

# Comparative Efficacy of Eletriptan 40 mg Versus Sumatriptan 100 mg

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**Objective.**—To confirm the efficacy advantage of eletriptan 40 mg over sumatriptan 100 mg.

**Background.**—Eletriptan 80 mg has demonstrated significantly greater efficacy when compared to both sumatriptan 50 mg and 100 mg in two studies. Eletriptan 40 mg demonstrated significantly greater efficacy than sumatriptan 100 mg in one previous trial.

**Methods.**—Two thousand one hundred thirteen patients with a diagnosis of migraine according to International Headache Society criteria were randomized using a double-blind, double-dummy, parallel-group design, and treated for a single migraine attack with either eletriptan 40 mg, sumatriptan 100 mg, or placebo. The primary endpoint was 2-hour headache response. Secondary endpoints included headache response rates at 1 hour, pain-free rates, absence of associated symptoms, functional response at 1 and 2 hours, and sustained headache response.

**Results.**—Headache response rates at 2 hours postdose were significantly higher for eletriptan 40 mg (67%) than for sumatriptan 100 mg (59%;  $P < .001$ ) and placebo (26%;  $P < .0001$ ). Eletriptan 40 mg consistently showed significant ( $P < .01$ ) efficacy over sumatriptan 100 mg across secondary clinical outcomes, including 1-hour headache response; 2-hour pain-free response; absence of nausea, photophobia, and phonophobia; functional improvement; use of rescue medication; treatment acceptability; and sustained headache response ( $P < .05$ ). Overall, treatment-related adverse events were low, nausea being the only adverse event with an incidence of 2% or higher (4.9% with eletriptan, 4.2% sumatriptan, 2.8% placebo).

**Conclusion.**—This trial confirmed that eletriptan 40 mg offers superior efficacy in treating migraine pain and associated symptoms and in restoring patient functioning when compared with sumatriptan 100 mg.

**Key words:** eletriptan, sumatriptan, triptan, migraine, acute treatment, headache

**Abbreviations:** AE adverse event

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The randomized, double-blind, placebo-controlled clinical trial is the cornerstone of evidence-based medicine.<sup>1</sup> In many illnesses such as migraine, well-controlled clinical trials have established the efficacy of a wide array of drugs. Choosing among treatments with established efficacy is an individualized clinical decision, and the gold-standard evidence that informs such decisions in clinical practice is the placebo-controlled, head-to-head comparator trial.<sup>2</sup> In the absence of such a trial, meta-analysis has been used to provide clinicians with indirect evidence

of relative efficacy among “triptans.”<sup>3</sup> But study-to-study differences in patient characteristics, as well as variations in design, procedures, and time of conduct, make the results from head-to-head trials stronger evidence of comparative efficacy than indirect evidence derived from meta-analyses.<sup>4,5</sup>

Placebo-controlled, head-to-head trials comparing two triptans have become more frequent in the past few years, most of them comparing newer triptans to oral sumatriptan.<sup>6</sup> Consistently superior efficacy, based on the results of two or more direct comparator trials, has yet to be demonstrated for rizatriptan, naratriptan, zolmitriptan, almotriptan, or frovatriptan. In contrast, three consecutive head-to-head comparator trials have found the 80-mg dose of eletriptan to have significantly greater efficacy than sumatriptan in terms of both the primary outcome measure (2-hour headache response) and other secondary clinical outcomes<sup>7,8</sup> (data on file, Pfizer Inc).

Similarly, two previous placebo-controlled, head-to-head trials have evaluated the comparative efficacy of the 40-mg dose of eletriptan versus sumatriptan 100 mg. In the first,<sup>8</sup> the 40-mg dose showed significantly greater efficacy than sumatriptan 100 mg on the primary outcome measure, while in the second it did not ( $P = .053$ ),<sup>7</sup> despite achieving a 10-point higher headache response rate.

Determination of the relative efficacy of two treatments for migraine cannot be based on differences in headache response alone, but should also include evaluation of treatment response across the multidimensional outcome domains that are typical of the clinical presentation of migraine.<sup>2</sup> The multidimensional clinical presentation of migraine is associated with significant impairment in work, social, and family activities and in quality of life.<sup>9-14</sup> Community surveys suggest that a typical migraine results in severe functional impairment or complete bed rest, or both, in approximately 50% of attacks.<sup>12</sup> This degree of impairment is equivalent or greater than that reported for other chronic medical illnesses including angina, diabetes, and hypertension. In fact, among adults aged 45 years and younger, the World Health Organization Global Burden of Disease survey identified migraine as one of the top 20 illnesses worldwide in terms of years lived with disability.<sup>15</sup> In light

of this, any comparison of the relative efficacy of two migraine treatments must assess functional response as one of the critical outcomes.

The current trial was designed with the primary goal of testing the hypothesis that the 40-mg dose of eletriptan was superior to the 100-mg dose of sumatriptan, both in terms of headache response at 2 hours and across the full range of migraine symptoms and functional improvement.

## PATIENTS AND METHODS

**Patients.**—The study sample consisted of men and women, aged 18 to 65 years, who met the International Headache Society (IHS) criteria for migraine with or without aura,<sup>16</sup> and who reported a monthly frequency of one to six attacks. Patients were excluded for the following reasons: presence of frequent concurrent nonmigrainous headache or treatment-resistant migraine (or both) or migraine variants (eg, familial hemiplegic or basilar migraine); coronary artery disease, heart failure, uncontrolled hypertension, or abnormal electrocardiogram (ECG); any clinically significant medical illness or laboratory abnormality; severe reduction in gastrointestinal absorption; hypersensitivity or known contraindication to treatment with eletriptan or sumatriptan; concomitant use of potent CYP3A4 inhibitors or use of monoamine oxidase (MAO) inhibitors in the 2 weeks prior to study entry; misuse or abuse of alcohol or other substances including analgesics or ergotamine; use of any experimental drug within the past month; and women who were pregnant or breast-feeding.

At screening, all patients had a physical examination, including a blood pressure test, a 12-lead ECG, and a urine pregnancy test (as appropriate). Study conduct was consistent with the Declaration of Helsinki. The study protocol was approved by institutional review boards (ethics committees) at each site. The study was explained to prospective patients and written informed consent was obtained prior to study entry.

**Study Design.**—This randomized, double-blind, parallel-group, outpatient study was conducted in 166 centers worldwide. Patients were randomly assigned in a 2:2:1 ratio to treat one attack with either 40 mg of eletriptan, 100 mg of sumatriptan, or placebo. The

study utilized a double-dummy design, and study medication consisted of plain white film-coated tablets of eletriptan or matching placebo and thin gelatin capsules containing sumatriptan or matching placebo capsules. The blinded sumatriptan was demonstrated to be both bioequivalent and clinically equivalent to the commercial tablet based on 4 categories of data: (1) an *in vitro* dissolution study conducted in deionized water (data on file, Pfizer Inc); (2) an *in vivo* gamma scintigraphy study showing no difference in dissolution rates (data on file, Pfizer Inc); (3) a bioequivalence study meeting standard regulatory criteria for equivalent area under the curve (AUC) and maximum concentration ( $C_{max}$ ) values (data on file, Pfizer Inc); and (4) a post hoc comparison of the therapeutic gain for the primary outcome measure in the current study, headache response at 2 hours. With regard to the last point, in the current study, encapsulated sumatriptan showed a 2-hour headache response of 59% (and therapeutic gain of 33%), which is equivalent to what has been reported across all available placebo-controlled studies of the 100-mg dose of sumatriptan, ie, 59% (29%, therapeutic gain).<sup>3</sup> Any concerns about the validity of encapsulation as a standard blinding methodology (eg, whether it subtly reduces bioavailability) do not appear to apply in this case since the therapeutic effect of sumatriptan reported is similar to that published in the literature. Objectivity is further supported by the fact that sumatriptan does not have a significant dose-response relationship; even a 50% reduction in dose (from 100 mg to 50 mg) has not been shown to have any effect on headache response.<sup>3</sup>

Patients were instructed to take study medication within 6 hours of the onset of a migraine headache. The headache was to be determined by the patient as moderate or severe in intensity and not improving. Furthermore, patients were instructed not to take study medication if they had taken an analgesic or antiemetic during the current attack or in the previous 6 hours; or if they had taken another triptan or ergotamine-containing or ergot-type medication (eg, dihydroergotamine) in the previous 48 hours.

Patients recorded migraine-related symptoms in a diary at baseline (immediately predose) and at 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, and 24

hours after dosing. Use of rescue medications was also recorded in the diary.

Patients who failed to achieve a headache response by 2 hours (defined below) were permitted to take rescue medication, but they were not permitted to take any other triptan, ergotamine, or ergotamine-like substance for 24 hours after taking the study medication. Patients who did achieve a 2-hour headache response, but experienced a recurrence, were permitted to take a second dose of study medication. The time of recurrence and the second dose, as well as information on rescue medication, were noted in the diary card. Headache intensity was recorded immediately prior to taking the second dose of study medication. Rescue medication was permitted 2 hours after the second dosing, if needed. The patient was asked to contact the investigator or his representative within 48 hours of study treatment to review adverse event (AE) information and to schedule the final appointment, which took place within 14 days of the index attack.

**Evaluation of Efficacy.**—Primary efficacy endpoints consisted of the percentage of patients who were headache responders, operationally defined as patients who, at 2 hours after ingesting the study drug, reported improvement in headache intensity to mild or pain-free levels from a pretreatment level of moderate or severe.

Secondary endpoints, designed to capture the full spectrum of symptom severity and disability associated with migraines, consisted of the following:

- change from pretreatment baseline in headache intensity (headache intensity was rated on a four-point global scale: none, mild, moderate, or severe)
- change from pretreatment baseline on a five-point patient-rated Global Impression of Efficacy scale (ranging from “much worse” to “much improved”)
- the presence or absence of nausea, vomiting, photophobia, and phonophobia
- change from pretreatment baseline in a 4-point functional impairment scale (3 = bed rest; 2 = severe impairment in work, study, or house-keeping activities, but not requiring bed rest;

1 = some impairment in work, study, or house-keeping activities; 0 = normal level of functioning [even if headache is present])

- change was reported as the percentage of patients whose functional status improved from 2 or 3 to 0 or 1
- headache recurrence (and time-to-headache recurrence), defined as the return of a moderate-to-severe headache, from a previously improved level of mild or no headache, at between 2 hours and 24 hours after ingestion of study medication
- time to use of rescue medication
- sustained relief, defined as headache response within 2 hours of study treatment with no subsequent headache recurrence and no use of rescue medication within 24 hours after the first dose of study medication
- acceptability of study medication compared to previous treatment, which was determined by the patient's answer to the following question: "Given the choice between this and any other previous medication you have used to treat a migraine attack, would you take this again?"

**Statistical Analyses.**—The primary efficacy parameter of this study was the proportion of patients with a headache response at 2 hours after the first dose of study treatment for the migraine attack. The primary efficacy comparison was between eletriptan 40 mg and sumatriptan 100 mg. The study was powered at 85% to detect as significant (alpha level = .05, two-tailed) an eight-point difference between eletriptan and sumatriptan in 2-hour headache response rates. The eight-point difference was considered to represent a clinically meaningful difference between the two medications. In addition, it was assumed that at least 75% of patients randomized would meet all eligibility criteria.

Baseline characteristics of the sample were compared for homogeneity across treatment groups. All efficacy analyses were performed on the intent-to-treat (ITT) sample, defined as all patients who took at least one dose of study medication and had a valid baseline and at least one postbaseline evaluation. The primary analysis was the 2-hour headache re-

sponder rate for the ITT group. This analysis was conducted using a categorical linear model based on the Statistical Analysis Systems (SAS) procedure, CATMOD, which included terms for treatment and baseline severity. In case of a statistically significant between-treatment difference at baseline, adjustments were made. Secondary endpoints were analyzed using a categorical linear model based on the SAS CATMOD procedure that includes terms such as treatment and baseline severity.

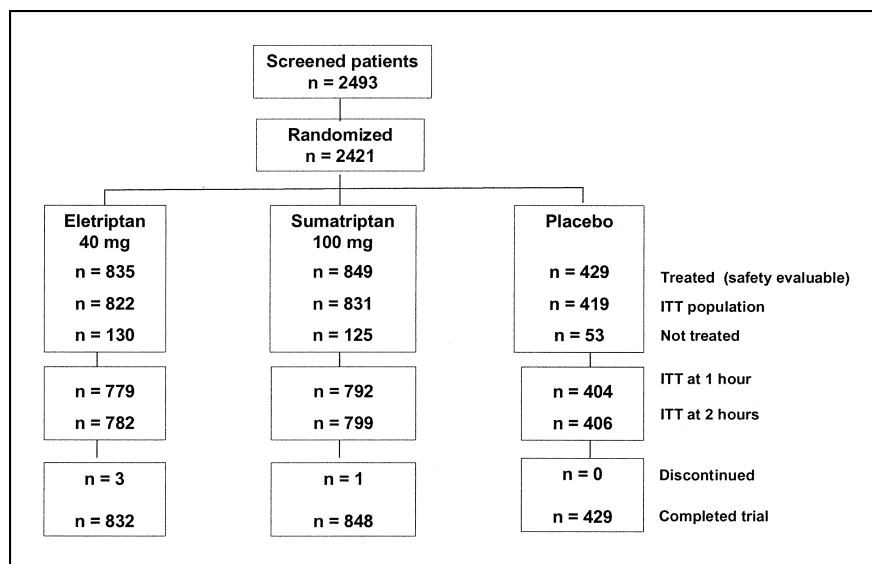
All statistical tests of significance were two-sided (unless otherwise specified), and all were performed at the 5% level of significance. No adjustment was made for multiple comparisons. Pair-wise comparisons were not performed unless the overall comparison of treatment groups was significant.

## RESULTS

**Study Sample.**—Two thousand one hundred thirteen patients were randomized to one of three treatment groups and received study treatment for a single migraine headache (the safety evaluable sample), with 2072 patients having a valid baseline assessment and at least 1 postdose assessment (the ITT sample) (Figure 1). The demographic and clinical characteristics of the patients in each treatment group (Table 1) are similar across the three treatment groups and are typical of patients entering short-term clinical trials in migraine.

**Efficacy.**—*Relief of Headache and Pain-Free Response.*—Eletriptan 40 mg showed significantly higher headache response rates versus sumatriptan 100 mg at both 2 hours (67% versus 59%;  $P < .001$ ) and at 1 hour (34% versus 27%;  $P < .01$ ) (Figure 2). Both active drugs were also superior to placebo at both time points. Eletriptan 40 mg showed higher pain-free response rates at 2 hours (36%) compared with both sumatriptan (27%;  $P < .0001$ ) and placebo (5%;  $P < .0001$ ). The sumatriptan pain-free response rate was also higher than placebo ( $P < .0001$ ).

*Relief of Associated Symptoms.*—Treatment with eletriptan 40 mg compared with sumatriptan 100 mg was associated at 2 hours with significantly lower incidence of nausea (74% absent versus 67%;  $P < .01$ ), photophobia (71% absent versus 63%;  $P < .01$ ), and phonophobia (74% absent versus 67%;  $P < .01$ ) (Fig-



**Fig 1.—Patient disposition.**

ure 3). The incidence of vomiting was too low to make a meaningful comparison.

*Improvement in Functioning.*—Patients treated with eletriptan showed a rapid return to normal or

near-normal levels of functioning with 33% of patients treated with eletriptan 40 mg showing a functional response within 1 hour postdose (Figure 4). From the 1.5-hour time point onward, patients treated

**Table 1.—Patient Characteristics**

Feature	Eletriptan 40 mg (n = 822)	Sumatriptan 100 mg (n = 831)	Placebo (n = 419)
Sex, female, %	87	86	87
Age, mean (SD), y	41.1 (10.8)	41.8 (10.4)	41.6 (10.6)
Range, y	18-64	18-65	18-65
Duration of illness, mean (SD), y*	13.4 (11.3)	14.0 (11.2)	13.6 (11.5)
Aura subtype, %			
Without aura	64	66	65
With aura	17	14	15
Mixed	19	20	20
Monthly attack frequency, mean (SD), No.†	2.7 (1.3)	2.7 (1.3)	2.8 (1.4)
Attacks rated as moderate to severe, %†	87	88	88
Characteristics of index attack			
Headache rated as severe, %	39	41	41
Incidence of associated symptoms, %			
Nausea	62	62	64
Photophobia	72	75	75
Phonophobia	64	67	64
Moderate to severe functional impairment, %	82	82	82

\*Time since first diagnosis.

†Average over 3 months prior to study entry.

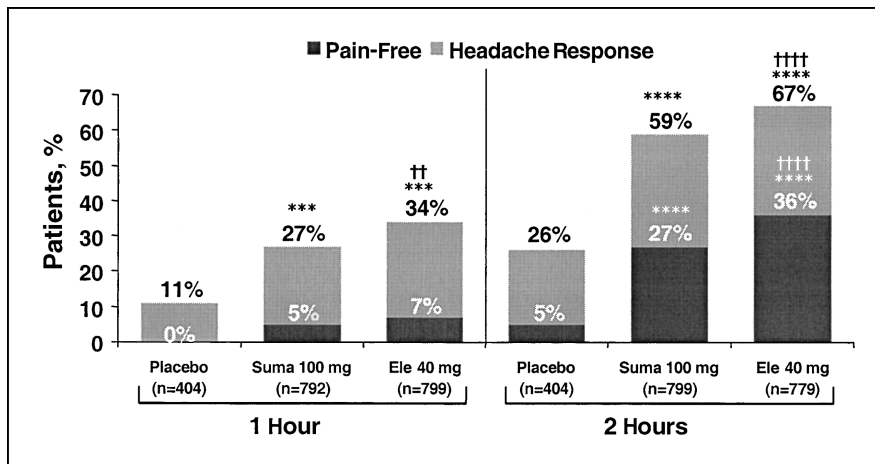


Fig 2.—Headache response rates at 1 hour and 2 hours and pain-free response at 2 hours. Ele triptan (Ele) or sumatriptan (Suma) versus placebo: \* $P < .05$ , \*\* $P < .01$ , \*\*\* $P < .001$ , \*\*\*\* $P < .0001$ ; ele triptan versus sumatriptan: † $P < .05$ , †† $P < .01$ , ††† $P < .001$ , †††† $P < .0001$ .

with ele triptan 40 mg showed significantly ( $P < .05$ ) greater improvement in functioning than those treated with sumatriptan 100 mg. Functional responses for ele triptan, sumatriptan, and placebo were 53%, 45%, and 26%, respectively, at 1.5 hours, and 68%, 61%, and 31%, respectively, at 2 hours.

**Use of Rescue Medication and Outcomes at 24 Hours Postdose.**—There was a significantly lower use of rescue medication among patients treated with ele triptan (20%;  $P < .0012$  versus sumatriptan;  $P < .0001$  versus placebo) compared to sumatriptan (27%;  $P < .0001$  versus placebo) and placebo (53%)

(Figure 5). In addition, among patients who achieved a 2-hour headache response, headache recurrence rates were significantly lower for ele triptan (31%;  $P < .0372$  versus sumatriptan;  $P < .0007$  versus placebo) compared to sumatriptan (37%;  $P < .0419$  versus placebo) and placebo (47%) (Figure 5). As a result, there was a significantly higher sustained headache response at 24 hours: 43% for ele triptan ( $P < .0003$  versus sumatriptan;  $P < .0001$  versus placebo), 34% for sumatriptan ( $P < .0001$  versus placebo) and 14% for placebo (Figure 6).

**Tolerability and Safety.**—Patients were asked to

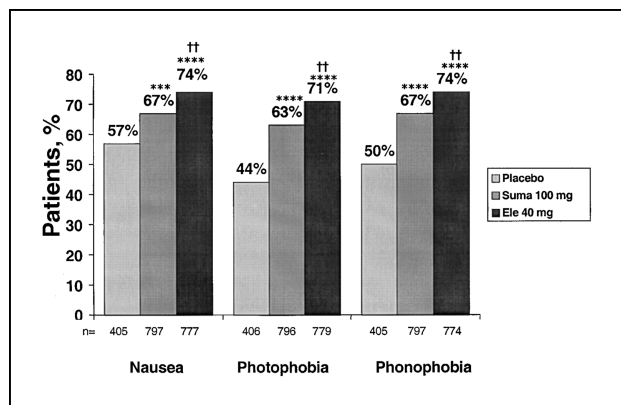


Fig 3.—Absence of associated symptoms at 2 hours. Ele triptan (Ele) or sumatriptan (Suma) versus placebo: \* $P < .05$ , \*\* $P < .01$ , \*\*\* $P < .001$ , \*\*\*\* $P < .0001$ ; ele triptan versus sumatriptan: † $P < .05$ , †† $P < .01$ , ††† $P < .001$ , †††† $P < .0001$ .

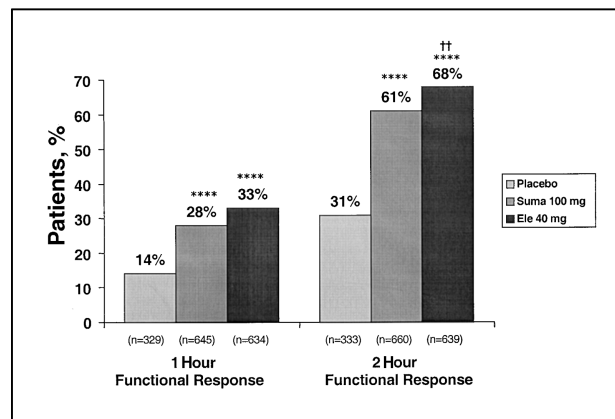
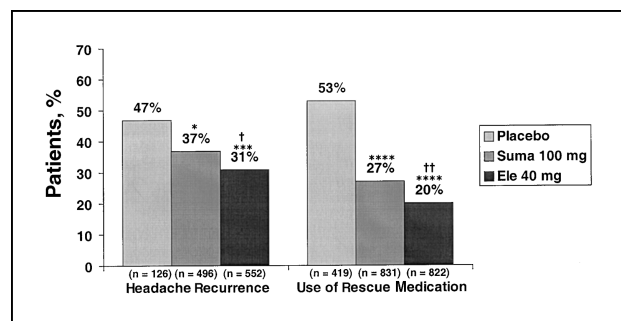
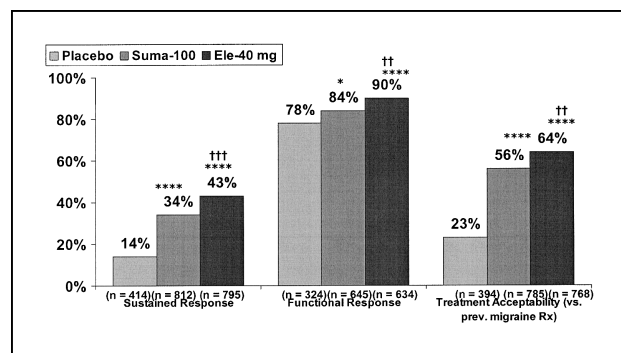


Fig 4.—Functional response at 1 hour and 2 hours. Ele triptan (Ele) or sumatriptan (Suma) versus placebo: \* $P < .05$ , \*\* $P < .01$ , \*\*\* $P < .001$ , \*\*\*\* $P < .0001$ ; ele triptan versus sumatriptan: † $P < .05$ , †† $P < .01$ , ††† $P < .001$ , †††† $P < .0001$ .



**Fig 5.—Headache recurrence and use of rescue medication. Eletriptan (Ele) or sumatriptan (Suma) versus placebo: \* $P < .05$ , \*\* $P < .01$ , \*\*\* $P < .001$ , \*\*\*\* $P < .0001$ ; eletriptan versus sumatriptan: † $P < .05$ , †† $P < .01$ , ††† $P < .001$ , †††† $P < .0001$ .**

report AEs, regardless of their causal relationship to the study drug. Adverse events that either arose within 7 days of dosing or, if present at baseline, increased in severity within 7 days of dosing were considered to be treatment emergent. Both eletriptan and sumatriptan were well tolerated and most AEs were mild and transient (Table 2). No serious treatment-related AEs occurred with either drug. The proportion of patients reporting at least one AE (most AEs were mild and transient) was 31% for eletriptan, 37% for sumatriptan, and 34% for placebo. No clinically significant laboratory abnormalities were recorded, and no clinically significant treatment-emergent ECG abnormalities were noted at the poststudy treatment visit. No patients exhibited clinically significant changes in pulse or blood pressure as defined by a change of more than 10 points in pulse



**Fig 6.—Assessments obtained at 24 hours. Eletriptan (Ele) or sumatriptan (Suma) versus placebo: \* $P < .05$ , \*\* $P < .01$ , \*\*\* $P < .001$ , \*\*\*\* $P < .0001$ ; eletriptan versus sumatriptan: † $P < .05$ , †† $P < .01$ , ††† $P < .001$ , †††† $P < .0001$ .**

**Table 2.—Treatment-Emergent Adverse Events\***

Adverse Event	Eletriptan 40 mg (n = 835)	Sumatriptan 100 mg (n = 849)	Placebo (n = 429)
Nausea	11.9	14.7	12.6
Vomiting	5.9	5.8	10.7
Photophobia	4.1	4.6	5.6
Asthenia	1.6	2.4	0.9
Chest symptoms	1.6	2.0	0.5
Paresthesia	1.1	2.4	0

\*Values are percent. All causality, with incidence  $\geq 2\%$ .

or a change of more than 10 mm Hg in diastolic or systolic blood pressure.

#### Patient Preference for Migraine Treatment.—

Overall, patient ratings of treatment acceptability (recorded at 24 hours for current versus prior migraine treatments) were significantly higher for eletriptan (64%;  $P < .01$  versus sumatriptan;  $P < .0001$  versus placebo) compared to sumatriptan (56%;  $P < .0001$  versus placebo) and placebo (23%) (Figure 6).

## COMMENTS

This double-blind, placebo-controlled, head-to-head comparator study was designed to evaluate the efficacy of the 40-mg dose of eletriptan versus the 100-mg dose of sumatriptan. The results show that 40 mg of eletriptan has significantly higher efficacy in migraine compared to 100 mg of sumatriptan across both primary and secondary endpoints. Eletriptan demonstrated a consistently significant efficacy advantage across the following a priori clinical outcomes: rapid headache response (1 hour); headache response at 2 hours; pain-free response at 2 hours; relief of nausea, photophobia, and phonophobia; functional response; use of rescue medication; sustained response over 24 hours; and overall treatment acceptability. In addition, the 40-mg dose of eletriptan showed a favorable tolerability profile with 31% of patients reporting any AE(s) compared to 37% of patients receiving sumatriptan.

The current study provides cross-validation of results from two previous placebo-controlled, head-

to-head trials. One of these studies found that 40 mg of eletriptan had significantly higher efficacy compared to 100 mg of sumatriptan on the primary outcome measure (2-hour headache response) as well as on secondary measures (pain-free response and functional response).<sup>8</sup> The second study showed an efficacy advantage (65% versus 55%),<sup>7</sup> but did not quite reach statistical significance on the primary outcome measure ( $P = .053$ ). Significantly higher efficacy on such secondary measures as headache response at 1 hour and functional response was also seen in this study.

The 2-hour headache response rate achieved on sumatriptan in the current study (59%) is similar to results reported in a recent comprehensive meta-analysis.<sup>2</sup> Furthermore, the placebo-subtracted headache response for sumatriptan measured as therapeutic gain (33%) is higher in the current study than in the recent meta-analysis.<sup>2</sup> This provides supportive evidence that the current results are valid and are not attributable to an artificially low headache response on sumatriptan. Any cross-study comparisons, however, even if based on large meta-analyses, must be interpreted with caution since multiple differences in study design, clinical characteristics of patients studied, and study procedures may significantly influence treatment response.

High rates of acute response are not always associated with low recurrence rates and high levels of sustained response at 24 hours.<sup>17</sup> The results of the current study, however, found that the 40-mg dose of eletriptan had a lower headache recurrence rate (31%) than sumatriptan (37%), resulting in a significantly higher sustained headache response rate for eletriptan, 43% versus 34% for sumatriptan ( $P < .0003$ ).

In conclusion, the results of the current study, taken together with two previous head-to-head comparator trials,<sup>7,8</sup> establish the superior efficacy and tolerability of the 40-mg dose of eletriptan compared to 100 mg of sumatriptan for the broad-spectrum relief of migraine pain and associated symptoms. The efficacy advantage of eletriptan was sustained for up to 24 hours and translated into significantly higher levels of functional improvement compared to sumatriptan.

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