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Times to pain relief and pain freedom with rizatriptan 10 mg and other oral triptans

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SUMMARY

Background: In the clinical trial setting, oral rizatriptan 10 mg has greater efficacy than other oral triptans in freedom from migraine headache pain 2 h after dosing. **Objective:** The study objective is to compare the effectiveness of rizatriptan 10 mg and other oral triptans for acute migraine attack in a naturalistic setting. **Methods:** A total of 673 patients took rizatriptan 10 mg or their usual-care oral triptans for two migraine attacks in a sequential, cross-over manner and recorded outcomes using a diary and a stopwatch. Mean and median times to pain relief (PR) and pain freedom (PF) for rizatriptan and other oral triptans were compared. The effect of rizatriptan on times to PR and PF, adjusting for potential confounding factors (treatment sequence, treatment order and use of rescue medication), was computed via a Cox proportional hazard model. **Results:** Significantly, more patients taking rizatriptan achieved both PR and PF within 2 h after dosing than other oral triptans. Times to PR and PF were shorter with rizatriptan than with other oral triptans (median time to PR: 45 vs. 52 min, $p < 0.0001$; median time to PF: 100 vs. 124 min, $p < 0.0001$). The adjusted proportional hazard ratios (rizatriptan vs. other oral triptans) for times to PR and PF were 1.32 (95% CI: 1.22–1.44) and 1.27 (95% CI: 1.16–1.39) respectively. **Conclusion:** The times to PR and PF in a 'naturalistic' setting were significantly shorter for patients treating a migraine attack with rizatriptan 10 mg than with other oral triptans.

What's known

Triptans are efficacious migraine-specific therapy for acute migraine. Rizatriptans, as compared with other oral triptans, have shown greater efficacy in treatment outcomes.

What's new

This article addresses an important question whether rizatriptan 10 mg is more effective than other oral triptans in aborting acute migraine in a real-world setting. With regard to research methodology, we strived for better measurement of time to treatment end-points (using stopwatch methodology) and minimising intra-patient variations by adopting cross-over study design.

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Disclosures

Drs Ng-Mak, Hu, and Chen, and Ma are currently employed by Merck & Co., Inc.

Introduction

Population-based surveys indicate that the 1-year prevalence rate of migraine is 18.2% for women and 6.5% for men (1), indicating that about 30 million people in the United States currently suffer from this condition. Migraine is typically manifest by episodic disabling headache lasting hours or days, with an average attack frequency of one per month (2). Triptans, the ergot alkaloids and non-steroidal anti-inflammatory drugs (NSAIDs) are the three main classes of drugs used to treat the pain and associated symptoms of a migraine attack (3).

The US Headache Consortium recommends a migraine-specific drug (triptan or ergotamine) for patients with severe migraine or for patients whose migraines respond poorly to NSAIDs or to combination analgesics (4). Several oral triptans (rizatriptan 10 mg, sumatriptan 100 mg and eletriptan 40–80 mg) have been shown to have greater efficacy than ergotamines in double-blind randomised clinical trials (5–7).

In randomised trials comparing different oral triptans head-to-head, rizatriptan 10 mg appears to have the greatest efficacy (8,9). A large randomised clinical trial ($n = 1268$) reports significant superior treatment efficacy of pain relief (PR) at 2 h and pain freedom (PF) at 2 h after dosing for rizatriptan 10 mg over sumatriptan 100 mg (9). No differences in PR and PF rates at 2 h are observed between rizatriptan 5 mg and sumatriptan 100 mg (9). Using freedom from pain 2 h after dosing as the outcome measure, which is recommended by the International Headache Society as the standard end-point for efficacy measurement (10), rizatriptan 10 mg has greater efficacy than sumatriptan 25 mg, sumatriptan 50 mg, sumatriptan 100 mg, naratriptan 2.5 mg and zolmitriptan 2.5 mg (8,11). In addition, patients taking rizatriptan 10 mg report more proportions of 24-h sustained PF rates than other oral triptans (8).

Overviews of placebo-controlled trials of individual oral triptans (12,13) indicate that rizatriptan 10 mg and eletriptan 80 mg exhibit placebo-subtracted values of PF at 2 h that are significantly higher

than those for the benchmark sumatriptan 100 mg, whereas values of PF for other triptan dosages – almotriptan 12.5 mg, eletriptan 20 and 40 mg, naratriptan 2.5 mg, sumatriptan 25 and 50 mg, zolmitriptan 2.5 and 5 mg – do not differ significantly from those for sumatriptan 100 mg (13).

It is unclear whether greater efficacy in randomised clinical trials translates into greater effectiveness in treating an acute migraine in a patient's everyday setting. Although there have been several open-label naturalistic studies of triptans (almost invariably rizatriptan) in comparison with patients' usual treatments, the 'usual treatment' comparator either non-triptans (14–16) or combined triptans with other non-triptan drugs (17). A recent open-label cross-over trial reports that rizatriptan 10 mg has enhanced PF rates at 2 h than almotriptan 12.5 mg (18). No naturalistic study has focused on a comparison of rizatriptan with other oral triptans, with time to headache PF at 2 h as an end-point. The objective of the current study is to investigate the effectiveness of rizatriptan 10 mg compared with the oral triptans usually taken by patients in a naturalistic setting. Given the bioavailability differences exist among oral triptans, comparison group was further categorised into (1) other oral triptans (2), sumatriptan only (3), fast-acting oral triptans (i.e. almotriptan, electriptan and zolmitriptan), and (4) slow-acting oral triptans (i.e. frovatriptan and naratriptan). The primary outcomes were times to achieve PR and PF.

Methods

Study overview

The methods of this trial have been reported in detail elsewhere (17). In brief, this was a multi-site, prospective, open-label, two-migraine-attack, cross-over study. Patients from across the United States were recruited in their primary care physicians' offices (see Appendix 1 for a list of participating physicians). After providing informed consent, consecutive rizatriptan-naïve patients completed a baseline questionnaire recording their demographic characteristics, migraine history and the use of acute and preventive migraine medications. Patients were then provided with a take-home kit containing two patient diaries, a stopwatch, two tablets of standard formulation oral rizatriptan 10 mg, instructions for data collection, and a stamped addressed envelope. Patients were instructed to treat their next two migraine attacks sequentially with either rizatriptan 10 mg or their usual migraine medication, in a cross-over manner. The sequence of medication use was left to the patient's discretion. Patients were asked to start the stopwatch upon taking the study medication, and to record in the diary the time to onset of PR and the time to PF. At the end of each treatment diary, patients recorded how satisfied they were with the prescription medication used to treat their migraine. At the conclusion of the cross-over phase, they were asked to indicate which acute migraine medication they would prefer to use in treating their next migraine. Patients treated their migraines as they usually would, so that additional prescription or over-the-counter medications were allowed. The study protocol and all patient materials used in this study were reviewed and approved by Schulman Associates Institutional Review Board, Inc. The study was carried out between September 2003 and February 2004.

Patients

Men and women were eligible to enter the study if they were 18 years of age or older, had physician-diagnosed migraine and a recent history of one or more migraines per month, were rizatriptan-naïve, had been prescribed an oral medication intended for the acute treatment of migraine, and were fluent in English. The criteria for exclusion from the study were pregnancy or any contraindication for the triptans used in the study.

Outcome measures

The primary study outcome measures were the times, in minutes, to migraine PR and PF, recorded by stopwatch. Patients recorded these exact times in the diaries provided in response to the questions 'After you took the first prescription drug, how long did it take before you started to feel onset of headache relief, i.e. you felt that the drug started working?' and 'After you took the first prescription drug, how long did it take before you felt your headache was completely gone?' Secondary outcome measures were patient satisfaction and patient medication preference. Patient satisfaction was measured on a five-point Likert scale (1, very satisfied; 2, satisfied; 3, neither; 4, dissatisfied and 5, very dissatisfied) and patient preference was evaluated in three categories (1, rizatriptan; 2, other oral triptan and 3, no preference).

Statistical analysis

This analysis is limited to patients whose previously prescribed migraine medication was an oral triptan (almotriptan, eletriptan, frovatriptan, naratriptan, sumatriptan or zolmitriptan, but not rizatriptan) in standard tablet formulation, and who used the stopwatch provided to record the times to PR and PF. The characteristics of patients who used rizatriptan for their first migraine attack and those who used

rizatriptan for their second attack were compared and the statistical significance of differences between these two patient sets was determined using an independent *t*-test for continuous variables and a chi-squared test for proportions.

Times to PR and PF were analysed both as categorical variables and as continuous. Comparisons were made between the following groups: (i) rizatriptan vs. all other oral triptans; (ii) rizatriptan vs. sumatriptan only; (iii) rizatriptan vs. fast-acting oral triptans (including almotriptan, electriptan and zolmitriptan) and (iv) rizatriptan vs. slow-acting oral triptans (including frovatriptan and naratriptan). For categorical measurement of time, statistical significance of differences in proportion of patients achieving PR and PF within 2 h after dosing was evaluated using McNemar's test. For continuous measurement of time, times to PR and PF were capped and censored at 3 days (i.e. 72 h or 4320 min) for patients who either achieved PF beyond 3 days or did not achieve PR and/or PF. The rationale of 3-day censoring was chosen because most migraine patients achieved PF within 3 days of attack. A paired *t*-test was applied to test treatment differences (e.g. rizatriptan vs. other oral triptans) in mean times to PR and PF. As the distributions of times to PR and PF were skewed, and parametric methods (which assume a normal distribution) are not strictly valid, non-parametric and semi-parametric methods were deemed more appropriate. Median times to PR and PF were presented by treatment groups, and the p-value associated with the treatment comparison was obtained from the Score Statistic in the Cox model, adjusting for clustering.

Cox proportional hazards modeling was considered the appropriate tool for testing treatment differences in times to PR and PF. To account for the clustering effect as a result of patients serving as their own controls in this cross-over study, the Cox proportional hazards model employed an independent working assumption and used a robust sandwich covariance matrix estimate. The variables controlled for included treatment sequence, treatment order and the use of rescue medications. Treatment sequence was a dichotomous variable that measured taking rizatriptan in the first attack. Treatment order was also a binary-coded variable that assessed the numerical order of treatment sequence. Use of rescue medication was coded as '1' if an affirmative response was given to the question 'Did you take any non-prescription medication after you took their prescription drug(s) to help relieve the migraine attack?' Patient satisfaction with rizatriptan in comparison with other oral triptans was evaluated in a cumulative logit model, in which the dependent variable was the satisfaction rating and the variables controlled for included treatment sequence, treatment order and the use of rescue medications. The proportion of patients indicating their preference for rizatriptan, other oral triptans and no preference was described. All analyses were performed with SAS, version 8. A p-value < 0.05 was considered to be statistically significant.

Results

Patient sample

A total of 2368 patients were enrolled in the study. Patients who did not follow the study protocol, who did not use a stopwatch, or who did not use an oral triptan as their comparator treatment were excluded, so that 673 patients, with 1346 migraine attacks, were included in the analysis presented here (Figure 1). The excluded population had a statistically significantly greater frequency of migraine-associated vomiting (22.6% vs. 14.3%), diarrhoea (10.7% vs. 6.2%) and blurred vision (32.5% vs. 26.5%). Stopwatch users and non-users were similar in terms of their educational levels, recent headache severity, health insurance coverage and treatment sequence. There were a slightly greater proportion of women among stopwatch non-users (90.9%), than among stopwatch users (83.4%).

The characteristics of the population included in the analysis are presented in Table 1. The mean age was 41.3 years, 83.4% were women, and the mean age at first diagnosis was 28.2 years. Patients' 'usual care' oral triptans were sumatriptan (49.6%), zolmitriptan (15.2%), eletriptan (13.8%), almotriptan (11.7%), frovatriptan (5.1%) and naratriptan (4.6%). A total of 386 patients (57.4%) used rizatriptan to treat their first migraine attack and 287 (42.6%) used rizatriptan to treat their second migraine attack (Table 1). There were no statistically significant differences between these two groups in age, gender, age at first diagnosis, migraine type, education, recent headache severity, number of headaches in the previous month or the use of rescue medications.

Times to pain relief and pain freedom

Proportions of achieving pain relief within 2 h after dosing

Using the International Headache Society's standard treatment end-points, proportions of patients achieved PR and PF within 2 h after dosing was shown in Table 2. Significantly more patients taking rizatriptan (88.1%) achieved PR within 2 h after dosing than patients taking other oral triptans (81.9%; $p = 0.0003$). Approximately nine of 10 patients

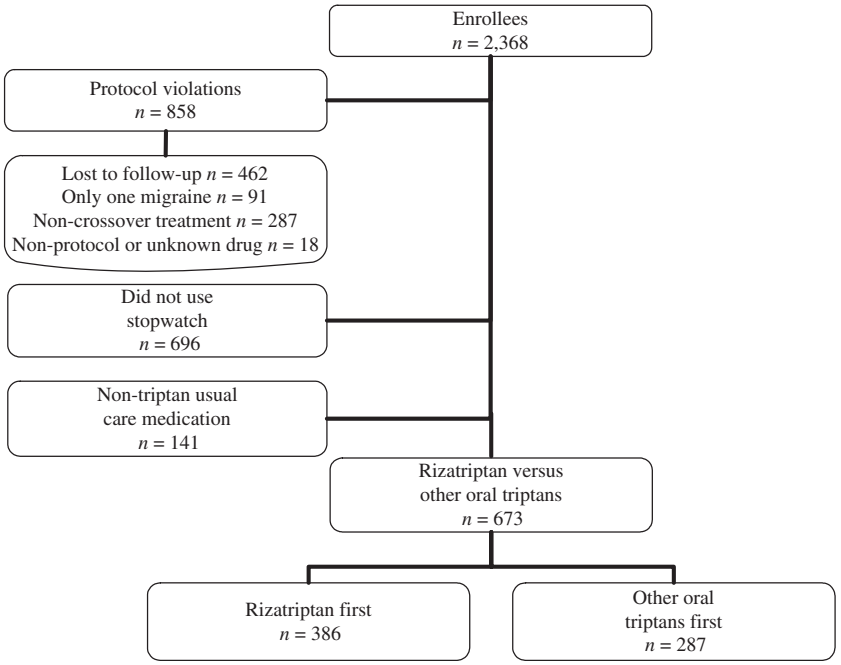

Figure 1 Patient sample

Table 1 Patient characteristics

		Sequence		
	Total (n = 673)	Took rizatriptan for first attack (n = 386)	Took rizatriptan for second attack (n = 287)	p-value
Age, mean years (SD)	41.3 (11.5)	42.0 (11.4)	40.3 (11.6)	0.06*
Women (%)	83.4	81.8	85.6	0.19
Age at first diagnosis, years (mean, SD)	28.2 (11.1)	28.6 (11.6)	27.7 (10.4)	0.29*
Migraine type (%)				
Without aura	53.3	52.3	54.8	0.76†
With aura	39.3	39.9	38.6	
Other	7.3	7.8	6.6	
Education (%)				
Less than eighth grade	0.3	0.3	0.4	0.83†
Some high school	3.9	4.2	3.5	
High school graduate	24.3	22.6	26.7	
Some college	29.7	29.4	30.2	
College graduate	29.4	30.7	27.7	
Postgraduate	12.3	12.9	11.6	
Recent headache severity (%)				
Mild	4.0	4.4	4.5	0.08†
Moderate	45.2	48.7	40.1	
Severe	50.6	46.9	55.4	
Number of headaches in past month (mean, SD)	5.5 (5.6)	5.6 (5.7)	5.4 (5.4)	0.55*
Use of rescue medication (%)				
None	86.4	84.9	88.4	0.18†
Used for one attack	8.2	8.3	8.1	
Used for both attacks	5.4	6.8	3.5	

*t-test. †Chi-square test.

Table 2 Proportions of patients achieving pain relief and pain freedom within 2 h after dosing

	Achieved pain relief within 2 h after dosing		Achieved pain freedom within 2 h after dosing	
Treatment groups	**%**	**p-value***	**%**	**p-value***
Rizatriptan (n = 673)	88.1	0.0003	60.9	<0.0001
Other oral triptans (n = 673)	81.9		49.9	
Rizatriptan (n = 334)	89.2	0.35	61.1	0.02
Sumatriptan (n = 334)	87.1		54.2	
Rizatriptan (n = 274)	87.2	0.0011	59.1	0.0008
Fast-acting oral triptans† (n = 274)	78.1		47.1	
Rizatriptan (n = 65)	86.2	0.012	67.7	0.0007
Slow-acting oral triptans‡ (n = 65)	70.8		40.0	

*McNemar's test. †Fast-acting oral triptans include almotriptan, electriptan and zolmitriptan. ‡Slow-acting oral triptans include frovatriptan and naratriptan.

taking either rizatriptan (89.2%) or sumatriptan (87.1%) achieved PR within 2 h after dosing. Patients taking rizatriptan disproportionately attained PR within 2 h of dosing than patients taking either fast- or slow-acting oral triptans.

Proportions of achieving pain freedom within 2 h after dosing

With regard to PF, significantly more patients taking rizatriptan achieved PF within 2 h after dosing (60.9%), than patients taking other oral triptans (49.9%; $p < 0.0001$) (see Table 2). Across all subgroup comparisons (i.e. sumatriptan, fast- and slow-acting oral triptans), patients disproportionately attained PF within 2 h after taking rizatriptan.

Mean and median times of pain relief

The mean and median times to PR by treatment groups were displayed in Table 3a. The mean time to PR was statistically significantly shorter with rizatriptan (87.2 min) than with other oral triptans (162.3 min), a mean difference of 75.1 min (95% CI:

Table 3 Treatment differences in times to pain (a) relief and (b) freedom

Treatment comparisons	Mean (SD)	Mean differences (95% CI)	p-value*	Median (95% CI)	p-value†
(a)					
Rizatriptan (n = 673)	87.2 (248.8)	75.1 (31.5–118.7)	0.0008	45 (40–45)	<0.0001
Other oral triptans (n = 673)	162.3 (546.9)			52 (45–60)	
Rizatriptan (n = 334)	90.0 (294.8)	20.3 (−27.2 to 67.7)	0.40	45 (40–45)	0.12
Sumatriptan (n = 334)	110.3 (370.8)			45 (42–48)	
Rizatriptan (n = 274)	89.2 (211.5)	131.4 (46.9–215.9)	0.002	45 (40–45)	<0.0001
Fast-acting oral triptans (n = 274)	220.6 (702.9)			60 (48–60)	
Rizatriptan (n = 65)	64.2 (79.9)	119.3 (−13.9 to 252.6)	0.078	45 (40–45)	0.0003
Slow-acting oral triptans (n = 65)	183.6 (538.3)			70 (60–90)	
(b)					
Rizatriptan (n = 673)	261.5 (637.6)	96.8 (33.8–159.9)	0.003	100 (90–110)	<0.0001
Other oral triptans (n = 673)	358.3 (776.7)			124 (120–135)	
Rizatriptan (n = 334)	268.4 (689.8)	71.4 (−15.1 to 157.8)	0.11	100 (90–110)	0.009
Sumatriptan (n = 334)	339.8 (798.3)			120 (112–128)	
Rizatriptan (n = 274)	279.9 (636.4)	93.2 (−12.9 to 93.2)	0.08	100 (90–110)	<0.0001
Fast-acting oral triptans (n = 274)	373.2 (767.3)			130 (120–147)	
Rizatriptan (n = 65)	148.2 (223.9)	242.9 (65.6–420.1)	0.008	100 (90–110)	0.006
Slow-acting oral triptans (n = 65)	391.1 (709.3)			180 (120–210)	

*Paired t-test. †p-value was obtained from the Score Statistic of the Cox model, adjusting for patient clustering.

Table 4 Multivariate proportional hazards models of times to pain (a) relief and (b) freedom for rizatriptan relative to other oral triptans

Treatment group comparisons	Adjusted hazard ratio*	95% CI	p-value†
(a)			
Rizatriptan vs. other oral triptans (n = 673)	1.32	1.22–1.44	<0.0001
Rizatriptan vs. sumatriptan (n = 334)	1.14	1.02–1.29	0.023
Rizatriptan vs. fast-acting oral triptans‡ (n = 274)	1.48	1.3–1.7	<0.0001
Rizatriptan vs. slow-acting oral triptans§ (n = 65)	1.67	1.33–2.11	<0.0001
(b)			
Rizatriptan vs. other oral triptans (n = 673)	1.27	1.16–1.39	<0.0001
Rizatriptan vs. sumatriptan (n = 334)	1.19	1.07–1.34	0.002
Rizatriptan vs. fast-acting oral triptans‡ (n = 274)	1.31	1.16–1.49	<0.0001
Rizatriptan vs. slow-acting oral triptans§ (n = 65)	1.46	1.19–1.78	0.0003

*Adjusted variables included treatment sequence, treatment order and use of rescue medications. †Chi-square test. ‡Fast-acting oral triptans include almotriptan, electriptan and zolmitriptan. §Slow-acting oral triptans include frovatriptan and naratriptan.

31.5–118.7) (Table 3a). Median time to PR was statistically shorter for rizatriptan (45 min) than other oral triptans (52 min, $p < 0.0001$). There was no statistical difference in mean or median times to PR between rizatriptan and sumatriptan, although there were some numeric advantages for rizatriptan. Patients taking rizatriptan, as compared with either fast- or slow-acting oral triptans, reported significantly shorter mean and median times to PR.

Mean and median times of pain freedom

The mean and median times to PF by treatment groups were displayed in Table 3b. The mean time to PF was statistically significantly shorter with rizatriptan (261.5 min) than with other oral triptans (358.3 min), a mean difference of 96.8 min (95% CI: 33.8–159.9). Likewise, the median time to PF was statistically shorter for rizatriptan (100 min) than other oral triptans (124 min, $p < 0.0001$). Compared with sumatriptan, patients taking rizatriptan reported shorter median time to PF and similar mean time to freedom. Patients taking rizatriptan, as compared with either fast- or slow-acting oral triptans, reported significantly shorter mean and median times to PF.

Multivariate analyses

In the Cox proportional hazards model comparing rizatriptan and other oral triptans (Table 4a), the adjusted time to PR was 32% faster with rizatriptan (hazard ratio 1.32, 95% CI: 1.22–1.44; $p < 0.0001$), after adjusting for treatment sequence, treatment period and the use of rescue medications. The adjusted time to PR was consistently faster with rizatriptan than all other subgroup comparisons (i.e. sumatriptan, fast- and slow-acting oral triptans).

Compared with other oral triptans (Table 4b), the adjusted time to PF was 27% faster with rizatriptan (hazard ratio 1.27, 95% CI: 1.16–1.39; $p < 0.0001$), after adjusting for treatment sequence, treatment period and the use of rescue medications. The adjusted time to PF was consistently faster with rizatriptan than all other subgroup comparisons (i.e. sumatriptan, fast- and slow-acting oral triptans).

Satisfaction and preference

A total of 668 patients completed the diary questions about their satisfaction with their current medication (Table 5). A greater proportion of patients indicated that they were very satisfied when treating a migraine attack with rizatriptan compared with other oral triptans (29.5% vs. 19.5%). A smaller proportion of patients reported that they were dissatisfied (12.3% vs. 14.9%) or very dissatisfied (5.4% vs. 7.0%) when treating a migraine attack with rizatriptan compared with other oral triptans. In the cumulative logit multivariate model, patients were 52% more satisfied when treating their attack with rizatriptan than when treating with another oral triptan (odds ratio 1.52, 95% CI: 1.25–1.85; $p < 0.0001$), after adjusting for treatment sequence, treatment order and the use of rescue medications. Of the 652 patients, who

Table 5 Patient satisfaction with rizatriptan and with other oral triptans

	Rizatriptan, n (%)	Other oral triptans, n (%)
Very satisfied	197 (29.5)	130 (19.5)
Satisfied	253 (37.9)	277 (41.5)
Neither satisfied nor dissatisfied	100 (14.9)	114 (17.1)
Dissatisfied	82 (12.3)	100 (14.9)
Very dissatisfied	36 (5.4)	47 (7.0)

responded to the diary question regarding medication preference, 304 (46.6%) expressed a preference for rizatriptan, 220 (33.7%) preferred another oral triptan and 128 (19.6%) expressed no preference.

Tolerability

One adverse event was reported by a 30-year-old female patient who experienced hives and itchy skin the day after taking rizatriptan. The symptoms subsided when treated with methylprednisolone. No other adverse events were reported for rizatriptan.

Comment

This was a prospective, open-label, cross-over study, in which patients took either oral rizatriptan 10 mg or their usual-care oral triptans sequentially for two consecutive migraine attacks, and timed the course of their migraine pain using a stopwatch. Compared with patients' usual oral triptans therapy, the mean time to PR was approximately 75 min shorter with rizatriptan 10 mg, and the mean time to PF was approximately 97 min shorter. Median times to PR and PF were, respectively, 7 and 24 min shorter with rizatriptan. Replicating the results in clinical trials, a significantly greater proportion of patients achieved PR and PF within 2 h of dosing with rizatriptan than with other oral triptans. The results of this naturalistic study are consistent with those of double-blind, randomised clinical trials, in which rizatriptan 10 mg has equal or greater efficacy for PF at 2 h postdose than all other triptan dosages (8,9).

The extent to which rizatriptan is a more effective acute migraine therapy than other oral triptans in a naturalistic setting has not been reported. Rizatriptan has previously been compared with patients' usual medications, which were either non-triptans or a mixture of triptans and non-triptans. These studies showed that rizatriptan had better treatment outcomes than non-triptan medications (15,16). In a study of the orally disintegrating formulation of rizatriptan, the percentage of patients reporting PR and PF at 2 h was more than twice as great with rizatriptan as with patients' usual, non-triptan medication (15). In a pharmacy-based study comparing patients who took rizatriptan with patients who took a non-triptan, the percentage of patients reporting PR and PF at 2 h was significantly greater with rizatriptan (16). The US Migraine Assessment Protocol study compared rizatriptan 10 mg with patients' non-triptan usual medication (14,19). Significantly more patients were symptom free at 2 h after dosing with rizatriptan than with patients' usual treatment (19). In studies in which the comparator included both oral triptans and non-triptan, rizatriptan was again found to have better treatment outcomes (17). In the previous publication by Bell et al. (17), 'usual treatment' included both triptan (80.6%) and non-triptan migraine medications (19.4%). Not surprisingly, when non-triptans were included in the usual treatment, a greater treatment benefit was observed with rizatriptan: the mean times to onset of PR and PF with rizatriptan compared to usual treatment were 85 vs. 107 min and 222 vs. 298 min respectively (17). Our study refines Bell et al. analysis by comparing rizatriptan with other oral triptans only. Consistent with the existing literature of treatment in naturalistic settings, we found that rizatriptan 10 mg provided shorter times to PR and PF than other oral triptans.

This report has made a number of improvements in terms of study design, outcome measurement and appropriate statistical analysis. Studies of triptans employing pretest to post-test or parallel group designs are vulnerable to certain biases. A pretest to post-test design is vulnerable to temporal drift in variables that might influence the results. A patient's migraine profile may change spontaneously from one attack to the next and changes in the migraine profile may be attributed incorrectly to the effect of the post-test intervention. In a non-randomised parallel-group design, a patient selection bias may result in non-comparable patient sets. The cross-over design employed in this and other studies (14,17,19) is meant to minimise these potential biases. A cross-over design reduces intraperson variability, because patients serve as their own controls. With this control for patient variability built into the study design, one can more confidently attribute differences in outcomes to differences in the intervention rather than to extraneous factors. With respect to the measurement of the primary end-points, we strove to time events precisely by asking patients to use a stopwatch. Thus, in contrast to previous studies, which categorised patients according to their pain status at fixed time points (14–16,19), we were able to document events continuously in real time. Precise measurement of the dependent variable enhances the ability to detect differences between treatments.

Both times to PR and PF were not normally distributed, but were skewed to the right, as a small proportion (3.8–5.9%) of migraine patients were not pain free 200 min after therapy (17). Mean times to events may be more intuitive, but results derived from means and parametric tests of statistical significance (e.g. *t*-test) may be inaccurate. In addition to mean times to events, we reported median times using semi-parametric (Cox proportional hazards modeling) methods. Our findings that patients taking rizatriptan for acute migraine had significantly shor-

ter times to PR and PF than patients taking other oral triptans, were supported by statistical tests of both mean and median time differences.

There are several caveats to the interpretation of these results. For unknown reasons, a majority of patients entering the study did not complete the protocol, introducing the possibility that the included and excluded populations may not have been comparable. We have noted that patients who were not included in the analysis because of protocol violations had a statistically significantly greater frequency of migraine-associated symptoms (17). In addition, there were a slightly greater proportion of women among stopwatch non-users (90.9%), than among stopwatch users (83.4%). Our results, therefore, are only strictly applicable to the migraine patients who followed the research protocol and used a stopwatch to track their time to headache events. Secondly, our definition of PR was different from the one generally used in clinical trials. In clinical trials, PR is typically defined as a reduction in headache pain severity from moderate/severe to mild/none (10). In this study, we asked patients to record the moment when they felt the onset of headache relief. Although both definitions are subjective, our definition may have exaggerated the degree of PR. It is reasonable to assume that patients evaluated their PR similarly whether taking rizatriptan or other oral triptans. Any non-differential exaggeration of PR would increase the noise in the estimation, thus decreasing the chance of finding any statistically significant difference. Thirdly, the open-label study design, in which patients were aware of the specific medications used for each attack, may have introduced a bias between treatments, so that subjectivity and/or loyalty to a particular brand name medication are potential threats to validity. We attempted to control for this type of artefact, by creating a numeric variable of the order of treatment options and adjusting for its effect in the multivariate analysis.

In conclusion, to the best of our knowledge, this was the first naturalistic study to compare rizatriptan 10 mg with other oral triptans using stopwatch methodology. The study employed a multi-centre, prospective, cross-over study design, with use of a stopwatch to measure the primary study end-points precisely. Rizatriptan was associated with shorter times to PR and PF than were other oral triptans. This study reproduced in a naturalistic setting the results of double-blind, randomised clinical trials, in which rizatriptan 10 mg has greater efficacy in terms of PF at 2 h postdose than the majority of other triptan dosages. Patients were more satisfied with rizatriptan than with other oral triptans and more patients preferred rizatriptan than other oral triptans for their next migraine attack.

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Appendix

Table 1 A list of participating physicians

Last name	First name	Title	City	State
Aaron	Maureen	MD	Martinsville	VA
Abdul-Wahab	Muhammed	MD	Los Angeles	CA
Absher	John	MD	Greenville	SC
Adams	Quentin	MD	Arlington	TX
Adkins	Edward	MD	Mansfield	OH
Agrawal	Anjula	MD	Washington	DC
Alexander	Michael	MD	Plantation	FL
Alexandrova	Natalia	MD	Arlington	VA
Alhabian	Oula	MD	Sylvania	OH
Allen	Chris	MD	Pittsburgh	PA
Allen	Thomas	MD	Overland Park	KS
Alway	David	MD	Alexandria	VA
Andrews	Roberta	MD	Macon	GA
Andrus	Dan	MD	Temecula	CA
Ansell	Jacqueline	MD	Northport	AL
Anstadt	David	MD	Warren	OH
Anthony	Jeff	DO	San Diego	CA
Aoki	Jeffrey	MD	Clovis	CA
Arastu	Jameel	MD	New Hartford	NY
Arikawa	Terry	DO	Granite Bay	CA
Arkin	Karen	MD	Overland Park	KS
Auld	Heather	MD	Fort Myers	FL
Avanzato	Joseph	MD	Yorktown Hgts	NY
Avey	Joseph	MD	Lehigh Acres	FL
Awerbuch	Gavin	MD	Bay City	MI
Baier	Charles	MD	Mandeville	LA
Bailey-Walton	Paula	MD	Beverly Hills	CA
Baill	Cori	MD	Orlando	FL
Baker	Keith	DO	Cape Coral	FL
Ballenger	Clarence	MD	Jacksonville	NC
Barboza	Beverly	MD	Los Gatos	CA
Barrett	Amelia	MD	Lonetree	CO
Barrington	Patricia	DO	Lawrenceville	GA
Bartkowiak	Anthony	MD	Altoona	PA
Bartnick	David	MD	Piqua	OH
Bartos	Paul	MD	North Canton	OH
Bartos	Sara	MD	Austin	TX
Baurichter	John	DO	Springfield	MO
Bayliss	Robert	MD	Greenville	SC
Baylor	Melissa	DO	Dover	PA
Beard	Mary	MD	Salt Lake City	UT

Table 1 (*Continued*)

Last name	First name	Title	City	State
Beck	Brian	DO	Davison	MI
Becker	Jeffrey	DO	Scottsdale	AZ
Becker	Teresa	MD	Friendship	TX
Beckert	John	DO	Kahoka	MO
Behm	John	MD	Wexford	PA
Belote	Robert	MD	Leesburg	VA
Benavides	Angela	MD	Ottawa	IL
Benchimol	George	MD	Gainesville	FL
Bennett	Nathan	MD	Pittsburgh	PA
Bennett	Suzanne	DO	Phoenix	AZ
Benzaquen	Max	MD	Chesterfield	MO
Berriesford	Gary	MD	Kingwood	TX
Berriman	Katherine	MD	Monroe	OH
Bertrand	V	DO	Frankfort	IL
Bevers	William	MD	Oklahoma City	OK
Bhupalam	Rukmaiah	MD	Louisville	KY
Birk	Harvinder	MD	Redding	CA
Birkmann	Lewiston	MD	Lincoln	NE
Black	Ross	MD	Cuyahoga Falls	OH
Blady	David	MD	Glen Ridge	NJ
Blanchard	Susan	MD	Mobile	AL
Blank	Benjamin	DO	Glendora	NJ
Bloodworth	James	MD	Greenville	SC
Blume	William	MD	Evansville	IN
Bodemann	Diane	MD	Hot Springs	AR
Bodemann	Stephen	MD	Hot Springs	AR
Bolinger	Jony	MD	Easley	SC
Borsheim	Mark	MD	Hayden Lake	ID
Boulware	William	MD	Florence	SC
Bowhay	Thomas	MD	Jackson	CA
Brandstater	Cherry	MD	Redlands	CA
Braun	Edward	MD	Tampa	FL
Breitenbach	Ray	MD	Waterford	MI
Bressler	Jill	MD	Englewood Cliffs	NJ
Brewer	Raymond	MD	Universal City	TX
Brodsky	Hal	MD	Gainesville	FL
Brooks	Mark	MD	Anderson Island	WA
Brown	Carl	DO	Odessa	TX
Brown	David	MD	Fayetteville	AR
Brown	Morris	MD	Dayton	OH
Brown	Raymond	MD	Cleveland	TN
Brown	Thomas	MD	San Antonio	TX
Brown	William	MD	Tyler	TX
Bryan	Angela	MD	Cape Coral	FL
Burnette	Thomas	MD	Brewster	NY
Butler-Sumner	Susan	MD	Cave Spring	GA
Buynak	Robert	MD	Portage	IN
C Quaglieri	Frank	MD	Reno	NV
Cagle	Mary	MD	Greenville	SC
Calise	Paul	MD	Ft Lauderdale	FL
Calland	Ann	DO	Westerville	OH
Cameron	Daniel	MD	Mount Kisco	NY
Campbell	James	DO	Broken Arrow	OK
Carlini	Walter	MD	Medford	OR

Table 1 (*Continued*)

Last name	First name	Title	City	State
Carmichael	Patrick	MD	Gainesville	FL
Carter	John	MD	Tucson	AZ
Castaldo	John	MD	Allentown	PA
Castor	Terrance	MD	Worthington	OH
Cavalier	Steven	MD	Baton Rouge	LA
Cerbone	Tracey	MD	Port Saint Lucie	FL
Cevasco	Robert	MD	Medina	OH
Chamikles	Jason	DO	Middle Vlg	NY
Chan	Kahing	MD	Opelika	AL
Chan	Kenneth	DO	Jonesboro	AR
Charani	Kimy	DO	Tucson	AZ
Charney	Jonathan	MD	New York	NY
Chehrenama	Mahan	DO	Alexandria	VA
Chequer	Rosemary	MD	Lancaster	CA
Chessin	Vicki	MD	Alma	MI
Clark	James	MD	Provo	UT
Clemens	Michael	MD	Palm Harbor	FL
Clendening	Marilyn	MD	North Canton	OH
Conard	Scott	MD	Irving	TX
Cook	Charles	DO	Bedford	TX
Cook	Jolanda	MD	Abihgdoh	VA
Cooley	Richard	MD	Baton Rouge	LA
Cooper	Kirsten	MD	Stanley	NC
Costa	Ralph	MD	Voorhees	NJ
Costin	Scott	MD	Bellefontaine	OH
Cottingim	Gary	MD	Greenville	SC
Counce	Diane	MD	Alabaster	AL
Crabtree	Yvette	MD	Mission	KS
Craig	William	MD	Greenville	SC
Crawford	Edgar	MD	Portland	OR
Crosnoe	Janna	MD	Cape Girardeau	MO
Crump	William	MD	Chicago	IL
Csepany	Emerico	MD	Cerritos	CA
Cuellar	James	MD	Wentzville	MO
Cushman	Kenneth	MD	Tyler	TX
Czulada	Gary	DO	Dover	PA
Davis	David	MD	Fayetteville	AR
Davis	Lloyd	MD	Des Plaines	IL
De Armitt	Don	MD	Harrisburg	PA
De Garmo	Ronald	DO	Greer	SC
De Haven	Joseph	MD	Savannah	GA
De Santis	Michael	MD	Hickory	NC
Debin	Susan	MD	Orange	CA
Decker	Andrew	MD	Yorktown Hts	NY
Delp	Robert	MD	Clawson	MI
Deyarmin	Brian	MD	Bethel Park	PA
Dibert	Steven	MD	Gastonia	NC
Doehring	Larry	DO	Northglenn	CO
Doghramji	Paul	MD	Pottstown	PA
Doran	Anne	MD	Midlothian	VA
Doreshow	Larry	DO	Philadelphia	PA
Dougherty	Richard	MD	Charlotte	NC
Dougherty	Nancy	MD	Portland	OR
Downey	Kathleen	MD	Cincinnati	OH
Drake	Alan	MD	Sparta	TN

Table 1 (*Continued*)

Last name	First name	Title	City	State
Drake	Robert	MD	Somerset	KY
Dresser	Lee	MD	Newark	DE
Drinnen	Jeffrey	MD	Knoxville	TN
Druzak	Karen	MD	Naperville	IL
Dugan	Thomas	MD	Monaca	PA
Dugano-Daphnis	Pamela	MD	League City	TX
Dumbacher	Perri	MD	Lake Mary	FL
Duncan Garcia	Stephanie	DO	Coral Gables	FL
Dure-Smith	Belinda	MD	San Diego	CA
D' Cruz	A	MD	Lubbock	TX
Ebersole	Philip	MD	Temecula	CA
Eck	Jeffrey	MD	Elkhart	IN
Edelmann	Karl	MD	Ann Arbor	MI
Elder	Robert	MD	Hartsville	SC
Elkind	Arthur	MD	Mount Vernon	NY
Ellis	Brian	MD	Melbourne	FL
Ellis	Paul	MD	Alpharetta	GA
Emerson	Russell	MD	Stanley	NC
Englert	Jack	MD	Huntsville	AL
Enns	Richard	MD	Huntington Beach	CA
Entin	Erik	MD	Plainview	NY
Eppinette	James	MD	West Monroe	LA
Erbay	Celal	MD	Gainesville	FL
Eshenaur	Oliver	DO	Orrville	OH
Eslami	Nasrollah	MD	Chicago	IL
Esposito	Anthony	MD	Anniston	AL
Estrada-Massey	Adahli	MD	Auburn	AL
Eubank	Geoffrey	MD	Columbus	OH
Evans	Bryan	MD	Huntsville	AL
Fahey	Patricia	MD	Englewood	CO
Fason	Jeff	MD	Florissant	MO
Feldman	Ludmila	MD	Staten Island	NY
Fesler	William	MD	Bartlesville	OK
Fields	Carolyn	MD	Greenville	SC
Fife	Terry	MD	Scottsdale	AZ
Finch	John	DO	Seattle	WA
Fink	Alan	MD	Wilmington	DE
First	Brian	MD	San Diego	CA
Fischer	Calvin	DO	Hoffman Estates	IL
Fisher	Robert	MD	Fort Smith	AR
Fisher	Tobin	MD	Huntsville	AL
Fisher	Todd	MD	Middletown	PA
Flechas	Jorge	MD	Hendersonville	NC
Fleming	Frank	MD	Greenville	NC
Fleming	Peter	MD	Watertown	MA
Fleshman	Daniel	MD	Hilliard	OH
Flitman	Stephen	MD	Phoenix	AZ
Ford	Don	MD	Sugar Land	TX
Ford	Jack	MD	Colorado Spgs	CO
Forner	Stephen	MD	Chico	CA
Foster	Carol	MD	Phoenix	AZ
Fox	Kenneth	DO	Levittown	PA
Franklin	Michael	MD	Saint Petersburg	FL
Freberg	Daniel	DO	Mesa	AZ
Friedman	Aaron	MD	New Orleans	LA

Table 1 (*Continued*)

Last name	First name	Title	City	State
Friedrich	Brian	DO	Drexel Hill	PA
Friend	Harold	MD	Boca Raton	FL
Fritz	John	DO	Jersey City	NJ
Fullemann	Susan	MD	Burlingame	CA
Fung	Wilson	MD	Santa Clarita	CA
Furey	William	DO	Stratford	NJ
Gaddis	Kenneth	MD	Thibodaux	LA
Gaikwad	Shilpa	MD	Oxnard	CA
Gardner	Jack	MD	Dallas	TX
Gardner	Raymond	MD	Mansfield	OH
Garg	Ram	MD	Woodhaven	MI
Garrett	David	MD	Bentonville	AR
Gatiwala	Indravadan	MD	Lumberton	NC
Gaya	William	MD	Ocala	FL
Gebel	Michael	MD	Winter Park	FL
Gehi	Chandra	MD	Anniston	AL
Gerard	William	DO	Milwaukee	WI
Gervais	Donald	MD	Houma	LA
Gill	Naurang	MD	Woodbridge	VA
Gilson	Paul	MD	Brick	NJ
Glapinski	Robert	DO	Capac	MI
Glasser	Michael	MD	New York	NY
Gluckman	Richard	MD	San Pedro	CA
Goering	Edward	DO	Portland	OR
Goldberger	Daniel	MD	Portage	MI
Goldstein	Gary	MD	Palm Harbor	FL
Golnick	Jan	MD	Omaha	NE
Golub	Bari	MD	Saint Louis	MO
Gordon	Colette	MD	Chicago	IL
Gordon	Norman	MD	E Providence	RI
Gosling	John	MD	Clinton	MI
Govindan	Srini	MD	Wheeling	WV
Graff	Justin	MD	Belden	MS
Grass	David	MD	Fairfax	VA
Graves	Christy	MD	Slidell	LA
Graves	Kurt	MD	Baton Rouge	LA
Green	Phillip	MD	Kalamazoo	MI
Greenberg	William	MD	Saint Petersburg	FL
Greenblatt	Lawrence	DO	Bellevue	WA
Greenwood	John	MD	Lenexa	KS
Greg Zoltani	John	MD	Tacoma	WA
Gregg Hardy	J	MD	Greenville	NC
Grellet	Catherine	MD	Los Gatos	CA
Grimball	Roger	MD	Sulphur	LA
Griner	Donald	DO	Mesa	AZ
Grote	Stewart	DO	Lansing	KS
Grover	Daniel	MD	Greenville	SC
Guin Johnson	Darlene	MD	Oklahoma City	OK
Haga	Edward	MD	Hampton	VA
Hallmark	Belton	MD	Castle Rock	CO
Halper-Erkkila	Ruby	MD	White House Station	NJ
Halpern	Betty	MD	Houston	TX
Halverson	James	DO	Newport News	VA
Hamo	Wael	MD	Sylacauga	AL
Hanley	Patricia	MD	Austin	TX

Table 1 (*Continued*)

Last name	First name	Title	City	State
Hanley	Thomas	MD	Voorhees	NJ
Hanrahan	Beth	MD	Clearwater	FL
Hanson	James	MD	Waukesha	WI
Hantos	Livia	MD	Buffalo Grove	IL
Hare	Ester	MD	Orangeburg	SC
Harris	Mark	MD	Atlanta	GA
Harrison	Stephen	MD	Fulton	IL
Harvey	Frank	MD	West Carthage	NY
Hatharasinghe	Roger	MD	Statesville	NC
Head	Gilbert	MD	Omaha	NE
Hegde	Hemant	MD	Ogden	UT
Henderson	Reggie	MD	Lexington	TN
Henson	Lois	DO	Vandalia	OH
Hernandez	Rafael	MD	Fredericksbrg	VA
Herrold	James	MD	Boise	ID
Hiebert	Pamela	MD	Bozeman	MT
Hilgeman	Joseph	MD	Manchester	MO
Hirsch	Jeffrey	MD	Oklahoma City	OK
Hoffman	Daniel	MD	Dunlap	IL
Holleman	Kevin	MD	Portage	MI
Holt	William	DO	Port Charlotte	FL
Homan	James	DO	Tampa	FL
Hosso-Cooper	Jennifer	DO	Oak Lawn	IL
Hostetter	Carol	DO	Westerville	OH
Howard	Jerome	MD	Charlotte	NC
Howe	Jeffrey	MD	Elkhart	IN
Howe	Steve	DO	Marietta	OH
Howell	Gregory	MD	Ocala	FL
Hrabarchuk	Eugene	MD	Franklin	NJ
Hsu	Jui	MD	Elkton	MD
Huddlestone	John	MD	Chicago	IL
Hudson	Ronald	MD	Columbus	GA
Hunt	Wade	MD	New Hartford	NY
Husain	Mohammad	MD	Valley Stream	NY
Husid	Marc	MD	Augusta	GA
Hutchison	Edward	MD	Brea	CA
Inamine	Gary	MD	Honolulu	HI
Ireland	Cliff	DO	Skokie	IL
Isenberg-Rawls	Judy	MD	Madison	AL
Ivy	Mary	MD	Lititz	PA
Izzo	Timothy	DO	Grand Ledge	MI
J Holladay	Dawnetta	MD	Athens	GA
Jackson	Rebecca	MD	Knoxville	TN
Jacobus	Brent	DO	Crown Point	IN
Jao	Kedy	DO	La Mirada	CA
Jeffries	Nancy	DO	Ephrata	PA
Jenckes	George	MD	Reading	PA
Jirovec	Richard	MD	Lincoln	NE
Johnson	Constance	MD	Clarksville	TN
Johnson	James	MD	Greenville	SC
Johnson	Mark	MD	Salt Lake Cty	UT
Johnson	Michael	MD	Bucyrus	OH
Johnson	Michael	MD	Sherwood	OR
Jones	Helen	MD	Fresno	CA
Joshi	Sanjeev	MD	Chicago Hts	IL

Table 1 (*Continued*)

Last name	First name	Title	City	State
Jurcik	Yvonne	MD	Buffalo Grove	IL
Justiz	William	MD	Naples	FL
Kafka	Christopher	DO	Gladstone	MO
Kagan	Jeffrey	MD	Newington	CT
Kailasam	Jayasree	MD	Houston	TX
Kalahasthy	Annadorai	MD	Dayton	OH
Kalra	Arun	MD	Monroe	LA
Kaplan	Ryan	MD	Fayetteville	AR
Karimi	Kambiz	MD	Indianapolis	IN
Kaville	Robert	MD	Scranton	PA
Keehbauch	Jennifer	MD	Orlando	FL
Keinarth	Paul	MD	Austin	TX
Kelemen	John	MD	Plainview	NY
Keller	David	MD	Hershey	PA
Kelsey	Alan	MD	White House Station	NJ
Kent	Robert	DO	Arlington	TX
Kersting	Clayton	MD	Newport	WA
Kessler	Thomas	MD	Mobile	AL
Khalid	Aijaz	MD	Columbus	GA
Kiefer	Peter	MD	Des Plaines	IL
Kilo	Charles	MD	Naples	FL
Kingston	Caroline	MD	Santa Fe	NM
Kipp	Joseph	MD	Newtown	PA
Kiser	Roy	MD	Richardson	TX
Kistler	Charles	DO	Columbus	OH
Klein	Jeffrey	MD	Westlake Vlg	CA
Knight	Rebecca	MD	Peoria	IL
Knipfer	Mark	MD	Spartanburg	SC
Knubley	William	MD	Fort Smith	AR
Koch	Stanley	MD	Morton	IL
Koffman	Brian	MD	Diamond Bar	CA
Koopman	Anton	MD	Columbus	IN
Kopp	James	MD	Newport News	VA
Kordish	Theresa	DO	Kalamazoo	MI
Kovacevic	Olga	MD	Strongsville	OH
Kovacs	Suzanne	MD	Spartanburg	SC
Kristl	Kevin	MD	South Bend	IN
Kritz	David	MD	Orange	CA
Krupitsky	Andrew	DO	Altamonte Spg	FL
Krusz	John	MD	Dallas	TX
Kumar	Ansuya	MD	Plano	TX
Kumar	Seema	MD	Alexandria	VA
Kunst	Edward	MD	Manchester	MO
Kurlander	Ronald	MD	Pompano Beach	FL
Kurtzer	Yitzchok	MD	Scranton	PA
Kurzawa	Mark	MD	Clinton Township	MI
Kwon-Hong	Grace	MD	Modesto	CA
Laeger	Jane	MD	Bangor	ME
Lamb	Chad	MD	Anderson	IN
Lambert	Lise	MD	Ft Lauderdale	FL
Larrison	Charles	MD	Hot Springs	AR
Lazarus	Kenneth	MD	Fayetteville	GA
Ledet	Michael	MD	Mobile	AL
Lee	Daniel	MD	Greenville	NC
Lee	Kang	MD	Ludington	MI

Table 1 (*Continued*)

Last name	First name	Title	City	State
Lee	Keung	MD	Asheboro	NC
Leeds	Leroy	MD	Houston	TX
Leitman	Jeffrey	DO	Stratford	NJ
Leitzinger	Linda	DO	Erie	PA
Leland	Richard	MD	Greenville	SC
Lele	Anju	MD	Mentor	OH
Lele	Geeta	MD	Hobbs	NM
Lele	Shreeniwas	MD	Mentor	OH
Levin	Kenneth	MD	Ridgewood	NJ
Lewison	Gary	MD	East Dundee	IL
Liebentritt	Matthew	MD	Longmont	CO
Lieux	Theodore	MD	Baton Rouge	LA
Lillo	Joseph	DO	Scottsdale	AZ
Lim	Andrew	MD	Wakefield	MA
Lin	Cheng-Te	MD	Lima	OH
Lindholm	Karin	DO	Chicago	IL
Lindley	Mark	MD	Plymouth	MI
Lipscomb	Geoffrey	MD	Foley	AL
Lisgar	Harvey	DO	Richboro	PA
Loftus	Brian	MD	Houston	TX
Look	Michelle	MD	San Diego	CA
Lucas	Cynthia	NP	Macon	GA
Lum	Katharine	MD	Vero Beach	FL
Luria	Eric	MD	Gig Harbor	WA
Lynn	Lon	DO	Tampa	FL
Ma	Sherry	MD	Saint Louis	MO
Magpile	Michael	MD	La Mesa	CA
Magre	Ann-Marie	MD	Fayetteville	AR
Maida	Gerald	MD	Bloomingdale	IL
Majid	Abdul	MD	Menasha	WI
Manning	Rickey	MD	Knoxville	TN
Mannix	Lisa	MD	Westchester	OH
Marlow	Robert	MD	Huntsville	AL
Marmel	Richard	MD	San Antonio	TX
Marquino	Rey	MD	Dennison	OH
Marraccini	Linda	MD	Miami	FL
Martin	John	MD	Edmond	OK
Mathew	Ninan	MD	Houston	TX
Matthews	Dale	MD	Washington	DC
Maurides	Peter	MD	Greenville	SC
Mauskop	Alexander	MD	New York	NY
May	James	MD	Shreveport	LA
Mayer	David	DO	Huntsville	AL
Mc Carren	Timothy	MD	Cincinnati	OH
Mc Carthy	Christopher	MD	Saint Louis	MO
Mc Clain	David	MD	American Fork	UT
Mc Daniel	Gregory	MD	Youngstown	OH
Mc Ghee	Terrence	MD	Asheville	NC
Mc Lean-Bennett	Jacquelyn	DO	Albany	NY
McCallum	Gary	MD	Bellingham	WA
Mcphee	Robert	DO	Crystal River	FL
Melton	Gary	MD	Crittenden	KY
Menachem	Allan	MD	Whiteville	NC
Mentock	Sabrina	MD	Durham	NC
Michel	Elliot	MD	Natrona Hts	PA

Table 1 (*Continued*)

Last name	First name	Title	City	State
Michelsen	Thomas	DO	Jacksonville	FL
Miller	Michael	MD	Chesterland	OH
Miller	Roger	MD	Jacksonville	FL
Miller	Tamara	MD	Fort Collins	CO
Millermaier	Edward	MD	Portage	MI
Millermaier	Janet	MD	Portage	MI
Mills	Richard	MD	Mount Pleasant	SC
Mingione	Donald	MD	Portsmouth	VA
Mir	Sarim	MD	Cumberland	MD
Moberly	Harold	MD	Winchester	KY
Mockler	Karen	MD	Dadeville	AL
Modi	Smita	MD	Iselin	NJ
Mogle	Douglas	MD	Melbourne	FL
Molter	Darron	MD	N Myrtle Bch	SC
Monje	Marile	MD	Crystal Lake	IL
Moon	Steven	MD	Fayetteville	AR
Moore	Harold	MD	Columbia	SC
Moore	Terrence	MD	Denton	TX
Moran	Joseph	MD	Statesville	NC
Morrill	Thomas	DO	Garland	TX
Morse	Michael	MD	Fayetteville	AR
Mueller	Nancy	MD	Englewood Cliffs	NJ
Mullowney	James	DO	Mesquite	TX
Munshower	John	MD	Marcus Hook	PA
Murillo	George	MD	Tomball	TX
Murphy	Ann	DO	Overland Park	KS
Murphy	Duffy	MD	Logansport	IN
Muse	Derek	MD	Salt Lake Cty	UT
Nakano	Kenneth	MD	Kailua	HI
Naples	Robert	DO	Cortland	OH
Natrajan	Puthugramam	MD	Augusta	GA
Navarro	Evelyn	MD	Grand Rapids	MI
Nayyar	Manmohan	MD	Apple Valley	CA
Nazario	Liliana	MD	Overland Park	KS
Neely	Kathryn	MD	Canton	GA
Nelson	Robert	MD	Norco	CA
Nestor	Gregory	MD	Saint Petersburg	FL
Newman	Stephen	MD	Plainview	NY
Ng	Ken	MD	Ocala	FL
Nieves	Alfredo	MD	Chattanooga	TN
Norman	Howard	DO	Avondale	AZ
Norys	James	MD	Fayetteville	AR
O'Carroll	Christopher	MD	Newport Beach	CA
Odio	Alberto	MD	Simi Valley	CA
Ohashi	Gary	MD	Westminster	CA
Olson	Michael	MD	Sioux Falls	SD
Ondrejicka	John	MD	Jacksonville Beach	FL
Oppy	James	MD	Connellsville	PA
Osio	Antonio	MD	Wichita	KS
Ottley	Barbara-Jean	MD	Hays	KS
Owusu-Yaw	Victor	MD	Danville	VA
Paley	Judith	MD	Denver	CO
Palmer	Madelyn	MD	Littleton	CO
Parcells	Patrick	MD	Newport News	VA
Pare	Bernard	MD	Mount Juliet	TN

Table 1 (*Continued*)

Last name	First name	Title	City	State
Park	Richard	MD	Universal Cty	TX
Parker	David	DO	Northglenn	CO
Parker	Richard	DO	San Diego	CA
Parmer	Keith	MD	Rome	GA
Parsley	Donna	DO	Pickerington	OH
Patel	Alpa	MD	Jacksonville	FL
Patel	Mrugendra	MD	Richlands	VA
Patterson	Brian	MD	Bellingham	WA
Paul	Alan	MD	Tyler	TX
Payne	Richard	MD	Encinitas	CA
Peacock	Mark	MD	Jacksonville	FL
Pearlman	Eric	MD	Savannah	GA
Peggy Jones	Mary	MD	Tucson	AZ
Perdikis	George	MD	Lancaster	CA
Perel	Allan	MD	Staten Island	NY
Perlman	Neil	MD	Vernon Hills	IL
Perry	William	MD	Centre	AL
Pham	Khoi	MD	Aurora	CO
Phelan	James	MD	Kingwood	TX
Pierce	Paul	MD	Vicksburg	MS
Pillow	Deborah	MD	Addyston	OH
Polyhronopoulos	Spiro	MD	Lebanon	KY
Porter	Andrew	MD	Gilbertsville	KY
Posgai	Scott	MD	Orlando	FL
Potts	Gregory	MD	Louisville	KY
Prater	Fredric	DO	Saint Louis	MO
Pratt	Joseph	MD	Corinth	MS
Prince	Vickie	MD	Jacksonville	FL
Pugach	Neil	MD	Chesapeake	VA
Putland	Kenneth	MD	Newport News	VA
Quick	Robert	MD	Crete	NE
R Holt	Raymond	MD	Baldwinsville	NY
R Raybourne	Susan	MD	Macon	GA
R. Bullard	Branch	MD	Monte Vista	CO
Rabovetskaya	Yevgeniya	MD	Brooklyn	NY
Raikhel	Marina	MD	Torrance	CA
Raj	Joseph	MD	New Hartford	NY
Rakowski	Tara	MD	Milwaukee	WI
Ralph	Lee	MD	San Diego	CA
Randall	William	MD	Dayton	OH
Ranieri	Joseph	DO	Philadelphia	PA
Rasor	Daniel	MD	Austin	TX
Ratcliff	Keith	MD	Washington	MO
Reeves	Robert	MD	Johnson City	TN
Rehm	Charles	MD	Saint Louis	MO
Reid	Randal	MD	Austin	TX
Rendziperis	Arthur	DO	White Lake	MI
Resnick	Harvey	MD	Lake Jackson	TX
Reyna	Oscar	MD	Latrobe	PA
Reznick	Louis	DO	Glendale	NY
Rhodes	Richard	DO	North Charleston	SC
Ringwala	Kirtida	MD	Oshkosh	WI
Riske	Terrance	MD	Hayden Lake	ID
Robin	Joseph	MD	Bellevue	WA
Rodberg	Nadia	MD	Southborough	MA

Table 1 (*Continued*)

Last name	First name	Title	City	State
Rodgers	Robert	MD	Apopka	FL
Roeshman	Robert	DO	Allentown	PA
Rogers	David	MD	Easley	SC
Rolfsen	Michael	MD	Baton Rouge	LA
Roller	Don	MD	Tulsa	OK
Rolston	B	MD	Covington	LA
Rosemore	Michael	DO	Hueytown	AL
Rosenberg	Mark	DO	Sterling Heights	MI
Rosenfeld	Jack	MD	Lansdale	PA
Ross	David	MD	Plantation	FL
Roth	Barbara	MD	Byesville	OH
Rubenstein	Robert	MD	Bremerton	WA
Ryan	Roger	MD	Little Rock	AR
S Asin	Gerald	MD	Phoenix	AZ
S Label	Lorne	MD	Thousand Oaks	CA
Salam	Yasser	MD	Racine	WI
Salvato	Patricia	MD	Houston	TX
Sarfraz	Naeem	MD	Norwalk	CT
Sarna	Paul	MD	Texarkana	TX
Satterfield	Benton	MD	Raleigh	NC
Savia	Philip	MD	Draper	UT
Savic-Dyrnas	Lydia	MD	Belvidere	IL
Savin	Andrew	MD	Chicago	IL
Schaffer	Robert	MD	Centerville	OH
Schecht	Howard	MD	Toledo	OH
Schmidt	Clinton	MD	Fayetteville	AR
Schmidt	Jay	MD	Hudson	NC
Schneider	Donald	DO	Highland Ranch	CO
Schwartz	Kenneth	MD	Saratoga Spgs	NY
Scrimenti	Michael	MD	Mahwah	NJ
Scroggins	John	MD	Tyler	TX
Seestedt	Richard	MD	Fairfax	VA
Seifer	Alan	MD	Miami	FL
Sengstock	Gregory	MD	Jacksonville	FL
Settles	Richard	DO	Scottsdale	AZ
Sharfman	Marc	MD	Winter Park	FL
Sharkey	Joseph	MD	Golden	CO
Sharlin	Kenneth	MD	Branson	MO
Sharman	Daryl	MD	Millsboro	DE
Siddiqui	Usman	MD	Lawrenceburg	IN
Sidney White	Ernest	MD	Paris	TX
Silverman	Marshall	MD	Charlotte	NC
Silverstein	Bruce	MD	Liverpool	NY
Simmons	Calvin	MD	Lewisville	TX
Simmons	Ronald	MD	Cadillac	MI
Simsarian	James	MD	Fairfax	VA
Singer	Jerry	MD	Altoona	PA
Sirken	David	DO	Huntington Valley	PA
Sklaver	Neal	MD	Dallas	TX
Sloan	Jerry	MD	New Hartford	NY
Smith	David	MD	Lincoln	NE
Smith	Robert	DO	Springboro	OH
Smith	Sally	MD	Tyler	TX
Smith	Theodore	MD	Spartanburg	SC

Table 1 (*Continued*)

Last name	First name	Title	City	State
Smith	Thomas	MD	Holdrege	NE
Snoddy	Neil	MD	Columbus	GA
Snyder	Marijo	MD	Kalamazoo	MI
Sockolov	Ronald	MD	Sacramento	CA
Sommers	Thomas	MD	O'Fallen	MO
Sparacino	Kathy	MD	Decatur	AL
Spivack	Jonathan	MD	Milwaukee	WI
Spuhler	Wanda	MD	Friendswood	TX
Squire	Karen	MD	West Chester	PA
Stalter	Marvin	MD	Bryan	OH
Stanton-Reid	Stephen	MD	Fairport	NY
Starke	Keith	MD	St Louis	MO
Starling	Wanda	MD	Landrum	SC
Steen	Susan	MD	Tampa	FL
Stephen	Albert	MD	Tyler	TX
Stine	Sandra	MD	Orlando	FL
Stoltz	Randall	MD	Evansville	IN
Stoner	Deborah	MD	Hiawatha	KS
Stoney	Scott	MD	Newport Beach	CA
Storey	George	MD	Huntsville	AL
Strutin	David	MD	Eugene	OR
Suetholz	David	MD	Taylor Mill	KY
Sukol	Roxanne	MD	Bedford	OH
Sullivan	Lori	MD	Hilliard	OH
Sunter	William	MD	Melbourne	FL
Sutherland	Katherine	MD	Mountain View	CA
Taber	Louise	MD	Phoenix	AZ
Tallo	Diane	MD	Columbus	OH
Tam	Henry	MD	Aiken	SC
Tambunan	Daniel	MD	Orlando	FL
Taradash	Michael	MD	Burlingame	CA
Taylor	Michael	MD	Richmond	VA
Taylor	Peggy	DO	Saint Louis	MO
Tejada	Albert	MD	Phoenix	AZ
Tellez	Luis	MD	Dayton	OH
Thorsen	Robert	MD	Southington	CT
Thurmer	Richard	DO	Portage	MI
Tidman	Raymond	MD	Blue Ridge	GA
Titus	Beverly	NP	Merriville	IN
Tolge	Bruno	MD	Schenectady	NY
Tom	Robert	MD	Mission Viejo	CA
Tranchina	Sara	MD	Dallas	TX
Truax	Walter	MD	Marrero	LA
Turner	Ira	MD	Plainview	NY
Ukwade	Philomena	MD	Friendswood	TX
Ulmer	Lawrence	DO	Portage	MI
Vacker	Mark	MD	Davies	FL
Vaisman	Sofia	MD	Woodland Hills	CA
Valone	Charles	DO	Fremont	OH
Van Sickle	Chris	MD	Tallahassee	FL
Vanderzyl	John	MD	Sugar Land	TX
Varughese	Thomas	MD	Douglasville	GA
Vashi	Dipak	MD	Atlanta	GA
Verrill	Peter	MD	Winter Haven	FL

Table 1 (*Continued*)

Last name	First name	Title	City	State
Vogel	Wendy	MD	Oberlin	KS
Waghray	Satesh	MD	North Olmsted	OH
Waldman	Wendy	MD	Des Moines	IA
Wallace	Mark	MD	Phoenix	AZ
Wansker	Pamela	DO	Greene	ME
Ward	Virginia	MD	New Bern	NC
Ware	William	MD	Aston	PA
Warlick	Thomas	MD	Bend	OR
West	James	MD	Roswell	GA
Wheless	James	MD	Concord	NC
Wiggers	Alan	DO	Twinsburg	OH
Wilcox	Patricia	MD	China Spring	TX
Wile	Larry	MD	Portage	MI
Williams	Barry	MD	Plano	TX
Williams	Benjamin	MD	Lubbock	TX
Wilson	Barbara	CRNP	Pittsburgh	PA
Wilson	Ian	MD	Columbus	OH
Winer	Norton	MD	Cleveland	OH
Winiger	Deborah	MD	Buffalo Grove	IL
Wiredu	Akua	MD	Lincoln	RI
Witt	John	MD	Murfreesboro	TN
Witt	Michael	MD	Chatsworth	GA
Witters	Gregory	MD	Hermitage	TN
Woan	Jin-Mei	MD	Tracy	CA
Wolfe	Warren	DO	Cherry Hill	NJ
Wong	Gene	MD	Richland	WA
Wongjirad	Chatree	MD	Bismarck	ND
Wrobel	Peter	MD	Waycross	GA
Yee	Robert	MD	Beckley	WV
Yoelson	Stephen	MD	Torrington	CT
Zelkowitz	Marvin	MD	Flossmoor	IL
Zhu	Jianhua	MD	Bowling Green	KY
Zwolinski	Ralph	MD	Port Orange	FL

