

# APPENDIX 1: Clinical Review Extraction and Quality Assessment Form (Systematic Review)

<b>Table 1: Triptans for migraine and cluster headache – clinical review data extraction and quality assessment.</b>		
<b>Date:</b>	<b>Reviewer’s initials:</b>	<b>ID number:</b>
Article identification (author, year): Full citation: Geographic location: Duration of study: Centre: Setting ( <i>e.g., hospital-based, clinic-based, community-based, referral criteria or process, other</i> ): Declared conflict of interest: Source(s) of funding:		
<b>Study Characteristics</b>		
Purpose or objective(s) of study ( <i>include among whom</i> ): Design (systematic review, meta-analysis): Protocol (a priori, appropriate consultation): Literature search (replicable, comprehensive, grey literature, manufacturer, limits, language): Abstract selection (inclusion and exclusion criteria, number of reviewers, flowchart of studies): Data extraction (two reviewers, independent extraction, consensus): Data analysis: Quality assessment (two reviewers, transparency, scale): Notes:		
<b>Systematic Review Findings</b>		
Number of systematic reviews: Treatment and comparator: Author’s outcomes (and definitions, if any): Quality assessment (if any): Limitations by author: Author’s conclusions: Review report outcomes (and definitions, if any): Review report assessment: Limitations by reviewers: Review report conclusions: Notes (calculations, if any):		
<b>Randomized Controlled Trial (RCT) and Observational Findings</b>		
Number of RCTs: Number of observational studies: Treatment and comparator: Author’s outcomes: Quality assessment (if any): Limitations by author: Author’s conclusions: Review report outcomes: Review report assessment: Limitations by reviewers: Review report conclusions: Notes (calculations, if any):		

## Assessment of Study Quality

### Quality of Meta-Analysis:

#### Oxman and Guyatt's index of the scientific quality of research overviews:

The purpose of this index is to evaluate the scientific quality (i.e. adherence to scientific principles) of research overviews (review articles) published in the medical literature. It is not intended to measure literary quality, importance, relevance, originality, or other attributes of overviews.

The index is for assessing overviews of primary (original) research on pragmatic questions regarding causation, diagnosis, prognosis, therapy, or prevention. A research overview is a survey of research. The same principles that apply to epidemiologic survey apply to overviews: a question must be clearly specified; a target population identified and accessed; appropriate information obtained from that population in an unbiased fashion, and conclusions derived, sometimes with the help of formal statistical analysis, as is done in meta-analyses. The fundamental difference between overviews and epidemiologic surveys is the unit of analysis, not the scientific issues that the questions in this index address.

Since most published overviews do not include a methods section, it is difficult to answer some of the questions in the index. Base your answers, as much as possible, on the information provided in the overview. If the methods that were used are reported incompletely relative to a specific item, score that item as "partially." Similarly, if there is no information provided regarding what was done relative to a particular question, score it as "can't tell," unless there is information in the overview that suggest either that the criterion was or was not met.

Questions	Yes, No, Partly; Score
1. Were the search methods used to find evidence (original research) on the primary question(s) stated? <i>Yes is attributed for meta-analysis that report the categories of sources, including years (e.g. databases-used), and whether these categories were named (e.g. MEDLINE). Partial points are given for the category of sources (e.g., electronic, hand, register).</i>	
2. Was the search for evidence reasonably comprehensive? <i>Yes is attributed if at least three categories, one of which must be electronic with key words stated, and any two others (e.g. hand, register) are reported. Key words and/or MeSH terms must be stated.</i>	
3. Were the criteria (inclusion or exclusion) used for deciding which studies to include in the overview reported?	
4. Was bias in the selection of studies avoided? <i>Yes is attributed if at least two reviewers independently assessed the studies for inclusion. A consensus must be reached.</i>	
5. Were the criteria (methodological quality) used for assessing the validity of the included studies reported? <i>It was felt that the issues relating to publication bias should not be included in the assessment of this. Yes is attributed to those meta-analysis reporting a priori methods of validity assessment (e.g. if the author(s) chose to include only randomized, double-blind, placebo controlled trials, or allocation concealment as inclusion criteria)</i>	
6. Was the validity of all studies referred to in text assessed using appropriate criteria (either in selecting studies for inclusion or in analyzing the studies that are cited)? <i>This item relates to validity assessment. Yes is attributed if there is a description of any criteria (either internal or external) used either for inclusion, or for analysis (e.g. sensitivity analysis).</i>	
7. Were the methods used to combine the findings of the relevant studies (to reach a conclusion) reported?	
8. Were findings combined appropriately, relative to the primary question that the overview addresses? <i>For question 8, if no attempt was made to combine findings, and no statement is made regarding the inappropriateness of combining the findings, check "no." If a summary (general) estimate is given in the abstract, the discussion, or the summary section of the paper, and it is not reported how the estimate was derived, mark "no," even if there is a statement regarding the limitations of combining the findings of the studies reviewed. If in doubt, mark "cannot tell."</i>	
9. Were the conclusions made by the author(s) supported by the data and/or analysis reported in the overview? <i>For an overview to be scored as "yes" on question 9, data (not just citations) must be reported that support the main conclusions regarding the primary question(s) that the overview addresses. If the overview concerns</i>	

<p><i>diagnostic or prognostic tests, “retest is not required” (this ensures that diagnostic and prognostic papers are not scored more rigorously than clinical papers).</i></p>	
<p>Overall score:          How would you rate the scientific quality of the review?          1 to 2=extensive flaws, 3 to 4=major flaws, 5 to 6=minor flaws, 7=minimal flaws  <i>The score for question 10, the overall scientific quality, should be based on your answers to the first nine questions. The following guidelines can be used to assist with deriving a summary score. If the “cannot tell” option is used <math>\geq 1</math> times on the preceding questions, a review is likely to have minor flaws at best and it is difficult to rule out major flaws (i.e. a score of <math>\leq 4</math>). If the “no” option is used on questions 2, 4, 5, or 8, the review is likely to have major flaws (i.e. a score of <math>\leq 3</math>, depending on the number and degree of the flaws).</i></p>	

## APPENDIX 2: Oxman-Guyatt Quality Assessment of DERP Report

Assessment of Study Quality	
Questions	Yes, No, Partially, Score
1. Were the search methods used to find evidence (original research) on the primary question(s) stated? <i>Yes is attributed to meta-analysis reporting categories of sources, including years (e.g., databases-MEDLINE) used, and whether these categories were named (e.g., MEDLINE). Partial points are given for the category of sources (e.g., electronic, hand, register).</i>	partially
2. Was the search for evidence reasonably comprehensive? <i>Yes is attributed if at least three categories, one of which must be electronic with key words stated, and any two others (e.g., hand, register) are reported. Key words or MeSH terms must be stated.</i>	partially
3. Were the criteria (inclusion and exclusion) used for deciding which studies to include in the overview reported?	yes
4. Was bias in the selection of studies avoided? <i>Yes is attributed if at least two reviewers independently assessed it for inclusion. A consensus must be reached.</i>	no
5. Were the criteria (methodological quality) used for assessing the validity of the included studies reported? <i>It was felt that the issues relating to publication bias should be excluded in the assessment of this point. Yes is attributed to those meta-analysis reporting a priori methods of validity assessment (e.g., If the author(s) chose to include only randomized, double-blind, placebo controlled trials, or allocation concealment as inclusion criteria).</i>	yes
6. Was the validity of all studies referred to in text assessed using appropriate criteria (either in selecting studies for inclusion or in analyzing the studies that are cited)? <i>This item relates to validity assessment. Yes is attributed if there is a description of any criteria (either internal or external used either for inclusion, or for analysis (e.g. sensitivity analysis).</i>	yes
7. Were the methods used to combine the findings of the relevant studies reported?	yes
8. Were findings combined appropriately, relative to the primary question that the overview addresses? <i>If no attempt was made to combine findings, and no statement is made regarding the inappropriateness of combining the findings, check "no." If a summary (general) estimate is given anywhere in the abstract, the discussion, or the summary section of the paper, and it is not reported how the estimate was derived, mark "no" even if there is a statement regarding the limitations of combining the findings of the studies reviewed. If in doubt, mark "cannot tell."</i>	partially
9. Were the conclusions made by the author(s) supported by the data or analysis reported in the overview? <i>For an overview to be scored as "yes," data (not just citations) must be reported that support the main conclusions regarding the primary question(s) that the overview addresses. If the overview concerns diagnostic-prognostic tests, a "retest is not required" (this ensures that diagnostic-prognostic papers are not scored more rigorously than clinical papers).</i>	yes
Overall score: How would you rate the scientific quality of the review? 1 to 2=extensive flaws; 3 to 4=major flaws; 5 to 6=minor flaws; 7=minimal flaws <i>The overall scientific quality should be based on your answers to the first nine questions. If the "cannot tell" option is used <math>\geq 1</math> times on the preceding questions, a review is likely to have minor flaws at best, and it is difficult to rule out major flaws (i.e., a score of <math>\leq 4</math>). If the "no" option is used on questions 2, 4, 5, or 8, the review is likely to have major flaws (i.e., a score of <math>\leq 3</math>, depending on the number and degree of the flaws).</i>	5 minor flaws

## APPENDIX 3: DERP Methods

### Inclusion Criteria

- adults with migraine (excluding other types of headaches): subgroups of interest included different races, ages, genders, pregnant or lactating women, patients with coronary artery disease, persons taking prophylactic migraine medication, and women with menstrual migraine
- studies comparing eligible oral triptan with another triptan, another anti-migraine drug (such as ergotamine) or placebo: eligible triptans included almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan; treatment included any level of migraine (during aura, or when pain was mild, moderate, or severe), but studies had to specify timing of treatment
- short-term efficacy outcomes: reduction or resolution of symptoms (pain, nausea, vomiting, photophobia), reduction of duration of symptoms, duration of improvement, consistency of effectiveness (proportion of headaches successfully treated per patient), functional outcome, quality of life, or adverse effect; pain measures included pain relief and PF response at various times after taking medication, sustained response, SPF response, and use of rescue medications; long-term efficacy included consistency, patient satisfaction and workplace productivity
- design: for short-term efficacy, published, double-blind RCTs conducted in outpatient setting (including emergency department) included; for long-term endpoints, longitudinal cohort studies included; to be considered for possible inclusion as systematic review, explicit criteria for inclusion in review had to be stated
- for safety and AEs, controlled clinical trials reporting the frequency of withdrawals or frequency or severity of specific AEs included; long-term observational studies of tolerability or withdrawals for one or more triptans also included.

### Exclusion criteria

Studies that were unpublished, had no original data, or evaluated complex interventions in which the effect of the triptan could not be determined were excluded, in addition to those with poor internal validity as judged by explicit criteria for quality. Studies that used encapsulated sumatriptan in a control group were excluded. A flowchart of studies was provided in the appendix of the DERP report.

### Literature Search

To identify potentially relevant studies to address each objective, the Cochrane Central Register of Controlled Trials, EBM Reviews-Cochrane Database of Systematic Reviews, MEDLINE, DARE, and Ovid Medline were searched from 1996 to 2004. Searching was limited to human studies published in the English language. Pharmaceutical manufacturers and subcommittee members were invited to provide additional citations, and reference lists of review articles were searched.

### Data Extraction and Synthesis

One reviewer abstracted the following data from included head-to-head trials: study design; setting; population characteristics; eligibility and exclusion criteria; interventions; comparisons; numbers screened; eligible, enrolled, and lost to follow-up; method of outcome ascertainment; and results. A second reviewer verified the data in the tables. One reviewer abstracted data from active-control trials.

The outcomes were summarized by outcome and by study. The absolute rate of response for each triptan per dose used and the statistical significance in difference were noted for each outcome measure of the included head-to-head trials.

## **Quality Assessment**

Pre-specified criteria were used to assess the internal validity of systematic reviews, RCTs, and longitudinal cohort studies. Appropriate randomization, blinding, and allocation concealment; similarity of groups at baseline and maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination were assessed. In short-term studies, patients who did not take the medication during the study period were excluded from further analysis. While excluding these patients violates the intention-to-treat principle, it does not introduce bias between compared groups. A selection bias is introduced in that individuals with milder headaches are more likely not to be captured. Potential threats to external validity were examined, including selection biases, intervention-related biases, and bias in reporting of results.

## APPENDIX 4: DERP Findings

### Quantity of Clinical Evidence

The DERP literature search resulted in 1,454 citations: 386 from the Cochrane Central Register of Controlled Trials, 401 from MEDLINE, 547 from EMBASE, 47 from manufacturer dossiers, and 53 from hand searching and reference lists.

### Summary of DERP Results

#### Results for DERP Objective 1: Systematic Reviews

*What are the comparative effectiveness and duration of response of different oral triptans in reducing the severity and duration of symptoms, improving functional outcomes, and improving quality of life in adult patients with migraine?*

Two Cochrane reviews were identified in the DERP review; one comparing rizatriptan with placebo and the other comparing eletriptan with placebo. Three self-described systematic reviews and a meta-analysis of the comparative efficacy of different triptans were also found. One review, Oldman, used predefined criteria (Jadad score) in assessing the trials' internal validity. Eletriptan 80 mg and rizatriptan 10 mg provided significantly superior headache relief at two hours than rizatriptan 5 mg, sumatriptan 50 mg, or naratriptan 2.5 mg. Eletriptan 80 mg and rizatriptan 10 mg provided significantly superior freedom from pain at two hours compared with naratriptan 2.5 mg, rizatriptan 5 mg, sumatriptan 50 mg and 100 mg, or zolmitriptan 2.5 mg. Eletriptan 80 mg provided significantly superior sustained relief over 24 hours compared with rizatriptan 5 mg or 10 mg or sumatriptan 50 mg or 100 mg.<sup>28</sup>

Ferrari *et al.*<sup>25</sup> conducted a meta-analysis of 53 trials, including 12 unpublished studies from manufacturers, but did not consider study quality. The investigators compared pooled results for each drug and dosage to sumatriptan 100 mg. Sumatriptan 50 mg and 100 mg, eletriptan 40 mg, zolmitriptan 2.5 mg and 5 mg, rizatriptan 5 mg, and almotriptan 12.5 mg had similar results for pain relief after two hours. Rizatriptan 10 mg was more likely to relieve pain after two hours than other triptans. Almotriptan 12.5 mg was more likely than sumatriptan 100 mg to provide freedom from pain by two hours (36% versus 29%), as was rizatriptan 10 mg (40% versus 29%). DERP reported that this meta-analysis was comprehensive, examined important outcome measures, and applied statistical methods appropriately, but the strategy for pooling was inappropriate, because the investigators gave equal weighting to the results of all studies without consideration for quality. In addition, recent studies of newer drugs were pooled with an older one conducted under different circumstances.<sup>28</sup>

Both Oldman and Ferrari pooled results of placebo-controlled trials in an effort to make inferences about the relative effectiveness of different triptans. The ability of indirect comparisons to predict the results of head-to-head trials has not yet been established. Ferrari *et al.* published a subsequent paper summarizing the 24-hour endpoint results of 22 head-to-head trials. Sumatriptan 100 mg was superior in efficacy to naratriptan 2.5 mg, equivalent to almotriptan 12.5 mg and zolmitriptan 5 mg, and inferior to eletriptan 40 mg and 80 mg and rizatriptan 10 mg. Sumatriptan 100 mg caused more AEs than almotriptan 12.5 mg and naratriptan 2.5 mg, but fewer AEs than eletriptan 80 mg. Sumatriptan 50 mg was inferior in efficacy compared with eletriptan 40 mg and 80 mg and slower on time to response compared with rizatriptan 10 mg. Sumatriptan 50 mg caused fewer AEs than eletriptan 40 mg and 80 mg or rizatriptan 5 mg. Sumatriptan 25 mg was inferior in efficacy compared with eletriptan 80 mg, rizatriptan 5 mg and 10 mg, and zolmitriptan 2.5 mg and 5 mg. Sumatriptan 25 mg caused fewer AEs for most parameters than other triptans.<sup>28</sup>

## Results for DERP Objective 1: Randomized and Observational Studies

Seventeen randomized controlled head-to-head trials of triptans were included in the DERP study, of which oral sumatriptan was the most common comparator. Twenty-five head-to-head trials were excluded because they were in abstract form or they were deemed to be of poor internal validity.

According to the DERP review, six placebo-controlled trials suggest that almotriptan 12.5 mg was similar in efficacy to sumatriptan 100 mg, and that frovatriptan was less likely than oral sumatriptan 100 mg to relieve pain within two hours. Two placebo-controlled trials suggest that patients taking fast-disintegrating, rapid-release formulations of sumatriptan experienced faster pain relief than those taking placebo.

Patients in the included head-to-head trials were reported to be similar in age, sex, and migraine history. Most recruited patients were not pregnant or experiencing coexisting medical conditions. Three trials were rated as having good internal validity according to DERP. Differences between compared groups were the most common reason for a “fair quality” rating. Conflicting results were reported regarding the effect of encapsulation on the pharmacokinetics of five trials involving eletriptan, sumatriptan, or another comparator. In the meta-analysis by Ferrari *et al.*, lower PF and SPF rates were reported in the Pfizer-conducted eletriptan versus sumatriptan comparator studies. In these studies, sumatriptan 100 mg did not perform as well as in studies conducted by other companies, perhaps because of encapsulation for blinding purposes. DERP conducted their meta-analysis to examine how encapsulation affects the results of head-to-head studies. For all triptans, encapsulation was associated with decreased efficacy. It was not possible to determine whether encapsulation was the cause of reduced efficacy. Sumatriptan was compared with eletriptan (three trials), naratriptan (one trial), rizatriptan, (two trials), and zolmitriptan (three trials). Four trials compared rizatriptan with naratriptan and zolmitriptan; and eletriptan with naratriptan and zolmitriptan.<sup>28</sup>

### Naratriptan versus Sumatriptan

One trial comparing various doses of naratriptan to sumatriptan 100 mg and placebo reported similar two-hour pain relief rates for naratriptan 2.5 mg and sumatriptan 100 mg (52% versus 60%). Four hours after dosing, headache relief was reported by significantly more sumatriptan 100 mg recipients (80%) than naratriptan 2.5 mg (48.4%) recipients ( $p < 0.001$ ).<sup>28</sup>

### Naratriptan versus Rizatriptan

A single-dose trial of 522 patients compared naratriptan 2.5 mg with rizatriptan 10 mg. A significantly higher percentage of rizatriptan 10 mg (68.7%) recipients reported two-hour pain relief compared to naratriptan 2.5 mg (48.4%,  $p < 0.001$ ) recipients; and significant satisfaction with rizatriptan (33% were “completely or very” satisfied versus 19% for naratriptan). Rizatriptan was more likely to result in PF response (44.8% versus 20.7%) and in normal function (39.3% versus 22.6%) at two hours after dosing. Significantly more rizatriptan recipients experienced a SPF response for 24 hours compared with naratriptan (29% versus 17%). Naratriptan and rizatriptan were similarly efficacious in relieving nausea and photophobia, while rizatriptan was better at relieving phonophobia. No significant difference was observed between groups regarding overall quality of life at 24 hours. Rizatriptan recipients experienced a significantly higher rate of AEs (most commonly asthenia or fatigue, dizziness, nausea, and somnolence) compared with naratriptan recipients (39% versus 29%,  $p < 0.05$ ).<sup>28</sup>

## Rizatriptan versus Sumatriptan

In a fair-quality trial of 1,099 patients receiving rizatriptan 5 mg or 10 mg or sumatriptan 100 mg, 60%, 67%, and 62% of patients respectively experienced pain relief at two hours.<sup>28</sup>

## Rizatriptan versus Zolmitriptan

A trial comparing zolmitriptan 2.5 mg to rizatriptan 10 mg reported no significant difference between groups regarding two-hour pain relief.<sup>28</sup>

## Sumatriptan versus Zolmitriptan

Three trials comparing zolmitriptan 5 mg with sumatriptan 50 mg or sumatriptan 100 mg reported insignificant differences in headache relief at two hours. Zolmitriptan 2.5 mg and 5 mg were superior compared with those receiving a lower, less commonly used dosage of sumatriptan 25 mg (67.1%, 64.8% versus 59.6%;  $p < 0.01$ ).<sup>28</sup>

## Eletriptan versus Sumatriptan, Naratriptan, and Zolmitriptan

Five trials compared eletriptan with encapsulated sumatriptan (three trials), naratriptan (one trial) and zolmitriptan (one trial). Significantly more eletriptan 40 mg users experienced two-hour pain relief than those taking encapsulated sumatriptan 100 mg in two of three trials and those taking encapsulated naratriptan 2.5 mg.<sup>28</sup>

## Satisfaction

Five trials reported two-hour patient satisfaction. One trial reported that a greater percentage of patients taking rizatriptan 10 mg were completely, very, or somewhat satisfied with treatment compared to those taking zolmitriptan 2.5 mg (62.7% versus 54.6%,  $p = 0.045$ ). One trial reported a higher mean satisfaction score for patients taking rizatriptan 10 mg than those taking naratriptan 2.5 mg (3.55 versus 4.2,  $p < 0.001$ ). Two trials suggested that the satisfaction of patients taking sumatriptan 100 mg did not differ from those taking naratriptan 2.5 mg. The two-hour satisfaction of sumatriptan 50 mg recipients did not differ from those taking zolmitriptan 2.5 mg. A greater proportion of eletriptan 40 mg and 80 mg recipients reported satisfaction compared to those taking encapsulated zolmitriptan 2.5 mg (64% versus 66% versus 55%,  $p < 0.01$ ).<sup>28</sup>

## Return to Normal Function

Six trials reported patients' perception of their functional disability. At two hours, four trials showed rizatriptan 10 mg to be superior to sumatriptan 50 mg (47% versus 42%,  $p = 0.033$ ), sumatriptan 100 mg (42% versus 33%,  $p = 0.015$ ), naratriptan (2.5 mg) (39.3% versus 22.6%,  $p < 0.001$ ), and zolmitriptan (2.5 mg) (45.4% versus 37%,  $p = 0.025$ ). Greater proportions of patients taking eletriptan 40 mg reported normal functions after two hours compared with those taking encapsulated sumatriptan 100 mg, according to two studies.<sup>28</sup>

## Endpoints at 24 Hours

Ferrari *et al.* suggest that there were no differences in the 24-hour SPF endpoint between sumatriptan 100 mg and almotriptan 12.5 mg, zolmitriptan 5 mg, or rizatriptan 10 mg. There was also no difference between sumatriptan 50 mg and zolmitriptan 2.5 mg, or rizatriptan 5 mg. Rizatriptan 10 mg was superior to zolmitriptan 2.5 mg and naratriptan 2.5 mg. Zolmitriptan 2.5 mg and 5 mg were superior to sumatriptan

25 mg. Eletriptan 40 mg was superior to encapsulated sumatriptan across two studies included in the meta-analysis by Ferrari *et al.*<sup>28</sup>

## Rescue Medication

Eight trials reported the use of rescue medication from two to 24 hours. Significantly fewer patients taking eletriptan 40 mg used rescue medication compared with those taking encapsulated naratriptan 2.5 mg, sumatriptan 100 mg, or zolmitriptan 2.5 mg.<sup>28</sup>

## Symptom Relief

Twelve trials reported the percentage of patients without migraine-related symptoms at two hours. Two trials reported significant differences in nausea among patients taking rizatriptan 10 mg and sumatriptan 100 mg (75% versus 67%,  $p < 0.05$ ) and zolmitriptan 2.5 mg (74.8% versus 67.5%,  $p = 0.046$ ). Eletriptan 40 mg was superior to encapsulated sumatriptan 100 mg in two of three trials and superior to encapsulated zolmitriptan 2.5 mg in treating nausea after two hours. Five trials reported insignificant differences in relief of nausea between rizatriptan 10 mg and naratriptan 2.5 mg or between sumatriptan 25 mg to 100 mg and any other triptan.<sup>28</sup>

Two trials reported significant differences in two-hour photophobia among patients taking rizatriptan 10 mg compared with naratriptan 2.5 mg (59.2% versus 47.2%,  $p < 0.05$ ) and zolmitriptan 2.5 mg (64.4% versus 56.5%;  $p = 0.029$ ). Rizatriptan 10 mg was equal to sumatriptan 100 mg regarding photophobia relief at two hours. Photophobia rates did not differ among sumatriptan 100 mg, naratriptan 2.5 mg, and zolmitriptan 5 mg. Eletriptan 40 mg was superior to encapsulated sumatriptan 100 mg, and eletriptan 80 mg was similar to encapsulated zolmitriptan 2.5 mg in treating photophobia at two hours.<sup>28</sup>

Five trials included the results of relief from vomiting. No significant differences were noted between the dosages of any triptans.<sup>28</sup>

## Consistency

Most head-to-head trials reported results for one to three migraine attacks. Two trials comparing zolmitriptan 2.5 mg and 5 mg with sumatriptan 25 mg and 50 mg suggested that the two-hour response is not a reliable indicator of consistency across multiple attacks. No difference in efficacy was reported between zolmitriptan 2.5 mg and 5 mg and sumatriptan 50 mg.<sup>28</sup>

## Preferences

Preference studies provide weak evidence of comparative effectiveness. While randomization ensures similar groups, it cannot correct the lack of blinding or the selection bias that is likely to occur. A randomized open-label cross-over trial found that more patients preferred rizatriptan wafer than sumatriptan 50 mg tablets (64.3 versus 35.7,  $p < 0.001$ ). In another study, migraine patients preferred zolmitriptan 2.5 mg over sumatriptan 50 mg tablets. Another study, where patients were given samples of four triptans, showed that preferences for sumatriptan, zolmitriptan, rizatriptan, and naratriptan were similar overall, but younger patients preferred oral dissolving rizatriptan.<sup>28</sup>

## Results for DERP Objective 2

*What are the comparative incidence and nature of complications (serious or life-threatening or those that may adversely effect compliance) of different triptans in adult patients being treated for migraine?*

### Serious or Life-threatening Events

There were no comparative studies of life-threatening events. A review of sumatriptan examined AEs in clinical trials and post-market surveillance data. In 1998, 103 serious cardiovascular events were reported after the use of subcutaneous sumatriptan and 38 after the use of oral sumatriptan. The review concluded that “serious events including myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following sumatriptan administration.”<sup>28</sup>

### Chest Pain and Tightness

Head-to-head trials suggest few differences among triptans regarding chest pain and tightness. In one trial, chest pain was more frequent among patients taking sumatriptan 100 mg than among those taking rizatriptan 5 mg (6% versus 1%,  $p < 0.05$ ), but not different for sumatriptan 100 mg and rizatriptan 10 mg (6% versus 3%). Subcutaneous sumatriptan 6 mg was associated with higher rates of mild to moderate chest pain compared to eletriptan 80 mg in an open trial including 1,696 migraine attacks.<sup>28</sup>

### Central Nervous System (CNS) Symptoms

No significant differences were reported between groups in trials assessing dizziness, paresthesia, or somnolence. In one trial, fatigue and asthenia was more frequent in patients taking sumatriptan 100 mg than those taking rizatriptan 5 mg (8% versus 2%,  $p < 0.05$ ), but was not different for sumatriptan 100 mg and rizatriptan 10 mg (8% versus 8%).<sup>28</sup>

## Results for DERP Objective 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 AEs?*

There is no evidence that any ethnic or racial group has a higher risk of AEs from triptans or that one triptan provides an advantage compared with the others in this respect. In a 12-attack randomized placebo-controlled trial, subcutaneous sumatriptan was equally effective among Caucasians, African Americans, Hispanics, and those of other ethnicities, in relieving headache, reducing disability, and experiencing adverse events. Two placebo-controlled trials involving Japanese migraineurs taking eletriptan and zolmitriptan reported similar results for pain relief and PF response at two hours, 24-hour recurrence, escape medication, relief of associated symptoms at two hours (nausea, photophobia, phonophobia, vomiting), and AEs (asthenia, paresthesia, somnolence) compared with placebo. Most trials excluded patients with cardiovascular disease, uncontrolled hypertension, liver disease, or other conditions. A retrospective meta-analysis of RCTs of subcutaneous sumatriptan, rizatriptan, and zolmitriptan suggested that triptans are equally effective for menstrual migraine.<sup>28</sup>

## APPENDIX 5: Literature Search Strategy

### Guide to Search Syntax (OVID®)

ab	Abstract
adj	Adjacent, any order
cp	Country of publication
ds	Diseases
exp	Explode (i.e., subject heading)
fs	Floating subject heading
hw	Heading word
pt	publication type
m	CAS registry #
sh	subject heading
ti	title
tn	trade name
\$	truncation symbol
*	Major subject heading (i.e., focus)

### Literature Search Strategy for clinical studies

DATABASES	LIMITS	SUBJECT HEADINGS/KEYWORDS
OVID®	Human Adolescent	<b>INTERVENTION SEARCH</b>
BIOSIS Previews® (1989-present)		Exp Tryptamines/ [MEDLINE]
EMBASE® (1980-present)		OR
MEDLINE® (1966-present)		Sumatriptan.sh. [MEDLINE]
		OR
		Tryptamine.sh. or Sumatriptan.sh. or Sumatriptan Succinate.sh. or Almotriptan.sh. or Eletriptan.sh. or Naratriptan.sh. or Rizatriptan.sh. or Zolmitriptan.sh. [EMBASE]
		OR
		464-06-2.rn. or 103628-46-2.rn. or 154323-57-6.rn. or 143322-58-1.rn. or 121679-13-8.rn. or 145202-66-0.rn or 144034-80-0.rn. or 139264- 17-8.rn.
		OR
		(tryptamine\$ or triptan\$ or indolyethylamine or tryptomine\$ or NSC 73938 or NSC73938).ti,ab.
		OR
		(GR 43175 or GR43175 or GR 43175X or GR43175X or BRN 6930870 or BRN6930870).ti,ab.
		OR

	<p>(sumatriptan\$ or imigran\$ or imitrex or sumatran or suminat or micranil or suvulan or migril or sumax or liotrex or somatran or imiject or sumigrene or diletan or arcoiran or dolmigral or novelian).ti,ab.</p> <p>OR</p> <p>(imigran or imigrane or imitrex or sumatran or suminat or micranil or suvulan or migril or sumax or liotrex or somatran or imiject or sumigrene or diletan or arcoiran or dolmigral or novelian).tn. [EMBASE]</p> <p>OR</p> <p>(almotriptan\$ or almogran or axert or almotrex).ti,ab.</p> <p>OR</p> <p>(almogran or axert or almotrex).tn. [EMBASE]</p> <p>OR</p> <p>(eletriptan\$ or relpax or UK 166,044 or UK166,044 or UK166044 or relert or relepax).ti,ab.</p> <p>OR</p> <p>(relpax or relert or relepax).tn. [EMBASE]</p> <p>OR</p> <p>(naratriptan or amerge or naramig or colatan or antimigrin or naragran).ti,ab.</p> <p>OR</p> <p>(naratriptan or amerge or naramig or colatan or antimigrin or naragran).tn. [EMBASE]</p> <p>OR</p> <p>(rizatriptan or maxalt or L 705,126 or L 705126 or L705,126 or L705126 or MK 0462 or MK 462 or MK0462 or MK462 or rizalief or rizalt or rizaliv).ti,ab.</p> <p>OR</p> <p>(rizatriptan or maxalt or rizalief or rizalt or rizaliv).tn. [EMBASE]</p> <p>OR</p> <p>(zolmitriptan or zomig or 311C90 or flezol or zomigoro or zomigon or AscoTop).ti,ab.</p> <p>OR</p> <p>(zolmitriptan or zomig or flezol or zomigoro or zomigon or</p>
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		<p>AscoTop).tn. [EMBASE]</p> <p><b>Note:</b></p> <ul style="list-style-type: none"> <li>• <i>Heading word was included for BIOSIS</i></li> </ul> <p><b>AND</b> <b>INDICATION SEARCH</b></p> <p>Exp Migraine Disorders/ or Cluster Headache.sh. [MEDLINE] [EMBASE]</p> <p>OR</p> <p>(Headache Disorders or Headache).sh. [MEDLINE]</p> <p>OR</p> <p>Trigeminal Autonomic Cephalalgias.sh. or Headache Disorders, Primary.sh. [MEDLINE]</p> <p>OR</p> <p>*Headache and Facial Pain/ or *Headache/ or *Sunct Syndrome/ or *Chronic Paroxysmal Hemicrania/ or *Hemicrania Continua/ or *Trigeminus Neuralgia/ [EMBASE]</p> <p>OR</p> <p>(Migraine or Cluster Headache).ds. [BIOSIS]</p> <p>OR</p> <p>(migrain\$ or migran\$.ti,ab.</p> <p>OR</p> <p>((sick adj headache\$) or (cluster adj headache\$) or (ciliary adj neuralgia\$) or (horton's adj syndrome\$) or (hortons adj syndrome\$) or (Horton adj syndrome\$)).ti,ab.</p> <p>OR</p> <p>(anti-migrain\$ OR antimigrain\$ Or anti-migrane\$ OR antimigrane\$.ti,ab.</p> <p>OR</p> <p>(histamine or histaminic or Horton\$.ti,ab. adj (cephalgi\$ or cephalalgi\$ or headache\$.ti,ab.</p> <p><b>Note:</b></p> <ul style="list-style-type: none"> <li>• <i>Heading word was included for BIOSIS</i></li> </ul> <p><b>AND</b> <b>POPULATION SEARCH</b></p> <p>Adolescent/ or exp Puberty/ or Minors/ [MEDLINE]</p>
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		<p>OR</p> <p>Exp Adolescent/ OR exp Adolescence/ OR exp Puberty/ [EMBASE]</p> <p>OR</p> <p>(adolescen\$ or teen or teens or teenager\$ or teen-ager\$ or youth or youths or juvenile\$ or puberty\$ or pubescen\$).ti,ab.</p> <p><b>Note:</b></p> <ul style="list-style-type: none"> <li>• <i>Heading word was included for BIOSIS</i></li> </ul> <p><b>AND</b></p> <p><b>SYSTEMATIC REVIEW FILTER</b></p> <p>Meta-Analysis.pt. [MEDLINE]</p> <p>OR</p> <p>Meta-Analysis.sh. or exp Technology Assessment, Biomedical/ [MEDLINE]</p> <p>OR</p> <p>(Meta Analysis or Systematic Review).sh. [EMBASE]</p> <p>OR</p> <p>((systematic\$ adj (literature review\$ or review\$ or overview\$)) or (methodologic\$ adj (literature review\$ or review\$ or overview\$))).ti,ab.</p> <p>OR</p> <p>((quantitative adj (review\$ or overview\$ or synthes\$)) or (research adj (integration\$ or overview\$))).ti,ab.</p> <p>OR</p> <p>((integrative adj2 (review\$ or overview\$)) or (collaborative adj (review\$ or overview\$)) or pool\$ analy\$).ti,ab.</p> <p>OR</p> <p>(data synthes\$ or data extraction\$ or data abstraction\$).ti,ab.</p> <p>OR</p> <p>(meta analy\$ or metaanaly\$ or met analy\$ or metanaly\$ or health technology assessment\$ or HTA or HTAs or biomedical technology assessment\$ or bio-medical technology assessment\$).ti,ab.</p> <p>OR</p> <p>(handsearch\$ or hand search\$).ti,ab.</p>
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		<p>OR</p> <p>(mantel haenszel or peto or der simonian or dersimonian or fixed effect\$ or latin square\$).ti,ab.</p> <p>OR</p> <p>(meta regression\$ or metaregression\$ or mega regression\$).ti,ab.</p> <p><b>Note:</b></p> <ul style="list-style-type: none"> <li>• <i>Heading word was included for BIOSIS</i></li> </ul> <p><b>OR</b></p> <p><b>CLINICAL STUDIES FILTER</b></p> <p>exp Controlled Clinical Trials/ [MEDLINE]</p> <p>OR</p> <p>(Multicenter studies or random allocation or double-blind method or single-blind method).sh. [MEDLINE]</p> <p>OR</p> <p>exp Epidemiologic Research Design/ or exp cohort studies/ [MEDLINE]</p> <p>OR</p> <p>(clinical trials or comparative study).sh. [MEDLINE]</p> <p>OR</p> <p>(Multicenter Study or Randomized Controlled Trial or Controlled Clinical Trial).pt. [MEDLINE]</p> <p>OR</p> <p>clinical trial.pt. [MEDLINE]</p> <p>OR</p> <p>exp Controlled Study/ or Randomized Controlled Trial/ or exp Evidence Based Medicine/ [EMBASE]</p> <p>OR</p> <p>(Major Clinical Study or Multicenter Study).sh. [EMBASE]</p> <p>OR</p> <p>(Randomization or double-blind procedure or single-blind procedure or latin-square design or crossover procedure or cohort analysis or longitudinal study or case control study or open study or case report or case study).sh. [EMBASE]</p> <p>OR</p>
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		<p>Exp Clinical trial/ [BIOSIS]</p> <p>OR</p> <p>(random\$ or sham\$ or placebo\$ or RCT\$ or (singl\$ adj (blind\$ or dumm\$ or mask\$)) or (doubl\$ adj (blind\$ or dumm\$ or mask\$))).ti,ab.</p> <p>OR</p> <p>((tripl\$ adj (blind\$ or dumm\$ or mask\$)) or (trebl\$ adj (blind\$ or dumm\$ or mask\$))).ti,ab.</p> <p>OR</p> <p>(control\$ adj (study or studies or trial\$)).ti,ab.</p> <p>OR</p> <p>((control\$ adj clinical) adj (study or studies or trial\$)).ti,ab.</p> <p>OR</p> <p>((multicent\$ or multi cent\$) adj (study or studies or trial\$)).ti,ab.</p> <p>OR</p> <p>((cohort or concurrent or incidence) adj (analys\$ or study or studies)).ti,ab.</p> <p>OR</p> <p>((case-control or case-base or case-comparison or case-referent or case-referrent or observational) adj (study or studies)).ti,ab.</p> <p>OR</p> <p>(latin square or control\$ or prospective\$).ti,ab.</p> <p>OR</p> <p>observational.ti,ab. adj (study or studies or trial\$).ti,ab.</p> <p><b>Note:</b></p> <ul style="list-style-type: none"> <li>• <i>Heading word was included for BIOSIS</i></li> </ul> <p><i>Searches performed: June 27 and 28, 2006</i>  <i>OVID alerts set up on same databases until October 3, 2006</i></p>
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## Literature Search Strategy for economic studies

DATABASES	LIMITS	SUBJECT HEADINGS/KEYWORDS
<b>Same pre-filter strategy for indication and intervention as previous with following economic filter</b>		
<p>OVID®</p> <p>BIOSIS Previews® (1989-present)</p> <p>EMBASE® (1980-present)</p> <p>MEDLINE® (1966-present)</p>		<p><b>ECONOMIC FILTER</b></p> <p>exp "Costs and Cost Analysis"/ [MEDLINE]</p> <p>OR</p> <p>(value of life or economics, medical or economics, pharmaceutical or models, economic or markov chains or monte carlo method or uncertainty).sh. [MEDLINE]</p> <p>OR</p> <p>economics.fs. [MEDLINE]</p> <p>OR</p> <p>(quality of life or quality-adjusted life years).sh. [MEDLINE]</p> <p>OR</p> <p>economics.sh. [MEDLINE]</p> <p>OR</p> <p>exp Health economics/ or exp Economic Evaluation/ or exp Pharmacoeconomics/ or exp Economic Aspect/ or Quality Adjusted Life Year.sh. or exp Quality of Life/ or pe.fs. [EMBASE]</p> <p>OR</p> <p>(Economic Impact or Economic Value or Pharmacoeconomics or Health Care Cost or Economic Factors or Economics or Cost Analysis or Cost or Economic Analysis or Cost-Effectiveness or Costs or "Quality of Life" or Health Care Cost or Cost Savings or Cost-Benefit Analysis or Hospital Costs or Medical Costs or Quality-of-Life).mp. [BIOSIS]</p> <p>OR</p> <p>((econom\$ or cost or costly or costing or costed or prices or pricing or discount or discounts or discounted or discounting or budget\$ or afford\$ or pharmacoeconomic\$ or pharmaco) adj1 economic\$).ti,ab.</p> <p>(decision adj1 (tree\$ or analy\$ or model\$)).ti,ab.</p> <p>((value or values or valuation) adj2 (money or monetary or life or lives)).ti,ab.</p> <p>(QOL or QOLY or QOLYs or HRQOL or QALY or QALYs).ti,ab.</p>

		<p>((quality adj1 life) or (willingness adj1 pay) or (quality adj1 adjusted life year\$) or sensitivity) adj analys?s) or (quality adjusted life expectanc\$)).ti,ab.</p> <p><b>Note:</b></p> <ul style="list-style-type: none"> <li>Heading word was included for BIOSIS</li> </ul> <p>Search performed: June 27 and 28, 2006  OVID alerts set up on same databases until October 3, 2006</p>
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### Literature Search Strategy for clinical practice guidelines

DATABASES	LIMITS	SUBJECT HEADINGS/KEYWORDS
Same pre-filter strategy for intervention as previous with following guideline and Canadian filters		
<p>OVID®</p> <p>BIOSIS Previews® (1989-present)</p> <p>EMBASE® (1980-present)</p> <p>MEDLINE® (1966-present)</p>		<p><b>GUIDELINE FILTER</b></p> <p>Exp Consensus development conferences/ [MEDLINE]</p> <p>OR</p> <p>(guidelines or critical pathways or health planning guidelines).sh. [MEDLINE]</p> <p>OR</p> <p>(guideline or practice guideline or Consensus Development Conference or Consensus Development Conference, NIH).pt. [MEDLINE]</p> <p>OR</p> <p>Exp practice guideline/ [EMBASE]</p> <p>OR</p> <p>(cpg or cpgs).ti,ab.</p> <p>OR</p> <p>((critical or clinical or practice) adj (path or paths or pathway or pathways or protocol or protocols or guideline or guidelines)).ti,ab.</p> <p>OR</p> <p>(care adj (path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab.</p> <p>OR</p> <p>Consensus.ti,ab. adj development.ti,ab.</p> <p><b>AND</b></p> <p><b>CANADIAN FILTER</b></p> <p>Canada.cp. [MEDLINE] [EMBASE]</p>

		<p>OR</p> <p>Canada.sh. [EMBASE]</p> <p>OR</p> <p>(Canada or Canadian\$ or (British adj Columbia\$) or Alberta\$ or Saskatchewan\$ or Manitoba\$ or Ontario\$ or Quebec\$.ti,ab.</p> <p>OR</p> <p>((Nova adj Scotia\$) or (New adj Brunswick\$) or (Prince adj Edward adj Island\$) or Newfoundland\$ or Yukon\$ or (Northwest adj Territor\$) or Nunavut\$.ti,ab.</p> <p><b>Note:</b></p> <ul style="list-style-type: none"> <li>• <i>Heading word was included for BIOSIS</i></li> </ul> <p><i>Search performed: June 27 and 28, 2006</i></p> <p><i>OVID alerts set up on same databases until October 3, 2006</i></p>
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### Additional searches

PubMed Cochrane Library, Issue 3, 2006	Same as in MEDLINE	Same MeSH headings and keywords as the original OVID <sup>®</sup> MEDLINE <sup>®</sup> search. “In Process” and “Publisher” filters were included in retrieve pre-MEDLINE records.  <i>Searches performed June 19, 2006</i>
Search of HTA, near- HTA websites for published, in-progress and planned reports	English or French	e.g., University of York NHS Centre for Reviews and Dissemination (CRD) databases, HEED, AHRQ, NCCHTA, NICE, NZHTA, ECRI, etc.

# APPENDIX 6: Clinical Review Abstract Selection Form

Triptans Study Inclusion and Exclusion Form

## Clinical Review

Title:

First author and year:

Abstract number:

Economic component:

Reviewer:

S. Membe

K. Cimon

## Inclusion Criteria

**Question 1: What is the evidence of comparative clinical effectiveness of available triptans?**

**Question 2: What is the evidence of the clinical advantage of sumatriptan versus placebo?**

- |   |     |    |             |
|---|-----|----|-------------|
| 1. Population:  | yes | no | cannot tell |
| • adolescents with acute migraine (with or without aura) or cluster headache  |     |    |             |
| 2. Intervention:  | yes | no | cannot tell |
| • almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, or zolmitriptan versus each other or placebo  |     |    |             |
| • sumatriptan versus placebo  |     |    |             |
| 3. Study Design:  | yes | no | cannot tell |
| • RCTs (efficacy and AEs)   |     |    |             |
| • observational studies (AEs)   |     |    |             |
| 4. Outcome Measures (any of):   | yes | no | cannot tell |
| • short-term efficacy: reduction or resolution or symptoms (pain, nausea, vomiting, photophobia, phonophobia); duration of improvement, proportion of headaches successfully treated per patient; functional outcome; quality of life |     |    |             |
| • long-term efficacy: consistency, patient satisfaction, academic or workplace productivity   |     |    |             |
| • AEs.  |     |    |             |

Exclusion Criteria: duplicate reports, dose-finding studies, studies combining interventions or comparisons with anticholinergic drugs

- 
- “yes” (1 to 4 inclusive): include study; or “no” (any of 1 to 4): exclude study
  - agreement between SM and KC:           yes           no
  - decision by third reviewer (MB) if SM and KC disagree: include           exclude

## APPENDIX 7: Clinical Review Data Extraction and Quality Assessment Form (Clinical Trials)

### Triptans for migraine and cluster headache

Date:	Reviewer Initials:	ID number:
Article identification ( <i>author, year</i> ): Full citation: Geographic location: Duration of study: Centre: Setting ( <i>e.g., hospital-based, clinic-based, community-based, referral criteria or process, other</i> ): Declared conflict of interest: Source(s) of funding:		
<b>Study Characteristics</b>		
Purpose or objective(s) of study ( <i>include among whom</i> ):		
Design ( <i>RCT, observational</i> ): Method of randomization: Blinding ( <i>patients, investigator, assessor</i> ): Sampling procedure ( <i>consecutive, selective, random, unreported, other</i> ): Number eligible for study: Number randomized: Number evaluated: Number completing study: Number of withdrawals and rationale: Participation rate ( <i>total eligible for inclusion, randomized, withdrawals and dropouts and reasons, total completing trial</i> ): Exclusion criteria:		
<b>Baseline Patient Characteristics</b>		
Inclusion Criteria	Triptan Treatment Group	Comparator Group
Mean age ( <i>years</i> ): Gender ( <i>male or female</i> ) (%): Ethnicity (%): Previous triptan use: History [ <i>Headache (HA) intensity, attack frequency, attack duration, aura, photophobia, phonophobia, nausea, vomiting</i> ]: Diagnosis: Pain severity: Time to treatment: Notes ( <i>calculations, if any</i> ):		

Treatment Description	Triptan Treatment	Comparator	Total (if given)
Description of treatment ( <i>drug and manufacturer</i> ) ( <i>almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, placebo</i> ): Dose: Administration ( <i>nasal, oral, subcutaneous, wafer</i> ): Duration: Notes ( <i>calculations, if any</i> ):			

Clinical Data Extraction	Triptan Treatment Group	Comparator Treatment Group
Outcomes as defined by study author:		
HA response at 1 hour		
HA response at 2 hour		
Pain outcomes at 0.5 hours		
Pain outcomes at 1 hour		
Pain relief by 2 hours		
PF at 2 hours		
Speed of response		
Sustained HA response		
Response of symptoms		
Functional status		
Satisfaction		
Health-related QOL		
Preference		
Short-term consistency		
Need for rescue medication		
Reliability and consistency of response		
Functional status, productivity, disability		
Notes ( <i>calculations, if any</i> )		

Adverse Events (AEs)	Triptan Treatment Group	Comparator Treatment Group
Total number of AEs		
Total number of serious adverse events (SAEs)		
Total number of deaths		
HA exacerbation		
Chest pain ( <i>% patients</i> )		
CNS ( <i>% patients</i> )		
Other AEs		
Total number of patients with SAEs		
Number of patients withdrawn because of AEs		
Notes ( <i>calculations, if any</i> )		

<b>Assessment of Study Quality</b>		
<b>Randomization</b>	<b>Yes, No, Unclear</b>	<b>Score</b>
Was the study described as randomized? <i>A trial reporting that it is “randomized” receives one point (yes=1, no=0)</i>		
Trials describing an appropriate method of randomization (table of random numbers, computer-generated) receive an additional point (appropriate=1)		
If the report describes the trial as randomized and uses an inappropriate method of randomization (date of birth, hospital numbers), a point is deducted (inappropriate=-1)		
<b>Blinding</b>	<b>Yes, No, Unclear</b>	<b>Score</b>
Was the study described as double-blind? <i>A trial reporting that it is “double-blind” receives one point (yes=1, no=0)</i>		
Trials describing an appropriate method of double-blinding (identical placebo, active placebo) receive an additional point (appropriate=1)		
If the report describes a trial as double-blind and uses an inappropriate method (comparison of tablets versus injection with no dummy) a point is deducted (inappropriate=-1)		
Was the treatment allocation masked from the participants?		
Was the treatment allocation masked from the investigators?		
Was the treatment allocation masked from outcome assessment?		
<b>Withdrawals and Dropouts</b>	<b>Yes, No, Unclear</b>	<b>Score</b>
Was there a description of withdrawals and dropouts? A trial reporting the number and reasons for withdrawals or dropouts receives one point. If there is no description, no point is given (yes=1, no=0)		
<b>Total Score (for categories above) (0 to 2=low, 3 to 5=high)</b>	<b>Low or High</b>	<b>Score</b>
<b>Adequacy of Allocation Concealment</b>	<b>Adequacy Level</b> Adequate, inadequate, unclear	
Central randomization; numbered or coded bottles or containers; drugs prepared by a pharmacy, serially numbered, opaque, sealed envelopes (adequate)		
Alternation; reference to case record number or date of birth (inadequate)		
Allocation concealment unreported or fits neither category (unclear)		
Notes:		

<b>Potential Biases</b> (mark with $\surd$ or ? if applicable)			
<b>Selection</b> <i>systematic (non-random) differences between those selected for study and those not selected</i>	<b>Performance</b> <i>systematic differences in study regarding how interventions were delivered</i>	<b>Measurement</b> <i>systematic differences in the study regarding how variables were measured (or how subjects were classified)</i>	<b>Attrition (loss to follow-up)</b> <i>systematic differences between those analyzed and those who withdrew or were lost from study</i>
Describe potential biases and estimated impact on results:			
Reporting of study details: (mark)	complete	incomplete	
Notes:			
Completeness of clinical information: (mark)	complete	incomplete	
Notes:			
<b>Limitations of study</b> (e.g., regarding test sensitivity and specificity, uninterpretable data, study design, potential biases, surprising results):			
<b>Population targeted by authors:</b>			
Results appear applicable and generalizable to authors' target:	yes	no	unclear
Results appear applicable and generalizable to another target:	yes	no	unclear
if so, which target(s):			
<b>Conclusions</b> , made by authors based on data (in words, related to objectives)			
Consistent with data and analysis? (mark)	yes	no	

First portion only applicable to RCTs; potential biases applicable to observational studies

## APPENDIX 8: Patient Characteristics of Adolescent Population

Author	Number Evaluated	Mean Age (SD)	Gender, n (%)	Previous Triptan Use
Rothner <i>et al.</i> , <sup>33</sup> naratriptan	300	12 to 17 years	M: 138 (46%) F: 162 (54%)	NR
Rothner <i>et al.</i> , <sup>30</sup> zolmitriptan	ITT 696	14.3 (1.7)	M: 288 (41%) F: 408 (59%)	NR
Visser <i>et al.</i> , <sup>31</sup> rizatriptan	476	14.2 (1.8)	M: 212 (44%) F: 264 (56%)	NR
Winner <i>et al.</i> , <sup>9</sup> Rizatriptan	296	14	M: 136 (46%) F: 160 (54%)	NR
Winner <i>et al.</i> , <sup>16</sup> sumatriptan	510	14.1 (1.6)	M: 250 (49%) F: 260 (51%)	41%
Winner <i>et al.</i> , <sup>32</sup> sumatriptan	738 (tolerability); 731 (ITT efficacy)	14.3 (1.7)	M: 331 (45%) F: 400 (55%)	54% to 59% of patients had never used triptans for acute treatment of migraines
Winner <i>et al.</i> , <sup>34</sup> sumatriptan	302	12 to 17 years	M: 127 (42%) F: 175 (58%)	NR
Winner <i>et al.</i> , <sup>35</sup> eletriptan	274	14.3 (1.7)	M: 117 (43%) F: 157 (57%)	25%

ITT=intention to treat; M=male; F=female; NR=not reported.

## APPENDIX 9: Clinical Outcomes and Adverse Events in Adolescent Population

### Naratriptan versus Placebo

The efficacy and safety of naratriptan 0.25 mg, 1.0 mg, and 2.5 mg were examined in a randomized, double-blind, placebo-controlled, 44-centre US study of 350 adolescent migraineurs.<sup>33</sup> Of 350 study participants, 300 treated a moderate to severe migraine attack at home and recorded clinical outcomes in a diary. Patients who experienced recurrence could take an identical blinded dose of the study drug. Headache relief at four hours was achieved in 72%, 67%, and 64% of naratriptan 0.25 mg, 1.0 mg, and 2.5 mg recipients respectively, compared with 65% of placebo recipients. No statistically significant differences were noted between active treatments and placebo. Patients receiving active treatment reported more AEs than placebo recipients (31% of the 0.25 mg group, 23% of the 1.0 mg group, 36% of the 2.5 mg group, versus 17% of placebo group). Nausea and vomiting were most commonly reported in all treatment groups and increased with administration of a second dose of the study drug.<sup>33</sup> Because this trial was presented in abstract form, no information was provided regarding patient selection, and there is uncertainty regarding the potential for selection, performance, measurement, and attrition bias.

### Zolmitriptan versus Placebo

A randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy of and patient tolerability to zolmitriptan 2.5 mg, 5 mg, and 10 mg compared with placebo for the treatment of one migraine attack in 696 adolescents.<sup>30</sup> Two-hour headache response rates were 54%, 53%, and 57% for zolmitriptan 10 mg, 5 mg, and 2.5 mg recipients respectively, and 58% for placebo recipients. Two-hour PF rates were 25%, 19%, and 23% for zolmitriptan 10 mg, 5 mg, and 2.5 mg recipients respectively, and 20% for placebo recipients. There was no statistically significant improvement in efficacy measures between groups at two hours. The most common AEs reported in zolmitriptan groups versus placebo were chest tightness (6.7% versus 1.1%); dizziness (6.1% versus 2.3%); nausea (5.5% versus 1.1%); and paresthesia (4.2% versus 0%) respectively. There was potential for selection bias, because treatment groups had more patients aged 12 to 14 years and more females (57% to 61%) than males. There was also potential attrition bias, because zolmitriptan recipients withdrew from the study after experiencing AEs, while no placebo recipients withdrew. Patients not experiencing a migraine during the study period were excluded from the ITT population (possible selection bias, because the study will potentially exclude patients with a lower incidence of or milder migraine).

### Rizatriptan versus Placebo

Two randomized, double-blind, placebo-controlled trials examined the efficacy and safety of rizatriptan (5 mg) for the treatment of moderate to severe migraine in adolescents.<sup>9,31</sup> In the first study, 296 adolescents, aged 12 to 17 years, received rizatriptan 5 mg or placebo to treat a moderate or severe headache with up to two recurrences. The percentage of patients with pain relief at two hours was 66% for rizatriptan 5 mg recipients versus 56% for placebo recipients ( $p=0.079$ ).<sup>9</sup> The percentage of patients who were pain-free at two hours was 32% for rizatriptan 5 mg recipients and 28% for placebo recipients ( $p=0.474$ ).<sup>9</sup> Compared with placebo, rizatriptan recipients expressed significantly improved functional disability at 1½ hours and at two hours; and nausea at one hour and at 1½ hours. A significant benefit was noted among those treated with rizatriptan on weekends (65% versus 36%,  $p=0.046$ ) compared with weekdays (66% versus 61%,  $p=0.365$ ).<sup>9</sup> There is possible selection bias, because it is unclear how patients were selected and randomized, and whether the outcome assessment was blinded. Six placebo patients and a rizatriptan recipient discontinued the study without an explanation being provided. Patients not experiencing a migraine during the study period were excluded from the ITT population.

In the second study, 473 adolescent migraineurs were instructed to treat a moderate to severe migraine (with up to two recurrences) with rizatriptan 5 mg or placebo only on non-school days, and to note their headache severity, associated symptoms, and functional disability.<sup>31</sup> The rizatriptan group had more females (59% versus 52%) and more patients with severe headache at baseline (47% versus 42%) than the placebo group. Patients were instructed to take their medication only on non-school days. The proportion of patients with pain relief at two hours was 68% in the rizatriptan 5 mg group and 69% in the placebo group.<sup>31</sup> A higher proportion of rizatriptan 5 mg recipients experienced freedom from pain at two hours than placebo recipients (39.1% versus 31.3%,  $p=0.053$ ).<sup>31</sup> Patients rated their ability to work, study, or play as normal, some, a little, or not at all. The proportion of patients with a “normal” rating in the rizatriptan 5 mg group was higher than in the placebo group one hour after dosing. There was no statistically significant difference between groups at any time with respect to functional ability or symptoms of photophobia, phonophobia, nausea, or vomiting. There is possible selective reporting, because not all outcomes described in the methods were reported; and weekday data were given even though weekend data were proposed in the methods. While 210 patients did not take any study medication, 120 were lost to follow-up, 48 did not have a headache during the study period, 33 withdrew from the study, and nine patients were unaccounted for. Patients not experiencing a migraine during the study period were excluded in the ITT population (possible selection bias, because the study will potentially exclude patients with a lower incidence of or milder migraine).

### Sumatriptan (nasal spray) versus Placebo

Two trials evaluated the efficacy and safety of sumatriptan nasal spray 5 mg, 10 mg, and 20 mg to identical placebo for the treatment of acute migraine in adolescents.<sup>15,32</sup> In the first study, 653 adolescents aged 12 to 17 years, with a history of migraine (with or without aura) based on the International Headache Society criteria for migraine, participated in taking study medication and noting headache relief, freedom from pain, symptoms, recurrence, and use of rescue medication. Headache relief at two hours was reported by significantly more sumatriptan nasal spray 5 mg recipients (66%) compared to placebo (53%,  $p<0.05$ ) and approached significance in sumatriptan nasal spray 20 mg recipients (63%) compared to placebo (53%,  $p=0.059$ ).<sup>15</sup> A significantly greater proportion of sumatriptan nasal spray 20 mg recipients achieved freedom from pain at 2 hours compared to placebo recipients (36% versus 25%,  $p<0.05$ ).<sup>15</sup> At 2 hours, photophobia was lower in recipients of sumatriptan nasal spray 20 mg compared with placebo recipients (36% versus 48%,  $p<0.05$ ). Phonophobia was lower in the group that received sumatriptan nasal spray 5 mg at two hours compared with placebo (28% versus 44%,  $p<0.05$ ). No significant differences were noted between groups regarding nausea and vomiting. Taste disturbance was the most commonly reported adverse event (2%, 19%, 30%, and 26% for placebo, 5 mg, 10 mg, and 20 mg sumatriptan nasal spray respectively).<sup>15</sup> Patient selection is unclear. Patients were issued a study drug after describing pre-treatment characteristics; it is unclear whether this may affect subsequent care. Not all outcomes were reported. While all withdrawals were reported, it is unclear whether there were differences between groups. Patients not experiencing a migraine during the study period were excluded from the ITT population (possible selection bias, as study will potentially exclude patients with milder or less incidence of migraine).

In the second study, 738 adolescents with a six-month history of migraine (with or without aura) self-treated one attack of moderate or severe migraine after being randomized to sumatriptan nasal spray 5 mg and 20 mg or identical placebo.<sup>32</sup> A greater proportion of sumatriptan nasal spray 20 mg treated patients reported headache relief at two hours than those who received placebo (68% versus 58%,  $p=0.025$ ).<sup>32</sup> Significantly more sumatriptan nasal spray 20 mg recipients reported freedom from pain at two hours than those who received placebo (45% versus 34%,  $p=0.014$ ), in addition to associated symptoms (41% versus 28%,  $p=0.003$ ). The most common adverse event, taste disturbance, was experienced by 2%, 19%, and 25% of placebo and sumatriptan nasal spray 5 mg and 20 mg recipients respectively.<sup>32</sup> In addition to taste disturbance, the sumatriptan 20 mg group experienced nausea (5%), vomiting (4%), and

burning/stinging (3%).<sup>32</sup> At least one patient randomized to sumatriptan 5 mg was 18 years of age (protocol specifies 12 to 17 years). Patients not experiencing a migraine during the study period were excluded from the ITT population, creating a possible selection bias.

### Sumatriptan versus Placebo

A 35-centre, randomized, double-blind, placebo-controlled study involving 355 adolescents was conducted to evaluate the efficacy and safety of oral sumatriptan 25 mg, 50 mg, and 100 mg versus placebo for the treatment of migraine with or without aura.<sup>34</sup> There were no statistically significant differences between groups at two hours. Significantly more sumatriptan 25 mg, 50 mg, and 100 mg recipients experienced headache relief at three hours and four hours ( $p < 0.05$ ).<sup>34</sup> Across attacks, sumatriptan 25 mg, 50 mg, and 100 mg showed similarly significant differences from placebo in pain-free rates, clinical disability, phonophobia, photophobia, and the use of rescue medication. Nausea and vomiting were the most common adverse events, which increased with an increasing dose of sumatriptan. Patient selection and randomization are unclear. While patients randomly treated up to four attacks of moderate or severe pain (three attacks with a matching placebo, and recurrences with a second, identical tablet), there is uncertainty regarding blinding. Patients not experiencing a migraine during the study period were excluded from the ITT population, creating possible selection bias.

### Eletriptan versus Placebo

The efficacy and safety of eletriptan 40 mg was compared with placebo for the acute treatment of migraine in 274 adolescents and reported in poster format.<sup>35</sup> At two hours, 57% of eletriptan 40 mg recipients and 57% of placebo recipients experienced headache relief. Twenty-two percent of eletriptan 40 mg recipients and 15% of placebo recipients were free of pain at two hours. Headache response and freedom from pain at two hours were similar between groups, and the functional response, nausea, photophobia, and phonophobia were also comparable. Eletriptan 40 mg recipients who achieved headache response at two hours had significantly lower recurrence rates than placebo recipients ( $p < 0.05$ ).<sup>35</sup> There was potential for attrition bias because the placebo group was smaller because patients were excluded if they used eletriptan as rescue medication.

## APPENDIX 10: Clinical-Effectiveness Measures in Adolescent Population

Author	HA Response (within 2 hours)	PF within 2 hours	Speed of Response	Sustained HA Response	Response of Symptoms	Endpoints at 24 hours	Need for Rescue Medication	Functional Status, Productivity, Disability
Rothner <i>et al.</i> <sup>33</sup>	NAR 0.25 mg 72%; NAR 1.0 mg 67%; NAR 2.0 mg 64%; PLC 65%	NR	NR	NR	all 3 doses demonstrated substantial symptomatic improvements over time	NR	NR	NR
Rothner <i>et al.</i> <sup>30</sup>	ZOL 2.5 mg 86 of 150 (57%); ZOL 5 mg 84 of 159 (53%); ZOL 10 mg 87 of 162 (54%); PLC: 93 of 160 (58%)	ZOL 2.5 mg 37 of 159 (23%); ZOL 5 mg 30 of 160 (19%); ZOL 10 mg 41 of 164 (25%); PLC 32 of 162 (20%)	ZOL 2-hour response rates: headache response 53% to 57%; PF 19% to 25%; PLC 2-hour response rate: headache response 58%; PF 20%	NR	NR	NR	NR	NR
Visser <i>et al.</i> <sup>31</sup>	RIZ 5 mg any day 159 of 233 (68.2%); weekend 54 of 73 (74%); PLC any day 165 of 240 (68.8%); weekend 42 of 72 (58.3%)	RIZ 5 mg any day 91 of 233 (39.1%); weekend 25 of 73 (34.2%); PLC any day 75 of 240 (31.1%); weekend 19 of 72 (26.4%)	NR	NR	slight numerical advantages found for RIZ compared with placebo for symptoms of photophobia and nausea from 1.5 hours onward; no statistically significant differences between groups	NR	NR	normal functional ability at baseline RIZ 5 mg 4%; PLC 4%; 2 hours RIZ 5 mg 45%; PLC 40%; 4 hours RIZ 5 mg 65%; PLC 60%

Winner <i>et al.</i> <sup>9</sup>	RIZ 5 mg 66%; PLC 56%	RIZ 5 mg 48 of 249 (32%); PLC 40 of 140 (28%)	NR	NR	nausea 1 hour, RIZ (5 mg) 26%; PLC 37%; 1.5 hours, RIZ 5 mg 22%; PLC 35%; 4 hours, RIZ 5 mg 16%; PLC 27%; vomiting, RIZ 5 mg 3%; PLC 5%; phonophobia 30 minutes, RIZ 5 mg 65%; PLC 54%; 2 hours, RIZ 5 mg 30%; PLC 31%; 4 hours, RIZ 5 mg 27%; PLC 16%	took 2 <sup>nd</sup> dose of study drug or additional migraine medication within 24 hours of initial dose, RIZ 5 mg 39%; PLC 46%	took 2 <sup>nd</sup> dose of study drug or additional migraine medication within 24 hours of initial dose, RIZ 5 mg 39%; PLC 46%; experienced recurrence after responding to treatment at 2 hours, RIZ 5 mg 11%; PLC 18%	resumed normal function at 1.5 hours, RIZ 5 mg 32%; PLC 25%; 2 hours, RIZ 5 mg 44%; PLC 36%
Winner <i>et al.</i> <sup>16</sup>	SUM 5 mg 66%; SUM 10 mg 85 of 128 (64%); SUM 20 mg 63%; PLC 53%	SUM 20 mg 36%; PLC 25%	NR	recurrence and time to recurrence, SUM 5 mg 18%, 7.2 hours; SUM 10 mg 20%, 8.0 hours; SUM 20 mg 16%, 8.2 hours; PLC 20%, 6.7 hours	nausea (baseline compared to 2 hours post-dose %), SUM 5 mg 46% to 20%; SUM 10 mg 49% to 17%; SUM 20 mg 51% to 21%; PLC 39% to 25%; vomiting (baseline compared to post-dose %), SUM 5 mg 3% to 7%; SUM 10 mg 4% to 5%; SUM 20	NR	SUM 5 mg 21%; SUM 10 mg 22%; SUM 20 mg 26%; PLC 33%; number of patients taking 2 <sup>nd</sup> dose, SUM 5 mg 14; SUM 10 mg 11; SUM 20 mg 9; PLC 12	NR

					mg 8% to 5%; PLC 5% to 5%; photophobia SUM 5 mg 87% to 38%; SUM 10 mg 83% to 43%; SUM 20 mg 84% to 36%; PLC 90% to 48%; phonophobia, SUM 5 mg 82% to 28%; SUM 10 mg 75% to 33%; SUM 20 mg 77% to 25%; PLC 83% to 44%			
Winner <i>et al.</i> <sup>32</sup>	SUM 5 mg 156 of 247 (63%); SUM 20 mg 160 of 236 (68%); PLC 58%	SUM 20 mg 44%; PLC 73 of 242 (30%)	SUM 20 mg 76%; PLC 65%	SUM 5 mg 37%; SUM 20 mg 41%; PLC 32%; proportion of subjects with sustained relief from 2 to 24 hours, SUM 5 mg 48%; SUM 20 mg 45%; PLC 38%	3 hour post- dose photophobia, SUM 5 mg 94 of 249 (38%); SUM 20 mg 74 of 237 (31%); PLC 102 of 244 (42%); phonophobia, SUM 5 mg 70 of 248 (28%); SUM 20 mg: 66 of 237 (28%); PLC 88 of 244 (36%); photophobia and phonophobia, SUM 5 mg 57	sustained relief from 1 to 24 hours, SUM 5 mg 33%; SUM 20 mg 40%	use of alternate rescue medications SUM 5 mg 29%; SUM 20 mg 32%; PLC 33%; use of 2 <sup>nd</sup> dose of investigational product, SUM 5 mg 16%; SUM 20 mg 11%; PLC 18%	NR

					of 248 (23%); SUM 20 mg 49 of 237 (21%); PLC 71 of 244 (29%); nausea, SUM 5 mg 45 of 248 (18%); SUM (20 mg) 42 of 237 (18%); PLC 48 of 244 (20%); vomiting, SUM 5 mg 3 of 248 (1%); SUM 20 mg 4 of 247 (2%); PLC 8 of 244 (3%); 1 hour post-dose, photophobia, SUM 5 mg 119 of 249 (60%); SUM 20 mg 102 of 237 (43%); PLC 126 of 244 (52%); phonophobia, SUM 5 mg 70 of 248 (28%); SUM 20 mg 66 of 237 (28%); PLC 107 of 244 (44%); photophobia and phonophobia, SUM 5 mg 73 of 248 (29%); SUM 20 mg 70			
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					of 237 (30%); PLC 87 of 244 (36%); nausea, SUM 5 mg 59 of 248 (24%); SUM 20 mg 50 of 237 (21%); PLC 57 of 244 (23%); vomiting, SUM 5 mg 3 of 248 (1%); SUM 20 mg 9 of 237 (4%); PLC 8 of 244 (3%)			
Winner <i>et al.</i> <sup>34</sup>	SUM 25 mg versus PLC, statistically significantly more patients reported relief at 3 hours; SUM 50 mg versus PLC, statistically significantly more patients reported relief at 3 and 4 hours; SUM 100 mg versus PLC, statistically significantly more patients reported relief at 2, 3, and 4 hours	NR, all 3 doses showed significant differences from placebo in PF rates	NR	NR	all 3 doses showed significant differences from placebo in presence of phonophobia and photophobia	NR	all 3 doses showed significant differences from placebo in use of rescue medications (no details given)	NR
Winner <i>et al.</i> <sup>35</sup>	ELE 40 mg 57%; PLC 57%	ELE 40 mg 22%; PLC 15%	NR	recurrence within 24-hours post-dose, ELE 40 mg 9%; PLC 27%; used rescue medication	nausea, ELE 40 mg 25%; PLC 22%; photophobia, ELE 40 mg 38%; PLC 36%; phonophobia,	sustained headache relief at 25 hours, ELE 40 mg 52%; sustained	ELE 40 mg 32%; PLC 39%	NR

				within 24 hours, ELE 40 mg 32%; PLC 39%	ELE 40 mg 30%; PLC 33%	headache relief, PLC 39%; sustained PF response, ELE 40 mg 22%; PLC 10%		
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NR= not reported; HA=headache; PF=pain free; ZOL=zolmitriptan; PLC=placebo; RIZ=rizatriptan; SUM=sumatriptan; ELE=eletriptan.

## APPENDIX 11: Adverse Events (AEs) in Adolescent Population

Author	HA Exacerbation	Chest Pain or Tightness (% Patients)	CNS (% Patients)	Other AEs	Total Number of Patients with AEs	Total Number of Patients with SAEs
Rothner <i>et al.</i> <sup>33</sup>	NR	NR	NR	nausea and vomiting most common individual events in all treatment groups; migraine and photophobia also commonly reported	NAR 0.25 mg 31%; NAR 1.0 mg 32%; NAR 2.5 mg 36%; PLC 17%	NR
Rothner <i>et al.</i> <sup>30</sup>	ZOL 5 mg 1 of 174 (<1%); PLC NR	ZOL 10 mg 20 of 178 (11%); ZOL 5 mg 10 of 174 (6%); ZOL 2.5 mg 5 of 171 (3%); PLC 2 of 176 (1%)	dizziness, ZOL 2.5 mg 8 of 171 (5%); ZOL 5 mg 8 of 174 (5%); ZOL 10 mg 16 of 178 (9%); PLC 4 of 176 (2%); paresthesia, ZOL 10 mg 11 of 178 (6%); ZOL 5 mg 8 of 174 (5%); ZOL 2.5 mg 3 of 171 (2%); PLC 0 of 176 (0%); asthenia ZOL 10 mg 9 of 178 (5%); ZOL 5 mg 2 of 174 (1%); ZOL 2.5 mg 3 of 171 (2%); PLC 2 of 176 (1%)	nausea, ZOL 10 mg 14 of 178 (8%); ZOL 5 mg 5 of 174 (3%); ZOL 2.5 mg 10 of 171 (6%); PLC 2 of 176 (1%); pain, ZOL 10 mg 9 of 178 (5%); ZOL 5 mg 3 of 174 (2%); ZOL 2.5 mg 3 of 171 (2%); PLC 0 of 176 (0%)	ZOL 10 mg 79 of 178 (44%); ZOL 5 mg 45 of 174 (26%); ZOL 2.5 mg 49 of 171 (29%); PLC 22 of 176 (13%)	ZOL 5mg 1 of 174 (<1%); PLC 0 of 176 (0%)
Visser <i>et al.</i> <sup>31</sup>	NR	NR	somnolence, RIZ 5 mg 19 of 234 (8.1%); PLC 14 of 242 (5.8%); dizziness, RIZ 5 mg 18 of 234 (7.7%); PLC 10 of 242 (4.1%)	nausea, RIZ 5 mg 11 of 234 (4.7%); PLC 13 of 242 (5.4%); dry mouth RIZ 5 mg 12 of 234 (5.1%); PLC 5 of 242 (2.1%)	RIZ 5 mg 80 of 234 (34.2%); PLC 73 of 242 (30.2%)	RIZ 5 mg 0 of 234 (0%); PLC 1 of 242 (0.4%)
Winner <i>et al.</i> <sup>9</sup>	NR	NR	somnolence, RIZ 5 mg 4 of 149 (2.7%);	nausea, RIZ 5 mg 4 of 149	RIZ 5 mg 50 of 149 (33.6%);	RIZ 0 of 149 (0%); PLC 0 of 147 (0%)

Author	HA Exacerbation	Chest Pain or Tightness (% Patients)	CNS (% Patients)	Other AEs	Total Number of Patients with AEs	Total Number of Patients with SAEs
			PLC 12 of 147 (8.2%); dizziness, RIZ 5 mg 7 of 149 (4.7%); PLC 7 of 144 (4.8%); asthenia, RIZ 5 mg 5 of 149 (3.4%); PLC 3 of 147 (2.0%)	(2.7%); PLC 12 of 147 (8.2%); dry mouth, RIZ 5 mg 1 of 149 (4.7%); PLC 5 of 147 (3.4%)	PLC 52 of 147 (35.4%)	
Winner <i>et al.</i> <sup>16</sup>	SUM 0 patients; PLC 1 patient (exacerbation of migraine symptoms requiring emergency department treatment)	SUM 0 patients; PLC 0 patients	triptan sensation (warmth, burning, and stinging; or paresthesia), SUM (5 mg) 1 patient (<1%); SUM (10 mg) 3 patients (2%); SUM (20 mg) 5 patients (4%); PLC 2 patients (2%)	2-hour post-dose, nausea, SUM 5 mg 20%; SUM 10 mg 17%; SUM 20 mg 21%; PLC 10 8%; vomiting, SUM 5 mg 7%; SUM 10 mg 5%; SUM 20 mg 5%; PLC 2 (2%); photophobia, SUM 5 mg 38%; SUM 10 mg 43%; SUM 20 mg 36%; PLC NR; phonophobia, SUM 5 mg 28%; SUM 10 mg 33%; SUM 20 mg 25%; PLC NR; taste disturbance, SUM 5 mg 24 patients (19%); SUM 10 mg 40 patients (30%); SUM 20 mg 31 patients (26%); PLC 2 patients (2%)	SUM 5 mg 45 patients (35%); SUM 10 mg 51 patients (38%); SUM 20 mg 47 patients (40%); PLC 23 patients (18%)	SUM, 0 patients; PLC 2 patients (SAEs related to exacerbation of migraine symptoms requiring emergency department treatment)

Author	HA Exacerbation	Chest Pain or Tightness (% Patients)	CNS (% Patients)	Other AEs	Total Number of Patients with AEs	Total Number of Patients with SAEs
Winner <i>et al.</i> <sup>32</sup>	SUM 0 patients; PLC 0 patients	SUM <1%; PLC <1%	burning and stinging sensation, SUM 5 mg 2 of 255 (<1%); SUM 20 mg 7 of 238 (3%); PLC 1 of 245 (<1%); paresthesia, SUM 5 mg 4 of 255 (2%); SUM 20 mg 5 of 238 (2%); PLC 2 of 245 (<1%); dizziness, SUM 5 mg 5 of 255 (2%); SUM 20 mg 4 of 238 (2%); PLC 1 of 245 (<1%)	taste disturbance, SUM 5 mg 48 of 255 (19%); SUM 20 mg 60 of 238 (25%); PLC 4 of 245 (2%); nausea, SUM 5 mg 5 of 255 (2%); SUM 20 mg 11 of 238 (5%); PLC 5 of 245 (2%); vomiting: SUM 5 mg 1 of 255 (<1%); SUM 20 mg 9 of 238 (4%); PLC 1 of 245 (1%); nasal signs and symptoms, SUM 5 mg 5 of 255 (2%); SUM 20 mg 4 of 238 (2%); PLC 1 of 245 (<1%)	at least 1 AE, SUM 5 mg 66 of 255 (26%); SUM 20 mg 79 of 238 (33%); PLC 20 of 245 (8%); at least 1 drug-related AE, SUM 5 mg 59 of 255 (23%); SUM 20 mg 76 of 238 (32%); PLC 15 of 245 (6%)	SUM 1 patient; PLC 0 patients
Winner <i>et al.</i> <sup>34</sup>	NR	NR	NR	SUM, nausea and vomiting most common AE; PLC NR	NR	NR
Winner <i>et al.</i> <sup>35</sup>	NR	NR	somnolence, ELE 40 mg 11 of 129 (8.5%); ELE 80 mg 0 of 12 (0%); PLC 7 of 113 (6.2%); dizziness, ELE 40 mg 10 of 129 (7.8%);	nausea, ELE (40 mg) 5 of 129 (3.9%); PLC 4 of 113 (3.5%)	ELE 40 mg 55 of 129 (42.5%); ELE 80 mg 4 of 12 (33.3%); PLC 26%	ELE 40 mg 3.1%; PLC 2.7%

Author	HA Exacerbation	Chest Pain or Tightness (% Patients)	CNS (% Patients)	Other AEs	Total Number of Patients with AEs	Total Number of Patients with SAEs
			ELE 80 mg 2 of 12 (16.7%); PLC 6 of 113 (5.3%); asthenia, ELE 40 mg 7 of 129 (5.4%); ELE 80 mg 0 of 12 (0%); PLC 2 of 113 (1.8%)			

HA=headache; NR=not reported; CNS=central nervous system; AEs=adverse events; SAEs=serious adverse events; NAR=naratriptan; PLC=placebo; ZOL=zolmitriptan; RIZ=rizatriptan; SUM=sumatriptan; ELE=eletriptan

## APPENDIX 12: Bias, Impact, Limitations, and Conclusions Regarding Adolescent Population

Author	Selection Bias	Performance or Intervention Bias	Measurement or Reporting Bias	Attrition Bias	Potential Impact of Bias on Results	Limitations of Study	Conclusions by Authors
Rothner <i>et al.</i> <sup>33</sup>	unclear	unclear	unclear	unclear	no information on patient selection, non-responders could take another dose	abstract provides few details of study design or outcomes; only headache relief at 4 hours reported	no statistically significant differences in 4-hour headache noted between naratriptan and placebo, or between naratriptan doses; percentage of patients reporting $\geq 1$ AEs higher in naratriptan recipients compared with placebo; patients commonly reported nausea, vomiting, migraine, and photophobia; overall incidence of AEs increased after 2 <sup>nd</sup> study dose administration in all treatment groups
Rothner <i>et al.</i> <sup>30</sup>	yes; treatment groups had more patients aged 12 to 14 years, and more females (57% to 61%) than males	no	no	yes, 5 zolmitriptan recipients withdrew from study because of AEs, while no placebo recipients withdrew	patients not experiencing migraine during study period excluded from ITT population (possible selection bias, because study will potentially exclude patients with lower incidence of or milder migraine)	delays in taking study medication and shorter duration of migraine headache in adolescents compared with adults could mean headache pain had resolved spontaneously 2 hours after treatment, nullifying advantage of drug therapy; adolescents may be more susceptible to genuine placebo effect because they are more likely than adults to believe treatment would reduce their pain; possible bias due to ITT excluding those not taking any medication (because of no migraine during study)	no statistically significant improvement when zolmitriptan 10 mg compared to placebo for headache response at 2 hours; 2-hour headache response rates 54%, 53%, and 57% for zolmitriptan 10 mg, 5 mg, and 2.5 mg respectively, and 20% for placebo; similar efficacy between zolmitriptan and placebo seems to be result of high placebo response rate

Author	Selection Bias	Performance or Intervention Bias	Measurement or Reporting Bias	Attrition Bias	Potential Impact of Bias on Results	Limitations of Study	Conclusions by Authors
Visser <i>et al.</i> <sup>31</sup>	yes, treatment group had more females and more severe headaches at baseline than placebo group; selection unclear; 2 18-year-olds included, in violation of protocol (unspecified treatment or placebo groups)	unclear	yes	yes	possible selective reporting; not all outcomes described in methods reported; weekday data given where weekend data proposed in methods; 210 did not take study medication; 120 lost to follow-up; 48 did not have headache during study period; 33 withdrew from study; 9 patients unaccounted for; patients not experiencing migraine during study period excluded from ITT population (possible selection bias, because study will potentially exclude patients with lower incidence of or milder migraine)	patients used study medication only on non-school days; previous study suggested high placebo response on weekdays may cause delays in treatment due to limited access to study medication within 30 minutes of headache onset; placebo response rates lower on weekends than weekdays; may limit generalizability of results; results at 3 and 4 hours after dosing may be confounded by use of NSAIDs or other analgesics taken between 2 and 24 hours after test drug by 36% of rizatriptan recipients and 42% of placebo recipients; 30% of patients used study medication on weekend, as recommended; authors suggest delays in treatment at school may contribute to high placebo response rate if attacks starting to resolve when treatment administered	rizatriptan 5 mg not more effective than placebo in treatment of 1 migraine attack in adolescents, but seemed to be more effective than standard care for treating multiple attacks occurring during 1 year; among patients treated on weekend, rizatriptan showed statistically significant advantage over placebo in percentage of patients reporting pain relief at 2 hours (74% versus 58%); not significant on any day
Winner <i>et al.</i> <sup>9</sup>	unclear; 1 18-year-old included, in violation of protocol (not specified treatment or	no	unclear	yes; 6 placebo recipients withdrew from study (no explanation given)	possible selection bias; unclear how patients selected and randomized, whether outcome assessment was	comparatively high placebo response rates obtained despite efforts intended to reduce likelihood of such results; rizatriptan treatment on weekends provided statistically superior relief	post-hoc analysis showed significant benefit of rizatriptan versus placebo in percentage of patients who had pain relief when migraine attacks treated on weekends (65% versus

Author	Selection Bias	Performance or Intervention Bias	Measurement or Reporting Bias	Attrition Bias	Potential Impact of Bias on Results	Limitations of Study	Conclusions by Authors
	placebo group)			compared with 1 from rizatriptan group	blinded; 6 placebo patients and 1 rizatriptan recipient discontinued study without explanation; patients not experiencing migraine during study period excluded in ITT population (possible selection bias, because study will potentially exclude patients with low incidence of or milder migraine)	versus placebo, whereas weekday treatment did not; delays in treatment during schooldays may mean headaches involved were closer to spontaneous resolution when treatment taken; may have contributed to high placebo response rate on weekdays	36%, p=0.046) compared with weekdays (66% versus 61%, p=0.365); weekend placebo response rate similar to that seen in adults; most commonly reported AEs were dry mouth, dizziness, asthenia or fatigue, nausea, and somnolence
Winner et al. <sup>16</sup>	unclear	unclear	no	unclear; more withdrawals from sumatriptan 20 mg group than others; withdrawal descriptions not broken down per group	patient selection unclear; patients issued study drug after describing pre-treatment characteristics; unclear whether this may affect subsequent care; not all outcomes reported; all withdrawals were reported; unclear whether there were differences between groups; patients not experiencing migraine during	elevated placebo response observed has adverse impact on treatment effect; shorter duration of migraine attacks in adolescents and instructions to wait until headache pain was moderate or severe before using study medication may contribute to elevated placebo effect; 15% of patients in study stayed on non-selective serotonin reuptake inhibitor prophylactic medications during study	sumatriptan nasal spray effective and well tolerated for treatment of acute migraine in adolescents, with 20 mg dose providing best overall efficacy and tolerability profiles

Author	Selection Bias	Performance or Intervention Bias	Measurement or Reporting Bias	Attrition Bias	Potential Impact of Bias on Results	Limitations of Study	Conclusions by Authors
					study period excluded from ITT population (possible selection bias, because study will potentially exclude patients with lower incidence of or milder migraine)		
Winner et al. <sup>32</sup>	no	no	no	yes; no details given for individual groups about reasons for withdrawal	at least 1 patient randomized to receive sumatriptan 5 mg was 18 years old (protocol specifies 12 to 17 years); patients not experiencing migraine during study period excluded from ITT population (possible selection bias)	choice of pain-free versus headache pain relief as primary endpoint for adolescent migraine remains unclear	sumatriptan nasal spray may be beneficial to some adolescents and is generally well tolerated in acute treatment of migraine
Winner et al. <sup>34</sup>	unclear	no	unclear	yes	patient selection and randomization unclear; while patients randomly treated up to 4 attacks of moderate or severe pain (3 attacks with matching placebo, and recurrences with 2 <sup>nd</sup> identical tablet), there is	abstract provides few details of study design or outcomes; no actual quantitative data provided	sumatriptan tablets 25 mg, 50 mg, and 100 mg similarly effective in acute treatment of migraine in adolescent patients; no clinically meaningful benefit to increasing dose in this population

Author	Selection Bias	Performance or Intervention Bias	Measurement or Reporting Bias	Attrition Bias	Potential Impact of Bias on Results	Limitations of Study	Conclusions by Authors
					uncertainty regarding blinding; patients not experiencing migraine during study period excluded from ITT population (possible selection bias, because study will potentially exclude patients with lower incidence of or milder migraine)		
Winner et al. <sup>35</sup>	unclear	no	yes; placebo group smaller because patients excluded if they used eletriptan as rescue medication	unclear	some placebo patients took eletriptan as second dose; patients not experiencing migraine during study period were not excluded (selection bias)	high placebo effect; may be necessary to use alternative primary endpoints to determine efficacy in adolescent populations	high placebo response observed; similarly high response seen for eletriptan; eletriptan 40 mg showed significant advantage over placebo in reducing headache recurrence and rescue medication use; in post-hoc analysis, eletriptan (40 mg) showed significant improvements in sustained headache response and SPF response rates

ITT=intention to treat.

