HEADACHE CARE
VOL. 3, NO. 1, 2006, 3–10

1742-3430
doi:10.1185/174234305X75207

ORIGINAL ARTICLE

Time to onset of efficacy of the fast-disintegrating/rapid-release formulation of sumatriptan tablets in the acute treatment of migraine

Reto Agosti[a], Carl G. H. Dahlöf[b], Wim M. Mulleners[c], Martin W. Jones[d], Chris Webster[e] and Colleen Few[e]

[a] *Headache Center Hirslanden Zürich, Zürich, Switzerland*

[b] *Gothenburg Migraine Clinic, Gothenburg, Sweden*

[c] *Department of Neurology, Atrium Medical Center, Heerlen, The Netherlands*

[d] *GlaxoSmithKline, Greenford, United Kingdom*

[e] *GlaxoSmithKline, Research Triangle Park, North Carolina, United States*

Address for correspondence: **Dr Reto Agosti, Headache Center Hirslanden, Kopfwehzentrum Hirslanden Zürich, Münchhaldenstr. 33, 8008 Zürich, Switzerland. Tel.: +41-43-499-13-30; Fax: +41-43-499-13-39; email: reto.agosti@kopfwww.ch**

Key words: **Headache – Migraine – Sumatriptan**

ABSTRACT

Objective: The time to onset of relief and to pain-free response with the fast-disintegrating/rapid-release form of sumatriptan tablets 50 mg and 100 mg were estimated from a randomized, double-blind, parallel-group, placebo-controlled study conducted in 119 European centers.

Methods: Sumatriptan 50 mg ($n = 454$), 100 mg ($n = 440$) or placebo ($n = 436$) was taken on an outpatient basis for a single moderate or severe migraine attack. Patients used a personal digital assistant (PDA) to record time of dosing, time of mild pain, and time of no pain (all in real time, a continuous variable). This method allowed calculation of elapsed times to mild and no pain, which were used to calculate times to onset of relief and pain-free response (defined as the earliest times at which statistically significant separation from placebo was achieved and maintained through 2 hours postdose for headache relief and pain-free response, respectively).

Results: Sumatriptan was significantly ($p \leq 0.05$) more effective than the placebo for pain relief as early as 17 minutes postdose with 100 mg and 30 minutes postdose with 50 mg, and, for pain-free response, as early as 39 minutes postdose with 100 mg and 49 minutes postdose with 50 mg. By 2 hours postdose, the cumulative percentages of patients with pain relief were 72% for 100 mg and 65% for 50 mg compared with 38% for placebo ($p < 0.001$ each dose versus placebo). The corresponding values for pain-free response by 2 hours were 47% for 100 mg, 39% for 50 mg, and 12% for placebo ($p < 0.001$ each dose versus placebo). Significantly more patients treated with either sumatriptan dose compared with placebo were migraine-free 2 hours postdose and experienced sustained pain relief and sustained pain-free response over 24 hours ($p < 0.001$ each dose versus placebo), and fewer patients had headache recurrence. The only drug-related adverse events reported in more than 2% of patients in a treatment group were nausea and paresthesia.

Conclusions: Onset of relief with the fast-disintegrating/rapid-release formulation of sumatriptan was observed as early as 17 minutes for 100 mg and as early as 30 minutes for 50 mg. Efficacy was maintained, compared with placebo, through the 24-hour postdose period. The fast-disintegrating/rapid-release formulation was well tolerated. This formulation of sumatriptan provides rapid pain relief in an oral tablet, the patients' preferred dosing form.

Introduction

Rapid onset of relief of migraine pain is a key determinant of the prompt restoration of functional ability and patients' satisfaction with migraine therapy[1–5]. The sumatriptan fast-disintegrating/rapid-release tablet has been developed as a reformulated product to allow for improved disintegration, while remaining bioequivalent to the conventional sumatriptan tablet[6,7] which relies on tablet surface erosion in the stomach to initiate the release of sumatriptan. The fast-disintegrating/rapid-release form of sumatriptan tablets has been developed to enhance tablet disintegration and drug dispersion, and potentially improve absorption in the context of gastric stasis that can accompany migraine[8,9]. The fast-disintegrating/rapid-release formulation is an oral tablet, which patients prefer[6,7]. In an *in vitro* study under conditions simulating gastric stasis, the fast-disintegrating/rapid-release tablet showed five times faster dissolution than the conventional tablet[10].

The improved disintegration and dispersion may lead to better absorption than with conventional tablets; a possibility supported by results of two pharmacokinetic studies[10,11]. One study employed gamma scintigraphy to image the gastrointestinal tracts of migraineurs given radiolabeled sumatriptan conventional tablets and sumatriptan fast-disintegrating/rapid-release tablets in a crossover fashion[11]. Compared to the conventional tablet, the mean time to tablet disintegration for the fast-disintegrating/rapid-release formulation was six times faster (6.2 minutes versus 38.8 minutes); the mean time to 50% gastric emptying was approximately 30 minutes faster; and plasma concentrations were more than five times higher 20 minutes postdose. In another pharmacokinetic study, the fast-disintegrating/rapid-release tablet was absorbed slightly more quickly than the conventional tablet during the early (0–2 hours) postdose period in healthy volunteers[10]. For the rapid-release formulation of sumatriptan, the sumatriptan t_{max} was estimated to be, on average, 10 minutes earlier for 50 mg and 15 minutes earlier for 100 mg, compared with the conventional tablet. However, the two formulations were shown to be bioequivalent as demonstrated by the finding that 24-hour exposure to sumatriptan did not differ between the fast-disintegrating/rapid-release form and the conventional tablet[10]. Whether the fast-disintegrating formulation also has improved absorption interictally in migraineurs remains to be determined. The fast-disintegrating/rapid-release tablet has been demonstrated to be effective for migraine. In a randomized, double-blind clinical trial of patients treating a migraine early, when pain was still mild (early intervention), the fast-disintegrating/rapid-release tablet was more effective than placebo for pain-free response and migraine-free response (no pain and no associated symptoms) 2 hours postdose, sustained pain-free response 2 through 24 hours postdose, and improvement of functional ability and reduction of productivity loss through 24 hours postdose[12,13]. Pain-free results 2 hours after dosing (primary endpoint) were reported by 51% and 66% of patients treated with sumatriptan tablets 50 mg and 100 mg, respectively, compared with 20% of patients treated with placebo. In placebo-controlled early-intervention studies with conventional sumatriptan tablets[14], pain-free response 2 hours after dosing was observed in 50% and 57% of patients taking the 50 mg and 100 mg doses, respectively, compared with 29% of placebo recipients.

In these early-intervention studies using the fast-disintegrating/rapid-release tablet and the conventional tablet[12,14], freedom from pain was measured as a discrete variable at specific postdose time points (i.e., 30 minutes, 1 hour, and 2 hours). This method of using specific time points, the norm in migraine clinical trials, is not optimal for estimating the time to onset of relief or pain-free response as onset times do not necessarily correspond with the specific time points sampled. To obtain a sensitive assessment of the time to onset of relief with the fast-disintegrating/rapid-release tablet, two randomized, double-blind, placebo-controlled studies assessed the times between dosing and onset of relief and pain-free response as continuous variables in real time (in minutes) through the patients' use of a hand-held, programmed electronic diary (i.e., a personal digital assistant [PDA])[15]. The results of the analyses of the combined data from these studies, one conducted in Europe and another conducted in the United States and Canada, are reported elsewhere[15]. This paper reports the results from the randomized, double-blind, placebo-controlled study conducted in Europe.

Methods

Patients

Males and females were eligible if they were between 18 and 65 years of age, had at least a 6-month history of migraine, with or without aura, as defined by the 1988 International Headache Society criteria[16], had one to six migraines monthly during the 3 months preceding the screening visit, and had a history of moderate to severe pain during migraine attacks. Females with childbearing potential were excluded, unless they had a negative pregnancy test at screening and agreed to use contraception throughout the study. General exclusion criteria included uncontrolled hypertension (sitting diastolic blood pressure > 95 mmHg or systolic blood

pressure > 160 mmHg) at screening, a history of epilepsy or seizures within 5 years before screening, confirmed or suspected cardiovascular or cerebrovascular disease, and basilar or hemiplegic migraine or headache on 15 or more days per month in any of the 3 months before screening. Other exclusion criteria included the use of migraine prophylactic medication containing ergotamine, an ergot derivative, or methysergide, use of a monoamine oxidase inhibitor within 2 weeks before screening, and, in countries where the combination of a selective serotonin reuptake inhibitor and a triptan is not allowed, the need for a selective serotonin receptor inhibitor. All patients provided written informed consent.

Procedures

Ethics committees or institutional review boards approved the protocol for this randomized, double-blind, placebo-controlled clinical trial (GlaxoSmithKline protocol SUM30053) for each of the 119 European study sites. The results of the analyses of combined data from protocol SUM30053 and an identically designed study conducted in the United States and Canada (GlaxoSmithKline protocol SUM30047), as well as selected data from each individual study, are reported elsewhere[15].

Eligible patients were randomized 1:1:1 to receive the fast-disintegrating/rapid-release form of sumatriptan tablets 50 mg, 100 mg, or placebo for the outpatient treatment of a single migraine attack characterized by moderate or severe pain. Prohibited medications included ergotamine-containing and ergot-type medications, as well as triptans (other than study medication), within 24 hours of the use of study medication, analgesics, antiemetics, and non-triptan acute migraine medications from 6 hours before to 2 hours after use of study medication, and monoamine oxidase inhibitors throughout the duration of the study. Patients with headache recurrence (i.e., a return of moderate or severe pain after having no or mild pain 2 hours after the initial dose of study medication) could take a second dose of study medication, or a non-prohibited acute migraine medication, between 2 and 24 hours postdose. Patients whose pain was not reduced to none or mild within 2 hours could take a non-prohibited acute migraine medication, as rescue medication, from 2 through 24 hours postdose.

Measures

Patients were trained to use a PDA that had been pre-programmed to function as a stopwatch and electronic diary to record data, including time and date of onset of the treated migraine attack, time and date of dosing with study medication, severity of migraine pain (mild, moderate, or severe) at attack onset and immediately before dosing, time of mild pain and time of no pain, pain severity 25 minutes, 30 minutes, and 1, 2, and 4 hours postdose, the presence or absence of nausea, vomiting, photophobia, and phonophobia 2 and 4 hours postdose, any use of a second dose of study medication, and headache recurrence between 2 and 24 hours postdose. Patients returned the electronic diary, and a paper record of the use of additional rescue medications, to the clinic at a visit occurring within 1 week following the treatment of the migraine attack. At that clinic visit, patients were queried about adverse events, defined as any untoward medical occurrences experienced at any time during the study, regardless of suspected cause. For each adverse event, investigators recorded whether or not it was considered to be caused by study medication.

Statistical methods

The primary efficacy endpoint was time to onset of pain relief, defined as the earliest time at which sumatriptan tablets 100 mg were statistically significantly more effective than placebo at reducing moderate or severe predose pain to mild or no pain and that statistical significance was maintained for 2 hours after dosing. Key secondary efficacy endpoints included time to onset of pain relief with sumatriptan tablets 50 mg and time to onset of pain-free response (moderate or severe predose pain reduced to no pain) during the 2-hour period after treatment with sumatriptan tablets 100 mg or 50 mg. Kaplan–Meier survival analysis techniques were used to derive time-to-event curves for sumatriptan tablets 100 mg, 50 mg, and placebo for the cumulative percentages of patients with pain relief and pain-free response through 2 hours postdose. Differences between each active treatment and placebo in the time-to-event curves for pain relief and pain-free response were tested with two-sided log-rank tests.

A sequential testing method was employed to control for a family-wise error rate of 0.05 for analysis of the time-to-onset endpoints. A comparison must have been statistically significant for the next comparison in the following sequence to be tested: (1) time to relief through 2 hours for sumatriptan tablets 100 mg versus placebo (the primary endpoint); (2) time to pain-free response through 2 hours for sumatriptan tablets 100 mg versus placebo and time to pain relief through 2 hours for sumatriptan tablets 50 mg versus placebo (key secondary endpoints); and (3) time to pain-free response through 2 hours for sumatriptan tablets 50 mg versus placebo (key secondary endpoint).

If a significant difference was observed between an active treatment and placebo in the 0 to 2-hour time-to-relief or time-to-pain-free curves, then the time to onset of pain relief, or to pain-free response, was

identified by evaluating the differences in the curves using time points in a predetermined sequence that decreased in time. The times to onset of pain relief and to onset of pain-free response were defined as the earliest times at which the time-to-event curves for pain relief or pain-free response, respectively, for sumatriptan statistically differed from that for placebo. Once statistical significance was lost, earlier time points were not considered.

Other efficacy endpoints included the categorical measures of the following: (1) the percentage of patients migraine-free (i.e., no pain and no associated symptoms of nausea, vomiting, photophobia, or phonophobia) 2 hours postdose; (2) the percentage of patients with sustained pain-relief and sustained pain-free response (i.e., pain relief or pain-free response from 2 hours through to 24 hours postdose, with no use of a second dose of study medication or rescue medication); (3) the percentage of patients taking rescue medication or a second dose of study medication during the 24-hour postdose period; and (4) the percentage of patients with recurrence (i.e., return of moderate or severe pain within 24 hours postdose in patients with pain relief 2 hours postdose). For all of these categorical endpoints, except headache recurrence, each active treatment was compared with placebo using Fisher's exact test.

Efficacy data were analyzed for the intent-to-treat population, defined as patients who treated a migraine attack and who provided at least one postdose efficacy assessment. The study was designed to compare each sumatriptan dose with placebo but not to compare the two sumatriptan doses. Sample size calculations revealed that approximately 457 patients in each group needed to treat a migraine attack in order to have 90% power to detect a difference at time t (time to onset) between a 12% incidence of pain relief for an active treatment and a 7% incidence for placebo.

Adverse-event data were summarized for the safety population, defined as patients who treated a migraine attack with study medication. The incidences of specific adverse events considered by investigators to be drug related were calculated. Inferential statistics were not performed on the adverse-event data.

Results

Patients

The numbers of patients randomized to treatment were 550 for sumatriptan 100 mg, 561 for sumatriptan 50 mg, and 555 for placebo (Table 1). The safety population included 1475 subjects (485 for 100 mg, 496 for 50 mg, 494 for placebo). The intent-to-treat population included 1330 subjects (440 for 100 mg, 454 for 50 mg, 436 for placebo). The percentage of patients who prematurely withdrew from the study was comparable between treatment groups (12% in each sumatriptan group and 11% in the placebo group) (Table 1). Not having the opportunity to treat a migraine episode accounted for most of the premature withdrawals (10% for 100 mg, 9% for 50 mg, and 9% for placebo) (Table 1).

Demographics and baseline clinical characteristics were comparable between treatment groups (Table 1). Most patients were women (82% for 100 mg, 85% for 50 mg,

Table 1. *Patient disposition, demographics, and clinical characteristics*

	Sumatriptan 100 mg	Sumatriptan 50 mg	Placebo
Patient disposition			
Number randomized	550	561	555
Safety population, *n*	485	496	494
Intent-to-treat population, *n*	440	454	436
Prematurely withdrew from study, *n* (%)	65 (12)	66 (12)	61 (11)
Did not treat a migraine	55 (10)	51 (9)	51 (9)
Lost to follow-up	5 (< 1)	7 (1)	3 (< 1)
Consent withdrawn	2 (< 1)	2 (< 1)	5 (< 1)
Protocol violation	0 (0)	1 (< 1)	1 (< 1)
Other	3 (< 1)	5 (< 1)	1 (< 1)
Demographics			
Mean (SD) age, years	40.2 (10.8)	39.9 (10.8)	39.2 (10.5)
Female, *n* (%)	361 (82)	387 (85)	378 (87)
White, *n* (%)	436 (> 99)	444 (98)	428 (98)
Clinical characteristics			
Migraine diagnosis, *n* (%)			
Migraine without aura only	309 (70)	296 (65)	290 (67)
Migraine with aura only	52 (12)	66 (15)	58 (13)
Migraine with and without aura	79 (18)	92 (20)	88 (20)

87% for placebo), and ≥ 98% of patients in each treatment group were white. Approximately two thirds of patients in each group had migraine without aura only. In each group, 84% of patients had a history of triptan use.

Onset of relief and onset of pain-free response

All patients reported moderate or severe pain before dosing. The time to onset of pain relief for sumatriptan 100 mg was 17 minutes ($p \leq 0.05$ versus placebo), when 5% of sumatriptan-treated patients and 2% of placebo-treated patients reported pain relief (Figure 1). The time to onset of pain relief for sumatriptan 50 mg was 30 minutes ($p \leq 0.05$ versus placebo), when 18% of sumatriptan-treated patients and 11% of placebo-treated patients reported pain relief (Figure 1).

The time to onset of pain-free response for sumatriptan 100 mg was 39 minutes ($p \leq 0.05$ versus placebo), when 7% of patients treated with sumatriptan 100 mg and 4% of placebo-treated patients reported a pain-free response. The time to onset of pain-free response for sumatriptan 50 mg was 49 minutes ($p \leq 0.05$ versus placebo), when 8% of patients treated with sumatriptan 50 mg and 4% of placebo-treated patients reported pain-free response.

Two-hour results: relief, pain-free response, and migraine-free response

By 2 hours postdose, the cumulative percentages of patients with pain relief were 72% for sumatriptan tablets 100 mg and 65% for sumatriptan tablets 50 mg, compared with 38% for placebo ($p < 0.001$ each sumatriptan dose versus placebo; Figure 2). The

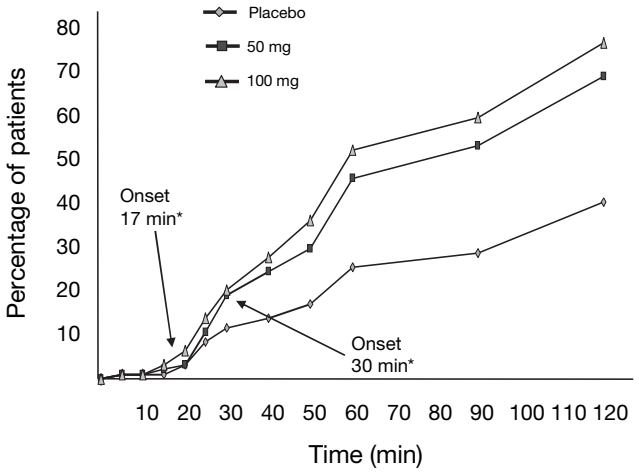

Figure 1. *Time to onset of pain relief in patients treating a migraine attack with sumatriptan tablets 50 mg or 100 mg in a fast-disintegrating/rapid-release formulation or placebo. Onset of pain relief is defined as the earliest time point at which relief was achieved and maintained (i.e., statistically significant separation from placebo through 2 hours postdose) *p ≤ 0.05 versus placebo*

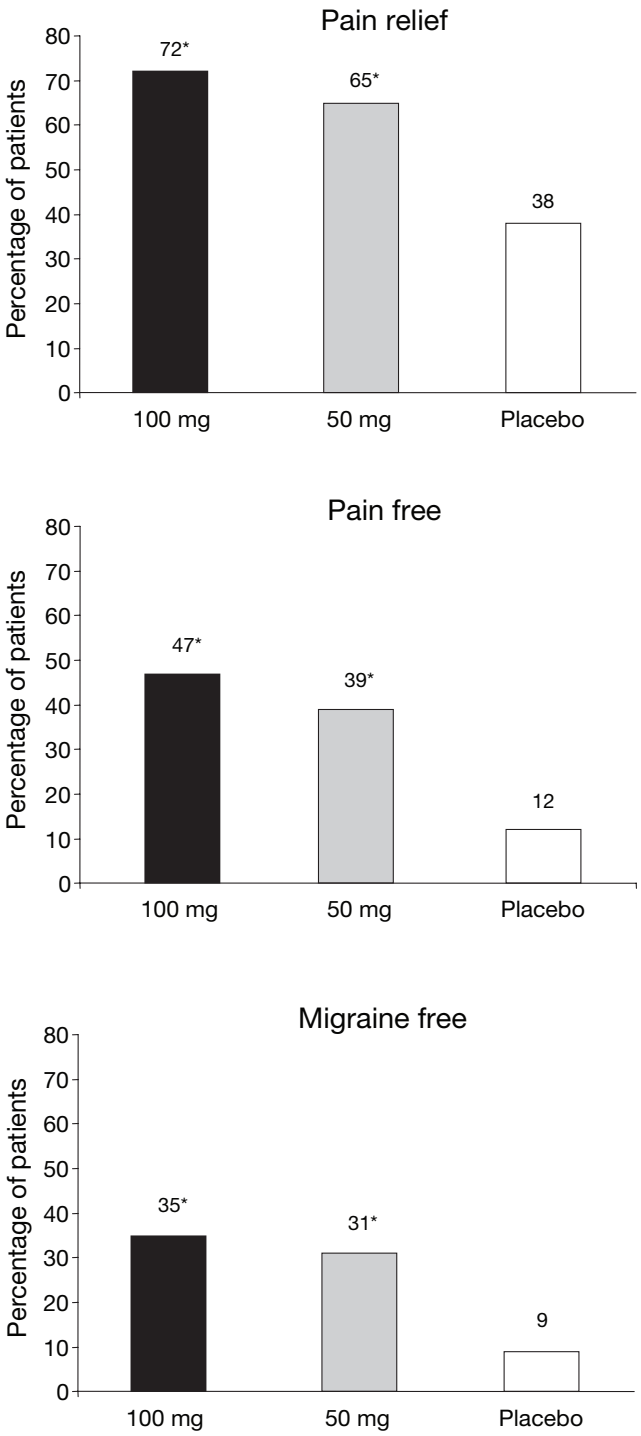

Figure 2. *Cumulative percentages of patients with pain relief and pain-free response, and percentage of patients migraine-free (i.e., no pain and no associated symptoms) 2 hours after dosing with sumatriptan tablets 50 mg or 100 mg in a fast-disintegrating/rapid-release formulation or placebo. *p ≤ 0.001 versus placebo*

cumulative percentages of patients with pain-free response 2 hours postdose were 47% for sumatriptan tablets 100 mg and 39% for sumatriptan tablets 50 mg, compared with 12% for placebo ($p < 0.001$ each sumatriptan dose versus placebo; Figure 2). The percentages of patients who were migraine free 2 hours postdose were 35% for sumatriptan tablets 100 mg and 31% for sumatriptan tablets 50 mg, compared with 9% for placebo ($p < 0.001$ each sumatriptan dose versus placebo; Figure 2).

Twenty-four hour results: sustained pain relief, sustained pain-free response, recurrence, and use of rescue medication

Significantly more patients treated with either dose of sumatriptan tablets reported sustained pain relief (43% with 100 mg, 40% with 50 mg, 16% with placebo) and sustained pain-free response (25% with 100 mg, 22% with 50 mg, 5% with placebo) through to 24 hours postdose ($p < 0.001$; Figure 3). Patients treated with either dose of sumatriptan were also less likely than placebo-treated patients to experience recurrence 2 to 24 hours postdose (95/319 [30%] with 100 mg, 81/293 [28%] with 50 mg, and 84/167 [50%] with placebo; differences not statistically tested) or to use rescue medication (162/440 [37%] with 100 mg, 187/454 [41%] with 50 mg, and 272/436 [62%] with placebo; $p < 0.001$ for each sumatriptan dose versus placebo).

Adverse events

No patient prematurely withdrew from the study because of adverse events. One serious adverse event (hospitalization for status migrainosus) was reported. This event occurred in a 53-year-old woman with a history of prolonged migraine attacks in the sumatriptan 50 mg group. The investigator judged the adverse event to be unrelated to treatment with study medication.

The percentages of patients with ≥ 1 adverse event considered possibly to be drug related were 19% with 100 mg, 12% with 50 mg, and 5% with placebo. The only possibly drug-related adverse events reported in > 2% of patients in any treatment group were nausea (3%, 100 mg; 2%, 50 mg; 1%, placebo) and paresthesia (3%, 100 mg; 1%, 50 mg; < 1%, placebo).

Discussion

The fast-disintegrating/rapid-release form of sumatriptan was developed to enhance tablet disintegration, drug dispersion, and to potentially improve absorption. It may be better absorbed than conventional tablets in the context of gastric stasis that can accompany migraine. Conventional and orally dissolving triptan tablets have been shown to have an onset of pain relief 30 minutes after dosing compared with placebo[17–19]. In the current study, using the fast-disintegrating/rapid-release form of sumatriptan, the onset of pain relief versus placebo was 17 minutes postdose with sumatriptan 100 mg, and 30 minutes postdose with sumatriptan 50 mg. The onset of action with this form is consistent with (1) the faster *in vitro* dissolution of sumatriptan in a fast-disintegrating/rapid-release tablet compared with the conventional tablet; (2) its slightly faster absorption during the early (0 to 2 hours) postdose period; and (3) the therapeutic gains with the new form compared with the conventional tablet for pain-free response 2 hours postdose[10,12,15]. As no head-to-head comparisons of

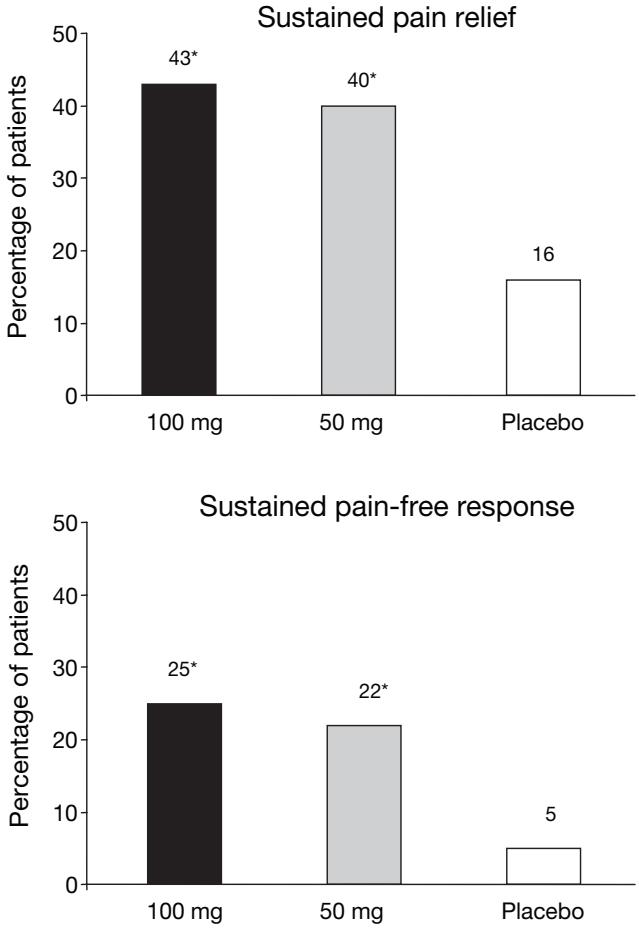

Figure 3. *Percentage of patients with sustained pain relief and sustained pain-free response (i.e., relief and pain-free response, respectively, from 2 through 24 hours postdose) after dosing with sumatriptan tablets 50 mg or 100 mg in a fast-disintegrating/rapid-release formulation or placebo.*
*p ≤ *0.001 versus placebo*

the onset of action of the fast-disintegrating/rapid-release form and the conventional tablets have been undertaken, no conclusions about the comparative time to relief with the two formulations can be drawn.

In the current study, the onset of efficacy of the fast-disintegrating/rapid-release form of sumatriptan was assessed by measuring times to onset of pain relief and pain-free response as continuous variables, with the use of PDAs to calculate elapsed time to mild pain or no pain. The measurement of pain relief and pain-free response as continuous variables is unique to this study and to a similarly designed study conducted in the United States and Canada[15]; previous migraine studies measured pain relief and pain-free response as discrete variables. The measurement of pain relief and pain-free response as continuous variables enables a more accurate assessment of the onset of therapeutic efficacy than is possible by measuring these parameters at discrete, predefined time points.

By 2 hours postdose, the cumulative percentages of patients with pain relief were 72% for sumatriptan tablets 100 mg and 65% for sumatriptan tablets 50 mg compared with 38% for placebo. The cumulative percentages of patients with pain-free response 2 hours postdose were 47% for sumatriptan tablets 100 mg and 39% for sumatriptan tablets 50 mg compared with 12% for placebo. The efficacy of the fast-disintegrating/rapid-release form of sumatriptan was maintained through the 24-hour postdose period, as demonstrated by the observations of sustained pain relief in more than twice as many sumatriptan-treated patients as placebo-treated patients, and of sustained pain-free response in approximately five times as many sumatriptan-treated patients as placebo-treated patients. The sustained efficacy of sumatriptan is also supported by the findings of less frequent headache recurrence and less need for rescue medication over the 24-hour postdose period in patients receiving sumatriptan 100 mg or 50 mg compared with those receiving placebo.

The fast-disintegrating/rapid-release form of sumatriptan had a benign adverse-event profile in this study. Both the type and the frequency of adverse events with the fast-disintegrating/rapid-release form of sumatriptan were comparable to those previously observed with the conventional sumatriptan tablet[19], a finding consistent with data from other studies of the fast-disintegrating/rapid-release form[12,15]. Nausea and paresthesia, both of which can occur as symptoms of migraine, were the only drug-related adverse events reported in more than 2% of patients in a treatment group.

In conclusion, results of this randomized, double-blind, placebo-controlled study show that sumatriptan tablets in a fast-disintegrating/rapid-release form have a rapid onset of efficacy in the acute treatment of migraine. Onset of pain relief was reported as early as 17 minutes postdose with the 100 mg dose, and 30 minutes postdose with the 50 mg dose. Sumatriptan tablets in this fast-disintegrating/rapid-release form provide rapid relief in an oral tablet, which is the patients' preferred dosing form.

Acknowledgements

Declaration of interest: The studies described in this manuscript were supported by GlaxoSmithKline. The authors acknowledge Jane Saiers, PhD, for assistance with writing the manuscript.

References

1. Cady RC, Ryan R, Jhingran P, et al. Sumatriptan injection reduces productivity loss during a migraine attack: results of a double-blind, placebo-controlled trial. Arch Intern Med 1998;158:1013-8
2. Lanteri-Minet M. What do patients want from their acute migraine therapy? Eur Neurol 2005;53(Suppl 1):3-9
3. Solomon GD, Santanello N. Impact of migraine and migraine therapy on productivity and quality of life. Neurology 2000;55(Suppl 2):S29-35
4. Davies GM, Santanello N, Lipton R. Determinants of patient satisfaction with migraine therapy. Cephalalgia 2000;20: 554-60
5. MacGregor EA, Brandes J, Eikerman A. Migraine prevalence and treatment patterns: the global Migraine and Zolmitriptan Evaluation survey. Headache 2003;43:19-26
6. Gruffydd-Jones K, Hood CA, Price DB. A within-patient comparison of subcutaneous and oral sumatriptan in the acute treatment of migraine in general practice. Cephalalgia 1998;17:31-6
7. Dahlöf CG, Saiers JA. Sumatriptan injection and tablets in clinical practice: results of a survey of 707 migraineurs. Headache 1998;38:756-63
8. Volans GN. Research review: migraine and drug absorption. Pharmacokinetics 1978;3:313-8
9. Boyle R, Behan PO, Sutton JA. A correlation between severity of migraine and delayed emptying measured by an epigastric impedance method. Br J Clin Pharmacol 1990;30: 405-9
10. Walls C, Lewis A, Bullman J, et al. Pharmacokinetic profile of a new form of sumatriptan tablets in healthy volunteers. Curr Med Res Opin 2004;20:803-9
11. Kori SH, Sandefer EP, McDonald SA, et al. Effect of tablet formulation on gastric transit time and drug absorption: evaluation by gastric scintigraphy. Headache 2005;45:816 [Abstract]
12. Carpay J, Schoenen J, Ahmad F, et al. Efficacy and tolerability of sumatriptan tablets in a fast-disintegrating, rapid-release formulation for the acute treatment of migraine: results of a multicenter, randomized, placebo-controlled study. Clin Ther 2004;26: 214-23
13. Barbanti P, Carpay JA, Kwong WJ, et al. Effects of a fast disintegrating/rapid release oral formulation of sumatriptan on functional ability in patients with migraine. Curr Med Res Opin 2004;20:2021-9

14. Winner P, Mannix LK, Putnam DG, et al. Pain-free results with sumatriptan taken at the first sign of migraine pain: 2 Randomized, double-blind, placebo-controlled studies. Mayo Clin Proc 2003;78:1214-22
15. Sheftell FD, Dahlöf CGH, Brandes JL, et al. Two replicate, randomized, double-blind, placebo-controlled trials of the time to onset of pain relief in the acute treatment of migraine with a fast-disintegrating/rapid-release formulation of sumatriptan tablets. Clin Ther 2005;27:407-17
16. Headache Classification Committee of the International Headache Society. Classification of headache disorders, cranial neuralgias and facial pain. Cephalalgia 1988;8(Suppl 7):1-96
17. Spierings LH, Rapoport AM, Dodick DW, et al. Acute treatment of migraine with zolmitriptan 5 mg orally disintegrating tablet. CNS Drugs 2004;18:1133-41
18. Sheftell F, Ryan R, Pitman V. Efficacy, safety, and tolerability of oral eletriptan for treatment of acute migraine: a multicenter, double-blind, placebo-controlled study conducted in the United States. Headache 2003;43:202-13
19. Pfaffenrath V, Cunin G, Sjonell G, et al. Efficacy and safety of sumatriptan tablets in the acute treatment of migraine: Defining the optimum doses of oral sumatriptan. Headache 1998;38:184-190

CrossRef links are available in the online published version of this paper:
http://www.librapharm.com
Paper HC-0126_3, *Accepted for publication*: 16 March 2006
Published Online: 26 April 2006
doi:10.1185/174234305X75207