Research Submission

Sumatriptan and Naproxen Sodium for the Acute Treatment of Migraine

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Objective.—To evaluate the efficacy and tolerability of treatment with a combination of sumatriptan 50 mg (encapsulated) and naproxen sodium 500 mg administered concurrently in the acute treatment of migraine.

Background.—The pathogenesis of migraine involves multiple peripheral and central neural mechanisms that individually have been successful targets for acute (abortive) and preventive treatment. This suggests that multimechanism therapy, which acts on multiple target sites, may confer improved efficacy and symptom relief for patients with migraine.

Design and Methods.—This was a multicenter, randomized, double-blind, double-dummy, placebo-controlled, four-arm study. Participants (n = 972) treated a single moderate or severe migraine attack with placebo, naproxen sodium 500 mg, sumatriptan 50 mg, or a combination of sumatriptan 50 mg and naproxen sodium 500 mg. In the latter two treatment arms, the sumatriptan tablets were encapsulated in order to achieve blinding of the study.

Results.—In the sumatriptan plus naproxen sodium group, 46% of subjects achieved 24-hour pain relief response (primary endpoint), which was significantly more effective than sumatriptan alone (29%), naproxen sodium alone (25%), or placebo (17%) ($P < .001$). Two-hour headache response also significantly favored the sumatriptan 50 mg plus naproxen sodium 500 mg therapy (65%) versus sumatriptan (49%), naproxen sodium (46%), or placebo (27%) ($P < .001$). A similar pattern of between-group differences was observed for 2-hour pain-free response and sustained pain-free response ($P < .001$). The incidence of headache recurrence up to 24 hours after treatment was lowest in the sumatriptan plus naproxen sodium group (29%) versus sumatriptan alone (41%; P = .048), versus naproxen sodium alone (47%; $P = .0035$), and versus placebo (38%; $P = .08$). The incidences of the associated symptoms of migraine were significantly lower at 2 hours following sumatriptan 50 mg plus naproxen sodium 500 mg treatment versus placebo ($P < .001$). The frequencies and types of adverse events reported did not differ between treatment groups, with dizziness and somnolence being the most common.

Conclusions.—This is among the first prospective studies to demonstrate that multimechanism acute therapy for migraine, combining a triptan and an analgesic, is well tolerated and offers improved clinical benefits over monotherapy with these selected standard antimigraine treatments. Specifically, sumatriptan 50 mg (encapsulated) and naproxen sodium 500 mg resulted in significantly superior pain relief as compared to monotherapy with either sumatriptan 50 mg (encapsulated) or naproxen sodium 500 mg for the acute treatment of migraine. Because encapsulation of the sumatriptan for blinding purposes may have altered its pharmacokinetic profile and thereby decreased the efficacy responses, additional studies are warranted that do not involve encapsulation of the active treatments and assess the true onset of action of multimechanism therapy in migraine. This study did show that the combination of sumatriptan and naproxen sodium was well tolerated and that there was no significant increase in the incidence of adverse events compared to monotherapy.

Key words: migraine, sumatriptan, acute treatment, NSAIDs, naproxen sodium, clinical trial

Abbreviations: NSAIDs nonsteroidal anti-inflammatory drugs, CGRP calcitonin gene-related peptide, IHS International Headache Society

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Many studies suggest that there are several different pathways activated during a migraine attack.[1] Collectively, the cascade of interrelated events causes the symptom complex of migraine that commonly includes disabling headache pain, nausea, sensitivity to light and sound, and a host of other autonomic symptoms including lacrimation and congestion.[1] Migraine symptoms are likely the result of changes in both the central and peripheral nervous systems, with specific activation of the trigeminal nerve. This suggests that multiple peripheral and central targets have the potential to offer therapeutic benefits for treatment.

Currently, the standard treatments available for migraine may be classified as either migraine-specific, such as the ergotamine alkaloid derivatives and triptans, or nonspecific, such as analgesics, narcotics, and barbiturates.[2] Since their introduction over 10 years ago, triptans are now considered first-line treatment for many patients with migraine.[3,4]

Triptans are very effective in relieving the pain associated with migraine and also in aborting the attack. Triptans prevent release of inflammatory substances from the nerve endings, block nociceptive transmission in the trigeminal system, cause vasoconstriction, and, when given early in the migraine attack, possibly prevent the development of central sensitization.[5,6] However, during a migraine attack triptans do not appear to have an effect on inflammatory substances already released or on inflammatory processes already activated. Therefore, drugs acting on this inflammatory component of migraine may also prove therapeutic. Medications that inhibit prostaglandin production, including nonsteroidal anti-inflammatory drugs (NSAIDs), are also effective antimigraine therapies.[3,4,7,8] NSAIDs also have been shown to block neurogenic dural plasma extravasation and to block trigeminal sensitization caused by calcitonin gene-related peptide (CGRP)-mediated dural vasodilatation.[9,10] Collectively, these studies demonstrate that triptans and NSAIDs work on distinct mechanisms involved in migraine, and therefore, when given concomitantly, may offer improved treatment for patients as compared to monotherapy treatment.

Previous open-label studies in small numbers of patients suggest that combining triptan and analgesic therapy offers improved therapeutic benefits, especially on specific parameters such as migraine recurrence. Krymchantowski initially reported the results of using sumatriptan 100 mg in combination with naproxen sodium 550 mg for the acute treatment of migraine.[11] An improvement in recurrence rate was noted, possibly due to the long half-life of naproxen sodium. This group further studied rizatriptan taken in combination with rofecoxib and again reported lower recurrence rates with consistent trends for improved headache response rates noted in the combination treatment group.[12] Similarly, in another open-label trial, the combinations of either rizatriptan and rofecoxib or rizatriptan and tolfenamic acid provided improved efficacy response rates, lower recurrence rates, and decreases in migraine-associated symptoms.[13] Collectively, these studies provide the initial reports that combination therapy consisting of triptans and anti-inflammatory medications may confer additional therapeutic benefits over single-therapy approaches. However, prospective, blinded, randomized controlled studies are needed to assess which specific endpoints may improve and the degree of improvement possible. To achieve this aim, this study further evaluated the relative efficacy and tolerability of sumatriptan 50 mg (encapsulated) plus naproxen sodium 500 mg versus placebo or monotherapy with naproxen sodium 500 mg or sumatriptan 50 mg. Although placebo tablets matching naproxen sodium 500 mg were available to the study sponsor, blinded sumatriptan 50 mg tablets and matching placebo were unavailable and therefore encapsulation of sumatriptan 50 mg (market-image) was required in order to double-blind treatment arms. Naproxen sodium 500 mg tablets were not encapsulated. As a result, a bias due to encapsulation of the triptan alone was present and any delay in the T_{max} of sumatriptan, as compared to an unencapsulated product, could have potentially affected the treatment responses in the two treatment arms containing sumatriptan.

DESIGN AND METHODS

Patients and Study Design.—This was a randomized, double-blind, placebo-controlled, multicenter study conducted at 32 centers in the United States. Subjects each treated a single migraine attack of moderate or severe intensity. The trial was designed in

accordance with the Ethical Principles of Good Clinical Practice as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki. All subjects provided informed consent prior to study enrollment. Participating clinical centers provided written approval from a central or local Institutional Review Board. A participating subject could receive a monetary stipend for time and travel expenses, as approved by the respective Institutional Review Board.

Males and nonpregnant females 18 years of age and older with a diagnosis of migraine with or without aura, according to the International Headache Society (IHS) Classification Criteria (1988[14] and 2004[15]) were recruited for participation. Eligible subjects had a history of at least 2, but not more than 6 migraine attacks per month during the preceding 12 months. Subjects had a history of tolerating oral treatment with a 5-HT agonist (triptans or ergotamine derivatives) for migraine. Each subject was instructed to treat a single migraine headache of moderate or severe pain intensity.

In order to blind the study treatments, sumatriptan 50 mg (market-image conventional tablet) was encapsulated (sumatriptan 50 mg-E). Each subject was randomly assigned to one of four treatment groups:

1. one sumatriptan 50 mg-E capsule and one tablet of naproxen sodium 500 mg.
2. one sumatriptan 50 mg-E capsule and one placebo tablet (matching the naproxen sodium tablet).
3. one placebo capsule (matching the sumatriptan 50 mg-E capsule) and one tablet of naproxen sodium 500 mg.
4. one placebo capsule and one placebo tablet.

Preparation of Study Treatments.—As noted previously, blinded sumatriptan 50 mg tablets and matching placebo were unavailable to the sponsor of this study. After preparation of the encapsulated sumatriptan 50 mg (market-image) tablets, the sponsor conducted a bioequivalence study that was a randomized two-way crossover study in 28 healthy volunteers. There was no difference between encapsulated and nonencapsulated sumatriptan 50 mg tablets for AUC_{0to24} for the market-image conventional sumatriptan 50 mg tablet versus the encapsulated tablet ($AUC_{0to24:}$ market-image 111.5 ng hour/mL vs. 111.0 ng hour/mL for sumatriptan 50 mg-E). The C_{max} also was similar for both preparations of sumatriptan: the C_{max} for the market-image conventional sumatriptan 50 mg tablet was 33.6 ng/mL and the C_{max} for the sumatriptan 50 mg-E capsule was 32.7 ng/mL. In this study, there was a delay (~30 minutes) in the T_{max} for sumatriptan 50 mg-E, with a T_{max} of 1.75 hours versus a T_{max} of 1.25 hours for the market-image conventional sumatriptan 50 mg tablet. Although the sponsor was aware that a delay of approximately 30 minutes in the T_{max} of sumatriptan could possibly influence early efficacy results, there was no other option available to provide for adequate blinding of the study treatments. Naproxen sodium tablets (500 mg) and matching placebo tablets were prepared by the sponsor for use in this study.

Assessments.—At the end of the screening visit, study medication (which was packaged in individual foil pouches) was dispensed to eligible subjects. Following onset of a moderate-to-severe migraine attack, subjects completed study diary cards just prior to taking study medication. Additional diary card assessments were subsequently recorded at 15-minute intervals for up 2 hours after dosing, and at 30-minute intervals between 2 and 4 hours after dosing. Hourly assessments were recorded between 4 and 24 hours while awake. Rescue medication was permitted no sooner than 2 hours after dosing. A 4-point scale (0 = no headache pain; 1 = mild headache pain; 2 = moderate headache pain; 3 = severe headache pain) was used to record headache responses over time throughout the 24 hours following treatment.

Subjects were required to return to the study center between 24 and 72 hours after taking study medication. At this time, the investigator reviewed diary card data, adverse event occurrences, and use of concurrent and/or rescue medication.

Efficacy Endpoints.—The primary efficacy endpoint was "sustained pain response" defined as: (1) having pain no greater than mild at 2 hours post dosing, (2) taking no rescue medication for 24 hours post dosing, and (3) having no recurrence of moderate or severe pain within 24 hours of the initial dose of study medication. Secondary endpoints included headache

Table 1.—Patient Demographics and Baseline Measures for All Patients in the Intent-to-Treat Population

	Sumatriptan 50 mg* + Naproxen Sodium 500 mg (N = 251)	Sumatriptan 50 mg* (N = 229)	Naproxen Sodium 500 mg (N = 250)	Placebo (N = 242)
Age, years (SD)	42.5 (11.0)	41.2 (11.3)	42.1 (10.7)	41.2 (10.2)
Sex (No.)				
Female	235	208	223	214
Male	16	21	27	28
Migraine history				
Duration (years)	21.0	21.5	19.6	20.0
With aura (%)	8	8	10	11
Without aura (%)	77	79	73	71
With/without aura (%)	15	12	18	19

*Sumatriptan 50 mg (encapsulated market-image conventional tablet).

response, pain-free response, sustained pain-free response, and headache recurrence (defined as achieving a reduction in pain response to score of 0 or 1 by 2 hours after dosing with a return of headache pain to 2 or 3 within the subsequent 22 hours). Migraine-associated symptoms were also assessed including nausea, photophobia, and phonophobia. Tolerability was assessed by physical examinations, standard laboratory tests, vital signs, and recording of adverse events.

Data Analysis.—The primary endpoint, sustained pain response, was ordered for purposes of analysis. The proportion of subjects achieving sustained pain response was summarized by treatment group. The SAS GENMOD procedure was used to test for treatment

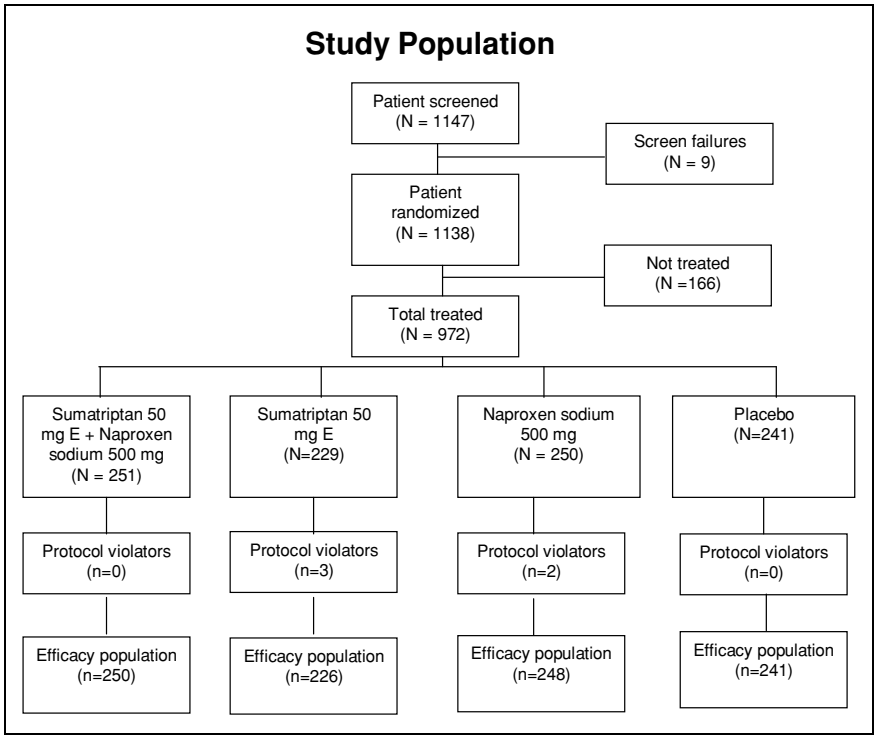

Fig 1.—Study enrollment and completion diagram.

differences using an ordered logistic regression model with site, treatment, and baseline pain as covariables. Sustained pain-free was analyzed by logistic regression since the potential outcomes were dichotomous (no pain vs. some pain). The logistic regression was performed using SAS GENMOD with model parameters as specified for the ordered logistic regression. Analysis of 2-hour pain response and pain-free were conducted using Cochran-Mantel-Haenszel (CMH) chi-square test corrected for continuity and stratified by sites. Incidence of nausea, photophobia, and phonophobia was also tested for differences from placebo using the CMH test.

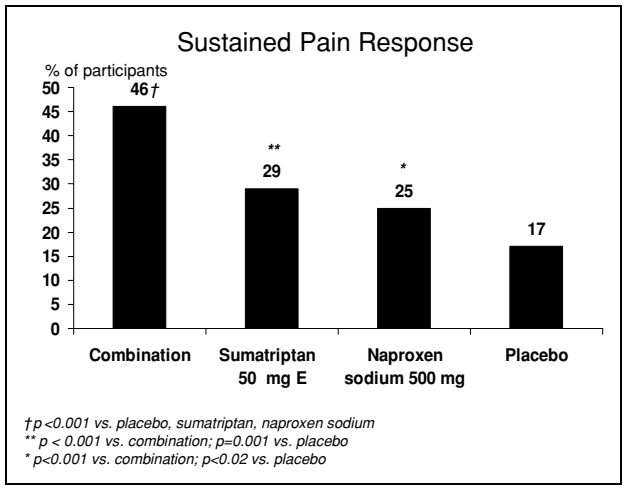

Fig 2.—Sustained pain relief was the primary endpoint for the study and was defined as patients having a headache response no greater than mild at 2 hours. Patients also did not use any rescue or escape medication and did not have any worsening of headache back to moderate or severe pain intensity for up to 24 hours post dose. Subjects treated with the combination sumatriptan 50 mg-E plus naproxen sodium 500 mg achieved the highest sustained pain response among the four treatment groups.

RESULTS

Demographic and Baseline Data.—Baseline characteristics were comparable among the four treatment groups. The majority of subjects were female with a mean age 41 years, and the mean duration of illness was 21 years (Table 1).

Of the 972 patients randomized, 3 were excluded from the efficacy analyses because these subjects failed to return a diary card to the investigator. In addition, 3 subjects treated when the headache intensity was mild, and one subject failed to record a rating of pain intensity at the time of treatment. These 7 subjects were considered to be protocol violators; therefore, 965 subjects comprised the efficacy population (Figure 1). All 972 study participants were included in the tolerability assessment.

Efficacy.—Sustained pain response (primary endpoint) was achieved in 46% of subjects treated with sumatriptan 50 mg-E and naproxen sodium 500 mg, and this was significantly greater than treatment with sumatriptan 50 mg-E only (29%), naproxen sodium 500 mg only (25%), or placebo (17%) (Figure 2).

By 2 hours, significantly more subjects achieved a headache response from sumatriptan 50 mg-E plus naproxen sodium 500 mg as compared to placebo, sumatriptan 50 mg-E alone, or naproxen sodium 500 mg alone. Sixty-five percent of the patients in sumatriptan 50 mg-E plus naproxen sodium 500 mg treatment group had a 2-hour pain response, compared with 49% and 46% of the patients who received sumatriptan 50 mg-E only or naproxen sodium 500 mg only, respectively (Table 2; Figure 3). The improvement noted in pain-free rates for the sumatriptan plus naproxen sodium treatment group were significantly higher than placebo and naproxen sodium alone starting at 1 hour following treatment (Table 2). Pain-free rates were highest for the sumatriptan plus naproxen sodium therapy at 2 and 4 hours following treatment. Headache recurrence between 2 and 24 hours was lowest in the sumatriptan plus naproxen sodium treatment group (29%) as compared to sumatriptan monotherapy (41%; $P = .048$), naproxen sodium monotherapy (47%; $P = .0035$), or placebo (38%; $P = .08$). Patients treated with sumatriptan plus naproxen were more likely to be free of nausea, photophobia, and phonophobia at 2 hours after dosing, compared to the other three treatment groups (Table 3).

Tolerability.—No serious adverse events were reported for patients in any of the treatment groups. The adverse event rate for the sumatriptan 50 mg-E plus naproxen sodium 500 mg group (23%) was not different from the sumatriptan 50 mg-E only group (24%). The adverse event rate in the group treated with naproxen sodium 500 mg only was 17%, while the placebo group had an adverse event rate of 15%.

Table 2.—Pain Responses Among Patients Evaluable for Efficacy

	Sumatriptan 50 mg† + Naproxen Sodium 500 mg (N = 250)	Sumatriptan 50 mg† (N = 226)	Naproxen sodium 500 mg (N = 248)	Placebo (N = 241)
Pain response (%)*				
30 minutes	5	8[a]	8[g]	3
1 hour	29[a]	23[a]	27[a]	12
2 hours	65[a,b,c]	49[a,d]	46[a,d]	27
4 hours	74[a,b,c]	56[a,d]	48[a,d]	29
Pain-free (%)*				
30 minutes	1	0	0	0
1 hour	8[a,f]	4[e]	3[e]	1
2 hours	34[a,b,c]	20[a,d]	18[a,d]	6
4 hours	54[a,b,c]	35[a,d,f]	27[a,d,h]	14
24-hour sustained pain response (%)*	46[a,b,c]	29[d,e]	25[a,d]	17
24-hour sustained pain-free (%)*	25[a,b,c]	11[d,e]	12[a,d]	5
Headache recurrence	29[f,h]	41[g]	47[g]	38
Rescue medication use 2–24 H (%)**	35[a,b,c]	51[a,d]	52[a,d]	64

[a]$P \leq .01$ vs. placebo; [b]$P \leq .01$ vs. sumatriptan; [c]$P \leq .01$ vs. naproxen sodium; [d]$P \leq .01$ vs. combination; [e]$P \leq .05$ vs. placebo; [f]$P \leq .05$ vs. naproxen sodium; [g]$P < .05$ vs. combination; [h]$P < .05$ vs. sumatriptan 50 mg-E.
*Logistic regression test; **Cochran-Mantel-Haenszel test; †Sumatriptan 50 mg-E (encapsulated market-image conventional tablet).

The listing of reported adverse events is shown in Table 4. There were no clinically significant differences in the types of adverse events reported from the individual treatment groups. The most common adverse events included dizziness (not vertigo) and somnolence. There were no serious adverse events reported.

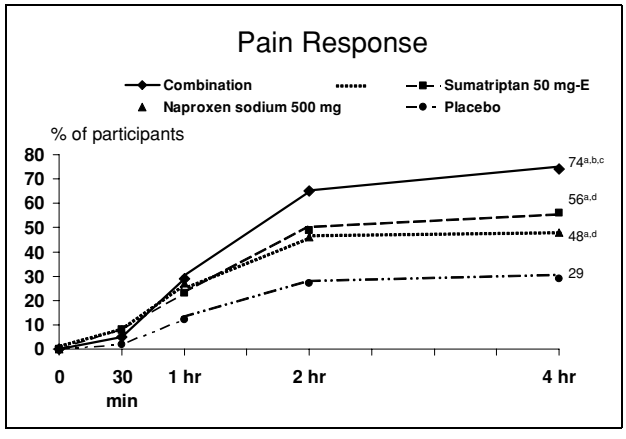

Fig 3.—The number of participants who achieved a headache response was highest in the sumatriptan 50 mg-E plus naproxen sodium 500 mg treatment group with significant differences noted as early as 1 hour after treatment. [a]$P \leq .001$ vs. placebo; [b]$P \leq .001$ vs. sumatriptan; [c]$P \leq .001$ vs. naproxen sodium; [d]$P \leq .001$ vs. combination.

COMMENTS

In this double-blind study, the combination of sumatriptan 50 mg-E (encapsulated market-image conventional tablet) and naproxen sodium 500 mg was significantly more effective for the acute treatment of migraine than placebo or the respective monotherapies and did not appear to have an increased risk of side effects. These results support the findings of a previous open-label study[11] that reported that naproxen sodium in combination with sumatriptan provided therapeutic benefits over triptan monotherapy, which has been the standard of care[3,4] for migraine since development of sumatriptan more than a decade ago.[16] Naproxen sodium is rapidly absorbed and the terminal half-life approaches 18 hours, thereby providing sustained plasma levels.[17,18] These pharmacodynamic properties of naproxen sodium, together with the potent effects of sumatriptan, are likely responsible for the benefits of improved acute efficacy, better sustained response, and lower recurrence rates observed with combination treatment.

Specifically, the 2-hour pain response with sumatriptan plus naproxen sodium (65%) was 33% higher than that of sumatriptan alone (49%); and the 24-hour sustained pain response was 57% higher (sumatriptan

Table 3.—Migraine-Associated Symptom Responses Among Patients Evaluable for Efficacy

	Sumatriptan 50 mg† + Naproxen Sodium 500 mg (N = 250)	Sumatriptan 50 mg† (N = 226)	Naproxen Sodium 500 mg (N = 248)	Placebo (N = 241)
Nausea-free at 2 hours (%)**	69[a,g]	60	65[a]	53
Photophobia-free at 2 hours (%)**	59[a,b,c]	46[a,d]	40[a,d]	30
Phonophobia-free at 2 hours (%)**	66[a,b,c]	52[a,d]	49[a,d]	37

[a]$P \leq .01$ vs. placebo; [b]$P \leq .01$ vs. sumatriptan 50 mg-E; [c]$P \leq .01$ vs. naproxen sodium; [d]$P \leq .01$ vs. combination; [e]$P \leq .05$ vs. placebo; [f]$P \leq .05$ vs. naproxen sodium; [g]$P < .05$ vs. sumatriptan 50 mg-E.
**The Cochran-Mantel-Haenszel test with site and baseline as strata; †Sumatriptan 50 mg-E (encapsulated market-image conventional tablet).

plus naproxen sodium 46% versus sumatriptan alone 29%). Thus, the greatest improvements afforded by the sumatriptan 50 mg-E and naproxen sodium 500 mg combination over sumatriptan monotherapy were noted in the sustained response measures (eg, sustained pain-free, sustained headache response, incidence of recurrence). The fact that multimechanism therapy can provide improved acute relief and better sustained response for 24 hours after a single administration is perhaps the most beneficial outcome from combining sumatriptan and naproxen sodium.

The results from this trial also support previous reports of improved 24-hour outcomes as assessed by lower recurrence rates with combining triptan and anti-inflammatory treatment.[11] In this study the recurrence rate in the combination treatment group was significantly lower than for either of the monotherapy treatment groups, but did not significantly differ from placebo. The low rate of recurrence in placebo recipients was likely due to the relatively small number of responders in the placebo group. Only 66/242 (27%) patients receiving placebo reported an initial headache response at 2 hours, and 25 of these patients subsequently reported recurrence. Low recurrence rates, sustained efficacy responses, and low use of rescue medication are identified as ongoing treatment goals among migraine patients.[3,4] Because monotherapy with triptans or NSAIDs commonly provide 2-hour response rates between 50% and 80%, and only about half of such patients achieve a sustained response by 24 hours,[19] acute treatments with longer durations of efficacy are needed.[1]

Table 4.—Adverse Events >2%

	Sumatriptan 50 mg† + Naproxen Sodium 500 mg (N = 251)	Sumatriptan 50 mg† (N = 229)	Naproxen Sodium 500 mg (N = 250)	Placebo (N = 242)
Chest tightness	5 (2%)	2 (1%)	4 (2%)	3 (1%)
Diarrhea (NOS)	0	4 (2%)	6 (2%)	3 (1%)
Dizziness (not vertigo)	9 (4%)	11 (5%)	4 (2%)	8 (3%)
Dry mouth	4 (2%)	4 (2%)	3 (1%)	1 (1%)
Fatigue	5 (2%)	1 (1%)	0	0
Nausea aggravated	1 (1%)	3 (1%)	2 (1%)	4 (2%)
Paresthesia	2 (1%)	4 (2%)	1 (1%)	1 (1%)
Somnolence	3 (1%)	6 (3%)	2 (1%)	0
Tinnitus	6 (2%)	4 (2%)	4 (2%)	2 (1%)

It should be noted that one aspect of the methodology employed in this study, specifically the use of encapsulated sumatriptan in both the combination and the sumatriptan monotherapy treatments, may have introduced a bias contributing to lower efficacy of these two study arms. Previous studies report that unencapsulated sumatriptan is quickly absorbed and reaches therapeutic plasma levels within 1 hour.[20] Encapsulation has been shown to decrease the speed of absorption of sumatriptan during a migraine attack.[21] In the prior pharmacokinetic study performed by the sponsor of the present study, although the encapsulated sumatriptan was bioequivalent to the marketed formulation based on AUC parameters over 24 hours, there was an approximate 30-minute delay in the T_{max} of sumatriptan with the encapsulated drug. This delay in T_{max} could have affected early time-point assessments such as time of onset of efficacy following treatment, but only in those treatment arms containing encapsulated sumatriptan. Despite this delay, the encapsulation of sumatriptan does not militate against the findings that the combination therapy was significantly more effective than either naproxen sodium monotherapy or encapsulated sumatriptan monotherapy. Such bias might serve to narrow the efficacy differences between each of the two sumatriptan-containing treatment arms and the naproxen sodium and placebo treatment arms. In fact, one might consider the hypothesis that removing the encapsulation might increase the between-group differences. Therefore, the onset of efficacy results should be interpreted with caution, and future studies that eliminate the encapsulation bias are needed to better define the onset of efficacy of multimechanism therapy utilizing triptans and anti-inflammatory drugs in the acute treatment of migraine.

Additional studies are also warranted that specifically examine pharmacodynamic interactions of combining different formulations of these classes of treatments, in order to explain the efficacy benefits, and also to assess safety and tolerability parameters.

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