Drug Class Review

Triptans

Preliminary Scan Report #2

April 2013

Last Report: Update #4 (June 2009)

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Update Report

Update #4, June 2009 (searches through January 2009)

Date of Last Preliminary Update Scan Report

April 2010

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Pacific Northwest Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The Participating Organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Participating Organizations approved the following key questions to guide this review:

1. How do effectiveness and efficacy outcomes (reduced severity and duration of symptoms, functional outcomes, quality of life, etc) differ for adult patients with migraine within the following treatment comparisons:
   1a. Monotherapy compared with monotherapy
   1b. Fixed-dose tablets containing a triptan compared with triptan monotherapy
   1c. Fixed-dose tablets containing a triptan compared with co-administration of its individual triptan and analgesic components

2. How do the incidence and nature of adverse effects (serious or life-threatening or those that may adversely effect compliance) differ for adult patients with migraine within the following triptan treatment comparisons:
   2a. Monotherapy compared with monotherapy
   2b. Fixed-dose tablets containing a triptan compared with triptan monotherapy
   2c. Fixed-dose tablets containing a triptan compared with co-administration of its individual triptan and analgesic components

3. Are there subgroups of patients based on demographics, other medications, or comorbidities for which one medication or preparation is more effective or associated with fewer adverse effects?

Inclusion Criteria

Populations

Adult patients with any level of migraine (mild, moderate, severe), with or without aura. Definition of migraine must be explicit, to exclude other types of headache (for example, tension headache).

Interventions

Table 1. Included drugs

Active ingredient	Form(s)	Brand name(s)
Almotriptan	Oral tablet	Axert®
Eletriptan	Oral tablet	Relpax®
Frovatriptan	Oral tablet	Frova®
Naratriptan	Oral tablet	Amerge®
Rizatriptan	Oral tablet, orally disintegrating tablet	Maxalt®, Maxalt-MLT®
Sumatriptan	Oral tablet, nasal spray, subcutaneous injection	Imitrex®, Imitrex® StatDose®, Sumavel DosePro®, Alsuma®
Sumatriptan	Iontophoretic transdermal system	Zecuity®[a]
Sumatriptan-naproxen sodium fixed dose combination product	Oral tablet	Treximet®
Zolmitriptan	Oral tablet, nasal spray, orally disintegrating tablet	Zomig®, Zomig-ZMT®

[a]Not in most recent DERP report; FDA approved 1/17/2013

Study designs

- For effectiveness/efficacy, study is a controlled clinical trial in an outpatient setting or a good-quality systematic review.
- For harms, the study is a controlled clinical trial or observational study.

Comparators

- Another triptan
- Placebo

Effectiveness outcomes

- Reduction or resolution of symptoms (pain, nausea, vomiting, photophobia, phonophobia), reduction of duration of symptoms, duration of improvement, consistency of effectiveness (proportion of headaches successfully treated per patient), functional outcome (for example, change in days of work lost), quality of life, or adverse effect (including drug interactions).
- Measures: Response, time to response, pain-free, sustained response, sustained pain-free, rescue (use of rescue medications), recurrence (reappearance of any degree of symptoms

within 24 or 48 hours) after response or becoming pain-free, time to relief, relief of associated symptoms, tablets per attack, and patient satisfaction.

Harms outcomes

- Overall withdrawals
- Withdrawals due to any adverse events
- Withdrawals due to specific adverse events (central nervous system effects, chest tightness)

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from April 2010 through March 26, 2013 using terms for included drugs. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) and the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/). All citations were imported into an electronic database (EndNote X1) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

Identified in this Preliminary Update Scan

Zecuity (sumatriptan iontophoretic transdermal system): Approved to treat acute migraine in adults with or without aura (1/17/2013).

Identified in previous Preliminary Update Scans

None.

New Indications

Identified in this Preliminary Update Scan

None.

Identified in previous Preliminary Update Scans
Almotriptan: Acute treatment of migraine in adolescents, aged 12 to 17 years (5/2009).

New Safety Alerts

Identified in this Preliminary Update Scan
None.

Identified in previous Preliminary Update Scans
None.

Comparative Effectiveness Reviews

Reviews identified in this Preliminary Update Scan

We identified 2 new comparative effectiveness reviews. One compares acute migraine treatments in emergency settings, and the other is a rapid review of clinical evidence on safety of the triptans. Abstracts of these reviews are attached in Appendix A, and links to the full reports are listed below.

From the AHRQ Effective Healthcare Program:
Acute Migraine Treatment in Emergency Settings. Sumamo Schellenberg E, Dryden DM, Pasichnyk D, Ha C, Vandermeer B, Friedman BW, Colman I, Rowe BH.
Comparative Effectiveness Review No. 84. (Prepared by the University of Alberta Evidence based Practice Center under Contract No. 290-2007-10021-I.) AHRQ Publication No. 12(13)-EHC142-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2012. Available at:
http://effectivehealthcare.ahrq.gov/ehc/products/289/1323/CER84_Migraine_FinalReport_20121119.pdf

From CADTH:
Triptans for Migraine Headaches: A Review of Clinical Evidence on Safety. Rapid Response Report, Summary with Critical Appraisal. March 2012. Available at:
http://www.cadth.ca/media/pdf/htis/mar-2012/RC0333%20Triptans%20Final.pdf

Reviews identified in previous Preliminary Update Scans
None.

Randomized Controlled Trials

Trials identified since the most recent Full Report
Medline searches this scan resulted in 47 citations. Of those, there were 19 potentially relevant new publications. Abstracts of these trials are attached in Appendix B. Since the most recent Update Report, we have identified 6 head-to-head trials (in 8 publications) and 16 placebo-controlled trials (Tables 2 and 3). We identified one placebo controlled trial of the newly approved product sumatriptan iontophoretic transdermal system.

Table 2. New head to head trials*

Author Year	Comparison	Focus
Ng-Mak 2009	Almotriptan vs rizatriptan	Time to response
Bartolini 2011 Bartolini 2012	Almotriptan vs frovatriptan	Pain relief, recurrence Menstrual migraine (subgroup analysis)
Savi 2011a Savi 2011b	Frovatriptan vs rizatriptan	Pain relief, patient satisfaction Menstrual migraine (subgroup analysis)
Allais 2011	Frovatriptan vs zolmitriptan	Menstrual migraine
Tullo 2010	Frovatriptan vs zolmitriptan	Pain relief, recurrence, tolerability
Muller 2011	Rizatriptan orally disintegrating tablet vs sumatriptan vs parecoxib	Acute migraine

*Shading indicates trials identified in this scan; others were identified in previous scan.

Table 2. New placebo controlled trials*

Author Year	Treatment	Focus
Allais 2011a	Almotriptan	Menstrual migraine
Merelle 2009	Eletriptan	Response, quality of life, absence from work
Diener 2011	Eletriptan vs placebo vs an oral CGRP antagonist	Phase II study
Spierings 2009	Frovatriptan	Time to response, recurrence
Latsko 2011	Frovatriptan	Prophylaxis for fasting-induced migraine
Barbanti 2012	Rizatriptan	Migraine with unilateral cranial autonomic symptoms
Cady 2009	Rizatriptan ODT	Early treatment, combined with patient education
Seeburger 2012	Rizatriptan orally disintegrating tablet	Patients taking topiramate for migraine prophylaxis
Seeburger 2011	Rizatriptan orally disintegrating tablet	Nonresponders to sumatriptan
Schulman 2012	Sumatriptan transdermal system	Migraine patients with baseline nausea
Djupesland 2010	Sumatriptan nasal powder	Device (Optinose®) not yet FDA-approved
Kostic 2010	Sumatriptan injection vs placebo vs intravenous prochlorperazine	Emergency department
Mathew 2009	Sumatriptan-naproxen fixed dose combination product	Poor responders to triptan monotherapy
Cady 2011	Sumatriptan-naproxen fixed dose combination product	Menstrual migraine
Derosier 2012a	Sumatriptan-naproxen fixed dose combination product	Adolescents (ages 12-17)
Derosier 2012b	Sumatriptan-naproxen fixed dose combination product vs placebo vs butalbital	Patients with moderate to severe migraine who had used butalbital-containing medications in the past

*Shading indicates trials identified in this scan; others were identified in previous scan.

Appendix A. Abstracts of new comparative effectiveness reviews of triptans (N=2)

Acute Migraine Treatment in Emergency Settings. Sumamo Schellenberg E, Dryden DM, Pasichnyk D, Ha C, Vandermeer B, Friedman BW, Colman I, Rowe BH. Comparative Effectiveness Review No. 84. (Prepared by the University of Alberta Evidence based Practice Center under Contract No. 290-2007-10021-I.) AHRQ Publication No. 12(13)-EHC142-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2012. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/289/1323/CER84_Migraine_FinalReport_20121119.pdf

Structured Abstract

Objectives. To compare the effectiveness and safe y of parenteral pharmacological interventions to treat migraine headaches in adults presenting to the emergency department (ED).

Data sources. In consultation with a librarian, we searched 10 electronic databases, conference proceedings, clinical trials registers, and reference lists.

Methods. Two reviewers independently selected studies, assessed risk of bias, extracted data, and graded the strength of evidence (SOE). Data were pooled using a random-effects model. A mixed-treatment analysis was performed for pain relief and akathisia.

Results. Nine classes of drugs were investigated in 71 controlled trials. Risk of bias was low for 28 percent of the trials, unclear for 61 percent, and high for 11 percent. Overall, active interventions were more effective than placebo for pain relief and headache recurrence. Most head-to-head comparisons for pain reduction were based on single trials resulting in insufficient SOE. The mixed-treatment analysis showed that the most effective treatments were combination therapy (i.e., dihydroergotamine [DHE] added to either neuroleptics or metoclopramide) or neuroleptic monotherapy (low SOE), with a pain reduction of approximately 40 mm on a visual analog scale (VAS). Metoclopramide monotherapy, opioids, and nonsteroidal antiinflammatories (NSAIDs) were the next most effective treatments, with a pain reduction of approximately 24 mm (low SOE). Other agents (e.g., DHE, triptans, orphan agents) were less effective, with a pain reduction of approximately 12-16 mm.

Short-term side effects were infrequent, and considered minor and self-limiting. No two studies reported the same side effects for the same pair of interventions; therefore, the SOE is insufficient to conclude which treatment results in more or fewer adverse effects. Based on the mixed-treatment analysis, the odds of experiencing akathisia symptoms following administration of metoclopramide or neuroleptic agents were 9.4 and 10.7 times greater than with placebo, respectively. The risk of sedation following administration of metoclopramide or neuroleptic agents was 17 percent. The most common short-term side effects for triptans were skin reactions, local reactions, and sedation. For patients receiving DHE, the most common side effects were skin and local reactions, sedation, digestive issues, nausea or vomiting, and chest symptoms. Few side effects were reported for NSAIDS or opioids. In patients receiving magnesium sulfate, high rates of skin flushing and local reactions were reported.

The available evidence failed to identify variable responsiveness based on subgroups.

Migraine relapse can be prevented with intravenous systemic corticosteroids provided in the ED, particularly in patients with prolonged headaches (>72 hours).

Conclusion. Many agents are effective in the treatment of acute migraine headache when compared with placebo. Several treatments provide insufficient evidence for continued use.

Neuroleptic monotherapy and DHE in combination with either metoclopramide or neuroleptics appear to be the most effective optionsfor pain relief (VAS). Systemic corticosteroids effectively prevent headache relapse, especially in patients with prolonged headaches. More research is required to identify the most effective parenteral treatments for adults with acute migraine.

Triptans for Migraine Headaches: A Review of Clinical Evidence on Safety. Rapid Response Report, Summary with Critical Appraisal. March 2012. Available at: http://www.cadth.ca/media/pdf/htis/mar-2012/RC0333%20Triptans%20Final.pdf

RESEARCH QUESTION

What is the clinical evidence on the safety and harms of triptans for migraine headaches?

KEY MESSAGE

While no consistent differences were found between triptans in the rates of overall AEs, a small number of studies suggest oral, intranasal and subcutaneous sumatriptan are associated with chest pain and tachycardia. The most common AEs include dizziness, drowsiness, paresthesia, nausea and fatigue. One study suggests that providing a clinical limit of 27 rizatriptan ODT 10 mg/month did not reduce the number of migraine days compared with providing a formulary limit of 9 tablets per month. Regardless of quantity, rizatriptan ODT 10 mg was well tolerated as AEs were similar between groups.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

A drug class review suggests there are no consistent differences between triptan monotherapies in rates of overall AEs. The most common AEs include dizziness, drowsiness, paresthesia, nausea and fatigue. Systematic reviews of sumatriptan and zolmitriptan suggest AEs are transient, mild and increase with dose but there is no significant difference between triptans and comparators for most AEs. Oral, intranasal and subcutaneous sumatriptan were associated with chest pain tachycardia. One in every 44 people treated with oral sumatriptan 100 mg experience chest pain. While no evidence was found regarding AEs as a result of triptan overuse, an observer-blind randomized parallel group study showed that providing a clinical limit of 27 rizatriptan ODT 10 mg/month did not reduce the number of migraine days compared with providing 9 tablets/month. Regardless of quantity, rizatriptan was well tolerated as AEs were similar between groups.

Appendix B. Abstracts of potentially relevant new trials of triptans

Head-to-head trials (N=5 new trials and 2 subgroup analyses)

Allais, G., V. Tullo, et al. (2011). "Efficacy of frovatriptan in the acute treatment of menstrually related migraine: analysis of a double-blind, randomized, multicenter, Italian, comparative study versus zolmitriptan." Neurological Sciences **32 Suppl 1**: S99-104.

Menstrually related migraine (MRM) is a particularly difficult-to-treat pain condition, associated with substantial disability. Aim of this study was to compare the efficacy and safety of frovatriptan and zolmitriptan in the treatment of MRM attacks, analyzing data from a multicenter, randomized, double blind, cross-over study. We analyzed the subset of 76 regularly menstruating women who participated in one head-to-head multicenter, randomized, double blind, cross-over clinical trial and who took the study drugs to treat MRM attacks. In a randomized sequence, each patient received frovatriptan 2.5mg or zolmitriptan 2.5mg: after treating three episodes of migraine in no more than 3months with the first treatment, the patient had to switch to the other treatment. MRM was defined according to the criteria listed in the Appendix of the last Classification of Headache disorders of the International Headache Society. A total of 73 attacks, classified as MRM, were treated with frovatriptan and 65 with zolmitriptan. Rate of pain relief at 2h was 52% for frovatriptan and 53% for zolmitriptan (p=NS), while rate of pain free at 2h was 22 and 26% (p=NS), respectively. At 24h, 74 and 83% of frovatriptan-treated and 69 and 82% of zolmitriptan-treated patients were pain free and had pain relief, respectively (p=NS). Recurrence at 24h was significantly (p<0.05) lower with frovatriptan (15 vs. 22% zolmitriptan). Frovatriptan proved to be effective in the immediate treatment of MRM attacks, similarly to zolmitriptan, but showed lower recurrence rates, and thus a better sustained relief.

Bartolini, M., M. A. Giamberardino, et al. (2011). "A double-blind, randomized, multicenter, Italian study of frovatriptan versus almotriptan for the acute treatment of migraine." Journal of Headache & Pain **12**(3): 361-368.

The objective of this study was to evaluate patients' satisfaction with acute treatment of migraine with frovatriptan or almotriptan by preference questionnaire. One hundred and thirty three subjects with a history of migraine with or without aura (IHS 2004 criteria), with at least one migraine attack in the preceding 6months, were enrolled and randomized to frovatriptan 2.5mg or almotriptan 12.5mg, treating 1-3 attacks. The study had a multicenter, randomized, double blind, cross-over design, with treatment periods lasting <3months. At study end patients assigned preference to one of the treatments using a questionnaire with a score from 0 to 5 (primary endpoint). Secondary endpoints were pain free and pain relief episodes at 2 and 4h, and recurrent and sustained pain free episodes within 48h. Of the 133 patients (86%, intention-to-treat population) 114 of them expressed a preference for a triptan. The average preference score was not significantly different between frovatriptan (3.1+/-1.3) and almotriptan (3.4+/-1.3). The rates of pain free (30% frovatriptan vs. 32% almotriptan) and pain relief (54% vs. 56%) episodes at 2h did not significantly differ between treatments. This was the case also at 4h (pain free: 56% vs. 59%; pain relief: 75% vs. 72%). Recurrent episodes were significantly (P<0.05) less frequent under frovatriptan (30% vs. 44%), also for the attacks treated within 30min. No significant differences were observed in sustained pain free episodes (21% vs. 18%).

The tolerability profile was similar between the two drugs. In conclusion, our study suggests that frovatriptan has a similar efficacy of almotriptan in the short-term, while some advantages are observed during long-term treatment.

Bartolini, M., M. A. Giamberardino, et al. (2012). "Frovatriptan versus almotriptan for acute treatment of menstrual migraine: analysis of a double-blind, randomized, cross-over, multicenter, Italian, comparative study." Journal of Headache & Pain **13**(5): 401-406.

The objective of the study was to compare the efficacy and safety of frovatriptan and almotriptan in women with menstrually related migraine (IHS Classification of Headache disorders) enrolled in a multicenter, randomized, double-blind, cross-over study. Patients received frovatriptan 2.5mg or almotriptan 12.5mg in a randomized sequence: after treating 3 episodes of migraine in no more than 3months with the first treatment, the patient was switched to the other treatment. 67 of the 96 female patients of the intention-to-treat population of the main study had regular menstrual cycles and were thus included in this subgroup analysis. 77 migraine attacks classified as related to menses were treated with frovatriptan and 78 with almotriptan. Rate of pain relief at 2 and 4h was 36 and 53% for frovatriptan and 41 and 50% for almotriptan (p=NS between treatments). Rate of pain free at 2 and 4h was 19 and 47% with frovatriptan and 29 and 54% for almotriptan (p=NS). At 24h, 62% of frovatriptan-treated and 67% of almotriptan-treated patients had pain relief, while 60 versus 67% were pain free (p=NS). Recurrence at 24h was significantly ($p<0.05$) lower with frovatriptan (8 vs. 21% almotriptan). This was the case also at 48h (9 vs. 24%, $p<0.05$). Frovatriptan was as effective as almotriptan in the immediate treatment of menstrually related migraine attacks. However, it showed a more favorable sustained effect, as shown by a lower rate of migraine recurrence.

Muller, T. and L. Lohse (2011). "Efficacy of parecoxib, sumatriptan, and rizatriptan in the treatment of acute migraine attacks." Clinical Neuropharmacology **34**(6): 206-209.

Triptans and analgetic nonsteroidal inflammatory drugs reduce acute pain syndromes in migraine. A further treatment option for an acute headache attack in patients with migraine may be the application of cyclooxygenase-2-specific inhibitors, as they have anti-inflammatory and analgesic properties. The objective of this pilot study was to investigate the effects of an oral fast-dissolving tablet of 10 mg of rizatriptan, an intravenous infusion of 40 mg of parecoxib, and a subcutaneous pen injection of sumatriptan (6 mg/0.5 mL) on pain relief in 3 cohorts of patients with episodic migraine. They were treated owing to the acute onset of a pain attack as a case of emergency. They were randomized to treatment with sumatriptan, rizatriptan, or parecoxib. The participants completed a visual analog scale for pain intensity at baseline before the drug administration and then after intervals of 20, 30, 60, and 120 minutes. Rizatriptan, parecoxib, and sumatriptan reduced pain symptoms. Twenty and 30 minutes after drug intake, rizatriptan was more efficacious than parecoxib and sumatriptan, and parecoxib was more effective than sumatriptan. Only a significant difference between rizatriptan and sumatriptan was found after 60 and 120 minutes. This trial demonstrates the effectiveness of a parecoxib infusion in the treatment of acute migraine and that the circumvention of the first pass effect of the liver by rizatriptan may be beneficial for fast pain relief.

Savi, L., S. Omboni, et al. (2011). "A double-blind, randomized, multicenter, Italian study of frovatriptan versus rizatriptan for the acute treatment of migraine." Journal of Headache & Pain **12**(2): 219-226.

The objective of this study was to assess patient satisfaction with acute treatment of migraine with frovatriptan or rizatriptan by preference questionnaire. 148 subjects with a history of migraine with or without aura (IHS 2004 criteria), with at least one migraine attack per month in the preceding 6 months, were enrolled and randomized to frovatriptan 2.5 mg or rizatriptan 10 mg treating 1-3 attacks. The study had a multicenter, randomized, double-blind, cross-over design, with treatment periods lasting <3 months. At the end of the study, patients assigned preference to one of the treatments using a questionnaire with a score from 0 to 5 (primary endpoint). Secondary endpoints were pain-free and pain relief episodes at 2 h, and recurrent and sustained pain-free episodes within 48 h. 104 of the 125 patients (83%, intention-to-treat population) expressed a preference for a triptan. The average preference score was not significantly different between frovatriptan (2.9+/-1.3) and rizatriptan (3.2+/-1.1). The rates of pain-free (33% frovatriptan vs. 39% rizatriptan) and pain relief (55 vs. 62%) episodes at 2 h were not significantly different between the two treatments. The rate of recurrent episodes was significantly ($p<0.001$) lower under frovatriptan (21 vs. 43% rizatriptan). No significant differences were observed in sustained pain-free episodes (26% frovatriptan vs. 22% rizatriptan). The number of patients with adverse events was not significantly different between rizatriptan (34) and frovatriptan (25, p=NS). The results suggest that frovatriptan has a similar efficacy to rizatriptan, but a more prolonged duration of action. Springer-Verlag 2010

Savi, L., S. Omboni, et al. (2011). "Efficacy of frovatriptan in the acute treatment of menstrually related migraine: analysis of a double-blind, randomized, cross-over, multicenter, Italian, comparative study versus rizatriptan." Journal of Headache & Pain **12**(6): 609-615.

The objectives of this study are to assess the efficacy and safety of frovatriptan, and rizatriptan in the subgroup of women with menstrually related migraine of a multicenter, randomized, double blind, cross-over study. Each patient received frovatriptan 2.5mg or rizatriptan 10mg in a randomized sequence: after treating 3 episodes of migraine in not more than 3months with the first treatment, the patient had to switch to the other treatment. Menstrually related migraine was defined according to the criteria listed in the Appendix of the last IHS Classification of Headache disorders. 99 out of the 125 patients included in the intention-to-treat analysis of the main study were of a female gender: 93 had regular menstrual cycles and were, thus, included in this analysis. A total of 49 attacks classified as menstrually related migraine were treated with frovatriptan and 59 with rizatriptan. Rate of pain relief at 2h was 58% for frovatriptan and 64% for rizatriptan (p=NS), while rate of pain free at 2h was 31 and 34% (p=NS), respectively. At 24h, 67 and 81% of frovatriptan-treated, and 61 and 74% of rizatriptan-treated patients were pain free and had pain relief, respectively (p=NS). Recurrence at 24h was significantly ($p<0.01$) lower with frovatriptan (10 vs. 32% rizatriptan). Frovatriptan was as effective as rizatriptan in the immediate treatment of menstrually related migraine attacks while showing a favorable sustained effect with a lower rate of migraine recurrence. These results need to be confirmed by randomized, double-blind, prospective, large clinical trials.

Tullo, V., G. Allais, et al. (2010). "Frovatriptan versus zolmitriptan for the acute treatment of migraine: a double-blind, randomized, multicenter, Italian study." Neurological Sciences 31 Suppl 1: S51-54.

The objective of this study is to assess patients' satisfaction with migraine treatment with frovatriptan (F) or zolmitriptan (Z), by preference questionnaire. 133 subjects with a history of migraine with or without aura (IHS criteria) were randomized to F 2.5 mg or Z 2.5 mg. The study had a multicenter, randomized, double-blind, cross-over design, with each of the two treatment periods lasting no more than 3 months. At the end of the study, patients were asked to assign preference to one of the treatments (primary endpoint). The number of pain-free (PF) and pain-relief (PR) episodes at 2 h, and number of recurrent and sustained pain-free (SPF) episodes within 48 h were the secondary study endpoints. Seventy-seven percent of patients expressed a preference. Average score of preference was 2.9 +/- 1.3 (F) versus 3.0 +/- 1.3 (Z; p = NS). Rate of PF episodes at 2 h was 26% with F and 31% with Z (p = NS). PR episodes at 2 h were 57% for F and 58% for Z (p = NS). Rate of recurrence was 21 (F) and 24% (Z; p = NS). Time to recurrence within 48 h was better for F especially between 4 and 16 h ($p < 0.05$). SPF episodes were 18 (F) versus 22% (Z; p = NS). Drug-related adverse events were significantly ($p < 0.05$) less under F (3 vs. 10). In conclusion, our study suggests that F has a similar efficacy of Z, with some advantage as regards tolerability and recurrence.

Placebo-controlled trials (N=12)

Allais, G., G. Bussone, et al. (2011). "Almotriptan 12.5 mg in menstrually related migraine: a randomized, double-blind, placebo-controlled study." Cephalalgia **31**(2): 144-151.

BACKGROUND: Menstrually related migraine (MRM) affects more than half of female migraineurs. Because such migraines are often predictable, they provide a suitable target for treatment in the mild pain phase. The present study was designed to provide prospective data on the efficacy of almotriptan for treatment of MRM.

METHODS: Premenopausal women with MRM were randomized to almotriptan (N = 74) or placebo (N = 73), taken at onset of the first perimenstrual migraine. Patients crossed over to the other treatment for the first perimenstrual migraine of their second cycle, followed by a two-month open-label almotriptan treatment period.

RESULTS: Significantly more patients were pain-free at two hours (risk ratio [RR] = 1.81; p = .0008), pain-free from 2-24 hours with no rescue medication (RR = 1.99; p = .0022), and pain-free from 2-24 hours with no rescue medication or adverse events (RR = 1.94; p = .0061) with almotriptan versus placebo. Nausea (p = .0007) and photophobia (p = .0083) at two hours were significantly less frequent with almotriptan. Almotriptan efficacy was consistent between three attacks, with 56.2% of patients pain-free at two hours at least twice. Adverse events were similar with almotriptan and placebo.

CONCLUSION: Almotriptan was significantly more effective than placebo in women with MRM attacks, with consistent efficacy in longer-term follow-up.

Barbanti, P., L. Fofi, et al. (2012). "Rizatriptan in migraineurs with unilateral cranial autonomic symptoms: a double-blind trial." Journal of Headache & Pain **13**(5): 407-414.

The objective and background is to confirm in a double-blind, placebo-controlled study the high triptan response rates we had previously reported in an open study in migraine patients with unilateral cranial autonomic symptoms. In this randomized, double-blind, placebo-controlled study 80 migraineurs with unilateral cranial autonomic symptoms were assigned to receive rizatriptan 10mg wafer or placebo (ratio 1:1) and treated for a single moderate or severe migraine attack. The primary endpoints were pain freedom at 2h and total migraine freedom at 2h. Secondary endpoints included pain relief, no associated symptoms and sustained pain freedom or relief. Significantly more patients reported pain freedom at 2h after taking rizatriptan (54%) than after placebo (8%) (therapeutic gain 46% [28%; 64%]; P<0.001). Similarly, significantly more patients reported total migraine freedom at 2h after rizatriptan (51%) than after placebo (8%) (therapeutic gain 43% [26%; 61%]; P<0.001). Rizatriptan was also more effective than placebo on most secondary endpoints. We confirm in a placebo-controlled study our previous data suggesting that the presence of unilateral cranial autonomic symptoms in migraineurs predicts a positive response to triptans, probably owing to intense trigeminal peripheral afferent activation which strongly recruits peripheral neurovascular 5-HT1B/1D receptors. Acute and preventive pharmacological trials in migraine should focus also on this subset of migraine patients.

Cady, R. K., M. L. Diamond, et al. (2011). "Sumatriptan-naproxen sodium for menstrual migraine and dysmenorrhea: satisfaction, productivity, and functional disability outcomes." Headache **51**(5): 664-673.

OBJECTIVE: To evaluate the impact of a sumatriptan/naproxen sodium combination tablet on patient satisfaction, productivity, and functional disability in menstrual migraine treated during the mild pain phase of a single menstrual migraine attack associated with dysmenorrhea.

BACKGROUND: Menstrual migraineurs with dysmenorrhea represent a unique patient population not previously studied. When health outcomes end points are analyzed alongside traditional efficacy end points in migraine studies, a more comprehensive and robust understanding of the many factors that may influence patients' choice of and adherence to pharmacological treatments for migraine is observed.

METHODS: In 2 replicate, multicenter, randomized, double-blind, placebo-controlled trials, participants with menstrual migraine and dysmenorrhea treated a single menstrual migraine attack with a single fixed-dose tablet of sumatriptan 85mg formulated with RT TechnologyTM and naproxen sodium 500mg (sumatriptan-naproxen sodium) or placebo.

RESULTS: Participants randomized to sumatriptan-naproxen sodium were significantly more satisfied than those randomized to placebo at 24 hours post dose, as demonstrated by higher satisfaction subscale scores for efficacy (P<.001 for both studies), functionality (P=.003 for study 1; P<.001 for study 2), and ease of use (P=.027 for study 1; P=.011 for study 2). There was little bothersomeness of side effects associated with either treatment. Use of sumatriptan-naproxen sodium was also associated with lower reported "lost-time equivalents" in work and leisure time (pooled analysis, P=.003) and lower rates of functional disability (P=.05, study 1; P<.001, study 2) compared with placebo.

CONCLUSION: A fixed-dose combination tablet containing sumatriptan and naproxen sodium significantly improved patient satisfaction, productivity, and restoration of normal

functioning in menstrual migraineurs with dysmenorrhea. 2011 American Headache Society.

Derosier, F., F. Sheftell, et al. (2012). "Sumatriptan-naproxen and butalbital: a double-blind, placebo-controlled crossover study." Headache **52**(4): 530-543.

OBJECTIVES: The primary objective was to compare the efficacy of a sumatriptan and naproxen combination medication (SumaRT/Nap-85mg sumatriptan and 500mg naproxen sodium), a butalbital-containing combination medication (BCM-50mg butalbital, 325mg acetaminophen, 40mg caffeine), and placebo when used to treat moderate to severe migraine headache pain in subjects who used BCMs in the past.

BACKGROUND: Despite the lack of Food and Drug Administration approval and the absence of placebo-controlled trials to demonstrate efficacy, butalbital-containing medications are among the most commonly prescribed acute migraine treatments in the United States. Butalbital-containing medications are associated with serious and undesirable side effects, and have been linked to the chronification of migraine and development of medication-overuse headaches. This study compares the relative efficacy, safety, and tolerability of a fixed dose SumaRT/Nap versus a BCM and placebo.

METHODS: Enrolled subjects were required to have treated at least 1 migraine with a butalbital medication in the past. Enrolled subjects treated 3 moderate to severe migraines using each of the 3 study treatments once in a randomized sequence. The primary endpoint compared SumaRT/Nap versus BCM for sustained pain freedom at 2-24 hours without the use of any rescue medication. This study combines data from 2 identical outpatient, randomized, multicenter, double-blind, double-dummy, 3 attack crossover studies in adult migraineurs (International Classification of Headache Disorders, 2nd edition).

RESULTS: A total of 442 subjects treated at least 1 attack with study medication. The majority of the treated subjects were female (88%) with a mean age 43 years, who reported that their migraines had a severe impact on their lives (78% with Headache Impact Test-6 of >59). At screening, 88% of subjects reported current butalbital use; 68% had used butalbital for more than 6 weeks; and 82% reported satisfaction with butalbital. Across treatment groups, 28-29% of subjects took study medication within 15 minutes of migraine onset, 34-37% of subjects took study medication >15 minutes to 2 hours after onset, and 32-36% of subjects took study medication more than 2 hours after onset. This study did not detect a difference at the nominal 0.05 level in percent sustained pain-free between SumaRT/Nap (8%), BCM (6%), and placebo (3%). SumaRT/Nap was superior to BCM for pain free at 2, 4, 6, 8, 24, 48 hours (P<=.044); pain relief (mild or no pain) at 2, 4, 6, 8, 24, 48 hours (P<=.01); sustained pain relief 2-24 hours (P<.001); migraine free (pain free with no nausea, photophobia, or phonophobia) at 4, 6, 8, 24, 48 hours (P<=.046); and complete symptom free (migraine free with no neck/sinus pain) at 4, 6, 8, 48 hours (P<=.031). Adverse event incidence was similar for all treatments (10%, 12%, and 9% for placebo, SumaRT/Nap, and BCM, respectively). Nausea was the most frequent adverse event (2%, 2%, and <1% for placebo, SumaRT/Nap, and BCM, respectively). Five serious adverse events were reported by 3 subjects: viral meningitis and colon neoplasm (placebo); chest pain and hypertension 17 days postdose (SumaRT/Nap); and breast cancer (BCM). Investigators judged no serious adverse events related to study medication.

CONCLUSIONS: This study primarily included subjects whose migraines significantly impacted their lives. Before the study, these subjects used butalbital-containing medications as part of their current migraine treatment regimen and were satisfied with it, suggesting they were butalbital responders who had found a workable treatment strategy for themselves. When treated with SumaRT/Nap versus BCM in this study, however, a significant proportion of subjects reported better treatment outcomes for themselves for both migraine pain and associated symptoms. Use of SumaRT/Nap was also associated with less rescue medication use and a longer time before use of rescue medication compared with both BCM and placebo. 2011 American Headache Society.

Derosier, F. J., D. Lewis, et al. (2012). "Randomized trial of sumatriptan and naproxen sodium combination in adolescent migraine." Pediatrics **129**(6): e1411-1420.

BACKGROUND: Treatment of adolescent migraine remains a significant unmet medical need. We compared the efficacy and safety of 3 doses of sumatriptan and naproxen sodium (suma/nap) combination tablets to placebo in the acute treatment of adolescent migraine.

METHODS: This randomized, parallel group study in 12 to 17 year olds required 2 to 8 migraines per month (typically lasting >3 hours untreated) for >= 6 months. Subjects entered a 12-week run-in phase, treating 1 moderate-to-severe migraine (attack 1) with single-blind placebo. Subjects reporting headache pain 2 hours after dosing were randomly assigned into a 12-week double-blind phase, treating 1 moderate-to-severe migraine (attack 2) with placebo (n = 145), suma/nap 10/60 mg (n = 96), 30/180 mg (n = 97), or 85/500 mg (n = 152). The primary end point was the percentage of subjects pain-free at 2 hours.

RESULTS: The attack 2 adjusted (age; baseline pain severity) 2-hour pain-free rates were higher with suma/nap 10/60 mg (29%; adjusted P = .003), 30/180 mg (27%; adjusted P = .003), and 85/500 mg (24%; adjusted P = .003) versus placebo (10%). Posthoc primary end-point analyses did not demonstrate differences among the 3 doses or an age-by-treatment interaction. Statistically significant differences were found for 85/500 mg versus placebo for sustained pain-free 2 to 24 hours (23% vs 9%; adjusted P = .008), 2-hour photophobia-free (59% vs 41%; adjusted P = .008), and 2-hour phonophobia-free (60% vs 42%; adjusted P = .008). Analyses of other pain, associated symptoms, rescue medication use, and health outcome end points supported higher efficacy for active doses versus placebo. All active doses were well tolerated.

CONCLUSIONS: All doses of suma/nap were well tolerated, providing similarly effective acute treatment of adolescent migraine pain and associated symptoms, as compared with placebo.

Diener, H.-C., P. Barbanti, et al. (2011). "BI 44370 TA, an oral CGRP antagonist for the treatment of acute migraine attacks: results from a phase II study." Cephalalgia **31**(5): 573-584.

METHODS: Four hundred and sixty-one adult subjects with migraine were randomised to one of five treatments, the oral antagonist at the calcitonin gene-related peptide (CGRP) receptor BI 44370 TA (50mg, 200mg, 400mg), active comparator eletriptan 40mg or placebo. The analysis included 341 subjects who took study medication.

RESULTS: The primary endpoint, pain-free after two hours, was reached by significantly more subjects in the BI44370TA 400mg (20/73=27.4%) and eletriptan 40mg (24/69=34.8%)

groups compared to placebo (6/70=8.6%, p=.0016), but not by subjects in the BI 44370 TA 200mg group (14/65=21.5%). The effect of 50mg BI44370TA (5/64=7.8%) was similar to that of placebo. Analysis of secondary endpoints supported the conclusion from the primary analysis. The frequency of adverse events was low in all groups.

CONCLUSION: Efficacy of BI 44370 TA was shown in a dose-dependent manner in the treatment of acute migraine attacks.

Djupesland, P. G., P. Docekal, et al. (2010). "Intranasal sumatriptan powder delivered by a novel breath-actuated bi-directional device for the acute treatment of migraine: A randomised, placebo-controlled study." Cephalalgia **30**(8): 933-942.

INTRODUCTION: Intranasal sumatriptan is an option for the treatment of migraine; however, nasal delivery using conventional spray pumps is suboptimal.

METHODS: Adult subjects (n = 117) with migraine were enrolled in a multicentre, randomised, double-blind, parallel group, placebo-controlled study. A single migraine attack was treated in-clinic with sumatriptan 10 mg, sumatriptan 20 mg or placebo administered intranasally by a novel bi-directional powder delivery device when migraine was moderate or severe.

RESULTS: A greater proportion of subjects who received sumatriptan were pain-free at 120 minutes compared with those who received placebo (10 mg/20 mg sumatriptan vs. placebo = 54%/57% vs. 25%, P < .05). Significant benefits were also observed for pain relief at 120 minutes (84%/80% vs. 44%, P < .001/.01) and as early as 60 minutes (73%/74% vs. 38%, P < .01) and for 48 hours sustained pain-free (P < .05). Treatment-related adverse events were rare, with a metallic taste being the most commonly reported (10%/13%).

CONCLUSIONS: Sumatriptan nasal powder administered using the new device during a migraine attack was effective and well tolerated.

Kostic, M. A., F. J. Gutierrez, et al. (2010). "A prospective, randomized trial of intravenous prochlorperazine versus subcutaneous sumatriptan in acute migraine therapy in the emergency department." Annals of Emergency Medicine **56**(1): 1-6.

STUDY OBJECTIVE: Intravenous (IV) prochlorperazine with diphenhydramine is superior to subcutaneous sumatriptan in the treatment of migraine patients presenting to the emergency department (ED).

METHODS: In this randomized, double-blind, placebo-controlled trial, after providing written informed consent, patients presenting to the ED with a chief complaint of migraine received a 500-mL bolus of IV saline solution and either 10 mg prochlorperazine with 12.5 mg diphenhydramine IV plus saline solution placebo subcutaneously or saline solution placebo IV plus 6 mg sumatriptan subcutaneously. Pain intensity was assessed with 100-mm visual analog scales (visual analog scale at baseline and every 20 minutes for 80 minutes). The primary outcome was change in pain intensity from baseline to 80 minutes or time of ED discharge if subjects remained in the ED for fewer than 80 minutes after treatment. Sedation and nausea were assessed every 20 minutes with visual analog scale scales, and subjects were contacted within 72 hours to assess headache recurrence.

RESULTS: Sixty-eight subjects entered the trial, with complete data for 66 subjects. Baseline pain scores were similar for the prochlorperazine/diphenhydramine and sumatriptan groups (76 versus 71 mm). Mean reductions in pain intensity at 80 minutes or time of ED

discharge were 73 mm for the prochlorperazine/diphenhydramine group and 50 mm for those receiving sumatriptan (mean difference 23 mm; 95% confidence interval 11 to 36 mm). Sedation, nausea, and headache recurrence rates were similar.
CONCLUSION: IV prochlorperazine with diphenhydramine is superior to subcutaneous sumatriptan in the treatment of migraine.

Latsko, M., S. Silberstein, et al. (2011). "Frovatriptan as preemptive treatment for fasting-induced migraine." Headache **51**(3): 369-374.

OBJECTIVE: To examine frovatriptan's efficacy as preemptive treatment for fasting-induced migraine.
BACKGROUND: Fasting is a common migraine trigger that cannot always be avoided. The development of a short-term preemptive approach would be of benefit. Because of its longer half-life, frovatriptan has been effectively used for short-term daily use to prevent menstrually related migraines and might prove useful in the prevention of fasting-induced migraine.
METHODS: This was a double-blind, placebo-controlled, randomized, parallel-group trial.
SUBJECTS: With a history of fasting-induced episodic migraine were randomly assigned to receive either frovatriptan (5.0mg) or placebo (ratio 1:1).
SUBJECTS: Took a single dose of study medication at the start of their 20-hour fast. Information about headache intensity, associated symptoms, and use of rescue medication was captured at defined time points from the start of the fast through 20 hours post-fast.
RESULTS: Of the 75 subjects screened, 74 subjects were randomized and 71 subjects completed the study. Demographic characteristics of the placebo and frovatriptan treatment groups were not statistically different. Thirty-three subjects received active drug. Twelve (36.4%) developed a headache between 6 and 20 hours after the start of the fast (1/33 mild, 11/33 moderate or severe). In the placebo group, 18/34 (52.9%) developed a headache (4/34 mild, 14/34 moderate or severe). The difference between the 2 treatment groups did not achieve statistical significance; Pearson chi-square, P=.172. Kaplan-Meier survival analysis showed no difference between the 2 treatment groups with respect to the time of onset of headache of any intensity (log rank, P=.264) and for the time of onset of a moderate or severe intensity (log rank, P=.634).
CONCLUSION: More subjects on placebo developed a headache than those on frovatriptan. Perhaps because of the small number of subjects involved, the differences in headache incidences observed did not achieve statistical significance.

Schulman, E. A. (2012). "Transdermal sumatriptan for acute treatment of migraineurs with baseline nausea.[Erratum appears in Headache. 2012 Jun;52(6):1062]." Headache **52**(2): 204-212.

OBJECTIVE: To evaluate the efficacy and safety of transdermal sumatriptan in migraine patients who have baseline nausea.
BACKGROUND: Migraine-associated nausea and vomiting can limit the effectiveness of acute treatment with oral agents by causing delays, avoidance, or incomplete absorption of medication due to post-dose vomiting.

METHODS: In a multicenter, randomized, double-blind, placebo-controlled study in adult (aged 18-66 years) migraineurs, 530 patients were randomized to receive transdermal sumatriptan or a placebo patch and remained in the study until they had treated a single moderate to severe migraine attack or had gone 2 months without treatment. At baseline (before applying the study patch), patients recorded headache pain intensity and the presence or absence of migraine-associated symptoms, including nausea. The use of analgesic or anti-emetic rescue medications within 2 hours of patch activation was prohibited. Post-hoc analyses were conducted to assess the proportion of patients with nausea at baseline who experienced headache relief and who were free from nausea, photophobia, and phonophobia at 1 and 2 hours post-activation.

RESULTS: A total of 454 patients were included in the intent-to-treat population for efficacy analyses. Baseline demographic and migraine headache characteristics were generally similar between the treatment groups. In the overall study population, transdermal sumatriptan was significantly superior to placebo at 1 hour post-activation for pain relief (29% vs 19%, respectively; P < .0135) and freedom from nausea (71% vs 58%, respectively; P < .05) and at 2 hours post-activation for freedom from pain (18% vs 9%, respectively; P < .009), pain relief (53% vs 29%, respectively; P < .0001), freedom from nausea (84% vs 63% respectively; P < .001), freedom from photophobia (51% vs 36%, respectively; P < .0028), freedom from phonophobia (55% vs 39%, respectively; P < .0002); and freedom from migraine (16% vs 8%, respectively; P < .0135). In the post-hoc analysis, transdermal sumatriptan was markedly superior to placebo for pain relief and freedom from pain, nausea, photo-, and phonophobia at 1 and 2 hours post-activation.

CONCLUSIONS: Transdermal sumatriptan is superior to oral triptans for migraine patients whose baseline nausea causes them to delay or avoid acute treatment. 2012 American Headache Society.

Seeburger, J. L., R. K. Cady, et al. (2012). "Rizatriptan for treatment of acute migraine in patients taking topiramate for migraine prophylaxis." Headache **52**(1): 57-67.

OBJECTIVE: To assess efficacy and tolerability of rizatriptan orally disintegrating tablet (ODT) for treatment of acute migraine in patients using topiramate for migraine prophylaxis.

BACKGROUND: There are limited data from prospective controlled trials demonstrating the benefit of triptans in patients who experience migraine attacks while taking prophylactic medication.

METHODS: This was a worldwide, randomized, placebo-controlled, double-blind, multiple-attack study in adults with a >1-year history of migraine taking a stable dose of topiramate for migraine prophylaxis and experiencing >=2 moderate/severe attacks per month. Participants treated 3 moderate/severe attacks in crossover fashion (2 with rizatriptan 10-mg ODT, 1 with placebo) following random assignment to 1 of 3 treatment sequences. The primary end point was 2-hour pain relief.

RESULTS: Two-hour pain relief was significantly greater with rizatriptan compared with placebo (55.0% vs 17.4%, P < .001). Response rates also favored rizatriptan for sustained pain relief from 2-24 hours (32.6% vs 11.1%, P < .001), 2-hour pain freedom (36.0% vs 6.5%, P < .001), normal functional ability at 2 hours (42.2% vs 12.7%, P < .001), and overall treatment satisfaction at 24 hours (60.8% vs 33.6%, P < .001). Few participants

reported adverse experiences (16 [15.8%] with rizatriptan, 3 [3.2%] with placebo); none were serious.
CONCLUSION: Rizatriptan 10-mg ODT was superior to placebo at all pain end points for treatment of acute migraine in patients using topiramate for migraine prophylaxis. Rizatriptan was generally well tolerated in this population. These results are comparable with those from clinical trials in patients not using prophylaxis, suggesting that the use of topiramate does not affect the efficacy or tolerability of rizatriptan for acute migraine treatment. 2011 American Headache Society.

Seeburger, J. L., F. R. Taylor, et al. (2011). "Efficacy and tolerability of rizatriptan for the treatment of acute migraine in sumatriptan non-responders." Cephalalgia **31**(7): 786-796.
OBJECTIVE: The study was carried out to assess the efficacy and tolerability of rizatriptan orally disintegrating tablet (ODT) for treating acute migraine in patients who are non-responders to sumatriptan.
BACKGROUND: Many migraineurs report dissatisfaction with sumatriptan efficacy. It is unclear whether sumatriptan 100mg non-responders will respond to other triptans.
METHODS: This was a randomized, placebo-controlled, double-blind study in adults with >1-year history of ICHD-II (International Classification of Headache Disorders, second edition) migraine who reported that they generally do not respond to sumatriptan (>=50% unsatisfactory response). In the baseline phase, participants treated a single moderate/severe migraine attack with open-label generic sumatriptan 100mg. Those who continued to experience moderate/severe pain at two hours post-dose were eligible to enter the double-blind treatment phase, during which participants treated three migraine attacks in crossover fashion (two with rizatriptan 10-mg ODT, one with placebo) after being randomly assigned to one of three treatment sequences (1:1:1 ratio). The primary endpoint was two-hour pain relief.
RESULTS: A total of 102 (94%) participants treated at least one study migraine. Pain relief at two hours was significantly greater with rizatriptan compared with placebo (51% vs. 20%, p<.001). Response rates also favored rizatriptan on two-hour pain freedom (22% vs. 12%, p=.013) as well as 24-hour sustained pain relief (38% vs. 14%, p<.001) and sustained pain freedom (20% vs. 11%, p=.036). Treatment was generally well tolerated.
CONCLUSION: Rizatriptan 10-mg ODT was superior to placebo at providing two-hour pain relief and two-hour pain freedom in the treatment of acute migraine in those who do not respond to sumatriptan 100mg. Rizatriptan was generally well tolerated in this population.