Responder analysis for pain relief and numbers needed to treat in a meta-analysis of etoricoxib osteoarthritis trials: bridging a gap between clinical trials and clinical practice

R Andrew Moore ¹ (andrew.moore@pru.ox.ac.uk),
Owen A Moore ² (droamoore@googlemail.com),
Sheena Derry ¹ (sheena.derry@pru.ox.ac.uk)
Paul M. Peloso³ (paul_peloso@merck.com)
Arnold R. Gammaitoni³ (arnold_gammaitoni@merck.com)
Hongwei Wang³ (hongwei_wang@merck.com)

1 Pain Research and Nuffield Department of Anaesthetics, University of Oxford, Oxford, UK
2 Department of Rheumatology, Musgrove Park Hospital, Stockman’s Lane Belfast, UK
3 Merck Research Laboratories, Rahway, New Jersey

Corresponding author and reprint request
RA Moore
Pain Research and Nuffield Department of Anaesthetics
University of Oxford
John Radcliffe Hospital
Level 6 West Wing
Oxford, OX3 9DU, UK
andrew.moore@pru.ox.ac.uk
Abstract

**Background:** Population mean changes from clinical trials are difficult to apply to individuals in clinical practice. Responder analysis may be better, but needs validating for level of response and treatment duration.

**Methods:** We obtained the number of patients with pain relief over baseline ($\geq 15\%$, $\geq 30\%$, $\geq 50\%$, $\geq 70\%$) at two, four, eight, and 12 weeks of treatment, using the WOMAC 100 mm visual analogue pain subscale score for each treatment group of seven randomised, placebo-controlled trials of etoricoxib in osteoarthritis lasting six weeks or longer. Dropouts were assigned 0% improvement from baseline from then on. Numbers needed to treat (NNTs) were calculated at each level of response and time point.

**Results:** 3,554 patients had placebo, etoricoxib 30 mg and 60 mg, celecoxib 200 mg, naproxen 1,000 mg, or ibuprofen 2,400 mg daily. Response rates fell with increasing pain relief; 60-80% experienced minimally important pain relief ($\geq 15\%$), 50-60% moderate pain relief ($\geq 30\%$), 40-50% substantial pain relief ($\geq 50\%$), and 20-30% extensive pain relief ($\geq 70\%$). NNTs for etoricoxib, celecoxib, and naproxen were stable over 2-12 weeks. Ibuprofen showed lessening of effectiveness with time.

**Conclusion:** Responder rates and NNTs are reproducible for different levels of response over 12 weeks, and have relevance for clinical practice at the individual patient level. An average 10 mm improvement in pain equates to almost 1 in 2 patients having substantial benefit.

Key words: Responder, clinical trials, osteoarthritis, individual patient, NNT
**Introduction**

Clinical trials are performed typically for regulatory purposes, with outcomes typically reported as statistical comparisons between treatment group population means. Clinical trial results can be difficult to translate into clinical practice. A report that an intervention shows an average 10 mm reduction more than placebo on a 100 mm visual analogue scale has little immediate impact.

Moreover, few of us are average. Most medicines provide good response in half or fewer of patients treated, [1,2] and true in postoperative pain, [3] neuropathic pain [4-6], migraine, [7] and TNF antagonists in rheumatoid arthritis. [8] An 80/20 rule seems to apply in osteoarthritis, with 80% of patients experiencing 20% pain relief, but only 20% experiencing 80% relief; about half have their pain halved. [9]


Average data from skewed distributions can produce misleading results. [17] Dichotomous responder analyses have been reported previously for acute [18] and chronic pain. [5,6,19] The validity of a dichotomous measure should be established before wide use. [20]

An added factor contributing to differences in treatment response observed in clinical practice vs. a clinical trial is the handling of dropouts. Commonly, a last observation carried forward technique used in clinical trials, where data from patients with good pain control but intolerable adverse events will still be included in an efficacy calculations using population mean. In clinical practice, this same patient would be considered a treatment failure.

We used individual patient data from seven randomised, placebo-controlled trials in osteoarthritis to investigate the effects of different levels of pain relief, assessed at various time points, on estimates of efficacy.
**Materials and methods**

Merck Research Laboratories provided pain response data from seven randomised, placebo-controlled trials of etoricoxib in osteoarthritis lasting six weeks or longer (protocols 007 [21], 018 [22], 019 [23], 071 [24], 073 [25], 076 [26], and 077). PDF copies of the company clinical trial reports were also available.

We calculated the number of patients in each treatment group in each trial achieving various Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) thresholds of pain relief over baseline of $\geq 15\%$ (minimal benefit), $\geq 30\%$ (moderate), $\geq 50\%$ (substantial), [27] and $\geq 70\%$, which we defined as extensive improvement. These were assessed at two, four, eight, and 12 weeks. All trials lasted 12 weeks except protocol 007, lasting six weeks.

In each study, patients were asked, "During the last 48 hours, how much pain do you have 1) Walking on a flat surface; 2) Going up or down stairs; 3) At night while in bed; 4) Sitting or lying; 5) Standing upright?". On a 100-mm visual analogue scale, patients placed an "X" ranging from 0 ("No pain") to 100 ("Extreme pain"). The Western Ontario and McMasters Universities (WOMAC) 100 mm visual analogue pain subscale score was calculated as the average of the responses to the five questions.

Criteria in defining responders included:
- For patients who did not drop out, only actual measured values were used for calculations. Last observation carried forward was not used.
- For patients who withdrew for any reason, measurements made within seven days of the last dose were used to calculate response.
- Thereafter, patients were assigned 0% improvement.

We calculated the number and percentage of responders for each level of response for each drug and time point, and NNT compared with placebo with 95% confidence interval (CI; [28]). Relative risk with 95% confidence interval was calculated using the fixed effects model, [29] and considered statistically significant when the 95% CI did not include one. Statistically significant differences between NNTs were established using the z test, [30] comparing different drug/dose combinations only in the trials in which they were used together.

Clinical trial reports were used to obtain, for each active treatment, the difference between active treatment and placebo for the WOMAC pain subscale score. This was defined in the company clinical trial reports as the mean time-weighted average change from baseline (flare/randomization...
visit) over the six or 12-week treatment period ([WOMAC baseline minus WOMAC treatment average] minus [WOMAC baseline minus WOMAC placebo average]). Average results for each treatment arm were pooled using RevMan 5.0.

**Results**

Information was available on 3,554 patients, two thirds women, and with an average age of 62 years (Additional file 1). Six trials involved patients with osteoarthritis of knee or hip, and one of knee only. Osteoarthritis was established clinically and radiographically. Initial pain had to be a minimum of 40/100 mm at inclusion, plus ≥15 mm increase and worsening in investigator global assessment since baseline. Additional file 1 includes the actual numbers of responders for each level of response for each drug, in each trial, and at each time point.

Table 1 gives percentage of responders and NNTs for each level of response for each drug, in each trial, and at each time point. They are also displayed graphically as percentage of responders (Figure 1) and NNT (Figure 2).
Table 1: Percent responders with treatment/placebo, and NNTs, after 2, 4, 8, and 12 weeks

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percent responders with treatment/placebo after different numbers of weeks</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Etoricoxib 30 mg; 5 trials, 1486 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥15%</td>
<td>70/41</td>
<td>70/45</td>
</tr>
<tr>
<td>≥30%</td>
<td>54/27</td>
<td>56/30</td>
</tr>
<tr>
<td>≥50%</td>
<td>35/13</td>
<td>40/18</td>
</tr>
<tr>
<td>≥70%</td>
<td>17/5</td>
<td>22/9</td>
</tr>
<tr>
<td>Etoricoxib 60 mg; 3 trials, 711 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥15%</td>
<td>77/46</td>
<td>76/51</td>
</tr>
<tr>
<td>≥30%</td>
<td>61/31</td>
<td>63/32</td>
</tr>
<tr>
<td>≥50%</td>
<td>43/16</td>
<td>46/19</td>
</tr>
<tr>
<td>≥70%</td>
<td>25/4</td>
<td>27/9</td>
</tr>
<tr>
<td>Celecoxib 200 mg; 2 trials, 714 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥15%</td>
<td>64/42</td>
<td>67/45</td>
</tr>
<tr>
<td>≥30%</td>
<td>53/27</td>
<td>54/29</td>
</tr>
<tr>
<td>≥50%</td>
<td>30/12</td>
<td>39/18</td>
</tr>
<tr>
<td>≥70%</td>
<td>15/6</td>
<td>22/10</td>
</tr>
<tr>
<td>Naproxen 1000 mg; 2 trials, 531 patients</td>
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<td></td>
</tr>
<tr>
<td>≥15%</td>
<td>78/54</td>
<td>75/57</td>
</tr>
<tr>
<td>Response (%)</td>
<td>Ibuprofen 2400 mg; 2 trials, 618 patients</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>≥30%</td>
<td>63/35 65/36 60/35 55/35</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.5 (2.6 to 5.5) 3.5 (2.6 to 5.4) 3.9 (2.8 to 6.4) 4.8 (3.2 to 9.2)</td>
<td></td>
</tr>
<tr>
<td>≥50%</td>
<td>44/20 47/22 45/22 44/23</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.1 (3.0 to 6.3) 3.9 (2.9 to 6.0) 4.3 (3.1 to 7.0) 4.8 (3.3 to 8.5)</td>
<td></td>
</tr>
<tr>
<td>≥70%</td>
<td>22/5 27/10 28/12 27/15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.9 (4.4 to 8.8) 5.8 (4.1 to 9.7) 6.1 (4.2 to 11) 8.0 (4.9 to 21)</td>
<td></td>
</tr>
</tbody>
</table>

Ibuprofen 2400 mg; 2 trials, 618 patients

<table>
<thead>
<tr>
<th>Response (%)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>≥15%</td>
<td>69/43</td>
<td>65/47</td>
<td>60/48</td>
<td>58/49</td>
</tr>
<tr>
<td></td>
<td>3.8 (2.9 to 5.5)</td>
<td>5.5 (3.8 to 10)</td>
<td>7.8 (4.8 to 22)</td>
<td>11 (5.8 to 121)</td>
</tr>
<tr>
<td>≥30%</td>
<td>49/29</td>
<td>51/33</td>
<td>51/36</td>
<td>49/41</td>
</tr>
<tr>
<td></td>
<td>5.0 (3.6 to 8.1)</td>
<td>5.6 (3.9 to 10)</td>
<td>6.6 (4.3 to 14)</td>
<td>not significant</td>
</tr>
<tr>
<td>≥50%</td>
<td>29/14</td>
<td>35/20</td>
<td>40/24</td>
<td>39/27</td>
</tr>
<tr>
<td></td>
<td>6.5 (4.6 to 11)</td>
<td>6.9 (4.6 to 14)</td>
<td>6.4 (4.3 to 12)</td>
<td>8.4 (5.1 to 24)</td>
</tr>
<tr>
<td>≥70%</td>
<td>16/6</td>
<td>20/8</td>
<td>22/13</td>
<td>26/18</td>
</tr>
<tr>
<td></td>
<td>10 (7.0 to 21)</td>
<td>7.9 (5.6 to 14)</td>
<td>11 (6.6 to 32)</td>
<td>13 (6.8 to 75)</td>
</tr>
</tbody>
</table>

Note: response with placebo is for placebo groups from trials in the particular comparison being made.
With placebo, the percentage of patients achieving levels of pain relief at each threshold rose between weeks 2 and 12 (Table 1). At the end of 12 weeks, the proportion of patients with response was about 45% for ≥15%, 35% for ≥30%, 25% for ≥50%, and 15% for ≥70%.

With, more patients achieved each level of response with active drug than with placebo (Table 1, Figure 1). Etoricoxib 30 mg and 60 mg daily and celecoxib 200 mg daily had similar response patterns, with constant percentages at lower response levels, but a tendency over time to increase the proportion achieving ≥70% pain relief by 12 weeks. Naproxen 1000 mg daily and ibuprofen 2400 mg daily had different response patterns, with stable or increasing percentages at higher levels (≥50%, ≥70%), but progressive decreases in percentage achieving lower levels of response of ≥15% and ≥30%.

NNTs calculated for ≥15%, ≥30%, and ≥50% pain relief were very similar to each other with etoricoxib 60 mg and 30 mg, celecoxib 200 mg, and naproxen 1000 mg (Table 1, Figure 2). NNT values were between 3 and 5 over the 12 weeks of measurement. The NNT for ≥70% pain relief was distinctly higher, with NNT values between 6 and 10. The pattern for ibuprofen 2400 mg was different, with NNTs generally much higher (worse) at longer study duration, and less consistency between various levels of response.

There were three direct comparisons, each in two trials, of daily doses of etoricoxib 60 mg and naproxen 1000 mg, etoricoxib 30 mg and celecoxib 200 mg, and etoricoxib 30 mg and ibuprofen 2400 mg. No statistically significant differences were found between them at any level of response or any duration of therapy.

The additional reduction in WOMAC pain subscale score for each active treatment over placebo between the flare/randomisation visit and end of treatment is shown in Figure 3. The smallest mean difference above placebo was 8 mm for ibuprofen 2,400 mg daily, and the largest was 15 mm for etoricoxib 60 mg daily. This shows that about 60% of patients have moderate benefit (Figure 1) while average reductions in pain over placebo appear modest.

**Discussion**

Population mean changes have no easy resonance outside a clinical trial. An average of 10 mm out of 100 mm (10% improvement; Figure 3) conveys no expectation of great benefit, with little to balance against known risks. A different approach is needed.
A pilot study of responder analysis in a single trial indicated that it might be a useful way of reporting pain results in osteoarthritis. [9] It suggested that at least 50% pain relief after six weeks of treatment could be a useful discriminator between interventions of greater and lesser efficacy. This needs validation with regard to different levels of pain relief, and especially duration, given that arthritis treatments are used in the medium to long term.

IMMPACT provided recommendations for interpreting clinical importance of treatment outcomes in clinical trials of chronic pain treatments. [27] For pain it suggested a 10-20% decrease in pain intensity to be minimally important, ≥30% moderately important, and ≥50% is substantial. This meta-analysis used these three discriminator points, together with the even higher discriminator of ≥70% pain relief, to perform a responder analysis, calculate NNTs, and examine effects of trial duration.

Response rates declined as the discriminator level increased, for all five active drugs and placebo (Figure 1, Table 1). Using the IMMPACT descriptions for commonly used NSAIDs, 60-80% of patients with osteoarthritis can expect minimally important pain relief, 50-60% moderate pain relief, 40-50% substantial pain relief, and 20-30% extensive pain relief.

With placebo and active drugs the proportion achieving higher levels of pain relief increased over time, perhaps due to a natural waning of pain inherent in the “flare” design. The tendency to less response at lower levels of pain relief over time with naproxen and ibuprofen may reflect higher withdrawal rates for traditional NSAIDs over cyclooxygenase-2 selective inhibitors. [31,32] Patients may be balancing benefit and harm, with lower levels of relief perhaps not worthwhile in the face of adverse events. In the responder approach, dropouts contribute to the denominator only, whereas with last observation carried forward they appear to continue to benefit after stopping withdrawal.

NNTs were comparable for pain relief of ≥15%, ≥30%, and ≥50%, with higher (worse) NNTs for ≥70%, for both doses of etoricoxib, celecoxib, and naproxen. For these three drugs NNTs were reasonably stable over two to 12 weeks. Ibuprofen 2400 mg daily was different, with NNT values generally increasing (worsening) with longer duration. The longitudinal responder analysis provides more insight than population average differences in Figure 3.

This apparently different behaviour with ibuprofen 2400 mg daily did not translate into a statistically significant difference in NNTs between ibuprofen and etoricoxib 30 mg, nor was a significant difference found between etoricoxib 30 mg and celecoxib 200 mg, or etoricoxib 60 mg and naproxen 100 mg. Establishing dose response in analgesic trials is known to be difficult even where direct comparisons are available in relatively simple models like postoperative pain. [33] Demonstrating an absolute difference in response of 10% requires a substantial number of trials and
patients. Confirming statistically that ibuprofen 2400 mg is inferior to other NSAIDs at commonly used doses in osteoarthritis will require more data.

A range of ±0.5 NNT was proposed to determine whether an NNT has “clinical relevance” - whether the NNT is within acceptable bounds of clinical “accuracy”. [34] A subsequent proposals was that ±0.5 NNT be used to determine that NNTs were different. [27] If a numerically different between NNTs of 1 (3.5 say compared with 5.0) was taken to be important, then application to NNTs in Table 1 would begin to differentiate between drugs, with ibuprofen particularly being judged less effective.

The results of the responder analysis achieve the same global conclusions as the original trials – that etoricoxib and its comparators have useful analgesic properties in osteoarthritis. Arguably the most important outcome from these analyses is that, for osteoarthritis, patients and professionals can be provided with trial data that translates into clinic practice, by using realistic estimates of the chance of achieving a particular level of benefit. For pain, a mean 10 mm difference over placebo translates into about 40% having substantial benefit, and 30% having not even minimal benefit. The majority of people with osteoarthritis treated with an NSAID at an appropriate dose can expect to get at least a minimal benefit (though 1 in 5 will not), almost 1 in 2 can expect a substantial benefit, and about 1 in 5 an extensive benefit. The prospect of a 1 in 2 chance of substantial benefit has considerably more impact than an average 10% improvement in pain. Moreover, the information is conveyed in terms of both the likelihood of benefit (1 in 2) and the extent of the benefit (substantial).

Patients and professionals are interested in the known associated risks, of both common and rare harm. These, too, can be conveyed in terms of likelihood of harm, and its consequences. [35] Balancing benefit and harm is easier when common language describes both. Providing information about the chance of response at various thresholds might produce a more realistic appreciation of benefits and risks of treatment. There is, of course, the caveat that these results come from flare designs in clinical trials where patient selection criteria may make the population different (less co-morbidity, perhaps) than a clinical practice population.

Responders are defined not just by the level of response, but by the outcome used to define response. We chose the WOMAC pain subscale, combining pain associated with walking, climbing stairs, sitting, lying down, and at night while in bed. Whether pain is the most appropriate outcome for responder analysis, or whether function, sleep, quality of life, or compound outcomes like the OMERACT-OARSI set of responder criteria [36] remains to be examined. Finally, this type of analysis may differentiate between treatments in a manner that is not possible with population mean changes in pain intensity, and discriminatory power may reside in different outcomes.
Responder analysis looks promising, and much more helpful than an average change of a few millimetres based on populations of responders combined with non-responders.

**Conclusion**

Population mean change in pain intensity reported in clinical trials may be difficult to translate into clinical decision-making and patient expectations of benefit. Responder analyses, and NNTs calculated from them, are reproducible for different levels of response and over at least 12 weeks of treatment with effective drug treatments. This offers the possibility of providing patients and professionals with information on the chance of achieving particular degrees of pain relief, improving clinical decision-making and patient communication.

**List of abbreviations**

CI – confidence interval  
NNT – number needed to treat  
NSAID – non-steroidal anti-inflammatory drug  
VAS – visual analogue scale

**Competing interests**

RAM has received research grants, consulting, or lecture fees from pharmaceutical companies, including Pfizer, MSD, GSK, AstraZeneca, Grunenthal, Menarini, Futura, and others. RAM, and SD have also received research support from charities and government sources at various times. RAM is the guarantor. RAM, OAM and SD have no direct stock holding in any pharmaceutical company. PMP, ARG and HW are employees of Merck Inc.
Authors’ contributions

RAM, ARG, PMP were involved with the original concept, planning the study, searching, writing it, analysis, and preparing a manuscript; HW provided the data; OAM and RAM performed calculations and analysis; OAM, and SD were involved with planning, and writing. All authors read and approved the final manuscript.

Acknowledgements

Pain Research is supported in part by the Oxford Pain Research Trust. Neither the Trust nor Merck Research Laboratories had any role in design, planning, execution of the study, or in writing the manuscript. No financial support was received from Merck Research Laboratories for this work. RAM is funded by NIHR Biomedical Research Centre Programme. We are grateful to Merck Research Laboratories for making available data from the original trials.

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Legends to Figures

Figure 1: Percentage of responders over baseline at various levels of reductions in pain intensity (PR) for placebo and five active drugs over 12 weeks of treatment

Figure 2: Numbers needed to treat compared with placebo for five active drugs over 12 weeks of treatment using various levels of reductions in pain intensity (PR) over baseline

Figure 3: Weighted mean difference between treatment and flare/randomisation visit for WOMAC pain subscale: active treatment minus placebo. Colours show upper and lower 95% confidence intervals

Additional file 1: Details of trials and numbers of patients at each level of response at each time

<table>
<thead>
<tr>
<th>Trial number</th>
<th>Description</th>
<th>Demographics</th>
<th>Duration weeks</th>
<th>Compliance Exposure</th>
<th>Treatments (N)</th>
<th>Weeks of treatment</th>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td>12</td>
</tr>
</tbody>
</table>
### OA Knee

#### Characteristics
- **Female**: 72%
- **White**: 89%
- **Mean age**: 61 years
- **Age range**: 40-87 years
- **Median duration**: 6 years
- **ARA Class II/III**: 85%

#### Inclusion Criteria
- At least 6/12 symptoms
- Minimum 40/100 mm at inclusion on flare visit, plus ≥15 mm increase and worsening in investigator global assessment since baseline visit

#### Efficacy Measures
- **At least 15% PR**
  - P: 18/58
  - E: 30: 69/99
  - At least 30% PR
    - P: 14/58
    - E: 30: 55/99
  - At least 50% PR
    - P: 5/58
    - E: 30: 39/99
  - At least 70% PR
    - P: 1/58
    - E: 30: 15/99

#### Notes
- All percentages refer to the proportion of patients responding to treatment compared to placebo.

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### OA Knee or Hip

#### Characteristics
- **Female**: 66%
- **White**: 91%
- **Mean age**: 62 years
- **Age range**: 40 to 92 years
- **Hip**: 19%
- **Knee**: 81%
- **Median duration**: 5 years
- **ARA Class II/III**: 76%

#### Inclusion Criteria
- At least 6/12 symptoms
- Minimum 40/100 mm at inclusion on flare visit, plus ≥15 mm increase and worsening in investigator global assessment since baseline visit

#### Efficacy Measures
- **At least 15% PR**
  - P: 30/54
  - E: 60: 167/219
- **At least 30% PR**
  - P: 17/54
  - E: 60: 135/219
- **At least 50% PR**
  - P: 8/54
  - E: 60: 60/141/211
- **At least 70% PR**
  - P: 3/54
  - E: 60: 97/219

#### Notes
- All percentages refer to the proportion of patients responding to treatment compared to placebo.

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### OA knee or hip

#### At least 40 years

- **Radiographic diagnosis**
  - At least 6/12 symptoms
  - Minimum 40/100 mm at inclusion on flare visit, plus ≥15 mm increase and worsening in investigator global assessment since baseline visit

<table>
<thead>
<tr>
<th>Group</th>
<th>Female</th>
<th>White</th>
<th>Mean Age</th>
<th>Age Range</th>
<th>Median Duration</th>
<th>ARA Class II/III</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>78</td>
<td>72%</td>
<td>63 years</td>
<td>35 to 84 years</td>
<td>4 years</td>
<td>81%</td>
</tr>
<tr>
<td>E60</td>
<td>81</td>
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<td></td>
<td></td>
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<tr>
<td>Pbo</td>
<td>73</td>
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</tr>
</tbody>
</table>

#### At least 6/12 symptoms

- Minimum 40/100 mm pain since baseline visit

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<tr>
<th>Group</th>
<th>Pain Increase</th>
<th>Investigator Global Assessment</th>
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<tbody>
<tr>
<td>P</td>
<td>≥15 mm</td>
<td>≥15 mm increase since baseline</td>
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#### Compliance

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<tr>
<th>Group</th>
<th>At least 15% PR</th>
<th>At least 30% PR</th>
<th>At least 50% PR</th>
<th>At least 70% PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>E60</td>
<td>60: 163/202</td>
<td>60: 169/233</td>
<td>60: 19/55</td>
<td>60: 134/202</td>
</tr>
<tr>
<td>Nap1000</td>
<td>77</td>
<td>60: 100/202</td>
<td>60: 103/202</td>
<td>60: 100/202</td>
</tr>
<tr>
<td>Pbo</td>
<td>73</td>
<td>60: 100/202</td>
<td>60: 100/202</td>
<td>60: 100/202</td>
</tr>
</tbody>
</table>

#### Clinical and radiographic criteria

- At least 6/12 symptoms
- Minimum 40/100 mm pain, increase of at least 15 mm from baseline, and worsening since baseline visit

<table>
<thead>
<tr>
<th>Group</th>
<th>Female</th>
<th>White</th>
<th>Mean Age</th>
<th>Age Range</th>
<th>Median Duration</th>
<th>ARA Class II/III</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>71%</td>
<td>89%</td>
<td>62 years</td>
<td>40 to 89 years</td>
<td>4 years</td>
<td>81%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Pain Increase</th>
<th>Investigator Global Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>≥15 mm</td>
<td>≥15 mm increase since baseline</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>At least 15% PR</th>
<th>At least 30% PR</th>
<th>At least 50% PR</th>
<th>At least 70% PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>39/99</td>
<td>60: 143/207</td>
<td>60: 137/207</td>
<td>60: 104/207</td>
</tr>
<tr>
<td>E60</td>
<td>60: 144/203</td>
<td>60: 135/208</td>
<td>60: 111/208</td>
<td>60: 82/208</td>
</tr>
<tr>
<td>Nap1000</td>
<td>77</td>
<td>60: 107/203</td>
<td>60: 106/208</td>
<td>60: 107/203</td>
</tr>
<tr>
<td>Pbo</td>
<td>56</td>
<td>60: 100/202</td>
<td>60: 100/202</td>
<td>60: 100/202</td>
</tr>
</tbody>
</table>

#### At least 15% PR

<table>
<thead>
<tr>
<th>Group</th>
<th>At least 15% PR</th>
<th>At least 30% PR</th>
<th>At least 50% PR</th>
<th>At least 70% PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>48/101</td>
<td>60: 135/208</td>
<td>60: 100/202</td>
<td>60: 82/208</td>
</tr>
<tr>
<td>E60</td>
<td>60: 135/208</td>
<td>60: 146/208</td>
<td>60: 100/202</td>
<td>60: 100/202</td>
</tr>
<tr>
<td>Nap1000</td>
<td>77</td>
<td>60: 122/208</td>
<td>60: 106/208</td>
<td>60: 107/203</td>
</tr>
<tr>
<td>Pbo</td>
<td>56</td>
<td>60: 100/202</td>
<td>60: 100/202</td>
<td>60: 100/202</td>
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</tbody>
</table>

#### At least 30% PR

<table>
<thead>
<tr>
<th>Group</th>
<th>At least 30% PR</th>
<th>At least 50% PR</th>
<th>At least 70% PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>58/207</td>
<td>60: 82/208</td>
<td>60: 12/202</td>
</tr>
<tr>
<td>E60</td>
<td>60: 56/203</td>
<td>60: 7/101</td>
<td>60: 13/202</td>
</tr>
<tr>
<td>Nap1000</td>
<td>77</td>
<td>60: 5/55</td>
<td>60: 13/202</td>
</tr>
<tr>
<td>Pbo</td>
<td>56</td>
<td>60: 8/208</td>
<td>60: 13/202</td>
</tr>
</tbody>
</table>

#### At least 50% PR

<table>
<thead>
<tr>
<th>Group</th>
<th>At least 50% PR</th>
<th>At least 70% PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>20/101</td>
<td>60: 12/202</td>
</tr>
<tr>
<td>E60</td>
<td>60: 22/101</td>
<td>60: 18/101</td>
</tr>
<tr>
<td>Nap1000</td>
<td>77</td>
<td>60: 7/101</td>
</tr>
<tr>
<td>Pbo</td>
<td>56</td>
<td>60: 8/208</td>
</tr>
</tbody>
</table>

#### At least 70% PR

<table>
<thead>
<tr>
<th>Group</th>
<th>At least 70% PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>12/101</td>
</tr>
<tr>
<td>E60</td>
<td>60: 4/208</td>
</tr>
<tr>
<td>Nap1000</td>
<td>77</td>
</tr>
<tr>
<td>Pbo</td>
<td>56</td>
</tr>
<tr>
<td>073</td>
<td>OA knee or hip Knee or hip and radiographic criteriaAt least 6/12 symptomsMinimum 40/100 mm pain, increase of at least 15 mm from baseline, and worsening since baseline</td>
</tr>
</tbody>
</table>
OA knee or hipClinical and radiographic criteria
At least 6/12 symptoms
Minimum 40/100 mm pain,
increase of at least 15
mm from baseline, and
worsening since baseline

Female 66%
White 88%
Mean age 62
years
Age range 41
to 88 years
ARA II/III 79%

Compliance 99%
Mean
days on
drug
E30 244C200
247Pbo 117

At least 15 % PRP:
50/108 E 30:
169/240 C
200: 161/245 At
least 30 % PRP:
35/108 E 30:
132/240 C 200:
132/245 At least
50 % PRP:
16/108 E 30:
88/240 C 200:
77/245 At least
70 % PRP:
4/108 E 30:
40/240 C 200:
42/245

At least 15 % PRP:
50/115 E 30:
178/241 C
200: 160/246 At
least 30 % PRP:
32/115 E 30:
144/241 C 200:
131/246 At least
50 % PRP:
22/115 E 30:
105/241 C 200:
98/246 At least
70 % PRP:
15/115 E 30:
56/241 C 200:
55/246

At least 15 % PRP:
46/114 E 30:
168/240 C 200:
158/245 At least
30 % PRP:
33/114 E 30:
135/240 C 200:
136/245 At least
50 % PRP:
25/114 E 30:
106/240 C 200:
97/245 At least
70 % PRP:
15/114 E 30:
65/240 C 200:
67/245

At least 15 % PRP:
47/117 E 30:
156/241 C 200:
153/244 At least
30 % PRP:
34/117 E 30:
139/241 C 200:
134/244 At least
50 % PRP: 23/117 E 30: 101/241 C 200:
105/244 At least
70 % PRP: 17/117 E 30: 68/241 C 200:
74/244
Responder analysis for pain relief and numbers needed to treat in a meta-analysis of etoricoxib osteoarthritis trials: bridging a gap between clinical trials and clinical practice

R Andrew Moore, Owen A Moore, Sheena Derry, Paul M Peloso, Arnold R Gammaitoni and Hongwei Wang

Ann Rheum Dis published online April 12, 2009

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