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

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ABSTRACT

Background: The gastric stasis that commonly accompanies migraine headache may impair absorption of conventional oral tablets in the stomach. A fast-disintegrating/rapid-release formulation of sumatriptan has been developed to enhance tablet disintegration and drug dispersion and potentially improve absorption.

Objective: Two studies were conducted comparing the time to onset of relief from moderate or severe migraine pain with the fast-disintegrating/rapid-release formulation of sumatriptan tablets 50 and 100 mg and placebo.

Methods: These were 2 identically designed randomized, double-blind, parallel-group studies. Sumatriptan 50 or 100 mg or placebo was taken on an outpatient basis to treat a single moderate or severe migraine attack. Using a personal digital assistant, patients recorded the time of dosing and the time at which pain severity reached none or mild (ie, pain relief) or none (ie, pain free) in real time so that the time to onset of relief could be measured as a continuous variable. Onset of relief was defined as the earliest time point at which a statistically significant difference in pain relief compared with placebo was achieved and maintained through 2 hours after dosing. Before dosing and at predetermined time points after dosing, patients also provided an assessment of migraine pain as none, mild, moderate, or severe. At a clinic visit within 1 week after treatment of the migraine attack, patients were queried about adverse events. For each adverse event, investigators recorded whether study medication was considered the cause. Data analyses were undertaken for each study individually and, in post hoc analyses of the primary and key secondary end points, on pooled data from both studies.

Results: The 2 studies comprised 2696 patients: 902 received sumatriptan 50 mg, 902 received sumatriptan 100 mg, and 892 received placebo. Patients' mean age ranged from 40.2 to 40.8 years across treatment groups, and most patients were female (83%–87%) and white (92%–93%). In the analysis of pooled data, sumatriptan tablets provided significantly more effective pain relief compared with placebo as early as 20 minutes after dosing with the 100-mg dose and as early as 30 minutes after dosing with the 50-mg dose ($P \leq 0.05$). Similar results were observed for the individual studies: in study 1, sumatriptan tablets were significantly more effective than placebo at 25 minutes with the 100-mg dose and at 50 minutes with the 50-mg dose; in study 2, sumatriptan tablets were significantly more effective than placebo at 17 minutes for the 100-mg dose and at 30 minutes for the 50-mg dose ($P \leq 0.05$). In the pooled data, the cumulative percentages of patients with pain relief by 2 hours after dosing were 72% for the 100-mg dose and 67% for the 50-mg dose, compared with 42% for placebo ($P \leq 0.001$, both sumatriptan doses vs placebo). The cumulative percentages of patients with a pain-free response by 2 hours were 47% for the 100-mg dose,

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40% for the 50-mg dose, and 15% for placebo ($P \leq 0.001$, both sumatriptan doses vs placebo). In the individual studies, significantly more patients receiving either sumatriptan dose were migraine free 2 hours after dosing and had sustained pain relief and a sustained pain-free response over 24 hours compared with placebo ($P \leq 0.001$, both sumatriptan doses vs placebo). The only drug-related adverse events reported in >2% of patients in any treatment group in either study were nausea (both studies: 3% sumatriptan 100 mg, 2% sumatriptan 50 mg, 1% placebo) and paresthesia (study 1: <1% sumatriptan 100 mg, <1% sumatriptan 50 mg, 0% placebo; study 2: 3% sumatriptan 100 mg, 1% sumatriptan 50 mg, <1% placebo).

Conclusions: In these studies, sumatriptan tablets in a fast-disintegrating/rapid-release formulation were effective for the acute treatment of moderate to severe migraine pain, were generally well tolerated, and achieved an onset of pain relief as early as 20 minutes for 100 mg and as early as 30 minutes for 50 mg. (*Clin Ther*. 2005;27:407–417)

Key words: migraine, sumatriptan, fast-disintegrating/rapid-release formulation.

INTRODUCTION

To facilitate customization of migraine therapy to patients' needs, triptans are available in several formulations, including oral tablets to be swallowed with liquid, orally dissolving tablets to be taken without liquid, subcutaneous injection, nasal sprays, and, in some countries, a suppository.[1] Overall, those with migraine prefer oral tablets to other forms of migraine medication for such reasons as convenience, familiarity, and ease of use.[2–4] Given a choice of formulations, patients generally prefer to use tablets for the initial treatment of migraine attacks compared with all other forms.[2] When they do choose an injectable or nasal spray form over tablets, it is often for speed of action, which is cited by migraineurs as a principal important attribute of migraine medication and a key determinant of their satisfaction with therapy.[2,5–9] In some patients, the onset of pain relief has been shown to differ significantly from placebo, occurring as early as 10 minutes after dosing with the injectable form, as early as 15 minutes after dosing with the nasal spray form, and as early as 30 minutes after dosing with oral tablets (including conventional tablets swallowed with liquid and orally dissolving tablets taken without liquid).[10–15]

A fast-disintegrating/rapid-release form of sumatriptan tablets has been developed to facilitate tablet disintegration and dispersion and potentially improve absorption. This form employs RT Technology™ (GlaxoSmithKline, Research Triangle Park, North Carolina), which draws water into the tablet to cause it to swell and break apart. This creates the potential for early absorption into the bloodstream. Hence, the fast-disintegrating/rapid-release formulation of sumatriptan may be better absorbed than conventional tablets in the context of the gastric stasis that can accompany migraine. In an in vitro study under conditions simulating gastric stasis, the fast-disintegrating/rapid-release tablet dissolved 5 times faster than the conventional tablet.[16] Additionally, a pharmacokinetic study in healthy volunteers showed quicker absorption 0 to 2 hours after dosing with the reformulated tablet.[16] Compared with the conventional tablet, the $AUC_{0–2}$ of the fast-disintegrating/rapid-release tablet was, on average, 1% (50 mg) and 8% greater (100 mg) and maximal sumatriptan levels were attained, on average, 10 minutes earlier (50 mg) and 15 minutes earlier (100 mg). Although the fast-disintegrating/rapid-release form appears to be absorbed more quickly than the conventional tablets, the reformulated tablet is considered bioequivalent to the conventional tablets in terms of C_{max} and overall 24-hour exposure ($AUC_{0–24}$) in healthy volunteers,[16] in accordance with US and European Union regulatory definitions of bioequivalence.[17,18] In a randomized, double-blind, placebo-controlled trial in patients treating a migraine attack when pain was mild, the fast-disintegrating/rapid-release tablet was more effective than placebo with respect to pain-free response and migraine-free results (no pain and no associated symptoms) 2 hours after dosing and sustained pain-free response from 2 through 24 hours after dosing.[19] In addition, the tolerability profile of the reformulated tablet appeared not to differ from that of the conventional tablet.

This article describes the results of 2 identically designed studies of the time to onset of pain relief with the fast-disintegrating/rapid-release form of sumatriptan tablets 50 and 100 mg in patients with moderate or severe migraine pain. The studies employed a personal digital assistant (PDA) and survival analysis methodology to assess the onset of pain relief. Use of the PDA, which was programmed to record the time to

pain relief and pain-free response in real time, permitted measurement of time to the onset of pain relief as a continuous variable and thereby provided a more accurate assessment of the onset of therapeutic efficacy in migraine compared with previous migraine studies.[10–15] Previous studies have measured pain relief as a discrete variable at certain time points (eg, 30 minutes, 1 hour, and 2 hours after dosing), a method that addresses efficacy at the specific time points but does not provide a sensitive estimate of the onset of pain relief.

PATIENTS AND METHODS

Inclusion and Exclusion Criteria

Eligible men and women were aged between 18 and 65 years, had a ≥6-month history of migraine with or without aura as defined in the 1988 International Headache Society criteria,[20] had 1 to 6 migraines per month during the 3 months before the screening visit, and had a history of moderate to severe pain during migraine attacks. Women could not be pregnant and were required to be using adequate contraception.

Patients were excluded if they had uncontrolled hypertension (sitting diastolic blood pressure >95 mm Hg or systolic blood pressure >160 mm Hg) at screening; a history of epilepsy or seizures within 5 years before screening; confirmed or suspected cardiovascular or cerebrovascular disease; basilar or hemiplegic migraine; or headache on ≥15 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 reuptake inhibitor. Previous experience with triptan therapy was not an exclusion criterion.

Study Procedures

The 2 trials were identically designed randomized, double-blind, placebo-controlled studies. The protocols were approved by ethics committees or institutional review boards for each study site. Study 1 (GlaxoSmithKline protocol SUM30047) was conducted at 153 centers in the United States and Canada. Study 2 (GlaxoSmithKline protocol SUM30053) was conducted at 119 centers in Europe. All patients provided written informed consent.

Patients meeting the eligibility criteria were randomized in a 1:1:1 ratio to receive the fast-disintegrating/rapid-release form of sumatriptan tablets 50 or 100 mg or placebo for the outpatient treatment of a single migraine attack characterized by moderate or severe pain. The randomization code was generated by the study sponsor and was not accessible to investigators. Each investigator was provided with a unique set of numbers to be assigned to patients. On study entry, patients who had given their informed consent were assigned the lowest available number based on the chronological order of their presentation at the study site. When a patient became eligible for randomization, study personnel phoned an automated registration and medication ordering system and received a randomization number corresponding to 1 of the 3 blinded treatments.

Prohibited medications included ergotamine-containing and ergot-type medications and triptans (other than study medication) within 24 hours of the use of study medication; analgesics, antiemetics, and nontriptan acute migraine medications from 6 hours before through 2 hours after the use of study medication; and monoamine oxidase inhibitors throughout the study. Patients experiencing a recurrence of headache (ie, a return of moderate or severe pain after having mild or no pain 2 hours after the initial dose of study medication) could take a second dose of study medication or a nonprohibited acute migraine medication between 2 and 24 hours after dosing. Patients whose pain was not reduced to mild or none within 2 hours of the first dose of study medication could take a nonprohibited acute migraine medication (ie, rescue medication) from 2 through 24 hours after dosing.

Study Assessments

Patients were trained in the use of a handheld PDA as an electronic diary for recording data. The PDA operated as a study tool only, and no other functions were available to patients. The device was programmed to record in real time the time to the onset of pain relief and to pain-free response. The data collection and management system was extensively tested, cross-checked, and verified before the studies to ensure accuracy, consistency, completeness, and reliability of the data. Research staff at the study sites were trained and certified in the use of the PDA to ensure standardization of methods and quality assurance procedures.

For the continuous measurement of pain, the patient tapped the PDA screen to record the time of dosing and tapped it again when pain severity reached none or mild (ie, pain relief) or none (ie, pain free). In addition, at predetermined discrete time points, pain was rated on the 4-point scale (ie, none, mild, moderate, severe) used in previous migraine trials to measure a medication's effects on pain severity.[10–15]

The PDA dated and time-stamped all entries. Electronic diary assessments included the time and date of onset of the treated migraine attack; the time and date of dosing with study medication; the severity of migraine pain (mild, moderate, or severe) at the onset of the attack and immediately before dosing; the time elapsed from dosing to mild pain and no pain; pain severity and the presence or absence of nausea, vomiting, photophobia, and phonophobia 2 and 4 hours after dosing; use of a second dose of study medication; and headache recurrence.

Patients returned the electronic diary and a paper record of their use of rescue medication to the clinic at a visit within 1 week after treatment of the migraine attack. At this 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 it was considered related to study medication.

Efficacy End Points

The primary efficacy end point was the time to onset of pain relief, defined as the earliest time at which sumatriptan 100 mg was significantly effective in reducing moderate or severe predose pain to mild or no pain compared with placebo and efficacy was sustained through 2 hours after dosing. Key secondary efficacy end points included the time to onset of pain relief for sumatriptan 50 mg compared with placebo and the time to onset of pain-free response for sumatriptan 50 and 100 mg compared with placebo. Pain-free response was defined as a reduction in moderate or severe predose pain to no pain.

Other efficacy end points included the following categorical measures: the percentage of patients who were migraine free (ie, no pain and no associated symptoms of nausea, vomiting, photophobia, or phonophobia) 2 hours after dosing; the percentage of patients with sustained pain relief and sustained pain-free response (ie, pain relief or pain-free response from 2 through 24 hours after dosing with no use of a second dose of study medication or rescue medication); the percentage of patients taking rescue medication or a second dose of study medication during the 24-hour period after dosing; and the percentage of patients with a recurrence (ie, return of moderate or severe pain in the 24 hours after dosing in patients who had experienced pain relief 2 hours after dosing).

Statistical Methods

Kaplan-Meier survival analysis techniques[21] were used to derive time-to-event curves for sumatriptan tablets 50 and 100 mg and placebo for the cumulative percentages of patients with pain relief and pain-free response through 2 hours after dosing. Differences between each active treatment and placebo in the time-to-event curves for pain relief and pain-free response were tested with 2-sided log-rank tests.[21] In the analyses of pooled data, the log-rank tests were stratified by study.

P values ≤0.05 were considered statistically significant. If a significant difference was observed between an active treatment and placebo in the time-to-pain-relief or time-to-pain-free curves for 0 to 2 hours, the time to the onset of pain relief or to pain-free response was identified by evaluating the differences in the curves using various time points in a fixed sequence. The times to onset of pain relief and onset of pain-free response were defined as the earliest times at which the respective time-to-event curves for sumatriptan differed significantly from those for placebo. Once statistical significance was lost, earlier time points were not considered statistically significant with respect to the onset of pain relief.

To control for type I error at 0.05 for all primary and key secondary comparisons, a testing method was employed with the following fixed sequence: (1) time to pain relief for sumatriptan tablets 100 mg versus placebo (the primary end point); (2) time to pain-free response for sumatriptan tablets 100 mg versus placebo and time to pain relief for sumatriptan tablets 50 mg versus placebo (key secondary end points); and (3) time to pain-free response for sumatriptan tablets 50 mg versus placebo (key secondary end point). The previous comparison in the sequence must have been statistically significant for the next comparison in the sequence to be tested. For all categorical end points except headache recurrence, the Fisher exact test was used to compare each active treatment with placebo in the individual studies.

Efficacy data were analyzed for the intent-to-treat (ITT) population, defined as patients who treated a migraine attack and provided ≥1 postdose efficacy assessment. The studies were designed to compare both sumatriptan doses with placebo but not to compare the 2 sumatriptan doses. Sample-size calculations revealed that in each study, ~457 patients in each group needed to treat a migraine attack for the study to have 90% power to detect a difference at time *t* between a 12% incidence of pain relief for an active treatment and a 7% incidence of pain relief for placebo (ie, a 5% difference at *t* <30 minutes). The 5% difference between an active treatment and placebo was used in the sample-size calculations on the basis of previous data suggesting that this amount of difference could be detected within 30 minutes after dosing.[22,23] The primary and key secondary end points were analyzed both for the individual studies and using pooled data from both studies. The analyses of pooled data were considered post hoc.

The main objective of the individual studies was to evaluate the speed of onset of efficacy of sumatriptan fast-disintegrating/rapid-release tablets compared with placebo. Because the 2 studies had identical designs and were conducted simultaneously, the data could be combined to obtain a single time to onset of pain relief and time to onset of pain-free response for sumatriptan tablets 50 mg and 100 mg. Although the pooled data analyses were post hoc, results from these analyses, along with the results from the individual studies, can be expected to provide an accurate description of the efficacy of both sumatriptan doses from the onset of a migraine attack through 2 hours after dosing for use in the clinical setting.

Adverse-event data were summarized for the safety population, defined as all patients who treated a migraine attack with study medication. The incidence of specific drug-related adverse events was calculated. Inferential statistical analyses were not performed on the adverse-event data, as there were no predetermined adverse events of special interest.

RESULTS

Patient Populations

In study 1, 1665 patients were randomized to treatment (556 sumatriptan 50 mg, 551 sumatriptan 100 mg, 558 placebo); 1477 patients treated a migraine attack with study medication and were included in the safety population (494 sumatriptan 50 mg, 488 sumatriptan 100 mg, 495 placebo); and 1366 treated a migraine attack and provided ≥1 postdose efficacy assessment and were included in the ITT population (448 sumatriptan 50 mg, 462 sumatriptan 100 mg, 456 placebo). Comparable numbers of patients were included in study 2 (1475 in the safety population, 1330 in the ITT population). Among randomized patients, the primary reason for exclusion from the safety and ITT populations was not having the occasion to treat a migraine attack during the study (study 1: 7%, 7%, and 8% for sumatriptan 50 mg, 100 mg, and placebo, respectively; study 2: 9%, 10%, and 9%), followed by loss to follow-up (study 1: 2%, 1%, and 2%; study 2: 1%, <1%, and <1%). Comparable proportions of patients across groups withdrew prematurely from the studies (**Table I**).

Demographic and baseline clinical characteristics were comparable among treatment groups and between studies. Using the pooled data, patients' mean age ranged from 40.2 to 40.8 years across treatment groups, and most patients were female (83%–87%) and white (92%–93%). In the individual studies, the majority of patients (65%–72%) had a history of migraine without aura. Across treatment groups and studies, most patients (77%–84%) were using triptans at study entry or had a history of triptan use (**Table I**).

Time to Onset of Pain Relief

Pain intensity immediately before treatment was moderate or severe in all patients in both studies. Using pooled data, the cumulative percentages of patients with pain relief by 2 hours after dosing were 67% for sumatriptan tablets 50 mg and 72% for sumatriptan tablets 100 mg, compared with 42% for placebo ($P \leq 0.001$, both sumatriptan doses vs placebo) (**Figure 1**). A similar pattern of results was observed in the individual studies (**Table II**).

In the analysis of the individual studies, the time to onset of pain relief for sumatriptan 100 mg was 25 minutes in study 1 and 17 minutes in study 2 (**Table II**). In the analysis of pooled data, the time to onset of pain relief with the 100-mg dose was 20 minutes (6% of patients reported pain relief vs 4% with placebo; $P \leq 0.05$) (**Figure 2**).

For sumatriptan 50 mg, the time to onset of pain relief was 50 minutes in study 1 and 30 minutes in study 2 (**Table II**). In the analysis of pooled data, the time to onset of pain relief was 30 minutes (19% of patients re-

Table I. Patient disposition and demographic and clinical characteristics.

	Sumatriptan 50 mg	Sumatriptan 100 mg	Placebo
Patient disposition			
Randomized, no.			
Study 1	556	551	558
Study 2	561	550	555
Pooled studies	1117	1101	1113
Safety population, no.			
Study 1	494	488	495
Study 2	496	485	494
Pooled studies	990	973	989
Intent-to-treat population, n/N (%)			
Study 1	448/494 (91)	462/488 (95)	456/495 (92)
Study 2	454/496 (92)	440/485 (91)	436/494 (88)
Pooled studies	902/990 (91)	902/973 (93)	892/989 (90)
Premature withdrawals, n/N (%)			
Study 1	72/556 (13)	67/551 (12)	75/558 (13)
Study 2	66/561 (12)	65/550 (12)	61/555 (11)
Demographic characteristics			
Mean (SD) age, y			
Study 1	41.6 (10.8)	41.5 (11.2)	41.2 (10.8)
Study 2	39.9 (10.8)	40.2 (10.8)	39.2 (10.5)
Pooled studies	40.7 (10.8)	40.8 (11.0)	40.2 (10.7)
Women, n/N (%)			
Study 1	380/448 (85)	389/462 (84)	401/456 (88)
Study 2	387/454 (85)	361/440 (82)	378/436 (87)
Pooled studies	767/902 (85)	750/902 (83)	779/892 (87)
White, n/N (%)			
Study 1	387/448 (86)	399/462 (86)	403/456 (88)
Study 2	444/454 (98)	436/440 (99)	428/436 (98)
Pooled studies	831/902 (92)	835/902 (93)	831/892 (93)
Clinical characteristics			
History of triptan use, n/N (%)			
Study 1	343/448 (77)	364/462 (79)	355/456 (78)
Study 2	380/454 (84)	368/440 (84)	367/436 (84)
History of migraine without aura only, n/N (%)			
Study 1	321/448 (72)	315/462 (68)	325/456 (71)
Study 2	296/454 (65)	309/440 (70)	290/436 (67)

ported pain relief vs 14% with placebo; $P \leq 0.05$) (**Figure 2**).

Other Efficacy Results

Using pooled data, the cumulative percentages of patients with a pain-free response by 2 hours after dosing were 40% for sumatriptan tablets 50 mg and 47% for sumatriptan tablets 100 mg, compared with 15% for placebo ($P \leq 0.001$, both sumatriptan doses vs placebo). A similar pattern of results was observed in the individual studies (**Table II**).

In the individual studies, significantly more patients taking either sumatriptan dose were migraine free 2 hours after dosing compared with those taking

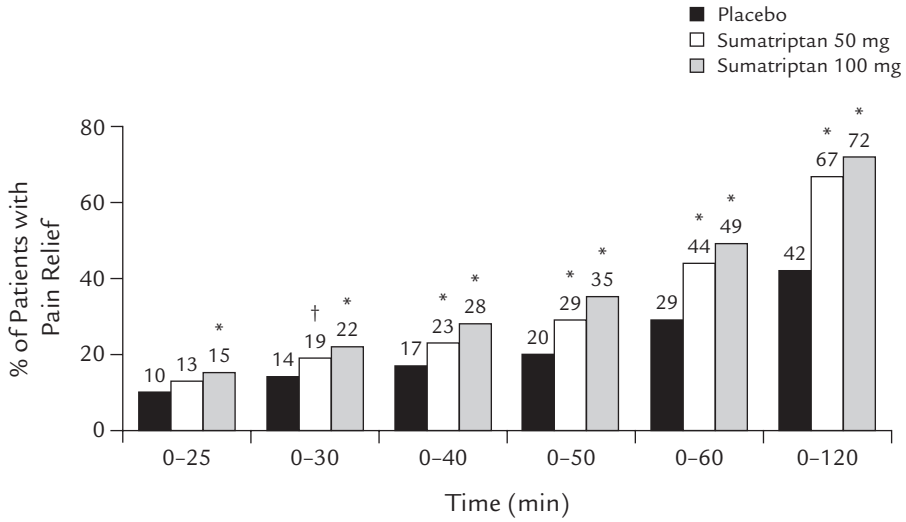

Figure 1. Cumulative percentage of patients with pain relief after treating a single migraine attack with sumatriptan tablets 50 or 100 mg in a fast-disintegrating/rapid-release formulation or placebo (pooled data from 2 studies). * $P \leq 0.001$ versus placebo; † $P \leq 0.05$ versus placebo.

placebo ($P \leq 0.001$, both sumatriptan doses vs placebo) (**Table II**). The percentages of patients with sustained pain relief and sustained pain-free response in the individual studies were also significantly higher with both doses of sumatriptan compared with placebo ($P \leq 0.001$).

In the individual studies, significantly fewer patients who took either dose of sumatriptan used rescue medication or a second dose of study medication during the 24 hours after dosing compared with those who took placebo ($P \leq 0.001$) (**Table II**). The percentage of patients with a recurrence in the individual studies ranged from 26% to 28% with sumatriptan 50 mg, from 28% to 30% with sumatriptan 100 mg, and from 43% to 50% with placebo.

Adverse Events

Both sumatriptan doses were generally well tolerated. The percentages of patients with ≥1 drug-related adverse event were 8% with sumatriptan 50 mg, 12% with sumatriptan 100 mg, and 3% with placebo in study 1 and a corresponding 12%, 19%, and 5% in study 2 (**Table III**). The only drug-related adverse events reported in >2% of patients in any treatment group in either study were nausea (2%, 3%, and 1%, respectively, in both studies) and paresthesia (study 1: <1%, <1%, and 0%; study 2: 1%, 3%, and <1%). No serious drug-related adverse events were reported. No patient withdrew from either study because of adverse events.

DISCUSSION

The gastric stasis that commonly accompanies migraine headache may impair absorption of conventional oral tablets in the stomach.[24,25] Therefore, a fast-disintegrating/rapid-release formulation of sumatriptan was developed to enhance tablet disintegration and drug dispersion and potentially improve absorption. Reports of faster in vitro dissolution of sumatriptan in the fast-disintegrating/rapid-release tablet compared with the conventional tablet and slightly faster absorption during the early period after dosing (0–2 hours) in healthy volunteers[16] suggested that this formulation may have a rapid onset of action. An earlier clinical trial of the fast-disintegrating/rapid-release formulation evaluated its efficacy and tolerability in the early-intervention treatment paradigm[19]; however, before the present studies, the efficacy and onset of pain relief with this formulation had not been evaluated in patients with moderate or severe migraine pain.

With respect to the onset of pain relief, previous migraine studies have assessed pain relief as a discrete variable at specific time points after dosing (eg, 30 minutes, 1 hour, and 2 hours),[10–15] a method that addresses efficacy at the specific time points but does not provide a sen-

Table II. Efficacy data for study 1 and study 2.

	Sumatriptan 50 mg	Sumatriptan 100 mg	Placebo
Time to significant difference in onset of pain relief vs placebo, min			
Study 1	50*	25*	NA
Study 2	30*	17*	NA
Pooled studies	30*	20*	NA
Cumulative incidence of pain relief 2 hours after dosing, n/N (%)			
Study 1	310/448 (69)†	331/462 (72)†	208/456 (46)
Study 2	293/454 (65)†	318/440 (72)†	167/436 (38)
Pooled studies	603/902 (67)†	649/902 (72)†	375/892 (42)
Time to significant difference in onset of pain-free response vs placebo, min			
Study 1	47*	29*	NA
Study 2	49*	39*	NA
Cumulative incidence of pain-free response 2 hours after dosing, n/N (%)			
Study 1	180/448 (40)†	219/462 (47)†	84/456 (18)
Study 2	178/454 (39)†	207/440 (47)†	53/436 (12)
Migraine-free response 2 hours after dosing, n/N (%)			
Study 1	139/442 (31)†	179/455 (39)†	69/455 (15)
Study 2	140/449 (31)†	155/437 (35)†	41/435 (9)
Sustained pain relief, n/N (%)			
Study 1	154/405 (38)†	163/420 (39)†	92/446 (21)
Study 2	173/437 (40)†	181/421 (43)†	69/429 (16)
Sustained pain-free response, n/N (%)			
Study 1	85/419 (20)†	107/426 (25)†	46/449 (10)
Study 2	96/442 (22)†	108/424 (25)†	21/430 (5)
Recurrence, n/N (%)‡			
Study 1	81/310 (26)	93/331 (28)	89/209 (43)
Study 2	81/293 (28)	95/319 (30)	84/167 (50)
Use of rescue medication or second dose of study medication, n/N (%)			
Study 1	192/448 (43)†	180/462 (39)†	257/456 (56)
Study 2	187/454 (41)†	162/440 (37)†	272/436 (62)

NA = not applicable.

*$P \leq 0.05$ versus placebo.

†$P \leq 0.001$ versus placebo.

‡Based on number of patients reporting pain relief 2 hours after dosing (discrete time-point data). The difference in the numbers of patients reporting pain relief using the personal digital assistant (PDA) and the numbers for the cumulative incidence of pain relief 2 hours after dosing is explained by 2 patients who reported pain relief at the 2-hour discrete time point, but not using the PDA. No statistical analysis of recurrence was planned or performed.

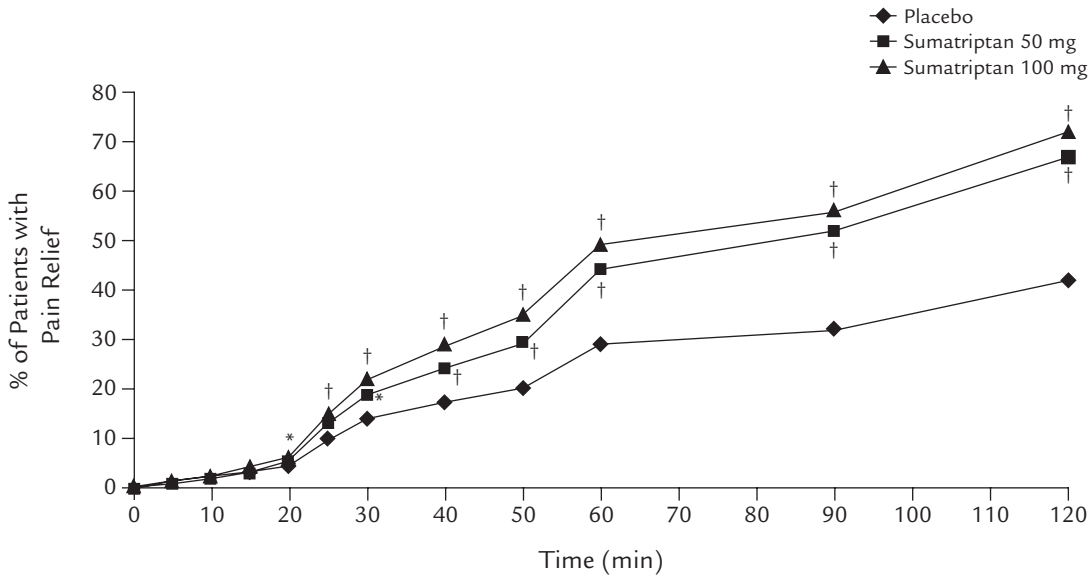

Figure 2. Time to onset of pain relief in patients treating a single migraine attack with sumatriptan tablets 50 or 100 mg in a fast-disintegrating/rapid-release formulation or placebo (pooled data from 2 studies). Onset of pain relief was defined as the earliest time point at which pain relief was achieved (ie, showed a statistically significant difference compared with placebo) and was maintained through 2 hours after dosing. *$P \leq 0.05$ versus placebo; †$P \leq 0.001$ versus placebo.

sitive estimate of the onset of pain relief. In contrast, patients in the present studies recorded the time elapsed to mild or no pain in real time, which permitted measurement of time to the onset of pain relief as a continuous variable, providing a more accurate assessment of the onset of therapeutic efficacy. Use of the PDA to measure elapsed time to mild or no pain and use of survival analysis methodology to analyze the onset of pain relief and pain-free response may have broad applications in migraine research.

In the pooled results from these randomized, double-blind, placebo-controlled studies, the time at which the onset of pain relief differed significantly from placebo occurred as early as 20 minutes after dosing with suma-

Table III. Adverse events (no. [%]) reported in >2% of patients in any treatment group in either study.

	Sumatriptan 50 mg	Sumatriptan 100 mg	Placebo
No. in safety population			
Study 1	494	488	495
Study 2	496	485	494
Any drug-related adverse event			
Study 1	40 (8)	57 (12)	17 (3)
Study 2	58 (12)	94 (19)	25 (5)
Nausea (drug-related)			
Study 1	11 (2)	13 (3)	5 (1)
Study 2	10 (2)	16 (3)	5 (1)
Paresthesia (drug-related)			
Study 1	4 (<1)	3 (<1)	0 (0)
Study 2	5 (1)	14 (3)	1 (<1)

triptan 100 mg and as early as 30 minutes after dosing with sumatriptan 50 mg. In the individual studies, the time to onset of pain relief ranged from 17 to 25 minutes for the 100-mg dose and from 30 to 50 minutes for the 50-mg dose. The cumulative percentage of patients with pain relief 2 hours after dosing was 67% for sumatriptan 50 mg and 72% for sumatriptan 100 mg, compared with 42% for placebo. An onset of pain relief as early as 30 minutes after dosing has been documented for oral tablet formulations of other triptans.[14,15,22] However, firm conclusions about the comparative onset of pain relief with the fast-disintegrating/rapid-release formulation of sumatriptan and other triptan tablets cannot be drawn, as no head-to-head clinical trials have been conducted. In addition, the design and methods of the present studies differed from those of past migraine trials in that the time to onset of pain relief was assessed as a continuous variable, survival analysis methodology was used, and cumulative percentages of patients with pain relief and pain-free response were calculated. These differences render comparisons between these and other studies difficult.

In assessing the profile of patient response over time, the data show the single time point at which active treatment and placebo separate and maintain their separation over the 2-hour period after dosing. By definition, this point of separation applies to a small proportion of patients. However, in these studies, after the initial point of separation at which the active treatments became significantly superior to placebo, the difference was not only maintained but continued to expand relative to placebo over the 2-hour interval after dosing. Thus, pain relief with sumatriptan 100 mg began in a small proportion of patients as early as 20 minutes after dosing, and up to 72% of patients achieved pain relief by 2 hours.

In addition to providing rapid pain relief, the fast-disintegrating/rapid-release form of sumatriptan was associated with sustained pain relief. Across sumatriptan doses and studies, up to 2 times more sumatriptan recipients reported sustained pain relief compared with placebo recipients (38%–43% vs 16%–21%, respectively) and 2 to 5 times more reported sustained freedom from pain (20%–25% vs 5%–10%). In addition, use of rescue medication or a second dose of study medication during the 24-hour period after dosing was significantly less frequent with both sumatriptan doses compared with placebo ($P \leq 0.001$).

Both doses of sumatriptan tablets were generally well tolerated. Nausea and paresthesia were the only drug-related adverse events reported in >2% of patients in any treatment group in either study. The safety profile of the fast-disintegrating/rapid-release formulation of sumatriptan tablets appears comparable to that of the conventional form[22] in terms of both the type and frequency of adverse events.

The exclusion criteria used in these studies, which are typical for migraine studies, may somewhat limit the extent to which the data can be generalized to all patients with migraine. Patients were excluded who had basilar or hemiplegic migraine or who had headache on ≥15 days per month in any of the 3 months before screening, as were patients residing in countries where the combination of a selective serotonin reuptake inhibitor and a triptan is not allowed who required a selective serotonin reuptake inhibitor. Also excluded were those using migraine prophylactic medication containing ergotamine, an ergot derivative, or methysergide, and those who had used a monoamine oxidase inhibitor within 2 weeks before screening.

CONCLUSIONS

In these 2 identical randomized, double-blind, placebo-controlled studies, a fast-disintegrating/rapid-release formulation of sumatriptan tablets was effective, was generally well tolerated, and provided a rapid onset of pain relief in the acute treatment of moderate or severe migraine pain. Onset of pain relief was detected as early as 20 minutes after dosing with the 100-mg dose of sumatriptan and 30 minutes after dosing with the 50-mg dose. Sumatriptan tablets in this formulation provided rapid pain relief and a rapid pain-free response in the acute treatment of migraine.

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