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.

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). Overview 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, eletriptan 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, eletriptan 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 (85.4%).

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...
Enrollees  
\[ n = 2,368 \]

Protocol violations  
\[ n = 858 \]

Lost to follow-up  
\[ n = 462 \]
- Only one migraine  
\[ n = 91 \]
- Non-crossover treatment  
\[ n = 287 \]
- Non-protocol or unknown drug  
\[ n = 18 \]

Did not use stopwatch  
\[ n = 696 \]

Non-triptan usual care medication  
\[ n = 141 \]

Rizatriptan versus other oral triptans  
\[ n = 673 \]

Rizatriptan first  
\[ n = 386 \]

Other oral triptans first  
\[ n = 287 \]

**Figure 1** Patient sample

**Table 1** Patient characteristics

| Sequence | 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.
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 sub-group 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 2 Proportions of patients achieving pain relief and pain freedom within 2 h after dosing

| Treatment groups          | Achieved pain relief within 2 h after dosing | Achieved pain freedom within 2 h after dosing |
|---------------------------|-----------------------------------------------|-----------------------------------------------|
|                           | %                              | 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                           |                                             |

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

### 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)          | 273.9 (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)   |          |

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

| 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, eletriptan and zolmitriptan. §Slow-acting oral triptans include frovatriptan and naratriptan.

| 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-triptan 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    | Lonestree    | 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    |
| Bayless        | Robert     | MD    | Greenville   | SC    |
| Baylor         | Melissa    | DO    | Dover        | PA    |
| Beard          | Mary       | MD    | Salt Lake City| UT   |
| 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      | Hanvinder  | 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    |
| Burnett   | 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    |
| 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       | Abilhghdoh | 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    |
| 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    |
| Espinette | 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 | Adahl    | 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    |
| 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        | Srinivasa  | 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    |
| Grellier        | 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-Erkkiila | 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    |
| 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    | Elkon      | 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    |
| Hutchinson    | 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    |
| Last name  | First name | Title  | City          | State |
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| Jurcik    | Yvonne     | MD     | Buffalo Grove | IL    |
| Justiz    | William    | MD     | Naples        | FL    |
| Kafka     | Christopher| DO     | Gladstone     | MO    |
| Kagan     | Jeffrey    | MD     | Newington     | CT    |
| Kalasam   | 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    |
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| Kumar     | Seema      | MD     | Alexandria    | VA    |
| Kunst     | Edward     | MD     | Manchester    | MO    |
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| Kurzawa   | Mark       | MD     | Clinton Township | MI |
| Kwon-Hong | Grace      | MD     | Modesto       | CA    |
| Laeger    | Jane       | MD     | Bangor        | ME    |
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| Lambert   | Lise       | MD     | Ft Lauderdale | FL    |
| Larrison  | Charles    | MD     | Hot Springs   | AR    |
| Lazarus   | Kenneth    | MD     | Fayetteville  | GA    |
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| Lee       | Daniel     | MD     | Greenville    | NC    |
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| 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    |
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| 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    |
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| Mathew    | Ninan      | MD    | Houston  | TX    |
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| Mauskop   | Alexander  | MD    | New York | NY |
| May       | James      | MD    | Shreveport | LA |
| Mayer     | David      | DO    | Huntsville | AL |
| Mc Carren | Timothy    | MD    | Cincinnati | OH |
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| Mc Clain  | David      | MD    | American Fork | UT |
| Mc Daniel | Gregory    | MD    | Youngstown | OH |
| Mc Ghee   | Terrence   | MD    | Asheville | NC |
| Mc Lean-Bennett | Jacqueline | DO | Albany | NY |
| McCallum  | Gary       | MD    | Bellingham | WA |
| Mcphee    | Robert     | DO    | Crystal River | FL |
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| Mentock   | Sabrina    | MD    | Durham   | NC    |
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| Millermaier | Janet     | MD    | Portage    | MI    |
| Mills     | Richard    | MD    | Mount Pleasant | SC |
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| 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    |
| Moler     | Darron     | MD    | N Myrtle Bch | SC |
| Monje     | Marie      | 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 |
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| Muse      | Derek      | MD    | Salt Lake Cty | UT  |
| Nakano    | Kenneth    | MD    | Kailua     | HI    |
| Naples    | Robert     | DO    | Cortland   | OH    |
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| Navarro   | Evelyn     | MD    | Grand Rapids | MI  |
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| Nazario   | Liliya     | MD    | Overland Park | KS  |
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| 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    |
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| Parcelli  | Patrick    | MD    | Newport News | VA   |
| Pare      | Bernard    | MD    | Mount Juliet | TN  |
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|-----------|------------|-------|---------------|-------|
| Park      | Richard    | MD    | Universal City| TX    |
| Parker    | David      | DO    | Northglenn    | CO    |
| Parker    | Richard    | DO    | San Diego     | CA    |
| Parmer    | Keith      | MD    | Rome          | GA    |
| Parsley   | Donna      | DO    | Pickerington  | OH    |
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| 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    |
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| 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    |
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| Rehm      | Charles    | MD    | Saint Louis   | MO    |
| Reid      | Randal     | MD    | Austin        | TX    |
| Rendzisperis | Arthur  | DO   | White Lake    | MI    |
| Resnick   | Harvey     | MD    | Lake Jackson  | TX    |
| Reyma     | 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    |
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|-------------|------------|-------|----------|-------|
| Rodgers     | Robert     | MD    | Apopka   | FL    |
| Roeshman    | Robert     | DO    | Allentown| PA    |
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| 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     | Naem      | 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    |
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| Schecht     | Howard     | MD    | Toledo   | OH    |
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| Schmidt     | Jay        | MD    | Hudson   | NC    |
| Schneider   | Donald     | DO    | Highland Ranch | CO |
| Schwartz    | Kenneth    | MD    | Saratoga Spgs | NY |
| Scriminati  | 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    |
| Sharmann    | Daryl      | MD    | Millsboro | DE    |
| Siddiqui    | Usman      | MD    | Lawrenceburg | IN |
| Sidney White | Estem    | 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    | Huntingdon Valley | PA |
| Sklaver     | Neal       | MD    | Dallas   | TX    |
| Sloan       | Jerry      | MD    | New Hartford | NY |
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| Smith       | Sally      | MD    | Tyler    | TX    |
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| Squire    | Karen      | MD    | West Chester | PA |
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| 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 |
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| Sukol     | Roxanne    | MD    | Bedford | OH |
| Sullivan  | Lori       | MD    | Hilliard | OH |
| Sunter    | William    | MD    | Melbourne | FL |
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| 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 |
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| Ukwade    | Philomena  | MD    | Friendswood | TX |
| Ulmer     | Lawrence   | DO    | Portage | MI |
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| Vaisman   | Sofia      | MD    | Woodland Hills | CA |
| Valone    | Charles    | DO    | Fremont | OH |
| Van Sickle| Chris      | MD    | Tallahassee | FL |
| Vanderzyl | John       | MD    | Sugar Land | TX |
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| Waldman   | Wendy      | MD    | Des Moines | IA   |
| Wallace   | Mark       | MD    | Phoenix   | AZ    |
| Wansker   | Pamela     | DO    | Greene    | ME    |
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| Ware      | William    | MD    | Aston     | PA    |
| Warlick   | Thomas     | MD    | Bend      | OR    |
| West      | James      | MD    | Roswell   | GA    |
| Wheelless | James      | MD    | Concord   | NC    |
| Wiggers   | Alan       | DO    | Twinsburg | OH    |
| Wilcox    | Patricia   | MD    | China Spring | TX |
| Wile      | Larry      | MD    | Plano     | TX    |
| Williams  | Barry      | MD    | Portage   | MI    |
| Williams  | Benjamin   | MD    | Lubbock   | TX    |
| Wilson    | Barbara    | CRNP  | Pittsburgh | PA   |
| Wilson    | Ian        | MD    | Columbus  | OH    |
| Winer     | Norton     | MD    | Cleveland | OH    |
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| 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    |
| Wongirad  | Charlee    | 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 |
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