forth Worth, TX; Larry Seidman, DO, Philadelphia Clinical Research, Philadelphia, PA; Egilius Spierings, MD, MedVadis Research Group, Wellesley Hills, MA; J. Christopher Stringer, MD, Central New York Clinical Research, Manlius, NY; Cynthia Strout, MD, Coastal Carolina Research Center, Mount Pleasant, SC; Michael Tuchman, MD, Palm Beach Neurological Group, Palm Beach Gardens, FL; Randal Von Seggern, PharmD, Headache Wellness Center, Greensboro, NC.

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