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Neurology 2002;59:1210-1217
DOI 10.1212/WNL.59.8.1210

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Migraine is a common disorder that, at its peak prevalence between ages 35 and 45 years, affects approximately 18% of women and 7% of men. Based on current population estimates, approximately 30 million Americans have migraine headaches, with 37% of these individuals reporting one to three attacks per month. The typical migraine lasts 15 to 20 hours and is accompanied by associated symptoms, such as nausea, photophobia, or phonophobia, which also contribute to the disability associated with migraine. Community surveys report that >50% of migraineurs rate their migraines as severe or incapacitating, resulting in combined direct and indirect costs in terms of missed work, reduced productivity, and utilization of medical services, estimated to be in the range of 10 billion euros in Europe and $20 to $30 billion in the United States.

Eletriptan is a compound that shows high affinity for 5-HT1B and 5-HT1D receptors in vitro, four- and eight-fold higher than sumatriptan. Eletriptan targets mechanisms that have been linked to migraine pathogenesis, reducing neurogenic inflammation and carotid blood flow in in vitro model systems. Pharmacokinetic studies show that oral doses are rapidly absorbed, with a median T_max of 1 hour in healthy individuals and a median T_max of 2 hours in migraineurs (data on file), suggesting that the reduced gastric motility associated with an attack may delay absorption. Bioavailability after oral dosing is 50%, with approximately linear pharmacokinetics across the therapeutic dose range. Eletriptan in oral doses of 40 mg and 80 mg has shown significant efficacy in controlled studies versus placebo at both 1 and 2 hours after dosing in treating the full range of migraine symptoms, including headache pain, nausea, photophobia, phonophobia, and functional response.

A previously published, placebo-controlled, head-to-head comparator study found eletriptan to have superior efficacy to oral sumatriptan 100 mg in treating a single acute migraine attack. The goal of the current study was to extend the findings of that study by examin
Table 1 Bioequivalence of encapsulated and unencapsulated sumatriptan

<table>
<thead>
<tr>
<th>Sumatriptan formulation</th>
<th>AUC&lt;sub&gt;0&lt;/sub&gt;&lt;sup&gt;→&lt;/sup&gt; [ng/mL · h]</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; [ng/mL]</th>
</tr>
</thead>
<tbody>
<tr>
<td>100-mg tablets, n = 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encapsulated, mean ± SD</td>
<td>204 ± 54.7</td>
<td>46.4 ± 13.5</td>
</tr>
<tr>
<td>Unencapsulated, mean ± SD</td>
<td>209 ± 54.0</td>
<td>51.1 ± 16.7</td>
</tr>
<tr>
<td>Ratio of encapsulated/unencapsulated (90% CI)</td>
<td>0.97 (0.910–1.029)</td>
<td>0.91 (0.836–0.998)</td>
</tr>
<tr>
<td>50-mg tablets, n = 34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encapsulated, mean ± SD</td>
<td>137 ± 41.3</td>
<td>33 ± 10.0</td>
</tr>
<tr>
<td>Unencapsulated, mean ± SD</td>
<td>139 ± 40.3</td>
<td>35.4 ± 10.6</td>
</tr>
<tr>
<td>Ratio of encapsulated/unencapsulated (90% CI)</td>
<td>0.99 (0.958–1.025)</td>
<td>0.93 (0.870–1.001)</td>
</tr>
</tbody>
</table>

The US Food and Drug Administration guidelines for bioequivalence specify the calculation of a 90% CI for the ratio of the geometric mean pharmacokinetic parameters (AUC and C<sub>max</sub>) of a new vs old formulation of a drug. If the ratios (±90% CI) fall within the 0.80 to 1.25 range, then the new formulation is said to be bioequivalent to the old formulation.

AUC = area under the curve; C<sub>max</sub> = maximum concentration.

The study was conducted in compliance with ethical principles in accordance with the Declaration of Helsinki, 1989.

Study treatment. Patients were randomly assigned to take eletriptan (40 mg or 80 mg), sumatriptan (50 mg or 100 mg), or placebo in a 2:2:2:1 ratio. The study was double-blinded, using a standard double-dummy design whereby eletriptan tablets were matched to placebo tablets, and sumatriptan, supplied in a thin gelatin capsule, was matched to its own placebo. Encapsulated sumatriptan was shown to have similar in vitro dissolution rates when compared with the commercially available formulation (Pfizer, data on file). In addition, the bioequivalence of the encapsulated formulation of sumatriptan to the unencapsulated commercial tablets was confirmed in a study consistent with Food and Drug Administration and EMEA guidelines (table 1). The bioequivalence of encapsulated sumatriptan in the current bioequivalence study was consistent with the results of a previous study by Fuseau et al. of a different capsule formulation based on standard bioequivalence criteria.

Study procedures. Patients were given a physical examination after a medical history had been taken. Patients received a migraine diary to take home with their study medication and were asked to record the time course of their symptoms, as well as any adverse events or need for concomitant medications. Patients were instructed to take a dose of study medication as soon as possible and within 6 hours of onset of the next migraine attack if the headache was moderate to severe in intensity and was not decreasing in intensity; if no other analgesic or antiemetic had been taken in the previous 6 hours; if no sumatriptan, ergotamine, or similar agent had been taken in the previous 48 hours; and if any aura phase had ended. Patients recorded their symptoms in the diary immediately before taking medication and at 0.5, 1, 2, 4, and 24 hours afterwards.

Patients were permitted to take a second, blinded, randomized dose of study medication if there was no response to treatment after 2 hours, or if there was a recurrence of headache (initial improvement to mild or no pain at 2 hours, followed by a return to moderate or severe pain within 24 hours of initial treatment). Data on the responses to the second dose will be presented in a separate publication, as they were prospectively collected in the de-
development program as part of a planned meta-analysis. If there was no improvement after a second dose, patients were permitted to take rescue medication, which could not include sumatriptan, ergotamine, or ergotamine-related compounds, from 2 hours after the second dose.

From 1 to 7 days after the first attack, patients returned for an assessment and were issued study medication and diaries for the next two attacks. Patients received the same study medication for the first, second, and third attacks. Patients were treated for up to three attacks or were withdrawn after 12 weeks (whichever came first). This form of protocol accounts for the large proportion of patients classified as withdrawals.

**Assessments and endpoints.** The primary endpoint of this study was the headache response at 1 hour after treatment of the first attack. Secondary endpoints measured at 0.5, 1, 2, 4, and 24 hours after treatment were headache severity, pain-free response, functional response, and presence or absence of nausea, photophobia, and phonophobia. Additional secondary endpoints included consistency of response and recurrence of headache, as defined here; use of a second dose of study medication; use of rescue medications; and treatment acceptability.

The severity of headache pain was assessed on a four-point scale from 0 (pain absent) to 1 (mild pain), 2 (moderate pain), and 3 (severe pain). Headache response was defined as an improvement from headache severity grade 2 to 3 at baseline to grade 0 or 1 after dosing. Headache recurrence was defined as initial improvement to mild or no pain at 2 hours followed by a return to moderate or severe pain within 24 hours of initial treatment.

Sustained headache and sustained pain-free response were also assessed post hoc. Sustained headache response was defined as headache response by 2 hours (severe or moderate pain to mild or no pain) with no recurrence (return of original headache) and no use of rescue medications within 24 hours. Sustained pain-free response was defined as going from severe or moderate pain to no pain by 2 hours, with no recurrence and no use of rescue medications within 24 hours.

The functional impairment of normal work and household activities was measured on a four-point scale. A functional response was defined as an improvement from a baseline severity score of severely reduced activity or bed rest to normal functioning or reduced activity at 2 hours after dosing.

Migraine-associated symptoms of nausea, photophobia, phonophobia, and vomiting were recorded as being present or absent.

The subjective acceptability of treatment was assessed by asking patients the question, “Given the choice between this and any other medication to treat a migraine attack, would you take this again?” Patients were questioned 24 hours after taking the first dose, or 24 hours after the second dose if one was taken.

Safety and laboratory tests. A full medical history was taken on entry to the study, and patients were given a medical examination, including pulse rate and blood pressure, routine laboratory measurements of hematology and clinical chemistry, and 12-lead EKG. These tests were repeated when patients visited the clinic after the first and third attacks.

All adverse events occurring at the time of, or following, treatment were recorded, regardless of their apparent relationship to study medication. Adverse events for a particular attack were considered to have occurred if they happened from the time the medication was taken until 7 days afterwards. If another attack (not a recurrence) occurred before the end of the 7-day period, the window for an adverse event from the previous attack was closed and a new one begun.

**Statistics and analyses.** The sample size per group was calculated to detect a difference between groups with 80% power. Assuming 1-hour headache responder rates of 14% for the placebo group, 19% for both sumatriptan groups, 37% for the eletriptan 40-mg group, and 41% for the eletriptan 80-mg group, 128 patients per active treatment group and 64 in the placebo group were required. These responder rates were based on data from a previous study. The sample sizes were increased to 200 per active treatment group and 100 patients in the placebo group in order to collect sufficient data for the secondary objective of determining the effect of a second dose of eletriptan.

All patients randomly assigned to receive study medication were included in an intent-to-treat analysis for both primary and secondary endpoints. The incidence rates or responder rates were analyzed using logistic regression with adjustments for covariates. Two families of comparisons were made using a step-down procedure: between eletriptan groups and placebo groups and between eletriptan and sumatriptan groups. In the first family, the first comparison was between eletriptan 80 mg and placebo. If this contrast was significant at the $p < 0.05$ level, a comparison between eletriptan 40 mg and placebo was made at the $p < 0.05$ level. For the second family, the first comparison was between the eletriptan 80-mg group and the sumatriptan 50-mg group. If this was significant at the 5% level, comparisons of eletriptan 80 mg versus sumatriptan 100 mg and eletriptan 40 mg versus sumatriptan 50 mg were performed. If either of these was significant at $p < 0.025$, the comparison between eletriptan 40 mg and sumatriptan 100 mg was made at the $p < 0.05$ level. No comparisons were performed between eletriptan groups, between sumatriptan dose groups, or between sumatriptan and placebo.

**Results.** Patient demographics and baseline characteristics. A total of 1,013 eligible patients were identified on screening evaluation; 1,008 were randomly assigned and 774 were treated (figure 1). These 774 patients constituted the safety evaluable sample. Of the 234 patients randomly assigned, but not treated, the majority (approximately 60%) did not have a migraine attack within the 12-week study period. Other reasons included patients who did not treat a migraine attack, were lost to followup, and withdrew consent. All five treatment groups were similar with respect to baseline demographic and clinical features (table 2). The typical study patient was a woman with a long history of moderate-to-severe migraine headaches that usually occurred without an aura and had one or more associated symptoms, such as nausea, photophobia, and phonophobia, as well as a high degree of functional impairment.

Headache response and pain-free response. At 1 hour after treatment of the first attack, the headache response rates (figure 2A) in both eletriptan treatment groups were significantly higher than the rate in the placebo group.
The 1-hour response rate for the 80-mg dose of eletriptan was higher than for the 50-mg dose of sumatriptan (37% [58/157] versus 24% [43/177]; p < 0.05). The eletriptan 80-mg response rate was comparable to the 100-mg dose of sumatriptan (37% [58/157] versus 27% [44/165]; p = 0.053). The 40-mg eletriptan dose gave a response rate of 30% (52/172), which was superior to placebo (p < 0.01). At 2 hours after treatment (see figure 2B), the headache response rates in both eletriptan groups (64% [108/169] for eletriptan 40 mg and 67% [107/160] for eletriptan 80 mg) were higher than both sumatriptan groups (50% [88/176] for sumatriptan 50 mg, 53% [85/160] for sumatriptan 100 mg), and 31% [25/80] for placebo; p < 0.01 for both eletriptan doses versus sumatriptan 50 mg; p < 0.05 for both doses versus sumatriptan 100 mg; and p < 0.0001 versus placebo. Significantly more patients achieved a pain-free state by 2 hours after treatment with either 40 mg (31% [52/169]) or 80 mg of eletriptan (37% [59/160]) compared with either sumatriptan 50 mg (19% [33/169]), sumatriptan 100 mg (18% [29/160]), or placebo (4% [3/80]) (see figure 2, A and B).

Need for second dose and use of rescue medication. The protocol design permitted patients to take a second dose of study drug either for nonresponse to the initial dose or for the treatment of headache recurrence. The proportion of patients reporting headache recurrence was 19% (21/109) for eletriptan 40 mg, 16% (17/105) for eletriptan 80 mg, 26% (23/89) for sumatriptan 50 mg, 27% (25/92) for sumatriptan 100 mg, and 25% (6/24) for placebo. The proportion of patients who took a second dose of study medication for the first attack was 39% (69/175) for eletriptan 40 mg, 36% (59/164) for eletriptan 80 mg, 56% (101/181) for sumatriptan 50 mg, 53% (89/169) for sumatriptan 100 mg, and 74% (62/84) for placebo.

Rescue medication was also permitted, beginning at least 2 hours after taking a second dose of study medication, for patients who reported either a headache recurrence or continued nonresponse. The proportion of patients who took rescue medication was 15% (26/175) for eletriptan 40 mg, 13% (22/164) for eletriptan 80 mg, 28% (50/181) for sumatriptan 50 mg, 25% (42/169) for sumatriptan 100 mg, and 48% (40/84) for placebo.

Sustained response. The difference in 2-hour headache response, as well as rates of recurrence and the use of rescue medication, resulted in a significantly higher level of sustained response for eletriptan compared with both sumatriptan and placebo (figure 3). The proportion of patients reporting sustained headache response was 50% (88/175) for eletriptan 40 mg, 54% (86/160) for eletriptan 80 mg, 34% (62/180) for sumatriptan 50 mg, 38% (64/169) for sumatriptan 100 mg, and 21% (18/84) for placebo. Sustained pain-free rates (see figure 3) were also higher than placebo (4% [3/84]) for eletriptan 40 mg (24% [42/175]; p = 0.0005), eletriptan 80 mg (29% [47/161]; p = 0.0001), and

### Table 2 Baseline demographic and clinical characteristics of study patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo</th>
<th>Sumatriptan 50 mg</th>
<th>Sumatriptan 100 mg</th>
<th>Eletriptan 40 mg</th>
<th>Eletriptan 80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean ± SD</td>
<td>37.5 ± 10.9</td>
<td>37.4 ± 10.2</td>
<td>38.2 ± 10.2</td>
<td>38.0 ± 10.1</td>
<td>39.9 ± 10.7</td>
</tr>
<tr>
<td>Sex, n/N (%)</td>
<td>75/84 (89)</td>
<td>162/181 (90)</td>
<td>148/170 (87)</td>
<td>154/175 (88)</td>
<td>142/164 (87)</td>
</tr>
<tr>
<td>Women</td>
<td>9/84 (11)</td>
<td>19/181 (10)</td>
<td>22/170 (13)</td>
<td>21/175 (12)</td>
<td>22/164 (13)</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine diagnosis, n/N (%)</td>
<td>10/84 (12)</td>
<td>19/181 (10)</td>
<td>25/170 (15)</td>
<td>24/175 (14)</td>
<td>16/164 (10)</td>
</tr>
<tr>
<td>With aura</td>
<td>53/84 (63)</td>
<td>129/181 (71)</td>
<td>108/170 (64)</td>
<td>99/175 (57)</td>
<td>111/164 (68)</td>
</tr>
<tr>
<td>Without aura</td>
<td>21/84 (25)</td>
<td>33/181 (18)</td>
<td>37/170 (22)</td>
<td>52/175 (30)</td>
<td>37/164 (23)</td>
</tr>
<tr>
<td>Both with and without aura</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional impairment, first attack, n/N (%)</td>
<td>72/84 (86)</td>
<td>165/180 (92)</td>
<td>153/168 (91)</td>
<td>157/174 (90)</td>
<td>139/164 (85)</td>
</tr>
</tbody>
</table>
Figure 2. (A) Percentage of patients with headache response at 1 hour after treatment, by treatment group. White bars denote headache response; black bars, pain-free response. Significance of response: *p < 0.05 versus placebo; **p < 0.005 versus placebo; ***p ≤ 0.001 versus placebo; †p < 0.05 versus sumatriptan 50 mg; ‡p < 0.005 versus sumatriptan 50 mg; ††p < 0.001 versus sumatriptan 50 mg; †‡p < 0.0005 versus sumatriptan 100 mg; ‡‡p < 0.0005 versus sumatriptan 100 mg. Suma = sumatriptan; Ele = eletriptan.

Figure 3. Sustained headache response and pain-free response at 24 hours, by treatment group. White bars indicate sustained headache response, black bars indicate sustained pain-free response. Significance of response: *p < 0.05 versus placebo; **p < 0.001 versus placebo; ***p ≤ 0.0001 versus placebo; ††p < 0.005 versus sumatriptan 50 mg; ‡‡p < 0.0005 versus sumatriptan 50 mg; †††p < 0.005 versus sumatriptan 100 mg; ‡‡‡p < 0.005 versus sumatriptan 100 mg.

Sumatriptan 100 mg (14% [23/169]; p < 0.05), but not for sumatriptan 50 mg (11% [20/180]). Treatment with eletriptan 40 mg resulted in higher sustained headache response and pain-free response rates, respectively, than both sumatriptan 50 mg (p < 0.005 for both comparisons) and sumatriptan 100 mg (p < 0.05 for both comparisons). Similarly, treatment with eletriptan 80 mg also showed higher sustained headache response and pain-free response rates than both sumatriptan 50 mg (p < 0.0005 and p < 0.0001, respectively) and sumatriptan 100 mg (p < 0.005 and p < 0.001, respectively).

Reduction in migraine-associated symptoms. To assess the efficacy of study treatment in reducing migraine-associated symptoms, we examined the presence of each symptom at baseline and at 2 hours after treatment. Patients were included if they reported nausea, photophobia, or phonophobia at baseline. Patients were also included who may not have had a symptom at baseline, but who may have developed a symptom over the course of treatment due to either illness progression or adverse events.

The 40- and 80-mg doses of eletriptan were significantly more effective than placebo in reducing the associated migraine symptoms of nausea, photophobia, and phonophobia (table 3). Only 10% (78/765) of patients reported vomiting with their attack at baseline. This incidence rate is too small to make meaningful comparisons between the treatment groups.

Improvement in functioning. Each dose of eletriptan was significantly more effective than placebo in alleviating functional impairment at 2 hours after treatment (figure 4). Functional improvement was also greater for the 40-mg dose of eletriptan (63% [96/152]) than for both sumatriptan 50 mg (46% [74/161]; p < 0.005) and sumatriptan 100 mg (46% [67/145]; p < 0.005). Functional improvement was noted as early as 1 hour in 30% (47/155) of patients treated with eletriptan 40 mg and in 34% (45/134) of patients treated with eletriptan 80 mg.

Consistency of response. Consistency of response was defined using two separate criteria: headache response at 2 hours in at least two of three attacks or in all three attacks. The percentage of patients showing consistency using the first criterion, response in at least two of three attacks (figure 5), was higher for eletriptan 80 mg (79% [64/81]) compared with sumatriptan 50 mg (53% [47/89]; p < 0.0005), sumatriptan 100 mg (61% [48/79]; p < 0.05), and placebo (29% [10/35]; p < 0.0001). Consistency of response (two of three, or more) was superior for eletriptan 40 mg (63% [52/82]) compared with placebo (p < 0.001). Using the more stringent three-of-three response criteria, consistency of response was higher for eletriptan 80 mg (49% [40/81]) compared with sumatriptan 50 mg (22% [20/89]; p < 0.0005), sumatriptan 100 mg (24% [19/79]; p < 0.005), and placebo (9% [3/35]; p < 0.0005). Again, consistency of response (three of three) was superior for eletriptan 40 mg (37% [30/82]) compared with placebo (p < 0.005) and sumatriptan 50 mg (p < 0.05).

Safety and tolerability. All 774 patients who received treatment with study drug were included in the analysis of adverse events. Adverse events occurring in >5% of patients in at least one treatment group, regardless of causality, following the first dose of medication for the first
attack are shown in Table 4. Most adverse events were mild or moderate in severity. Seven patients withdrew from the study due to treatment-emergent adverse events (one each from eletriptan 40 mg/40 mg, eletriptan 40 mg/placebo, eletriptan 80 mg/placebo, sumatriptan 50 mg/50 mg, sumatriptan 100 mg/100 mg treatments, and two patients treated with placebo/placebo). There were no serious treatment-related adverse events.

Laboratory abnormalities were observed at a similar rate in all study groups. No serious laboratory abnormalities were observed, and no patients were withdrawn from the trial due to laboratory abnormalities.

Acceptability of treatment. Following treatment, patients were asked whether they would choose to take the study medication again. Among patients who took one or two doses of study medication, 80% (107/133) of those taking eletriptan 40 mg as a first dose and 78% (104/133) of those taking eletriptan 80 mg found it acceptable, compared with 67% of those taking 50 mg (89/132) or 100 mg (83/123) sumatriptan as a first dose, and 43% (27/63) of those taking placebo. The acceptability of both eletriptan doses was higher than that of sumatriptan 50 mg (both comparisons) and placebo (p < 0.0001 both comparisons), whereas eletriptan 40 mg showed an improvement compared with sumatriptan 100 mg (p < 0.05).

Discussion. The results of the current study confirm the efficacy of both the 40- and 80-mg doses of eletriptan across the key clinical dimensions of migraine, including headache response, relief of associated symptoms, and pain-free response. In addition, the 40- and 80-mg doses of eletriptan showed significant superiority to both doses of sumatriptan in sustained headache response and pain-free response up to 24 hours. The multidimensional efficacy of both doses of eletriptan was reflected in significant improvement in functioning and high levels of patient acceptance.

The primary outcome of the study was headache response at 1 hour after treatment. Based on this criterion, eletriptan 80 mg achieved significance versus sumatriptan 50 mg (see figure 2A). Subsequent

![Figure 4](image-url)

Figure 4. Percentage of patients with a functional response at 1 and 2 hours after treatment, by treatment group. White bars denote 1-hour response; black bars, 2-hour response. Significance of response: *p < 0.05 versus placebo; **p < 0.005 versus placebo; ***p < 0.0001 versus placebo; †p < 0.05 versus sumatriptan 50 mg; ††p < 0.005 versus sumatriptan 50 mg; †††p < 0.0001 versus sumatriptan 50 mg; †††p < 0.005 versus sumatriptan 100 mg; ‡p < 0.005 versus sumatriptan 100 mg.

![Figure 5](image-url)

Figure 5. Percentage of patients with a headache response in two of three attacks and three of three attacks, by treatment group. White bars indicate a response in two of three attacks; black bars indicate a response in three of three attacks. Significance of response: *p < 0.05 versus placebo; **p < 0.005 versus placebo; ***p < 0.0001 versus placebo; †p < 0.05 versus sumatriptan 50 mg; ††p < 0.005 versus sumatriptan 50 mg; †††p < 0.0005 versus sumatriptan 50 mg; †††p < 0.005 versus sumatriptan 100 mg; ‡‡p < 0.005 versus sumatriptan 100 mg.

### Table 3 Effect of eletriptan, sumatriptan, and placebo on the presence of migraine-associated symptoms by 2 hours

<table>
<thead>
<tr>
<th>Treatment (n at baseline/n at 2 h)</th>
<th>Nausea</th>
<th>Photophobia</th>
<th>Phonophobia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>2 h</td>
<td>Baseline</td>
</tr>
<tr>
<td>Placebo 57/84 (68)</td>
<td>42/80 (53)</td>
<td>63/84 (75)</td>
<td>46/80 (58)</td>
</tr>
<tr>
<td>Sumatriptan 50 mg 114/181 (63)</td>
<td>70/174 (40)</td>
<td>134/179 (75)</td>
<td>85/174 (49)</td>
</tr>
<tr>
<td>Sumatriptan 100 mg 122/169 (72)</td>
<td>66/159 (42)</td>
<td>125/167 (75)</td>
<td>73/159 (46)</td>
</tr>
<tr>
<td>Eletriptan 40 mg 113/174 (65)</td>
<td>48/167 (29)</td>
<td>138/175 (79)</td>
<td>67/167 (40)</td>
</tr>
<tr>
<td>Eletriptan 80 mg 109/164 (66)</td>
<td>55/159 (35)</td>
<td>116/164 (71)</td>
<td>49/161 (30)</td>
</tr>
</tbody>
</table>

Values are n/N (%) for first attack, first dose.

Significance of eletriptan response vs sumatriptan 50 mg: †p < 0.05; ††p < 0.01; †††p < 0.001; vs sumatriptan 100 mg: ‡p < 0.05; ‡‡p < 0.01; ‡‡‡p < 0.001; vs placebo: *p < 0.05; **p < 0.01; ***p < 0.001.
to the completion of this study, IHS guidelines for conducting clinical trials in migraine have recommended 2-hour pain-free response as a more clinically relevant primary efficacy measure for acute treatment studies. Using this outcome, both eletriptan 40 mg and 80 mg demonstrated a significant efficacy advantage over the 50- and 100-mg doses of sumatriptan (see figure 2B). Furthermore, on the most widely used primary outcome, headache response at 2 hours, both doses of eletriptan demonstrated significantly greater responses when compared with the 50- and 100-mg doses of sumatriptan (see figure 2B). These results extend the findings of a previous head-to-head comparator study that found a significant 1- and 2-hour efficacy advantage for eletriptan 80 mg compared with sumatriptan 100 mg.

Sustained response, especially sustained pain-free response, has recently emerged as a stringent outcome criterion in recognition of the extent to which relapse is a major problem with effective migraine treatments. The current study confirms results reported previously showing that both the 40- and 80-mg doses of eletriptan are significantly superior to oral sumatriptan in achieving and sustaining both headache response and pain-free response at 24 hours (see figure 3). The sustained pain-free response rates achieved in the current trial, 24% for eletriptan 40 mg and 29% for eletriptan 80 mg, are among the highest that have been reported, especially when the low placebo rate is taken into account.

Relatively few studies have been published that report data on consistency of response across multiple attacks using a randomized, double-blind, placebo-controlled design. As the IHS clinical trials guidelines point out, long-term studies that are not placebo controlled are not optimal for evaluating consistency of response. To our knowledge, this study provides the first data evaluating consistency of response for two triptans based on a double-blind, placebo-controlled, head-to-head comparison. Both doses of eletriptan and sumatriptan achieved significantly higher headache response rates than placebo on all three migraine attacks treated in the study. Eletriptan 80 mg demonstrated significantly superior consistency of response compared with both the 50- and the 100-mg doses of sumatriptan in three of three attacks (see figure 5).

The ability to achieve and sustain headache response and pain-free response and the ability to consistently provide pain relief are important components of the management of migraine headaches. The multi-dimensional nature of a migraine attack requires that effective acute treatment also provide relief of associated symptoms and restoration of normative levels of functioning. The results of the current study demonstrate that both doses of eletriptan rapidly provided relief of nausea, photophobia, and phonophobia when compared with placebo (see table 3). At 2 hours, treatment with the 80-mg dose of eletriptan resulted in significantly greater relief of photophobia and phonophobia than either dose of sumatriptan. Similarly, the 40-mg dose of eletriptan also resulted in significantly greater relief of nausea and photophobia than the 50-mg dose of sumatriptan, as well as significantly greater relief of nausea and phonophobia compared with the 100-mg dose of sumatriptan. The net effect of 2-hour relief of both headache pain and associated symptoms was a significant return to normal levels of functioning for both doses of eletriptan and both doses of sumatriptan compared with placebo (see figure 4). No dose-response effect was evident for either active drug. The lack of significant dose-response effects on functional improve-

### Table 4 All-causality adverse events reported (≥5% incidence in any group) within 2 hours of the dose

<table>
<thead>
<tr>
<th>Adverse events, first attack, first dose</th>
<th>Placebo, n = 84</th>
<th>Sumatriptan 50 mg, n = 181</th>
<th>Sumatriptan 100 mg, n = 169</th>
<th>Eletriptan 40 mg, n = 175</th>
<th>Eletriptan 80 mg, n = 164</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthenia</td>
<td>2 (2) 3 (4)</td>
<td>9 (5) 11 (6)</td>
<td>7 (4) 14 (8)</td>
<td>15 (9) 18 (11)</td>
<td>15 (9) 18 (11)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (2) 2 (2)</td>
<td>9 (5) 13 (7)</td>
<td>8 (5) 9 (5)</td>
<td>15 (9) 18 (11)</td>
<td>15 (9) 18 (11)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (2) 2 (2)</td>
<td>11 (6) 12 (7)</td>
<td>5 (3) 9 (5)</td>
<td>15 (9) 20 (12)</td>
<td>6 (4) 7 (4)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2 (2) 4 (5)</td>
<td>2 (1) 5 (3)</td>
<td>3 (2) 5 (3)</td>
<td>12 (7) 12 (7)</td>
<td>6 (4) 7 (4)</td>
</tr>
<tr>
<td>Chest symptoms*</td>
<td>2 (2) 3 (4)</td>
<td>2 (1) 4 (2)</td>
<td>0 (0) 1 (1)</td>
<td>1 (1) 2 (1)</td>
<td>7 (4) 9 (5)</td>
</tr>
<tr>
<td>Sweating</td>
<td>2 (2) 3 (4)</td>
<td>0 (0) 0 (0)</td>
<td>3 (2) 4 (2)</td>
<td>8 (5) 10 (6)</td>
<td>3 (2) 5 (3)</td>
</tr>
<tr>
<td>Discontinuations†</td>
<td>2 (2.4) 1 (0.6)</td>
<td>1 (0.6) 1 (0.6)</td>
<td>2 (1.1) 1 (0.6)</td>
<td>1 (0.6)</td>
<td></td>
</tr>
</tbody>
</table>

Values are n (%).

The total columns refer to adverse events that occurred from the time the first dose was taken until 7 days afterward. If another attack (not a recurrence) occurred before the end of the 7-day period, the window for an adverse event from the first attack was closed at that time.

* Incidence ≥4% in any group.
† Due to treatment-related adverse events.
ment is consistent with previously published literature for sumatriptan. In contrast, there is previous evidence for a dose-response effect on functional improvement for eletriptan, so the reasons for the lack of dose-response effect in the current study are unclear.

Overall, both sumatriptan and eletriptan were well tolerated. A similar pattern of treatment-related adverse events was observed in the eletriptan and sumatriptan groups and showed modest increases with increasing dose. Adverse events were generally mild or moderate in severity and transient in nature. The high level of tolerability is confirmed by a 78% (104/133) to 80% (107/133) treatment acceptability rating for both doses of eletriptan, which compares favorably with the 67% (89/132 and 83/123) acceptability rating for both sumatriptan 50 mg and 100 mg.

In summary, the results of the current study provide evidence for the efficacy, safety, and tolerability of oral eletriptan 40 mg and 80 mg in the acute treatment of migraine headache and associated symptoms. Acute symptomatic improvement translated into significant improvement in the ability to function. Both doses of eletriptan demonstrated significantly higher rates of sustained headache and pain-free response when compared with either dose of sumatriptan, which was highly correlated with less need for additional treatment with eletriptan. Finally, the current study provides some of the only data available regarding the consistency of response of two triptans based on head-to-head comparator data, with the 80-mg dose of eletriptan demonstrating significantly more consistent efficacy than sumatriptan.

References