Reporting and other biases in studies of Neurontin for migraine, psychiatric/bipolar disorders, nociceptive pain, and neuropathic pain

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Executive Summary

Reporting bias occurs when the dissemination of research findings is influenced by the nature and direction of the results. There is extensive, even shocking, evidence of reporting biases in the studies of Neurontin that I reviewed for this report.

Although bias is a statistical term, when it is applied to the design or analysis of research studies, it can have important consequences to knowledge and ultimately to human life and health. Research has clearly established that positive results are selectively reported, reported more often as full length articles, published more quickly, more often in duplicate, in English, in easier to access literature, and cited more frequently. Furthermore, research has shown repeatedly that industry funding is associated with biased reporting of positive results over other findings. If the biomedical literature is a biased representation of what is known from research, then as a consequence physicians' knowledge of a drug's efficacy, and prescription-writing based on that knowledge, is likely to be wrong. Thus, the end result of reporting biases is that patients may be harmed and resources wasted on ineffective treatments. For these and other reasons, bias in reporting of study findings represents unethical behavior and scientific misconduct.

With respect to Pfizer-supported studies of Neurontin in the areas of migraine, bipolar disorders, and pain, there is extensive evidence of reporting bias. Those that I observed, most of them many times over, included failure to publish negative results; selective outcome reporting where a secondary outcome or newly defined outcome was reported because the desired findings were not obtained for the primary outcome; selective analyses where, for example, patients were inappropriately excluded from or included in the analyses; multiple publication of desirable results; hiding of negative results in abstracts, letters to the editor, or other "grey literature"; and differential citation of Pfizer results to highlight actual or claimed positive findings. In addition, I observed extensive evidence of "reframing" or "spin" to make negative results appear positive. This was often accomplished by a "ghost author" working with a commercial company hired to accomplish Pfizer's marketing goals related to its "publication strategy" (ie, the plan to successfully market Neurontin through selective publication of study results). There is also evidence that many of the studies were biased in their design, rendering their scientific value questionable.

The documents I reviewed represent a remarkable assemblage of evidence of reporting biases that amount to outright deception of the biomedical community, and suppression of scientific truth concerning the effectiveness of Neurontin for migraine, bipolar disorders, and pain. Although each of the biases I observed has been individually reported and decried in the biomedical research literature, these biases have not typically been examined collectively as part of an overall "publication strategy" taken on by product sponsors. A publication strategy, meant to convince physicians of Neurontin's effectiveness and misrepresent or suppress negative findings, is clearly spelled out and executed when one views the Neurontin documents as a whole. I find the behavior and actions visible through these documents highly unethical, harmful to science, wasteful of public resources, and potentially dangerous to the public's health.

Qualifications

1. I have attached my curriculum vitae, which includes a listing of my publications, as Appendix C to this report.

2. I received my MA in zoology (specializing in cell biology) from the University of California, Berkeley in 1975, and my PhD in epidemiology from Johns Hopkins University, School of Hygiene and Public Health, in Baltimore, Maryland, in 1989. I was appointed as Professor of Epidemiology and the Director of the Center for Clinical Trials at Johns Hopkins in 2005, where I oversee the clinical trials curriculum in the Bloomberg School of Public Health (JHSPH). Prior to this appointment, I served as Assistant Professor and Associate Professor at the University of Maryland School of Medicine in Baltimore, Maryland for nearly 10 years (1989-1998) and as Associate Professor and Professor at Brown University School of Medicine in Providence, Rhode Island for seven years (1998-2005). At these institutions I have taught graduate level courses on clinical trials, systematic reviews and meta-analysis, and medical undergraduate courses on evidence-based healthcare and health policy.

3. I was a founding member of the Cochrane Collaboration, an endeavor dedicated to synthesizing high quality research evidence in systematic reviews and making it easily accessible to the public, and have directed a US-based Cochrane Center since 1994. I currently serve as the Director of the US Cochrane Center (USCC), one of 13 Centers worldwide participating in The Cochrane Collaboration.

4. My major research contributions are methodological and related to clinical trials, systematic reviews, publication bias, trials registers, and evidence-based healthcare. My research over the years has demonstrated the need for global trial registration, as a means to combat publication bias, and I have led a variety of successful efforts designed to achieve this goal.

   I have served as principal investigator (PI) for federally-funded, multicenter trials in both ophthalmology (PI of the Data Coordinating Center for The Ischemic Optic Neuropathy Decompression Trial [IONDT]) and women's health, (PI for the Surgical Treatment Outcomes Project for Dysfunctional Uterine Bleeding [STOP-DUB]), and as a co-investigator in the data coordinating center in a number of other clinical trials.

5. I have been honored for my research contributions, including election to the Institute of Medicine (IOM) in 2007, and the American Epidemiological Society in 1999. I am currently President of the Society for Clinical Trials and co-chair the World Health Organization's (WHO) Scientific Advisory Group to the International Clinical Trials Registry Platform. Other appointments have included the National Cancer Advisory Board (appointed by President William Jefferson Clinton); the Centers for Disease Control and Prevention (CDC) Task Force on Community Services; a dozen advisory committees for the IOM and National Research Council; international and national data and safety monitoring boards; grant review panels; and the Editorial and Advisory Boards of major journals in the field of clinical trials (*Clinical Trials* and *Trials*), as well as

the *BMJ*, *Health Expectations* and *BioMed Central*. I have also received numerous awards for my consumer advocacy contributions, most recently in 2007 from the American Association for Cancer Research for my "Contributions and Enduring Commitment to the Eradication of Cancer".

6. In the past 5 years, I have not testified at deposition or trial in any cases. I am not accepting any compensation for consulting in this case. Instead, I have requested that funds equivalent to what I would have received as compensation be deposited in an account at Johns Hopkins University to be used to support development of teaching materials related to publication bias. The hourly rate this fund will be compensated for my work is $400 per hour. I have relied on the documents referenced in this report, and upon my experience in the field of epidemiology, clinical trials, and publication bias, in preparing this document. I reserve the right to supplement this report with additional material if need be.

1. Reporting biases in the dissemination of biomedical knowledge

1.1 The ethical and scientific imperative to communicate knowledge gained from biomedical research

All healthcare should be "evidence-based," that is, decisions about individual patient care should be based on "the conscientious, explicit, and judicious use of current best evidence" (Sackett et al., 2000). Practically speaking, knowledge is generated by studies of an intervention's effectiveness and safety, and the "best" evidence (bias is minimized) is derived from the results of *randomized clinical trials* (RCTs). A randomized clinical trial is an experimental study on human beings in which the intervention is assigned using a random process. When there is more than one trial that addresses a clinical question, *systematic reviews* and *meta-analyses* of trial results form the "best available evidence". A systematic review is a review of existing knowledge that uses explicit scientific methods, including a comprehensive search for all relevant research, a critical appraisal of the identified trials, a summary of the available evidence, and, if appropriate, a quantitative synthesis of data (or meta-analysis). Systematic reviews are, in turn, used as a basis of evidence-based practice guidelines and other tools for summarizing knowledge in a format useful for doctors and healthcare practitioners (IOM, 2008).

Ethical principles derived from the Nuremberg Code (http://ohsr.od.nih.gov/guidelines/nuremberg.html), the Declaration of Helsinki (http://www.wma.net/e/ethicsunit/helsinki.htm), The Belmont Report (http://ohsr.od.nih.gov/guidelines/belmont.html), 45 CFR 46 (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm), and other sources serve as a foundation for modern biomedical research involving human volunteers. A critical element of this foundation is approval of individual research projects by a research ethics review board or institutional review board (IRB). A responsible IRB requires an "informed consent" process involving both the research volunteer and investigator(s), and, among other things, transmission of valid information to the participant about the potential benefits and harms associated with participation in the research study. One benefit of participation that is typically described in the consent document, regardless of the topic or project, is that the research participant will be contributing to scientific knowledge that will in turn contribute to the care of others. In the case of intervention studies, knowledge gained will help future patients regardless of the study findings, by identifying beneficial, harmful, and ineffective treatments.

But research can only contribute to knowledge if it is communicated from the investigators to the biomedical community. The generally accepted primary means of communication is "full" publication of the study methods and results in an article published in a scientific journal. Sometimes, investigators choose to present their findings at a scientific meeting as well, either through an oral or poster presentation. These presentations are included as part of the scientific record as brief "abstracts" which may or may not be recorded in publicly accessible documents typically found in libraries or the worldwide web.

Sometimes, investigators fail to publish the results of entire studies. This effectively means that the covenant between the investigators and study participants, reflected in the

informed consent document, has been broken, and the knowledge gained in the study is lost to the community. Sometimes study results are published in full, but not all outcomes examined are reported, or only selected analyses (for example, on a select group of participants) are reported; this is called selective outcome reporting. This, too, represents a failure to communicate knowledge and can result in an ethical breach if key efficacy or safety information is omitted or falsely described in the scientific record. The Declaration of Helsinki ((http://www.wma.net/e/ethicsunit/helsinki.htm), the American Association of Medical Colleges (Korn and Ehringhaus, 2006), and others have issued consensus documents on the ethical obligation to make results from clinical trials publicly available.

> "Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication." (World Medical Association Declaration of Helsinki, 2004)

Failure to publish study findings is not only unethical, it is also scientific misconduct (Chalmers, 1990). When failure to publish research findings is "random" it harms our knowledge base. When failure to publish is "differential," that is, on the basis of some systematic factor, it results in a "biased" knowledge base and the scientific literature, overall, may provide incorrect information.

1.2 Reporting biases

Reporting bias occurs when the dissemination of research findings is influenced by the nature and direction of the results (Higgins and Green, 2008), and encompasses a number of different subtypes (see Table 1). The phrase *nature and direction of research results* encompasses a number of possible situations. It can refer to a difference, or no difference, observed between two or more interventions being compared, the direction of that difference, the size of the difference, and the statistical significance of the difference. *Statistical significance* is common research jargon communicating that as a result of statistical analyses, there appears to be a low probability (usually set at less that 1 chance in 20) that the results obtained in a given study are due to chance. The contribution made to the totality of knowledge, or of the evidence in systematic reviews, by studies with statistically non-significant results is as important as that from studies with statistically significant results.

Positive results is a term most commonly used to describe a study finding that one intervention is better than another, and that the observed difference between the two interventions, however small, is statistically significant. We might also use "positive results" to refer to unexpected findings that a new or existing intervention is not inferior to a standard intervention. The term *negative results* has been broadly used to refer both to the direction of findings (that is, results favoring the comparison intervention or *null results* favoring neither intervention), and to the lack of statistical significance of the findings, regardless of whether they are positive, negative, or null.

Table 1. Definitions of some types of reporting biases[1]

Type of reporting bias	Definition
Publication bias	The *publication* or *non-publication* of research findings, depending on the nature and direction of the results.
Selective outcome reporting bias	The *selective reporting* of some outcomes but not others, depending on the nature and direction of the results.
Multiple (duplicate) publication bias	The *multiple* or *singular* publication of research findings, depending on the nature and direction of the results.
Location bias	The publication of research findings in journals with different *ease of access* or *levels of indexing* in standard databases, depending on the nature and direction of results.
Language bias	The publication of research findings *in a particular language*, depending on the nature and direction of the results.
Time lag bias	The *rapid* or *delayed* publication of research findings, depending on the nature and direction of the results.
Citation bias	The *citation* or *non-citation* of research findings, depending on the nature and direction of the results.

[1] Adapted from Sterne J et al., 2008.

To understand reporting biases in context, one must first understand the full spectrum of decisions when reporting study findings. As noted earlier, study investigators and sponsors could choose *not to publish* a study's findings or to publish multiple times. The timing of manuscript submission for publication is also under an author's control. One could also choose to *selectively report* a study's findings, selectively presenting or omitting outcomes, analyses, or populations described in the study protocol, or reframing the questions addressed in the study.

Investigators must also decide *where* to present their findings and the *format* in which they will be accessed. For example, they may elect to present at a conference, using an "abstract" or other abbreviated format, or they may publish a full length article. Conference abstracts are by definition short summaries of a study's methods and findings and often omit key details essential to understanding the reliability and validity of the results. For example, it is often not clear whether a report is describing interim or final results.

In addition to selecting the format of their reports (abstract or full length), investigators choose the publication *source* for their articles. This includes a decision about the desired

impact of the report (for example choosing a journal with a high "impact factor"), the language of the report, and the bibliometric databases in which the report will be included. Not all forms of publication are equally accessible to those seeking information. The "grey" literature, which is not easily accessed, includes conference abstracts, letters to the editor, some journal supplements, books, theses, technical documents, and other reports outside the mainstream scientific literature. Commonly used bibliometric databases, such as MEDLINE, may tend to favor higher impact, English-language journals. Location and language biases are associated with this aspect of study reporting.

1.2.1 Publication bias

Over the past two decades, evidence has accumulated that failure to publish research studies, including clinical trials testing intervention effectiveness, is pervasive (Dickersin, 2005). Studies demonstrating failure to publish have included research conducted in many countries, for example the United States, England, Australia, France, Germany, Switzerland, and Spain, and have found that, depending on the setting, only 21% to 93% of all studies are published.

Publication bias can be due to investigators failing to *submit* study findings, or due to journal editors failing to *accept* manuscripts for publication because of the findings. According to numerous surveys of investigators, almost all failure to publish is due to failure of the investigator to submit (Godlee and Dickersin, 2003); only a small proportion of studies are not published because of rejection by journals (Olson, 2002; Okike et al, 2008).

The main factor associated with failure to publish is negative or null findings (Dickersin, 1997). A meta-analysis of data from five cohort studies that followed research from its inception found that overall, the odds of publication for studies with positive findings was about two and one half times greater than the odds of publication of studies with negative or null results (Dickersin, 1997).Thus, the preponderance of evidence indicates that a higher proportion of studies with positive results are published compared to studies with negative results.

Does biased knowledge lead to use of ineffective and potentially harmful treatments? This would appear to be the case, assuming clinical practice is based on the literature. In an examination of 122 meta-analyses published in *The Cochrane Library* based on 'comprehensive' literature searches, Sterne and his colleagues identified 39 that included unpublished trials. Overall, published trials estimated a greater beneficial effect of the intervention compared to unpublished trials (ratio of odds ratios = 1.12 [95% CI 0.99 to 1.26]), and this association was strengthened after controlling for factors associated with trial quality (Sterne et al., 2002). Thus, failure to publish negative results leads to overestimates of treatment effect in meta-analyses, which in turn can lead doctors and decision makers to believe a treatment is effective when it is not.

We know from many studies that when initiated studies are not reported in full, some are not published in any form whatsoever, and some are published in abstract form only. Scherer and colleagues combined data from 79 reports (follow-up of 29,729 abstracts) on how often studies initially presented as abstracts reach "full" publication (Scherer et al., 2007). She

found that fewer than half of all abstracts were published in full, and that positive results are positively associated with full publication, regardless of whether 'positive' results are defined as any 'statistically significant' result or as a result favoring the experimental treatment.

Though publication of findings in conference abstracts is perhaps better than no publication at all (the biomedical community at least knows of a trial's existence), there are numerous problems with relying only on an abstract for valid information. First, data presented in abstracts are frequently preliminary or interim results and thus may not be reliable representations of what was found once all data were collected and analyzed (Chokkalingam et al., 1998; Toma et al., 2006; Hopewell et al., 2006). For example, an investigator could publish "positive" preliminary results, and then fail to publish final "negative" results. The scientific community might rely on the abstract results, without knowing that the final results are any different. Second, abstracts are often not accessible to the public through journals, MEDLINE, or easily accessed databases. Many are published in conference programs, conference proceedings, or on CD-ROM, and are made available only to meeting registrants. Thus, if those performing systematic or other reviews of the literature depend on searches of electronic databases such as MEDLINE, they are thus likely to miss identifying abstracts and will have to rely on fully published papers and the disproportionately positive results they represent.

It is now well-established that publication bias is associated with the source of funding for the study. Lexchin (Lexchin et al, 2003) systematically reviewed the literature on whether industry funding of drug studies is associated with outcomes favorable to the funder (30 research studies). Examination of relevant studies revealed that, overall, research funded by the pharmaceutical industry was less likely to be published than research funded by other sources. In addition, studies sponsored by pharmaceutical companies were more likely to have outcomes favoring the sponsor than were studies with other sponsors. Numerous new studies have been published since this review and provide additional support for these findings (Sismondo, 2008).

There are several possible explanations for why industry support is strongly associated with failure to publish negative results. Industry may selectively publish findings supporting a product's efficacy. It is also possible that industry is more likely to undertake studies with a high likelihood of a positive outcome, for example, by selecting a comparison population likely to yield results favoring the product. Neither of these actions would be ethical. The results presented may also vary by dissemination medium, for example articles reporting negative findings for efficacy, or reporting adverse events associated with an exposure, may be published but "hidden" in harder to access sources (Bero et al., 1996). It is also possible that journals are more likely to publish studies with negative results if they are funded by government sources. No evidence of selective acceptance for publication by journal editors based on source of funding was seen, however, in a study of controlled trials submitted to *JAMA* between 1996 and 1999 (Olson et al., 2002).

1.2.2 Selective outcome reporting

The classic textbook *Fundamentals of Clinical Trials* (Friedman et al., 1999) is clear that selective outcome reporting is not acceptable if one is seeking unbiased results.

"**Fundamental Point**
Excluding randomized participants or observed outcomes from analysis and subgrouping on the basis of outcome or response variables can lead to biased results of unknown magnitude or direction."

As noted earlier, a study may be published in full, but outcomes omitted or misrepresented. It is generally accepted that a study's primary outcome should be stated in the protocol *a priori*, before the study begins, to minimize bias that may be introduced by *post hoc* selection of outcomes (Friedman et al., 1999). Why is this important? Standard practice assumes that a difference observed between treatments is "statistically significant" if the p-value is less than 0.05. This means that the probability is less than 5%, or 1 in 20, that the result obtained, or one more extreme, is due to chance, assuming no true association exists between the treatment/exposure and outcome. In other words, if 100 statistical tests are done as part of a study analysis, then 5 associations tested will be "statistically significant," just by chance, even though none of the associations truly exist. If the primary outcome of interest was determined after the statistical testing was done, outcomes found to be statistically significant by chance would be commonly reported and much of the medical literature would be wrong. Analysis of outcomes chosen *post hoc* are properly done first as "exploratory analyses," and then planned for *a priori* in subsequent study protocols.

Two pieces of additional information seem relevant here: first, a statistically significant result does not mean that the difference observed between two treatments is actually valid or true, as explained above. Second, a statistically significant result does not mean that the finding is clinically significant. For example, a statistically significant 1 point difference in pain scores between treatment groups may not represent an important difference to the person experiencing that pain.

Several recent studies have had a major impact on our understanding of selective outcome reporting. Chan and his colleagues compared published articles to study protocols approved in 1994-1995 by two ethics committees in Denmark. They found that 62% of the time at least one outcome planned for assessment in the trial was changed, introduced, or omitted in the published article (Chan et al., 2004). In a separate study of randomized trials funded by the Canadian Institutes of Health Research from 1990-1998, Chan and his colleagues found that primary outcomes differed between the protocol and published article 40% of the time (Chan et al., 2004). In both studies, efficacy outcomes that were statistically significant had a higher chance of being fully published compared to those that were not statistically significant.

In a recent landmark study, Turner and colleagues identified considerable selective outcome reporting for 12 antidepressant agents submitted for review to the Food and Drug Administration (FDA). The authors examined reviews submitted to FDA associated with 12 antidepressant agents, matched them with publications, and compared outcomes (Turner et al., 2008). Only 31% of the 74 FDA-registered studies had been published, and publication was associated with a positive outcome (as determined by the FDA). Studies the FDA considered to have negative or questionable results (n=36) were either not published (22 studies), reported with a positive interpretation (11 studies), or reported in a manner consistent with the FDA interpretation (3 studies). Thus, if one only considered evidence from the published literature it

appears as if 94% (48/51) of studies had positive findings, while the FDA analysis concluded that 51% were positive. The appendix of the Turner article highlights key results that apparently were not submitted to the FDA but which were reported in the published articles, or that were reported differently between the FDA-submitted review and the publication.

Selective reporting of suspected or confirmed adverse treatment effects is an area for particular concern because of the potential for patient harm. In a study of adverse drug events submitted to Scandinavian drug licensing authorities, reports for published studies were less likely than unpublished studies to record adverse events (for example, 56 vs 77% respectively for Finnish trials involving psychotropic drugs) (Hemminki, 1980). Recent attention in the lay and scientific media on failure to accurately report adverse events for drugs (eg, selective serotonin uptake inhibitors (Healy, 2006), rosiglitazone (Drazen et al., 2007), rofecoxib (DeAngelis and Fontanarosa, 2008) has resulted in additional publications, too numerous to review here, indicating substantial selective outcome reporting (mainly suppression) of known or suspected adverse events.

Selective presentation of analyses and *analyses of selected populations* are special forms of selective outcome reporting that are well-known threats to validity. To expand, unbiased analyses of RCT data is generally agreed to be *intention to treat*, where all study participants are analyzed as part of the group to which they were randomly assigned, regardless of their compliance with the assignment or subsequent participation. The key principles of an intention to treat (or ITT) analysis are:

- "Keep participants in the intervention groups to which they were randomized, regardless of the intervention they actually received;
- Measure outcome data on all participants;
- Include all randomized participants in the analysis." (Higgins and Green, 2008).

An intention to treat analysis maintains the original randomization scheme, and minimizes biases associated with, for example, omitting patients from an analysis because they stopped taking a drug due to its side effects. The favored analytic approach is to conduct intention to treat analysis as the primary analysis, with a *per protocol* or *as treated* analysis secondarily and in conjunction with the primary analysis. In a secondary analysis, investigators may explore the effect of not including noncompliers, withdrawals, those found to be ineligible, and those lost to followup in the analysis.

Presentation of the per protocol analysis, without an accompanying intention to treat analysis, can represent a form of selective outcome reporting that we will refer to as *analysis of selected populations*. Melander and colleagues reported on 42 placebo-controlled studies associated with five SSRIs (selective serotonin reuptake inhibitors) submitted to the Swedish drug authorities for marketing approval between 1989 and 1994 (Melander et al, 2003). Of the 42 studies conducted, half found the test drug to be statistically significantly superior to placebo, and 90% of these (19/21) were published in stand-alone publications. Only 28% (6/21) of studies not showing a statistically significant effect were published. Although Melander and colleagues found that all but one of the study reports submitted to the drug agency included both an intention to treat and a per protocol analysis, most of the publications

only reported the more favorable analysis. Exclusion of patients in per protocol analyses increased the estimate of the treatment effect (ie, the treatment was estimated to be more beneficial) compared to intention to treat analyses.

"Reframing" of negative results in positive terms has been reported many times over the years, for example, Ioannidis reported that HIV/AIDS drug trials reporting a negative finding for a primary outcome typically reported results in a positive frame, and included positive results for subgroups and surrogate outcomes in the reports (Ioannidis et al., 1997). Attention has also been drawn to the practice of stating conclusions in the Abstract and the article's text that do not reflect the true study findings (Barnes and Bero, 1998) and multiple observations that article conclusions are associated with author affiliation. In particular, articles describing primary research and with acknowledged sponsorship from the pharmaceutical industry tend to draw pro-industry conclusions (Davidson, 1986; Rochon PA et al., 1994; Cho and Bero, 1996; Als-Nielsen et al., 2003). A specific concern is the data presented and conclusions drawn in the article's Abstract (Gøtzsche, 2006), since the Title and Abstract are what is included in online bibliographic databases such as MEDLINE, and may be the only portion of the article that is read.

1.2.3 Multiple publication bias

Investigators may also publish the same findings multiple times. The World Association of Medical Editors (WAME) Publication Ethics Policies for Medical Journals provides guidance on when this is acceptable:

> "Redundant publication occurs when multiple papers, without full cross reference in the text, share the same data, or results. Republication of a paper in another language, or simultaneously in multiple journals with different audiences, may be acceptable, provided that there is full and prominent disclosure of its original source at the time of submission of the manuscript. At the time of submission, authors should disclose details of related papers they have authored, even if in a different language, similar papers in press, and any closely related papers previously published or currently under review at another journal." (WAME, 2008)

The International Committee of Medical Journal Editors, (ICMJE), editors of the world's most prestigious biomedical journals, have made it clear that they consider duplicate publication without a clear acknowledgment of prior publication at best potentially harmful and potentially illegal:

> "Readers of primary source periodicals, whether print or electronic, deserve to be able to trust that what they are reading is original unless there is a clear statement that the article is being republished by the choice of the author and editor. The bases of this position are international copyright laws, ethical conduct, and cost-effective use of resources. Duplicate publication of original research is particularly problematic, since it can result in inadvertent double counting or inappropriate weighting of the results of a single study, which distorts the available evidence." (ICMJE, 2007)

As noted by the ICMJE, one of the challenges of multiple publications from a single study is that it can be difficult to identify their common origin. The numbers reported, authors, and other features may differ from report to report, leading the reader to believe that multiple studies have obtained similar findings. "Multiple publication bias" can be an outgrowth of this phenomenon.

Von Elm and colleagues (Von Elm et al., 2004) identified several patterns of duplicate publication in full length papers: (1) identical samples and outcomes, (2) identical samples and different outcomes, (3) increasing or decreasing samples and identical outcomes, and (4) different samples and different outcomes. About 33% of the duplicates overall were funded by the pharmaceutical industry; duplicates with the same sample and outcomes, with two or more "main" articles assembled to create a third article, were supported by industry 81% of the time. Most of these duplicates (63%) were published in journal supplements, potentially difficult to access literature. Positive results appear to be published more often in duplicate, which can lead to overestimates of a treatment effect (Tramèr et al., 1997).

1.2.4 Location bias

There is also evidence that, compared to negative or null results, statistically significant results are on average published in journals with greater impact factors (Easterbrook et al.,1991), and that publication in the mainstream (non grey) literature is associated with an overall 9% greater treatment effect compared to the grey literature (Hopewell et al. 2007). Furthermore, even when studies initially published in abstract form are published in full, negative results are less likely to be published in high impact journals than positive results (Timmer et al., 2002).

1.2.5 Language bias

There is evidence that investigators choose to publish their negative findings in non-English language journals and reserve their positive findings for English language journals. For example, for pairs of reports of clinical trials by the same author, one published in English the other in German, only statistically significant results predicted publication in an English language journal (Egger et al., 1997). Other authors have found that in certain cases, language restrictions in systematic reviews can change the results of the review (Grégoire et al., 1995; Pham et al., 2005).

1.2.6 Time lag bias

It is difficult to assign a uniform time that it should take to report study findings after data collection has been completed. More complex studies may take longer to report, for example if multiple investigators need to help draft and approve a manuscript. Nevertheless, an overarching scientific goal is to make knowledge generally available as quickly as possible. When the time between study completion and publication is influenced by the nature and direction of results, this can result in *time lag bias*.

Scientifically and ethically, the faster study results are published the faster doctors and consumers can benefit from the findings, for example by getting a beneficial treatment faster or by avoiding harm. From a business perspective, faster publication of positive results leads to increased sales, and lengthier time to publication of negative results delays a potential decrease in sales. In a systematic review of the literature, Hopewell and her colleagues (2007) found that overall, trials with "positive results" (statistically significant in favor of the experimental arm) were published about a year sooner than trials with "null or negative results" (not statistically significant or statistically significant in favor of the control arm). Regardless of how time to publication is measured, (eg, time between publication and funding start date [Misakian and Bero, 1998], research ethics review board approval [Stern and Simes, 1997], enrollment of the first patient, or completion of the followup [Ioannidis,1998]), studies with negative findings take longer to be published. There is no evidence that the increased time to publication for negative results is associated with delay at the editorial level (Dickersin et al., 2002).

1.2.7 Citation bias

Citation of a study in a published article renders it more easily identified by the casual reader, the researcher looking for evidence, the investigator proposing a new study, and by the systematic reviewer. For example, it is easy to search online databases of cited articles to find those on a topic similar to an already identified report. Surprisingly, authors do a poor job of citing prior relevant work, even when it is the "best" work in a field (Fergusson et al., 2006). This might not be a problem if relevant articles were cited at random, but they are not. Instead, authors tend to cite positive results over negative or null results, and this has been established over a broad cross section of topics (Gøtzsche, 1987; Ravnskov, 1992; Ravnskov, 1995; Kjaergard and Gluud, 2002; Schmidt and Gøtzsche, 2005; Nieminen et al., 2007). Differential citation may lead to a perception in the community that an intervention is effective when it is not, and it may lead to over-representation of positive findings in systematic reviews if those left uncited are difficult to locate.

Selective pooling of results is a form of citation bias that is particularly insidious in its potential to influence knowledge. With the advent of systematic reviews and meta-analysis (see Section 3.6), there has been an increase in pooling of data from similar studies. To minimize bias, such pooling requires an exhaustive search for all relevant studies and anything less is subject to possible selection bias. Selective pooling of results that are chosen by the authors will not reflect the true state of research evidence, rather it is likely to reflect what the authors want us to know.

1.2.8 Ghost authorship

The practice of hiring a commercial firm to company to write up the results from a clinical trial is common in industry trials (Sismondo, 2007). In these cases, the author listed rarely includes the hired writer, though the Acknowledgments section may list the writer(s) or writing company by name. The named authors may include investigators who worked to collect data, industry representatives, and others.

The problem with paid medical writers who are unnamed is that they have a potential conflict of interest, in that they are paid to write the paper by the company hiring them. In this capacity they may be asked to address company interests in the way that methods and results are presented. In this way, unnamed or "ghost" authors help to shape science.

There is extensive evidence that publication is strongly influenced by pharmaceutical industry funding (Lexchin et al., 2003; Sismondo 2007). It follows that when the writer is working for the company funding the study, the company has influence on the way in which the study is communicated to the biomedical community. Gøtzsche and colleagues estimated that 75% of industry-initiated studies approved by two ethics committees in Denmark had ghost authors (Gøtzsche et al., 2007). Sismondo provides an example of ghost authorship and its influence from records emanating from a lawsuit related to sertraline and manuscripts being coordinated for Pfizer. Between 1998 and 2000, an estimated 18-40% of articles on sertraline were managed by Pfizer through one company (CMD). CMD's articles were found to be published in more prominent journals, be more positive, and cited more often than other articles. This proportion is sufficiently large to shape the literature and thus opinion about the drug (Healy and Cattell, 2003). The World Association of Medical Editors has made it clear it considers ghost authorship to be dishonest,

> "Ghost authorship exists when someone has made substantial contributions to writing a manuscript and this role is not mentioned in the manuscript itself. *WAME considers ghost authorship dishonest and unacceptable* (emphasis mine). Ghost authors generally work on behalf of companies, or agents acting for those companies, with a commercial interest in the topic, and this compounds the problem."
> (http://www.wame.org/resources/policies accessed August 1, 2008)

1.3 Conclusions on the effects of reporting biases

Overall, it has been clearly established that positive results are selectively reported, reported more often as full length articles, published more quickly, more often in duplicate, more often in English, in easier to access literature, and cited more frequently. Furthermore, we know that industry funding is associated with biased reporting of studies, tending to report positive results over other findings. The end result is that the biomedical literature is a biased representation of what is known from research, and thus our biomedical knowledge as a whole is inaccurate.

The term *bias* is a statistical term and may not convey to most people the seriousness of the practical implications. The biomedical literature is the basis of evidence-based healthcare. If the literature is biased, then physicians' knowledge of a drug's efficacy, and prescription-writing based on that knowledge, is likely to be wrong. The end result of reporting biases is that patients may be harmed, and resources wasted. Moreover, if reporting biases are deliberate, they represent unethical behavior (World Medical Association, 2004) and scientific misconduct (Chalmers 1990; Antes and Chalmers, 2003). When reporting biases favor commercial interests, and industry withholds or manipulates data from trials it has sponsored, ethical issues are of particular concern.

2. Review of Neurontin documents for evidence of reporting and other biases

Overall, the documents examined by me for the purpose of this report indicate suppression and manipulation of data, such that the information on the effectiveness of Neurontin in treating migraine, psychiatric conditions, nociceptive pain, and neuropathic pain available to the public is inaccurate, incomplete, and potentially harmful to patients. I recommend that the documents reviewed by me (including sealed documents) and other expert witnesses in the case be made publicly available for the education of the public, students, clinicians, payers and other decision-makers, as well as scholarly work that can be used to guide future understanding of and potential change in how drugs are marketed and used.

My analysis of events and reporting biases is not intended to be comprehensive, for example, I may not note all instances of "ghost authorship" identified. Rather, my description is a representation of the types of deliberate reporting biases and other biases that I noted in review of the documents made available to me.

Tables 1-8 for each of the indications (migraine, psychiatric/bipolar disorders, nociceptive pain, and neuropathic pain) are located in Appendix A. These tables provide detailed information used to support the statements made in this report, particularly regarding reporting biases. The tables were developed using the study protocols, internal research reports, drafts of reports, submissions to journals and publications (including posters, abstracts and journal articles). In each table, text extracted from available documents is in quotation marks. My comments are within [square brackets].

Table 1 Table of Citations
: Lists documents summarizing research results of which we are aware for each study

Table 2 Summary of Reporting Biases
: Notes key reporting biases observed, comparing published reports to the study protocol

Table 3 Comparison of Study Reports by Authors and Funding Source
: Indicates where authorship not properly acknowledged and where new authors were added to publications

Table 4 Comparison of Study Reports by Participant Inclusion/Exclusion Criteria
: Notes information about study population, including inclusion criteria, enrollment dates, and number of study sites

Table 5 Interventions and Run-in Phase
: Description of intervention, including dosages, use of run-in, design characteristics, and length of followup

Table 6 Risk of Bias
Summarizes key trial design and operational items acknowledged to increase the risk of bias in clinical trials

Table 7 Primary Outcome and Number of Patients Assessed
Description of primary outcome and type of analysis performed, including whether and when patients were excluded from analyses

Table 8 Comparison of Study Reports by Results and conclusions
Direct comparison of Results section of report and Conclusions and Discussion sections

2.1 The "publication strategy" is a key element of Marketing Assessments and the marketing strategy for Neurontin

In its Marketing Assessments, Parke-Davis frequently compared two alternatives for "Neurontin Development" in terms of costs and sales: a "Publication Strategy" and "Full Development" for an indication. The "publication strategy" scenario was discussed in terms of a strategy for increased sales of Neurontin, not in terms of moving medical knowledge forward or of fulfilling an ethical obligation to patients participating in the trials. The publication scenario also frequently noted that in comparable cases publication had resulted in increased off-label use and increased sales.

2.1.1 Migraine

The covering memo of the Marketing Assessment summarized a "publication strategy" for migraine, specified to relate to positive findings only:

> "The decision is to conduct only publication study(ies) in the U.S. due to the current patent situation in the U.S., limited use of anticonvulsants in the EC, and favorable pre-clinical results in analgesia seen with CI-1008.
>
> The results, if positive, will therefore be publicized in medical congresses and published in peer reviewed journals." (WLC_Franklin_0000081255)

The Marketing Assessment concluded that ..."an indication strategy cannot be justified since an NDA filing would occur close to patent expiration" (WLC_FRANKLIN_0000081278). The recommendation was to pursue a "publication strategy," "It is recommended that the initial studies with Neurontin would be trials for only publication"....with presentation of the data to the American Academy of Neurology during 1Q'98. The full publication in a peer-reviewed journal would require 12 months after finalization of the study, i.e. 3Q-4Q '98. The estimate of market share and sales was provided in terms of time elapsed since initiating the "two publication trial" (WLC_FRANKLIN_0000081279).

2.1.2 Psychiatric (bipolar) disorders

The Marketing Assessment for psychiatric disorders, and specifically bipolar disorder, also implies that publication alone would have the effect of increasing sales:

> "- Start an exploratory study in acute mania and highlight the results through peer-reviewed publication and key psychiatric congresses. (WLC_Franklin_0000179644)
>
> - Start two well designed Phase II trials in panic disorders and social phobia and apply the same publication strategy and congress activity as mentioned above...The use generated by the 3 studies in the US [nb: proposed above] ($0 to $60 million a year when patent extension ends) would largely justify investment in the clinical program...." (WLC_Franklin_0000179644)

This recommendation further implies that positive results would not be required for implementation of the publication strategy,

> "In addition, due to the lack of scientific rationale, since Neurontin has a different mechanism of action than the mood-stabilizing anti-epileptics, it is recommended to implement only an exploratory study in outpatients with bipolar disorders with the results highlighted through a peer reviewed publication. Should the results be positive and the patent situations change, a full development program would be considered." (WLC_Franklin_0000179645)

This recommendation to follow a "publication strategy," as described above, is based on an analysis in the section of the Marketing Assessment "Neurontin 'Development'". As with the recommendation for migraine, the recommendation for marketing of Neurontin for bipolar disorder is based on what Parke-Davis views as a successful strategy undertaken by Abbott (presumably to win FDA approval to market Valproic acid):

> " This strategy would mirror Abbott's...when only data from the first pivotal study was available. With these results Abbott was able to generate a tremendous interest in the psychiatric community and consequently the use indicated earlier." (WLC_Franklin_0000179658)

The Forecast also implies that the publication strategy would be useful in increasing off label use:

> "The first scenario (publication only) is modeled after valproic acid and carbamazepine which both have 17% to 20% of their therapy days derived from off label use in bipolar disorder. It is assumed that Neurontin use would approach 4% to 6% of therapy days in 1999, five years after a positive exploratory trial has been published. (WLC_Franklin_0000179659)

2.1.3 Nociceptive pain

The Marketing Assessment for nociceptive pain focuses on the potential market and regulatory approval/patent issues for combination products and does not discuss a publication strategy per se. (Pfizer_MPierce_0000798)

2.1.4 Neuropathic pain

The covering memo of the Marketing Assessment summarizes a "publication strategy" for neuropathic pain, specified to relate to positive findings only:

> "The results of the recommended exploratory trials, if positive, will be publicized in medical congresses and published, but there is no intention to fully develop this indication at this point...." (WLC_Franklin_0000166608)

Medical Actions Communications was a company providing strategic marketing and pharmaceutical branding. A Medical Actions Communications (MAC) Action Report summarized a variety of publication strategy issues discussed at the Neurontin Publications Subcommittee (PSC) meeting held on 18 July 2001 (Pfizer_RGlanzman_0044634), including but not limited to:

- "Journal and Congress profiling
- Publications Process Timelines
- Key Message Development Update"

The Report makes it clear that "publication strategy" in general is a marketing issue:

> "The PSC members will then be asked to review the list and indicate which journals and congresses they feel are the top priorities for full profiling". (Pfizer_RGlanzman_0044635)

> "MAC updated the PSC regarding the development of key messages, indicating that the branding guide had been received and that it was anticipated that the draft key message list would be circulated to the team by 25-July." (Pfizer_RGlanzman_0044636)

> Authorship strategy is discussed as follows:

> "The issue of Pfizer authors on Neurontin manuscripts was raised. RG [Robert Glanzman] indicated that he was under the impression that it was Pfizer policy that no Pfizer author should be included on manuscripts....it was suggested that this may not be a global Pfizer policy....The general agreement is that Pfizer employees should not be 1st or last authors and a ratio of >/=3/1 (outside to Pfizer) in authors should be maintained." (Study 945-306 Pfizer_RGlanzman_0044636)

2.2 Reporting and other biases observed

There is ample evidence of *reporting bias* across the studies and indications I reviewed. The most common are also arguably the most insidious, *publication bias, selective outcome reporting*, and *time lag bias*.

Publication was rare when the final study results were "negative". For the indications I reviewed, most of the studies had "negative" findings at the end of the study for the primary outcome (16/21 studies plus substudies). While 4/5 studies with positive findings were published in full, only 6/16 of the studies with negative results were published and 2/6 of these were published in a format other than full journal article (ie, they would be difficult to locate as individual studies). This provides good evidence of *publication bias*, as well as *location bias*. A deliberate delay in publication of negative results (time lag bias) is evident from memos and emails for a number of studies.

In nearly every case, published studies focused on *analysis of selective populations*, with randomized participants excluded even in the "intention to treat" population. Manipulation of the numbers included in the analysis ("presentation of selective analyses") results in a form of bias that can easily invalidate study findings, since randomization is destroyed and the design becomes effectively an observational study. The study reports frequently obscured manipulations of the analysis by using terminology that made it appear as if the exclusions were legitimate and by using a variety of terms. For example, analyses included the following: "efficacy analysis", "intention to treat analysis", "modified intention [or intent] to treat" analysis, "safety analysis", "evaluable patients", "efficacy evaluable population", "safety evaluable population." Most of these terms do not have a generally agreed definition in the epidemiology, statistics, and clinical trials community. In contrast, "intention to treat" does have a generally agreed definition (analysis of all randomized patients as part of the group to which they were originally assigned–see Section 1.2.2), but this was not applied in the analyses done under this rubric. For example, the Research Report for Study 879-201 says, "In the intent to treat analysis all patients were included who had received at least a single dose of study medication". I observed one additional highly unusual manipulation of the study population. Study 879-201 included two patients treated in an open label fashion with gabapentin as part of the randomized trial data.

By and large, published reports were consistent in accurately stating their *a priori* choice of primary outcome, as described in the protocol. However, more focus was frequently placed on secondary outcomes, especially in the conclusion sections of the abstracts and full length articles. Focus on statistically significant outcomes, that is, *selective presentation of analyses*, regardless of whether the findings were clinically significant or whether the findings were seen for only a few time points or quality of life domains, is a form of selective outcome reporting or undue weighting of an outcome. In most cases, even the statistically significant results obtained would be considered unreliable because of potential bias related to exclusions from the analysis.

Published reports from studies of Neurontin frequently placed undue weight on an outcome. This form of *selective outcome reporting* bias is particularly insidious in that it takes

advantage of the fact that most clinicians are untrained in recognizing and understanding most forms of bias and have little time to devote to reading an article in detail. There are several opportunities for undue weight on an outcome in a conference abstract or article. In the Results section, more space can be devoted to outcomes the authors want to emphasize, and additional confirmatory analyses can be presented at length. In the articles I reviewed, the primary outcome was frequently presented summarily, with more emphasis placed on positive secondary outcomes. The Discussion section offers the opportunity to provide a rationale for negative findings and to emphasize positive findings. In the studies I reviewed, a rationale for negative results (for example, high response rate in the placebo group) was frequently invoked and repeated in subsequent articles, in turn providing an explanation for undesirable findings that could be cited by the medical community.

The Conclusions section of the abstract and of the article itself is arguably the most important place in an article to place undue weight on an outcome, because readers may look at only this section. This opportunity to *reframe* or "*spin*" the results was almost always used, at times diverting meaningfully from the truth.

When emails were available, I observed evidence of *ghost authorship* by a company engaged in medical writing. Only rarely was the writing by an unnamed author even acknowledged. In the cases observed, the ghost authors were frequently asked to "spin" or frame the message.

Citation bias was an important component of the overall strategy used by Pfizer to promote the desired message of Neurontin efficacy. For example, I observed several examples of citing only studies with positive results, or of implying the cited studies all had positive findings when they did not. Perhaps the most egregious example of citation bias is a selective pooled analysis (meta-analysis) of Neurontin data (Backonja 2003).

The following sections will highlight specific instances of reporting biases in each of the studies reviewed, organized by indication.

2.2.1 Migraine

All three migraine studies (879-201, 945-217, and 945-220) obtained negative results for the primary outcome examined. One study (879-201) published preliminary results only. Another study (945-217) was not published. And the third study (945-220) was published in both abstract and full journal article form.

Table 1 summarizes my assessment of the reporting and other biases present in the migraine studies. Multiple reporting biases are present and it appears data have been manipulated by re-defining the primary outcome. Three studies were conducted but the final results were only published for one (Mathew). The final results for all three studies were negative. Nevertheless, positive preliminary results were published for one study, and one study was published in full, after a long time lag. In this study (945-220), statistically significant primary results were presented in the article and this was not consistent with the findings in the research report. It appears this positive result was obtained by redefining the primary outcome

as it applied only to a select group of patients (those who had received a stable dose of 2400 mg/day). Thus, the number analyzed in the Neurontin group was greatly reduced from the number randomized.

Table 1. Migraine: Reporting and other biases

Study	Article(s)	Bias	Example
879-200	Wessely 1987	Publication bias	Final negative primary results not published, only positive preliminary results
		Selective outcome reporting	Outcome reported was not primary or secondary outcome
		Selective statistical analyses	Two nonrandomized patients assigned Neurontin were included with randomized. Reported numbers "investigated," failed to report number randomized
		Spin	Emphasis on "positive" outcomes other than the primary outcome (ie, cumulative distribution of percent change)
945-217	None	Publication bias	Final, "negative", results not published
945-220	Mathew 2001	Selective analyses	Reported only analysis with major patient exclusions. Definition of "evaluable patients" in publication different from research report, for the primary outcome
		Primary outcome redefined in publication	Primary outcome changed to reduce number of evaluable patients, result is that p-value and findings in research report are not the same as publication
		Multiple publication	The 2 conference abstracts, presented at different times, are nearly duplicates. Neither cited the other abstract
		Time lag bias	Three years to publication from end of study

Study	Article(s)	Bias	Example
		Citation bias	No mention of other negative results (eg, Wessely 1987, 945-217)
		Spin	Conclusions do not match actual study findings per research report

2.2.2 Psychiatric disorders - bipolar

Table 2 summarizes my assessment of the reporting and other biases present in the psychiatric disorders/bipolar studies. Two of the three studies of Neurontin for bipolar disorders had "negative" results for the primary outcome, and all three were published. The study with "positive" results used an open label design which is not useful for determining efficacy. The bipolar publications were marked by extensive spin and misrepresentation of data. One method of spin was to provide an extensive rationale for negative findings, which would establish a counter argument that could be more broadly employed in the community. Misrepresentation of data was most obvious for study 945-291 in which a different outcome measure (Clinical Global Impression scale for Bipolar Illness, Modified) was reported in the publication than what was described in the protocol and research report (Clinical Global Impression of Severity).

Table 2. Psychiatric disorders - bipolar: Reporting and other biases

Study	Article(s)	Bias	Example
945-209	Pande 2000b	Location bias	Published in a journal with circulation of 455, in contrast to Study 945-203 (social phobia article), which was published in a journal with circulation of 8,000 (PFIZER_LKNAPP_0026006). Not distributed to physicians in same manner as social phobia articles (WLC_CBU_134928)
		Time lag bias	Three years to publication from end of study
		Citation bias	Did not cite Guille, published during same time period [Guille C, Demopulos CM, Shriver AE, Sachs GS. American Pain Association. 1999]

Study	Article(s)	Bias	Example
		Possible misrepresentation of data	The values differed for difference from baseline scores (YMRS and HAM-D outcomes) between the letter to investigators and the journal publication
		Spin	Extensive rationale for negative findings in letter to investigators and the journal publication
945-291	Vieta	Selective outcome reporting	Outcome reported was not primary or secondary outcome
		Selective analysis	Analysis excluded approximately half of patients randomized, including for reasons such as "lack of efficacy" (though article claimed ITT)
		Misrepresentation of data	Research report findings do not agree with publication
		Spin	Discussed the lack of statistical significance of secondary outcomes (patient-rated) to support significance found with primary outcome (physician-rated) as indication of longer-term benefits reflected by the primary outcome
		Design bias	Primary outcome variable based on physician report: change at 12 months in Clinical Global Impression Scale, a physician-rating instrument
		Design bias	Opportunity for manipulation of randomization: the randomization was generated by sponsor prior to use of SAS software. No attempt to conceal allocation was mentioned
945-250	Wang	Spin	Despite no group for comparison, article states "adjunctive GBP is effective"
		Design bias	Open label trial of Neurontin added to current psychotropic regimen

2.2.3 Nociceptive pain

Table 3 summarizes my assessment of the reporting and other biases present in the studies of nociceptive pain. None of the five+ studies of Neurontin combined with other analgesics for nociceptive pain showed a statistically significant benefit of Neurontin when it was added to either naproxen or hydrocodone. And none of these studies, all with negative results, were published. When a statistically significant benefit of a Neurontin combination regimen *was* found to be beneficial compared to placebo, it was apparent that the beneficial effect was due to the naproxen or hydrocodone not the Neurontin. For example, both Neurontin 250/naproxen 250 and Neurontin 125/naproxen 250 were significantly more effective than placebo in terms of pain relief for dental pain. Nevertheless, Neurontin 250 alone and Neurontin 125 alone were not more effective than placebo. Firthermore, both Neurontin 250/naproxen 250 and Neurontin 125/naproxen 125 were more effective than Neurontin 250, indicating that the naproxen (even at a lower dose), not Neurontin, is the effective agent in the combination regimen.

Of interest is the fact that 1032-001 NPN 550 had 79 patients and other groups had about 50 patients. Similar numbers were proposed in the protocol, yet it is not clear how this was achieved from the description of the randomization. These numbers and the protocol description suggest that allocation to group may not have been concealed, effectively negating the goal of randomization, to minimize selection bias.

Table 3. Nociceptive pain: Reporting and other biases

Study	Article	Bias	Example
1032-001 (Post-op dental pain)	None	Publication bias	Neurontin added to naproxen did not significantly increase pain relief over naproxen alone
1032-002 (Acute osteo-arthritis pain of the knee)	None	Publication bias	"…no treatment group (GBP125/NPN250, GBP125, NPN250, or NPN550) was significantly different from placebo on the primary efficacy endpoint, the SPID6... No differences between GBP125/NPN250 and NPN550 were detected."

Reporting and other biases in studies of Neurontin - Dickersin (cont'd)

Study	Article	Bias	Example
1032-003 (open label exten-sion of 1032-002)	None	Publication bias	"Because earlier double-blind trials showed no strong superiority of GBP125/NPN250 over NPN550, the study was terminated prior to completion." "Efficacy data and all other data were not summarized."
1032-004 (Protec-tive effects of Neuron-tin on naprox-en sodium-induced upper gastro-intestin-al mucosal injury)	None	Publication bias	"At the doses studied, GBP [gabapentin] in combination with NPN [naproxen sodium] did not provide a protective effect from NPN-induced mucosal injury as measured by endoscopy."
1035-001 (Post-op dental pain)	None	Publication bias	Overall, the analgesic effect of [Neurontin and hydrocodone] treatment was similar to [hydrocodone] treatment alone. Acetaminophen + hydrocodone significantly better than all treatment groups
1035-001 Add-endum-B (Post-op dental pain)	None	Publication bias	No differences between groups were statistically significant

Study	Article	Bias	Example
1035-002 (Pain following major orthopedic surgery)	None	Publication bias	"The GBP250/HC10 group did not significantly outperform the HC10 group on any of the efficacy measures examined."

2.2.4 Neuropathic pain

Table 4 summarizes my assessment of the reporting and other biases present in the studies of neuropathic pain. Four of the nine randomized trials conducted for treatment of neuropathic pain had negative findings, and seven were published, four with "positive" and three with "negative" results. As with all the trials I reviewed, selective analyses (ie, no intention to treat analyses, despite the company's saying so) could explain any positive findings observed. So even the studies with positive findings are suspect. Published studies with negative findings were presented with considerable "spin" and misrepresentation of data.

In addition, it is likely that a *design bias* was present in Neurontin trials, at least for studies in which Neurontin was titrated to high doses. As seen in various documents (see Section 3.5), there is a high probability that patients and physicians were unblinded by adverse events in patients, especially those on high doses of Neurontin. Since the primary and other outcomes in the trials were entirely subjective, unblinding could have led to positive findings favoring Neurontin. The likelihood of unblinding is covered in Dr. Jewell's report.

Table 4. Neuropathic pain: Reporting and other biases

Study	Article	Bias	Example
945-210	Backonja	Selective analyses	Analyses to examine possible association of side effects and primary outcome, requested by those outside and inside company, were not produced

Reporting and other biases in studies of Neurontin - Dickersin (cont'd)

Study	Article	Bias	Example
		Design bias	Investigators aware that CNS side effects at high doses could unmask patients to active intervention, potentially biasing self-reported response. (This possibility was demonstrated to be highly likely, see expert report by Dr. Nicholas P. Jewell)
945-224	Reckless	Publication bias	Final primary results not published in full article
		Selective outcome reporting	Secondary outcomes reported (in selective meta-analysis) with greater emphasis and conclusions based on secondary outcomes
		Selective analysis	Study's findings used in selective meta-analyses by another author (Backonja 2003) to show overall effectiveness
		Time lag bias	Internal memos indicate company delayed publication
		Ghost authorship	Both drafts written by unacknowledged commercial source to include "key messages"
945-271	POPP	Publication bias	Negative results never published in full
		Spin	Discussion and conclusions focused on positive outcomes despite negative findings for primary outcome
945-276	Caraceni	Misrepresentation of facts	Inaccurate reporting of dates of enrollment (start/end) In Research report: May 1999/June 2002; In Caraceni 2004: August 1999/May 2002
		Misrepresentation of facts	No description of allocation concealment in Research Report, yet described in publication

Reporting and other biases in studies of Neurontin - Dickersin (cont'd)

Study	Article	Bias	Example
		Misrepresentation of facts	Patients included in ITT analysis defined differently in Research Report and publication
945-306	Serpell	Selective analysis	Use of transformation to obtain statistical significance; outcomes significant only for selected time points, not at time point specified in protocol; effectiveness in post-herpetic neuropathy population influences overall result.
		Selective analysis	Analyzed populations were different from those presented in protocol
		Citation bias	Citation of only positive findings in a conference poster
		Ghost authorship	Full length article written by hired medical writers (Synergy)
		Spin	Negative findings reported to sound positive
		Design bias	Excluded patients who were "non-responders" to gabapentin in the past resulting in a selective study population
945-411	Gomez-Perez	Citation bias	Cited Gorson and Serpell as positive findings
		Ghost authorship	Companies thanked in acknowledgments but not named authors
		Design bias	Compared "effective" dose (Backonja) to "ineffective" dose (Gorson)
		Design bias	Open label

Study	Article	Bias	Example
		Design bias	Investigators aware that central nervous system (CNS) side effects at high doses could unmask patients to active intervention, potentially biasing self-reported response. (This possibility was demonstrated to be highly likely, see expert report by Dr. Nicholas P. Jewell)
A945-1008	No publication	Publication bias	Statistically significant but not clinically significant results (difference in pain score = -0.765)
Number unavail-able	Dallocchio	Citation bias	Did not cite Morello, a randomized trial published one year before and showing no evidence of benefit
		Design bias	Open label, designed to counter Morello (Pfizer_RGlanzman_0040034)
Number unavail-able	Gorson	Location bias	Final (negative) results were published as Letter to the Editor and conference abstract/poster
		Time lag bias	Internal memos indicate company delayed publication
		Spin	Conclusions modified between draft sent to Magistro (WLC_Franklin_0000100279) and draft circulated internally by Magistro (WLC_Franklin_0000088375). Also, comments on why the study found negative results are different between the two drafts. In addition, conclusions differ between conference abstract, Gorson 1998 and letter to editor sent by Gorson 1999

3. Case studies of suppression and "spinning" of study results

The following case studies provide a narrative description and sequence of events related to reporting biases associated with five specific Pfizer-sponsored studies. I have used internal emails and memos available to me as a source of information, in addition to documents such as the protocol, research reports, and the Marketing Assessment, as needed. Exact quotations are provided with the source document referenced in parentheses. Taken both individually and together, these cases reflect clear intent to suppress information, deceive the medical community, and manipulate messages regarding the results of biomedical research. This represents a distortion of knowledge that is inexcusable and unethical.

3.1 Study 945-224 (Reckless)

Study 945-224 is an example of suppression of negative results (publication bias), multiple forms of selective outcome reporting, spin, time lag bias, ghost authorship, and a form of citation bias.

Study 945-224 was a multicenter, placebo controlled trial, conducted at 59 sites in the UK, France, Germany, Italy, Spain, and 2 in South Africa, comparing three doses of Neurontin® for treatment of neuropathic pain. Statements in the informed consent document that those enrolling would benefit others by their participation were carefully made:

> "Information gained in this study may eventually benefit other persons with painful diabetic neuropathy." (RR 720-04130 p.259)

The studied period was May 1998 to September 1999. No statistically significant differences were observed between any of the three Neurontin dosage groups and the placebo group for the primary endpoint (mean pain score). Several secondary outcomes were statistically significant, depending on the dosage group. After study completion, the company sent investigators a 3-page "Summary of Results from Study 945-224 (International Diabetic Neuropathy Dose-finding Study)," dated 8 March 2000. (Pfizer_LeslieTive_0020979)

On 18 April 2000, Dr. Reckless, a UK investigator in the 945-224 study, complained to the Clinical Trials Monitor for Parke-Davis about failure to publish the study. Parke-Davis staff communicated with one another about his concern and planned for next steps in a series of emails. These emails indicate a plan to delay and even suppress publication. For example,

- "I don't think we should be too hasty with this request," and
- "I agree with your answer. Although I would love to publish SOMETHING about 945-224, Donna McVey made it very clear that we should take care not to publish anything that damages neurontin's marketing success." and
- "It probably needs someone locally to go back to him and explain why at this time point we will not be publishing the data. Also, it would be the ideal opportunity to present him with our UK study results, confidentially as someone valued in the diabetes area? ...I agree that until we have our action plan we don't phone him to tell him that." (Pfizer_TMF_CRF_015316)

A Parke-Davis representative met with Dr. Reckless June 19, 2000, where Dr. Reckless presented his views on the reasons the study results should be published. These included his own explanations for the nonsignificant findings, high satisfaction with Neurontin among clinicians, the fact that the clinical community was expecting results, and ethical arguments favoring publication.

> "He was pleasant enough throughout the meeting, although I didn't miss the veiled threats in his words – if we don't publish, they will (an option that doesn't reflect well on the investigators or ourselves). I feel he had some very valid points and that any publication would take time to make it into the public domain (ie, it would be too late to affect the launch period). It would be a publication that the MLE's could handle and train the reps on but clearly it would need to be carefully written." (Pfizer_TMF_CRF_015320)

> A response from Beate Roder (Senior Clinical Scientist [Germany], Pfizer GmbH) said,

> "I am glad that Dr. Reckless has a positive view of the study results and that he agrees with our line of reasoning as to explanation of the negative outcome.
> If there is no threat to the marketing of gabapentin or maybe even some benefit (to correct misperceptions about the negative outcome), it might be worth pursuing a publication in my mind." (Pfizer_TMF_CRF_015319)

A response from Sean Buckland (Senior Regional Medical & Research Specialist [UK], Pfizer Ltd) noted,

> "..We would need to have 'editorial' control, but would certainly involve Dr. Reckless in the process, asking for his expert comment." Pfizer_TMF_CRF_015314).

This suggestion was met with a rebuff, reminding Parke-Davis staff that "PD has ownership of the data." Internal communications make it apparent that decision-making on publication was in the hands of marketing, not those doing the clinical research. "Dave is finding out through International marketing their intentions on publication and money to do this...." (Pfizer_TMF_CRF_015314)

By August 2000, after Pfizer had acquired Parke-Davis, a decision had been made to publish 945-224, with a UK company, Synergy, writing the manuscript, and Dr. Reckless serving as lead author. From Michael Rowbotham on September 11, 2000:

> "Overall the study was not positive in terms of efficacy but there were some positive aspects of the secondary measures". (Pfizer_LCastro_0002679)

Publication would be allowed to proceed under the following conditions:

- "What is critical is that -224 is NOT submitted to any publication until we know WHEN the 2 UK studies are going to be published."

- "This will allow us to ensure that 224 is not published before the UK studies." "We must delay publication of -224, as its results were not positive" (Pfizer_LCastro_002680)

- "I think that we can limit the potential downsides of the 224 study by delaying the publication for as long as possible and also from where it is published. More importantly it will be more important to how WE write up the study. We are using a medical agency to put the paper together which we will show to Dr. Reckless. We are not allowing him to write it up himself." (Pfizer_LeslieTive_0020985)

The company sent another letter to investigators describing 945-224 findings dated 14 November 2000. This investigator letter differed from the letter sent 8 March 2000 , in that the results were interpreted more positively. Certain messages were written in bold; a reader focusing on the messages in bold could easily miss the message that the results were negative for the primary outcome variable, instead linking the word "primary" with statistically significant findings related to other measures.

> "...unfortunately none of the gabapentin treatment groups showed statistically significant efficacy for the treatment of painful diabetic neuropathy, if judged by the **primary** outcome parameter....Therefore, the minimal effective dose of gabapentin could not be defined in this study.
>
> However, the **1200 mg/day gabapentin group** showed **statistically significant results** compared to placebo for **the responder rate**..., the **weekly mean sleep interference score**, the **Clinical Global Impression of Change** (CGIC), and 5 domains of the SF-36, indicating an improvement in **quality of life**.....Furthermore, there were several patients who became **totally pain-free**, but there was no totally pain-free patient in the placebo group. In addition to that, an exploratory analysis showed a significant difference between the 1200 mg/day gabapentin and placebo group when pain scores, sleep interference scores, and the 8 items of the SF-36 from end of the double-blind treatment phase were combined to a global test statistic. (Pfizer_LeslieTive_0020982)

By November 13, 2000, a revised draft manuscript had been sent from Synergy to Pfizer and further revisions were requested by Pfizer:

> "please find attached some minor changes we would like to make to the revised draft....These changes mainly concern wording in the statistical section...I will then forward a copy of the draft publication to Dr. Reckless for review (in close co-operation with Dr. Uzman Azam)." (Pfizer_LeslieTive_0020922)

Key suggested changes in the revised Abstract were likely to change the reader's interpretation of at least one outcome:

> "further improvements were seen in the four-month open-label phase in terms of mean pain scores, mean sleep interference scores, and ~~two~~ most of the SF-36 domains." (Pfizer_LeslieTive_0020927)

In addition, inappropriate emphasis was added:

> "Conclusion: The evidence from secondary endpoints indicates that patients receiving gabapentin 1200 mg experience an overall benefit from treatment despite the lack of a signficant effect on pain scores." (Pfizer_LeslieTive_0020927)

Despite these changes, Pfizer was still not anxious to publish. Angela Crespo (Senior Marketing Manager [Major Markets], Pfizer Worldwide Marketing, Pfizer Pharmaceuticals Group [PPG]), sent the revised manuscript draft to Leslie Tive (Neurontin Medical Team Worldwide Leader, Pfizer Medical and Regulatory Operations, PPG) with a comment:

> "This is the negative study we were talking about....As you can imagine, I am not in a hurry to publish it." (Pfizer_LeslieTive_0020922).

The final version of the manuscript, ready for submission to *Diabetic Medicine*, was sent to Leslie Tive and others on 12 January 2001. She circulated a comment that her "instinct would be to continue to wait" [on the manuscript submission], until after acceptance of the UK studies (225 and 226), currently undergoing a second rewrite following a rejection by the *BMJ*. (Pfizer_LKnapp_0053962)

Delay was further recommended in a Medical Actions Communications (MAC) Action Report, dated 18 July 2001 (Pfizer_RGlanzman_0044634):

> "The team agrees that this study should not be pushed for publication."

The manuscript was submitted to *Diabetic Medicine* 14 February 2002 (Pfizer_LeslieTive_0020885) and a successful upload confirmation was sent on 11 March 2002. (Pfizer_LeslieTive_0020884). The covering letter sent with the submission emphasized, to an extent which I find dishonest, the study's positive results:

> "The study reported in this manuscript examined the efficacy, dose response characteristics, and tolerability of gabapentin for the symptomatic relief of painful diabetic neuropathy. The results obtained reveal that gabapentin has significant beneficial effects on responder rate, weekly mean sleep interference score, Clinical Global Impression of Change, and several domains of quality of life. These results are consistent with those seen in previous trials and further establish gabapentin as a useful and well-tolerated treatment option for painful diabetic neuropathy." (Pfizer_LeslieTive_0020885)

In an email dated 13 May 2002, *Diabetic Medicine* rejected the 945-224 manuscript, with an invitation to resubmit after responding to reviewer comments. Reviewers comments included concerns about company bias and inappropriate statistics:

> "As stated by the statistical advisors, the quality of the statistics appears to be poor, and hence the conclusions are not justified....The authors are advised to perform an appropriate statistical analysis which should allow them to draw a less biased interpretation..." (Pfizer_Leslie_Tive0020881)
>
> "First, I believe the stat section should use the Bonferroni correction....With this redo of the data, it is probable that NO statistical measures were positive. Thus, this trial would be considered a failure and the paper rewritten accordingly....Third, there are many areas of company bias that need elimination." (Pfizer_LeslieTive_0020882)

The statistical reviewer also raised the concern that some groups appeared to have been combined (ie, the 1200 and 2400 mg/d groups for sleep interference score) and 'very much' and 'much improved' in Figure 3. Combining data for two categories would be one way of manipulating data to obtain desired results and should not be done unless the collapsing of categories were proposed *a priori* for a specific reason, or was done consistently across all analyses, or was done for exploratory purposes. It would not be done inconsistently, for example for a single outcome or analysis. (Pfizer_LeslieTive_0020883)

The peer reviewers were also concerned about inconsistencies across the study data and in comparison with the US study (945-210), where the mean effective dose was found to be 1800 mg. They were concerned that only the middle dose (1200 mg) appeared to have a beneficial effect, and yet was associated with the fewest adverse effects and the lowest dropout rate. For example, why was the lowest dose (600 mg) associated with the worst of all outcomes including adverse events, even worse than placebo? A reviewer raised the issue that investigators or patients may possibly have been unblinded to a treatment being taken by a given patient if that patient experienced one or more adverse events, and this may have influenced their assessment of study outcomes, all of which were subjective. (Note that this issue was also raised for Study 945-210, and would have been a consideration for all studies of Neurontin, particularly those in which high dosages were administered). (Pfizer_LeslieTive_0020882)

On 21 October 2002, Pfizer submitted the manuscript to *Diabetologia*, a second journal. The cover letter was essentially identical to that sent to *Diabetes Medicine*, including the inappropriate and perhaps dishonest summary of findings noted earlier. (Pfizer_LeslieTive_0020844). In addition, neither the *Diabetologia* or *Diabetes Medicine* manuscripts, nor the cover letters acknolwedged the ghost authorship by Synergy (the company providing the manuscript preparation). The manuscript was rejected 14 November 2002. Reviewer comments included:

- "I am concerned as to whether these patients really did have painful neuropathy"
- "Why did the authors elect to do a 7-week study which seems rather short?"
- "There is no apparent dose-response curve"
- "No change in VAS or PPI normally gold standard measures of therapeutic efficacy in clinical trials of pain"
- "Is there a benefit in sleep scores, is this as a consequence of the side effect somnolence?"

- "Why did only 67 patients continue in the open-label study? If the drug is truly effective would you not expect more patients to have gone to open label." (Pfizer_LeslieTive_0020843)

Email correspondence (13 December 2002) between Pfizer Marketing and the company providing the manuscript preparation indicates that the article remained a low priority at Pfizer:

> "By the way, Christine, from a MKT point of view we are not interested at all in having this paper published because it is negative!! So don't put this as a high priority on your list...." (FAL_007964)

Elizabeth Mutisya (Neurontin Medical Director [Major Markets], Pfizer Medical and Regulatory Operations, PPG), informed Beate Roder that it would not be possible to work with the medical writers any more on revising and submitting an article (February 3, 2003) and Dr. Reckless was asked soon thereafter for a decision on whether or not he would like to pursue publication any further.

> "...given our limited budget for Neurontin this year, and the number of projects Fallon Medica is currently handling for us, the agency will not be able to take the lead in revising the manuscript again. Dr. Reckless will have to take the lead this time." (Pfizer_LeslieTive_0020838)

Emails within Pfizer indicated that Dr. Reckless would need to take the lead on revisions. He requested copies of all previous submissions, statistical analyses, and references. The previous submissions and references (only) were sent 11 February 2003. (Pfizer_LeslieTive_0020837)

Ultimately, results from the trial were not published as a stand alone paper, but were incorporated into a selective pooling of data from three Pfizer studies of painful diabetic neuropathy; the paper was submitted 14 October 2002 and published in 2003 with a Pfizer-associated investigator and Pfizer co-author (Backonja M and Glanzman R. *Clinical Therapeutics* 2003; 25:81-103). The article emphasized the positive findings of study 945-224 and provides a possible explanation for the negative findings. The data from three studies of painful diabetic neuropathy (Pfizer studies 945-210, 945-224, 945-306) were pooled and showed an overall statistically significant benefit on "the efficacy of gabapentin in diabetic neuropathy" compared to placebo for doses $\geq$1800 mg (see Table 5 of article). The article refers regularly to the "efficacy" of gabapentin, and the "most efficacious dose" even though these were not primary outcomes nor were they clearly defined. The text notes that "patients treated with gabapentin did statistically better (lower mean pain scores at end point; $P< 0.001$) than patients who received placebo...." (Pfizer_LeslieTive_0038526). This article does not follow standard methods for performing a systematic review (Egger et al 2001), and its methodology is unclear. Although it is written authoritatively, it would not be considered to be a reliable source of high quality research evidence.

3.2 Study 945-271 (POPP)

Study 945-271 is an example of suppression of negative results (publication bias), time lag bias, and "spin".

Study 945-271 (POPP) was a multicenter crossover trial conducted between November 1998 and November 2001 at 9 centers in Sweden, Denmark, Finland, and Norway. The study aimed to evaluate the efficacy and safety of gabapentin compared with placebo for symptomatic relief of neuropathic pain due to peripheral nerve injury. The primary efficacy outcome was daily pain intensity (a 0-100 score, where 0 is no pain) recorded on awakening and evening. Secondary outcomes were sleep interference (how much did pain interfere with sleep, recorded using a visual analogue scale of 0 to 100), the SF-36, pain relief (measured by two questions), clinical global impression of change (CGIC), and patient global impression of change (PGIC), and safety outcomes. The Final Report notes one "publication" emanating from the research, a poster presentation we were unable to locate (*Gabapentin in chronic peripheral post-operative and post-traumatic neuropathic pain. T Gordh et al. Poster presentation at IASP, August 2002, Abstract p 406-407).*

Gabapentin did not reduce mean pain intensity score compared to placebo, but a statistically significant benefit was found for some secondary outcome variables. The Final Report (dated 2003-03-07), section titled Efficacy Results, states:

> "Thus, no difference between the treatments could be seen, p=0.16" (Pfizer_LCastro_0043359)

Yet the Discussion and Overall Conclusions of the Final Report states:

> This study indicates that gabapentin treatment may be of benefit for patients with neuropathic pain. Although the primary efficacy variable did not reveal any difference in pain reducing effect of gabapentin as compared with placebo, a variety of secondary outcomes did so....In conclusion, this study indicates that gabapentin may be of benefit for patients with neuropathic pain." (Pfizer_LCastro_0043329)

Study 945-271 included a substudy (ie, it was part of the larger POPP study) conducted at 4 of the 9 sites, with a purpose of examining the effects of gabapentin on hyperalgesia and allodynia, on pain evoked by cold, touch and pinprick in patients with neuropathic pain due to peripheral nerve injury. According to the Final Report, no publication emanated from this study either. No benefit of gabapentin was observed for any of the tested variables. The Final Research Report for the substudy (dated 2003-09-18) concludes:

> "In conclusion, the results from this sub-study could not reveal any difference between placebo and gabapentin, a finding that may be misleading due to the low number of patients studied and the complexity of the study...." (Pfizer_LCastro_0027137)

Email correspondence in September 2001 indicates that Pfizer aimed to manage publication decisions (ie, establish explanations for negative results, possibly combine data

from the main study and substudy, and delay publication) in view of the negative results for both the main study and the substudy. The following suggestions were made:

- Propose possible explanations for lack of observed efficacy, and possible post-hoc analyses to look for differences between groups

- Wait for substudy to be completed and include those data "if we want to avoid the appearance of 'handpicking' which data we present....The delay created by completion of the substudy would allow us to optimise timing between the release of the two studies. At the next Publications Subcommittee Meeting, we need to discuss how we would like the results to be disseminated. The investigators are open to our suggestions. My initial thoughts...IASP might be a good venue for an abstract. We can see if they are still interested in a journal submission after that." (Pfizer_LeslieTive_0076418)

- "...Of course these kind of things can always be a delicate issue, but I am sure that everyone can appreciate our desire to "take our time" to review it carefully."

- "I assume that we would like to maximize the time interval between the Reckless paper and the POPP study" (Pfizer_JMarino_0000809)

And, an email from Kirk Taylor (Lyrica Medical Team Leader, Pfizer Medical and Regulatory Operations, PPG) to the Pfizer group noted that comments made by the Nordic investigators indicated current perceptions that were of concern.. For example, he noted,

> "...the negative halo about Neurontin's efficicay and the negative POPP study....This perception must be corrected in terms of DPN and PHN. Journal clubs with OL's [opinion leaders] and internal people may help." (Pfizer_LeslieTive_0076417)

He also noted concerns about possible adverse events (visual field loss) in the eye and that:

> "a perception was borne as to the frequency of such event". (Pfizer_LeslieTive_0076417)

Elizabeth Mutisya also noted that the Nordic investigators believe that "we had a minimally effective drug" and that some were concerned about the possibility of visual problems, "the conclusion being that we had a slightly effective drug with significant risks". She concludes by noting the opportunity to obtain the desired study results (design bias) as well as suppression of negative results:

> "The choices are to do nothing (and hope that our competitors don't notice the negative -224 study and this study) or to proactively design a study based on our experiences that may provide better results. Both negative studies will likely be in the public domain in 2002." (Pfizer_RGlanzman_0040034)

It appeared from all the documentation that I reviewed that Pfizer was successful in suppressing full publication of final results of Study 945-271.

3.3 Study 945-306 (Serpell)

Study 945-306 represents a particularly interesting example of selective outcome reporting, citation bias, and ghost authorship. In this case, Pfizer also learns the identity of a peer reviewer for a submitted manuscript and establishes a relationship intended to be useful in the future.

Study 945-306 was a randomized clinical trial conducted at 32 centers in the UK and two in Ireland,1999-2000, evaluating the efficacy and safety of gabapentin up to a maximum dose of 2400 mg/day compared to placebo in relieving symptoms of neuropathic pain, for a wide range of neuropathic pain syndromes. The primary efficacy measure was weekly mean overall pain scores from the daily pain diary (11 point Likert scale), secondary outcomes were weekly mean pain scores for four pain symptoms from the daily pain diaries, Short Form- McGill Pain Questionnaire, Clinical and Patient Global Impression of Change and the SF-36. The results showed statistically significant differences between gabapentin and placebo for the primary outcome weekly pain score, but only for weeks 1, and 3-6, not in weeks 7 and 8, the final weeks of the study. None of the individual pain symptoms showed a significant difference at the end of treatment, but there was a treatment effect seen for some of other variables at the end of treatment.

Furthermore, examination of these and other data at a meeting of consultants September 6, 2001 at the Crowne Plaza in Ann Arbor, Michigan, hosted by Pfizer to discuss securing [from the FDA] the broad neuropathic pain indication, indicates that the consultants believed that the statistical significance in Study 945-306 could be explained by effectiveness for post-herpetic neuropathy (PHN), and that there was no supporting evidence for a broad neuropathy pain claim. (Pfizer_LKNAPP_0050385)

> "...the evidence is not convincing to support a broad neuropathic pain claim. Opinion on the Neurontin neuropathic pain package is that neither the FDA nor the Advisory Committee is likely to agree that adequate evidence is provided for a broad indication. New analyses/data not only do not support a broad claim, they provide evidence to the contrary to a broad indication."
>
> "...Statistical significance in 945-306 is predominantly the result of the PHN patients (in addition to a small number of DPN patients) in the study. (Pfizer_LKNAPP_0050386)

The first attempt at publication was submission to the *BMJ*, but the manuscript was rejected.

An internal document (Pfizer_LeslieTive_0020632) states that rejected BMJ papers cannot be resubmitted, and that the referee identity is known (Henry McQuay from Oxford Pain Research Group) since it is an open peer review system. The referee was concerned about:

- "Exclusion criteria: The referee was grieved by the fact that patients who had previously had little or no response to gabapentin were excluded from the trial. He felt this to be a source of bias.
- Analysis of the gabapentin group as a whole rather than the three separate dose groups.
- 'Badging' of the trial. The referee felt that named authors are from the sponsoring company and that this put an overtly company favourable spin on the paper." (Pfizer_LeslieTive_0020631)

The proposed strategy was to:

- Revise and resubmit to *Pain*.
- "Contact Henry McQuay - We have very good relationships with this individual and we can reassure him that most of his comments will be incorporated. This action is important as it is highly likely that he will review these papers in his capacity as the world authority on pain and clinical trial methodology." (Pfizer_LeslieTive_0020632)

The second publication attempt, a submission to *Pain* (submitted 10 April 2001, revised and resubmitted 28 June 2002) was successful and an article was published later that year (Serpell MG, Neuropathic Pain Study Group. *Pain* 2002;99:557-566. The results were carefully described and conclusions were presented as positive in the Abstract:

> "Over the 8 week study this score decreased (ie, improved) by 1.5 (21%) in gabapentin treated patients and by 1 (14%) in placebo treated patients (P=0.048, rank-based analysis of covariance). Significant differences were shown in favour of gabapentin (P<.05) for the Clinician and Patient Global Impression of Change, and some domains of the Short Form-McGill Pain Questionnaire....This study shows that gabapentin reduces pain and improves some quality-of-life measures in patients with a wide range of neuropathic pain syndromes."

The article's text also presented a positively presented conclusion, obscuring the negative findings.

As noted in Section 1 of this report, research has shown that conclusions frequently do not match study results in journal articles (Barnes and Bero 1998) and this mismatch is disproportionately found in industry-sponsored studies (Yank 2007; Gøtzsche 2006; Als-Nielsen et al 2003). There is evidence from internal Pfizer memos that there was a deliberate action on Pfizer's part to spin the results of Study 945-306.

A letter to the editor of *Pain* (dated 22 November 2002) indicated that at least one reader believed that the conclusion of reduction in cardinal symptoms of neuropathic pain was not valid, in part because it did not correspond to the data observed (FAL_007867 , FAL_007868, FAL_007869 and FAL_007986).

Communication between Medical Action Communications and Pfizer Marketing indicated they recognized that the findings did not support the efficacy of gabapentin, and

worked to find language for two poster presentations that included data from study 945-306 (Backonja 16792.pdf, Serpell 16889.pdf) that would "spin" the findings positively (note subject line on emails):

"To: Crespo, Angela (Pfizer)
From: David Cooper (MAC)
Subject: spinning Serpell

20 September 2002 16:53

> "I am certainly familiar with the Serpell study in detail. We have discussed the merits of publishing, republishing, and creating promotional campaigns around these results in the past.
>
> We know Alison wants to make sure that we align publication messages with your global marketing efforts.
>
> Our concern, not having seen any of Penny's PR spin on the results as part of your promotional campaign on this manuscript, is that we make sure that we don't make up different ways of explaining away the results to different audiences. It is our understanding that you publicized the study as supporting the use of gabapentin for these difficult mixed NeP patients." (MAC_0003664)

To: David Cooper@ Qunitiles.com
From: Crespo, Angela, Senior Marketing Manager, Neurontin
Subject: Spinning Serpell
09/20/2002 11:04 am

> "The problem we are facing with the poster is that is (sic) comparing 5 studies and there is when you can see differences with the Mix paper and the rest...Obviously we are not analyzing this at the PR stuff....Did you understand what was really my issue? Try to compare all dosing and QoL graphs between them. The Serpell is the worst. We knew that but we should try to balance that negative effect at least with a short sentence." (MAC_0003665)

To: Crespo, Angela
From: David Cooper
Subject: spinning Serpell
09/20/2002 12:37 pm

> "If Pfizer wants to use, present, and publish this comparative data analysis in which 2 of 5 studies compared make the overall picture look bad, how do we make it sound better than it looks on the graphs."
>
> "There just isn't a lot of room in a poster to make that case, but I'll add in the following to the discussion of the mean pain score results after the comment on DPN II.

> **'While gabapentin was significantly more efficacious than placebo in the mixed neuropathic pain study, the smaller response seen in both gabapentin and placebo groups in the study is likely due to intractable and chronic nature of the pain in the population'.**"
>
> Allison has asked us to present our ideas going forward for the 2003 plan, and we look forward to presenting an alternative to continued republication of study data at that meeting" (MAC_0003664)

In my opinion, the poster describing Study 945-306 and ultimately presented at the 2002 ICMTNP meeting (Serpell 16889.pdf) exhibits multiple forms of reporting bias. The Results section lists 13 bulleted points, with the data not presented until bullet number 6. Prominent graphs display visual differences between treatment groups, which are only statistically significant at selected time periods. The prominent boxed conclusions (below) imply that gabapentin is effective in treating neuropathic pain, though the focus is not on the primary outcome, and neither comparisons with placebo, nor statistical significance, nor time point of measurement are provided. In addition, outcomes are blurred in ways that imply a stronger result (eg, self-reported quality of life was statistically significantly better for gabapentin for only 3/8 of the quality of life domains):

Boxed conclusions:

- "Gabapentin, at doses up to 2400 mg/day, reduced pain in difficult to treat patients with a variety of resistant neuropathic pain syndromes, such as complex regional pain syndrome (28%), postherpetic neuralgia (14%), other post-surgical pain (9%), radiculopathy (9%), and postlaminectomy pain (7%). The majority of these patients (97%) had pain that was refractory to other treatments.

- Both patients and clinicians rated significantly more patients in the gabapentin group as "very much" or "much improved" compared to patients in the placebo group.

- Patients in the gabapentin group experienced significantly greater improvements in outcome measures reflecting quality of life.

- Except for dizziness and somnolence, adverse events were comparable in the treatment and placebo groups. Dizziness and somnolence, when they occurred, were generally mild to moderate and transient". (16889.pdf)

The poster describing Study 945-306 also exhibits "citation bias," citing four articles, one related to classification of chronic pain and the other three studies supporting the effectiveness of gabapentin (Backonja,1998; Rowbotham 1998; Rice 2001). Pfizer studies with negative findings are not cited.

3.4 "Gorson" (study number not available)

A placebo controlled, double blind crossover trial of Neurontin vs placebo was conducted by Dr. Kenneth Gorson at St. Elizabeth's Hospital in Boston, Massachusetts (WLC_Franklin_0000100237). Confirmation of the investigator-company agreement, including a final payment for manuscript completion, is dated August 1, 1995. The agreement says,

> "You may publish the results of the study, provided you give Warner a copy of any proposed publication at least 45 days before submitting it for publication and that you allow Warner to review and comment on the contents of such publication." (WLC_Franklin_0000100237)

Submission of the trial protocol to the St. Elizabeth's institutional review board was signed by Dr. Gorson on January 15, 1996, and Phil Magistro from Parke-Davis on February 12, 1996. (WLC_Franklin_0000100239)

Dr. Gorson submitted a draft manuscript by fax to Phil Magistro at Parke-Davis on August 25, 1997, and asked him for quick turnaround and suggestions "in the text or margins" (WLC_Franklin_0000100279). Dr. Gorson indicated that he wanted to submit to the journal *Neurology*.

Using various documents available to me, including the sample size estimate, I judged the planned primary outcome to be mean visual analogue scale (VAS) score. The draft manuscript reports (in the Abstract), "There was modest improvement in the MPQ score only, with a mean reduction of 8.9 points compared to 2.2 points with placebo (p=0.03)...Gabapentin, at a dose of 900 mg/day, is probably no more effective than placebo in the treatment of painful diabetic neuropathy". And from the Results, "no differences between the [gabapentin and placebo] mean change in the composite VAS or PPI scores." Further, the manuscript states, "The results of this study suggest that gabapentin is probably ineffective or is only minimally effective for the treatment of painful diabetic neuropathy at a dosage of 900 mg/day." Dr. Gorson concludes that there is a need for further study of gabapentin at higher doses (up to 3600 mg/day). Margin notes, presumably made by individuals at Parke-Davis in response to Dr. Gorson's request, note questions or areas where changes to the manuscript might be made.

I did not receive documentation of any correspondence occurring between the initial manuscript and a revised manuscript, circulated by Phil Magistro to Parke-Davis colleagues on January 7, 1998 (WLC_Franklin_0000088375). Mr. Magistro says in his covering memo, "...a significant difference vs placebo was noted only on the McGill Pain Questionnaire."

The revised, circulated, manuscript presents a much changed "spin" of the study findings. The Results section in the Abstract begins by noting changes between baseline and follow-up for each treatment group separately (ie, this was a within treatment (before & after treatment) group comparison and not a comparison of gabapentin and placebo), "There was a substantial reduction in the mean MPQ (P<0.005), VAS (p=0.001), and PPI (p=0.008) scores in patients treated with gabapentin, but there was also significant improvement in the mean VAS score (p<0.005) in patients treated with placebo." The Abstract next reports only the statistically

significant MPQ outcome for the comparison of gabapentin and placebo. The Abstract concludes, "Gabapentin may be effective in the treatment of painful diabetic neuropathy. Our results suggest that further studies evaluating higher dosages of gabapentin are warranted". Wording similar to that in the Abstract is used in the text of the manuscript.

Dr. Gorson presented a poster at a 1998 conference (Neurology Apr 1998; 50 (suppl 4):A103 P02.055), with wording that was nearly identical to the wording in the Abstract of the revised manuscript.

I have received no additional correspondence or manuscripts concerning the Gorson Study, and as far as I know it was never published in full. Instead, results were published in a Letter to the Editor (*J Neurolog Neurosurg Psychiatr* 1999; 66:251-2). The data were not presented accurately, for example although 53 patients were randomized, the letter did not report this correctly. Instead the letter reported the number analyzed after exclusions,

"Nineteen patients were randomized to the active drug and 21 to placebo..."

In the text, the letter also establishes more than one explanation for the negative results, and sets the stage for future trials at higher dosages, "The low dosage of gabapentin was chosen to minimize adverse effects that might compromise blinding." (Note that this also indicates an awareness by Parke-Davis that patients may have been unblinded to active treatment at doses higher than 900 mg/day); and "The results of this study suggest that gabapentin is probably ineffective or only minimally effective for the treatment of painful diabetic neuropathy at a dosage of 900 mg/day".

3.5 Backonja (945-210)

In 1998, Backonja and colleagues published the findings from study 945-210 in *JAMA* (1998; 280:1831-6), a high impact journal almost guaranteeing high visibility for the study and Neurontin. The article, however, glossed over several important facts. For one, it claimed that,

> "Because this was the first trial to evaluate gabapentin's efficacy in this patient population, all patients' dosages were titrated to tolerability up to 3600 mg/d regardless of any efficacy achieved at lower dosages."

First, this was not the first trial, Gorson's trial was. There is evidence from several sources that Bakconja was aware of this. On January 7, 1998, Phil Magistro at Parke-Davis circulated an edited draft of Gorson's manuscript which was unchanged from a version that was faxed on November 13, 1997 (WLC_CBU_086698). One of the recipients of the memo was Elizabeth Garofalo, who was a co-author of the Backonja publication. Another recipient of the memo was Leslie Magnus Miller (Director of Medical Affairs, Parke-Davis). On March 30, 1998, Clinical Communications notified others at Parke-Davis that Backonja's manuscript was submitted to *JAMA* on March 25, 1998. This memo was copied to Leslie Magnus Miller.(WLC_CBU_093708)

Second, in the published *JAMA* article, the investigators state that they recognized that the subjective outcomes in the study required blinding [of the patient, physician, and investigator] to protect against bias in attribution of benefit (or not) as a result of knowledge of the treatment. Thus, the investigators

> "explored the possibility that the occurrence of adverse events resulted in the unblinding of the study, biasing the result of our efficacy analysis."

They reported that their analysis (not presented in the article) demonstrated to them that

> "...inclusion of patients who experienced these central nervous system adverse effect [dizziness and somnolence] in the original analysis did not account for the overall efficacy seen in the trial."

They conclude the article text with:

> "Gabapentin is a promising new agent for use in patients with neuropathic pain when therapeutic options are limited and offers advantages over currently available treatments as a first-line agent."

The Abstract conclusion also promotes use of gabapentin for diabetic neuropathy,

> "Gabapentin monotherapy appears to be efficacious for the treatment of pain and sleep interference associated with diabetic peripheral neuropathy and exhibits positive effects on mood and quality of life."

Pfizer clearly recognized the likelihood that unblinding due to adverse events could result in corruption of the study's validity. An internal Pfizer January 7, 1998 memo requested additional analyses for Study 945-224:

> "Rationale: at a pain experts' meeting, it was proposed that we should look for a correlation of maximum CNS-related Adverse Event severity with mean pain score, assuming that patients with more severe AEs tend to believe that they are on study drug (which would be a good guess) and therefore tend to have better efficacy data, thus unblinding and corrupting the study." (Pfizer_TMF_CRF_061890)

Analyses similar to Study 945-210 were suggested (see Pfizer_LLaMoreaux_0038148) but were not undertaken. (Pfizer_TMF_CRF_062490) Other indicators of Pfizer's awareness of the unblinding issue are seen in Minutes of the Meeting with the French Drug Agency, Concerning Neurontin in Pain, June 18, 1998 (Pfizer_LLaMoreaux_0009058), as well as comments made in the published literature (eg, for another Parke-Davis Neurontin study, Miller et al., *Neurology* 1996; 47:1383-1388).

3.6 Cochrane reviews

It is evident from the documents reviewed that Pfizer exerted considerable control over publication of findings and messages disseminated to the biomedical community. The existence of a "publication strategy," covered in Section 2.1 of this report, indicates the importance of Pfizer-driven publications to the marketing success of Neurontin.

Before the 1990s, the "traditional" narrative review article was a common way of summarizing the literature on, for example, the effectiveness of a treatment or treatments for a given disorder. The traditional review was highly subjective and also offered a platform for disseminating the author's message. With the advent of the "systematic review" and "meta-analysis," a scientific approach to the synthesis of similar but separate studies, the situation changed. In systematic reviews, selection of included studies, as well as the qualitative and quantitative synthesis, is subject to rigorous and transparent methodology.

The Cochrane Collaboration, founded in 1993, is an international organization dedicated to conducting, maintaining and disseminating systematic reviews of healthcare interventions. Cochrane reviews are conducted using standardized, evidence-based methods, for example an exhaustive search for all evidence addressing a topic that includes unpublished and "grey literature" data. The Cochrane Collaboration has, since its inception, recognized the risk that reporting biases may influence the validity of outcomes of a systematic review, and thus has advocated requesting unpublished data from sponsors and investigators as part of standard protocol. These data are requested as a scientific courtesy from the pharmaceutical industry and others, usually by mail or email. There is no way to "demand" or "subpoena" data from sponsors or investigators.

For bipolar disorders, migraine, and neuropathic pain, Pfizer was approached by systematic reviewers affiliated with the Cochrane Pain, Palliative and Supportive Care Review Group, and asked to provide data from unpublished trials and for published variables where additional information was needed to conduct the review. I reviewed documents indicating that Pfizer was not willing to provide these data but did not want to appear noncompliant. According to documents I reviewed, Pfizer ultimately agreed to assist with a migraine review or reviews, with Henry McQuay, the head of Oxford Pain Group, a prominent pain specialist who also served as the *BMJ* peer reviewer on Study 945-306.

3.6.1 Cochrane review - gabapentin for bipolar disorders

On November 5, 2001, Dr. Atul Pande (Vice-President, Worldwide Portfolio Leader, Pfizer Global Research & Development Headquarters) responded to a Cochrane request (original 22 October 2001 request not available to me) by providing a list of references, including Pande 2000b (already noted as identified by the Cochrane reviewers), a study by Vieta (2000) and an abstract from Wang (2000). (Pfizer_APande_0005005) On July 8, 2003, Cochrane authors again contacted Pfizer staff by email asking for help in identifying randomized trials of gabapentin in the treatment of bipolar disorder (Pfizer_APande_0003413). A further request in October [2003], for original data relating to the Pande study (baseline and endpoint scores on TMRS, HAM_D, and CGIS, Internal States Scale, and the Quality of Life

Questionnaire, as well as other numbers needed for an intention to treat analysis, led to a promise that Dawn Carroll at Pfizer would "look into the matter." (Pfizer_BParsons_0030122) After another request in December 2003, a list of published studies was sent to Karine Macritchie (Cochrane), and she again requested raw data. A December 23, 2003 email discussion within Pfizer resulted in "I would not send unpublished data to anyone outside Pfizer". (Pfizer_BParsons_0030122)

The Cochrane request was then sent to another group within Pfizer, with quite a bit of back and forth about whether Pfizer bipolar studies existed and if so, what should be done. There was a reference made to the Pande 2000b study and reiteration that Cochrane wanted "data that is not in the publication". (Pfizer_Knapp_0112244) The emails indicate a disinclination to share data and a preference to let Cochrane know about published data and "let it go at that if possible". On February 10, 2004, Dawn Carroll sent an email to Lloyd Knapp (Re: Gabapentin - Bipolar Data action required) saying,

> "The decision is ultimately yours as to what data we send this group - the risk is that in the cochrane review there is a statement saying Pfizer declined to provide the information requested! which does not look good for the company." (Pfizer_LKnapp_0112245)

On February 23, 2004, Anitra Fielding from the UK Pfizer team sent an email to Lloyd Knapp, Dawn Carroll and others asking them to please get back to the Cochrane team (Pfizer_LKnapp_0112829). Accordingly, a teleconference was arranged for March 23, 2004 to "confirm some details". This call did not take place as arranged but apparently occurred in April 2004. After that call, a request identical to previous requests was made by the Cochrane group and internal Pfizer emails resumed discussing how to respond. On November 7, 2004, the Cochrane group again reminded Lloyd Knapp of its request. This is the last email I have access to. The Cochrane protocol was eventually withdrawn (ie, the review was never completed).

3.6.2 Cochrane review - gabapentin for migraine prophylaxis

Cochrane authors also requested information from Pfizer about trials of gabapentin for migraine prophylaxis (15 March 2002; Pfizer_RGlanzman_0140655) and their request was met with a response similar to the one given for the bipolar systematic review:

> "If they are looking for unpublished data, I would be reluctant to send it." (Pfizer_RGlanzman_0140656)

> "The suggestion I would throw out there is to have someone from medical just tell them that we are not indicated for this condition and that we are only aware of two double-blind placebo controlled trials done independently of Pfizer and which we had no involvement and send them the reference...."We definitely will not supply any internal data, we all agree on that." (Pfizer_RGlanzman_0140655)

The emails concluded that this issue was one related to global messages and provision of information in a consistent way.

> "...it seems to me that it would be easier to have NYHQs follow up with request like this, especially when it is as influential and the Cochrane group...." (Pfizer_AFannon_0012222)

3.6.3 Systematic review by Cochrane authors - gabapentin for neuropathic pain

On January 3, 2001, Michael Rowbotham circulated an email (Pfizer_CTaylor_00334400) drawing attention to a systematic review of anticonvulsants for migraine (Henry McQuay et al. 1995 BMJ 31:1047-52), and responding to a colleague's December 15, 2000 email regarding a new published review by the same group (J Pain Symptom Manage 2000;20:449-450). A Reuters article copied into the email described Dr. McQuay's 2000 review and noted that the review found that "....gabapentin was as effective as older anticonvulsants." Dr. Rowbotham said,

> "We have drafted a field letter for our reps, which we will be sending out in the next week, to brief them on how to handle any potential objections....Henry is known for not going out on a limb, and he was only able to analyse data that had been published upto [sic] about a year ago." (Pfizer_CGrogan_0012128)

> The letter to the field reps described the McQuay findings and cautioned them,

> "In the near future you might be engaged in conversations with customers regarding this article. This document will help you handle queries that may arise as a result of this publication....This study at first glance does not put Neurontin in a favourable position as the drug of choice for all types of neuropathic pain. However there are ways that this study could be handled if customers raise this article with you and used to our advantage." (Pfizer_CGrogan_0012131, Pfizer_CGrogan_0012132)

Various reasons for dismissing the findings are then provided in the letter.

The Pfizer team learned a few days later (January 5, 2001) that the two UK Neurontin pain studies had been rejected for publication in *BMJ.* Henry McQuay, who headed the Oxford Pain Group, and who was first author on the systematic review, was the single *BMJ* reviewer. The reasons for rejection included "2 of the three named authors are from the company" (Pfizer_WSigmund_0000241) (termed "badging" of the trials); patients having been excluded from the trial if they had not responded to gabapentin in the past; and combining data for the three separate dosage groups (Pfizer_LeslieTive_0020631). The Pfizer group planned for immediate revision by contracted medical writers, submission to the journal Pain, and personal contact with Henry McQuay. And on January 29, 2001 Michael Rowbotham wrote:

> "For your info, we have agreed to commission a meta-analysis of all NTN Pain studies through the Oxford Pain group...." (Pfizer_DProbert_0007525).

On January 31, 2001, Michael Rowbotham wrote to Pfizer colleagues:

> " We also need to get from Henry and Andrew about what is a good outcome - and where the results of the analysis will lead us in the future. In other words, we need to start with the end in mind!"(Pfizer_DProbert_0007543)

On March 2, 2001, Michael Rowbotham wrote again:

> "This is a potentially a big opportunity for Pfizer as we can formulate and shape the area....The meatanalysis [sic] that we are planning to do through the Oxford pain group (Henry McQuay) could look into the patient improvements on the SF 36, the McGill questionnaire and the sleep data. As you mentioned previously, we need to be very clear about what is a good outcome!" (Pfizer_RGlanzman_0001383)

And on March 20, 2001, he wrote:

> "Can I take it from the message from Joe that...the next steps are for the UK team to develop a clear proposal with the specific criteria and outcomes laid out? Obviously we need to be very clear what we want to get out of the analysis and why. We also need to be clear what we believe what the outcome will be (sic) from our understanding of the data." (Pfizer_LeslieTive_0035819)

On March 28, 2001, Michael Rowbotham wrote:

> "Henry presented his slides at our sponsored symposium last night and a number of positive points came out....He also gave Neurontin some very good coverage and positioned it strongly, saying that although it is not his first line choice at the moment, it is the gold standard in the states." (Pfizer_DProbert_0007581)

It appears from the documents I reviewed that the interaction with Henry McQuay led to several important outcomes for Pfizer: a positive relationship with an important opinion leader, and potential reviewer of journal manuscripts; influence on one or more Cochrane reviews; and influence on use of a measure of association favored by doctors but of concern to Pfizer – the Number Needed to treat (NNT).

The progress of the review was held up by Cochrane, per Pfizer's request, in anticipation of the publication of Serpell's paper on study 945-306 in *Pain*. (Pfizer_RGlanzman_00053506)

According to the documents I reviewed, the Oxford Pain Group and Pfizer continued to work together, with optimism on Pfizer's part regarding input on the Cochrane review, as well as the potential for influence on analyses using NNT (number needed to treat). (Pfizer_DProbert_0007581; Pfizer_DProbert_0007559; MAC_0001691;MAC_0001296; MAC_0002919; MAC_E_0051950; Pfizer_RGlanzman_0146211; Pfizer_RGlanzman_0146213; Pfizer_LeslieTive_0033161;Pfizer_LeslieTive_0033286; Pfizer_MGarcia_0002899).

4. Conclusions

The documents I reviewed on clinical trials of Neurontin for migraine prophylaxis, as well as treatment of bipolar disorders, nociceptive, and neuropathic pain, indicate a clear and deliberate pattern of reporting biases, including but not limited to publication bias, selective outcome reporting; selective analyses; multiple publication; location bias; time lag bias; and citation bias. In addition, I observed extensive evidence of "reframing" or "spin" to make negative results appear positive; "ghost" authorship; and bias in study design. These biases render information about Neurontin's effectiveness, as disseminated in the published literature (as stand-alone reports of trials or as included in systematic reviews), untrustworthy and invalid.

5. References cited

Als-Nielsen B, Chen W, Gluud C et al. Association of funding and conclusions in randomized drug trials: A reflection of treatment effects or adverse events? *JAMA* 2003; 290 (7):921-928.

Antes G, Chalmers I. Under-reporting of clinical trials is unethical. *Lancet* 2003; 361:978-1979.

Barnes, DE, Bero LA. Why review articles on the health effects of passive smoking reach different conslusions. *JAMA* 1998; 279 (19):1566-1570.

Bero LA, Rennie D. Influences on the quality of published drug studies. *Int J Technol Assess Health Care* 1996;12:209-237.

Chalmers I. Underreporting research is scientific misconduct. *JAMA* 1990; 263:1405-1408.

Chan AW, Krleža-Jerić K, Schmid I, Altman D. Outcome reporting bias in randomized trials funded by the Canadian Institutes of Health Research. *CMAJ* 2004;171:735-40.

Chan AW, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical Evidence for selective reporting of outcomes in randomized trials. Comparison of protocols to published articles. *JAMA* 2004; 291:2457-65.

Cho MK, Bero LA. The quality of drug studies published in symposium proceedings. *Ann Intern Med* 1996;124:485–489.

Chokkalingham A, Scherer R, Dickersin K. Agreement of data in abstracts compared to full publications. *Controlled Clin Trials* 19:61S-62S, 1998.

Davidson RA. Source of funding and outcome of clinical trials. *J Gen Intern Med* 1986;1:155–158.

DeAngelis CD, Fontanarosa PB. Impugning the integrity of medical science, the adverse effects of industry influence. *JAMA*. 2008 299:1833.

Dickersin K. How important is publication bias? A synthesis of available data. *AIDS Educ Prev* 1997; 9(1 Suppl):15-21.

Dickersin K, Olson CM, Rennie D, Cook D, Flanagin A, Zhu Q, Reiling J, Pace B. Association between time interval to publication and statistical significance. *JAMA* 2002; 287:2829-2831.

Dickersin K. Publication bias: Recognizing the problem, understanding its origins and scope, and preventing harm. In: Rothstein H, Sutton A, Borenstein M (eds). *Publication Bias in Meta-analysis: Prevention, Assessment, and Adjustments*. London: John Wiley and Sons, Ltd. 2005.

Directives for Human Experimentation: Nuremberg Code. 1949, (available at: http://ohsr.od.nih.gov/nuremberg.php3)

Drazen JM, Morrissey S, Curfman GD. Rosiglitazone--continued uncertainty about safety. N Engl J Med. 2007; 357:63-4.

Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. *Lancet* 1991; 337:867-872.

Egger M, Zellweger-Zahner T, Schneider M, Junker C, Lengeler C, Antes G. Language bias in randomised controlled trials published in English and German. *Lancet* 1997; 350:326–329.

Egger M, Smith GD, Altman D (eds). *Systematic Reviews in Health Care: Meta-analysis in Context*. London: BMJ Publishing Group, 1995, 2001.

Federal Policy for the Protection of Human Subjects, 45 CFR 46, Subpart A (2001). (available at: http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm)

Fergusson D, Glass KC, Hutton B, Shapiro S. Randomized controlled trials of aprotinin in cardiac surgery: Could clinical equipoise have stopped the bleeding? *Clin Trials* 2005; 2:218-29.

Friedman LM, Furberg CM, DeMets DL. Chapter 16. Issues in Data Analysis. *Fundamentals of Clinical Trials.* 3rd Edition 1999; New York: Springer.

Godlee F, Dickersin K. Bias, subjectivity, chance, and conflict of interest in editorial decisions. In: Godlee F, Jefferson T (eds). *Peer Review in Health Sciences*. London: BMJ Books, 2nd Edition, 2003.

Gøtzsche, PC. Believability of relative risks and odds ratios in abstracts: cross sectional study. *BMJ* 2006; 333:231-234.

Gøtzsche PC, Hrobjartsson A, Johanseen HK et al. Ghost authorship in industry-initiated randomised trials. *PloS Medicine* 2007; 4 (1):47-52.

Gøtzsche PC. Reference bias in reports of drug trials. *Br Med J* (Clin Res Ed) 1987; 195:654-56.

Grégoire G, Derderian F, Le Lorier J. Selecting the language of the publications included in a meta-analysis: is there a Tower of Babel bias? *J Clin Epidemiol* 1995; 48:159–163.

Healy D, Cattell D. Interface between authorship, industry and science in the domain of therapeutics. *Br J Psychiatry* 2003; 183:22-27.

Healy D. Did regulators fail over selective serotonin reuptake inhibitors? *BMJ* 2006; 333:92-95.

Hemminki E. Study of information submitted by drug companies to licensing authorities. *Br Med J* 1980; 280:833–836.

Higgins JP, Green S (eds). Cochrane Handbook for Systematic Reviews of Interventions, Version 5.0.0 (updated February 2008). The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org).

Hopewell S, Clarke M, Askie L. Reporting of trials presented in conference abstracts needs to be improved. *J Clin Epidemiol* 2006; 59:681-684.

Hopewell S, McDonald S, Clarke M, Egger M. Grey literature in meta-analyses of randomized trials of health care interventions. *Cochrane Database of Systematic Reviews* 2007, Issue 2. Art. No.: MR000010. DOI: 10.1002/14651858.MR000010.pub3.

Hopewell S, Clarke M, Stewart L, Tierney J. Time to publication for results of clinical trials. *Cochrane Database of Systematic Reviews* 2007, Issue 2. Art. No.: MR000011. DOI: 10.1002/14651858.MR000011.pub2.

Institute of Medicine (IOM) Committee on Reviewing Evidence to Identify Highly Effective Clinical Services. *Knowing what Works in Health Care. A Roadmap for the Nation*. 2008; Washington, DC: The National Academies Press.

ICMJE. Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. Publication Ethics: Sponsorship, Authorship, and Accountability. Updated October 2007. http://www.icmje.org/ accessed July 13, 2008.

Ioannidis JP. Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. *JAMA* 1998; 279:281-286.

Ioannidis JPA, Cappelleri JC, Sacks HS, Lau J. The relationship between study design, results, and reporting of randomized clinical trials of HIV infection. *Controlled Clin Trials* 1997; 18:431-444.

Kjaergard LL, Gluud C. Citation bias of hepato-biliary randomized clinical trials. *J Clin Epidemiol* 2002; 55:407-410.

Korn D, Ehringhaus S. Principles for strengthening the integrity of clinical research. *PloS Clinical Trials* 2006; 1:1-4.

Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003; 326:1-10.

Melander H, Ahlqvist-Rastad J, Meijer G, Beermann B. Evidence-b(i)ased medicine – selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications. *BMJ* 2003; 326:1171-3.

Misakian AL, Bero LA. Publication bias and research on passive smoking. Comparison of published and unpublished studies. *JAMA* 1998; 280:250-253.

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Washington, DC: DHHS, 1979. (availalbe at: http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm)

Nieminen P, Rucker G, Miettunen J, Carpenter J, Schumacher M. Statistically significant papers in psychiatry were cited more often than others. *J Clin Epidemiol* 2007; 60:939-946.

Okike K, Kocher MS, Mehlman CT, Heckman JD, Bhadhari M. Publication bias in orthopaedic research: An analysis of scientific factors associated with publication in *The Journal of Bone and Joint Surgery (American Volume)*. *J Bone Joint Surg* 2008; 90:595-601.

Olson CM, Rennie D, Cook D, Dickersin K, Flanagin A, Hogan J, Zhu Q, Reiling J, Pace B. Publication bias in editorial decision making. *JAMA* 2002; 287:2825-2828.

Pham B, Klassen TP, Lawson ML, Moher D. Language of publication restrictions in systematic reviews gave different results depending on whether the intervention was conventional or complementary. *J Clin Epidemiol* 2005; 58:769-776.

Ravnskov U. Frequency of citation and outcome of cholesterol lowering trials. *BMJ* 1992; 305 (6855):717.

Ravnskov U. Quotation bias in reviews of the diet heart idea. *J Cin Epidemiol* 1995;48:713-719.

Rochon PA, Gurwitz JH, Simms RW, Fortin PR, Felson DT, Minaker KL, Chalmers TC. A study of manufacturer supported trials of non-steroidal anti-inflammatory drugs in the treatment of arthritis. *Arch Intern Med* 1994; 154:157-163.

Sackett D, Straus S, Richardson WS, Rosenberg W, Hayes RB. *Evidence-based Medicine, How to Practice and Teach EBM*. 2000; Philadephia: Churchill Livingstone.

Scherer RW, Langenberg P, Von Elm. Full publication of results initially presented in abstracts (Cochrane Methodology Review). In: *The Cochrane Library*, 2007, Issue 2. Art. No.: MR000005. DOI: 10.1002/14651858.MR000005.pub3

Schmidt LM, Gøtzsche PC Of mites and men: reference bias in narrative review articles: a systematic review. *J Fam Practice* 2005; 54: 334-8.

Sismondo S. Ghost management: How much of the medical literature is shaped behind the scenes by the pharmaceutical industry? *PloS Medicine* 2007;4 (9):1429-1433.

Sismondo, S. Pharmaceutical company funding and its consequences: A qualitative systematic review. *Contemp Clin Trials* 2008; 29:109-113.

Stern JM, Simes RJ. Publication bias: evidence of delayed publication in a cohort study of clinical research projects. *BMJ* 1997; 315):640-5.

Sterne J, Egger M, Moher D on behalf of the Cochrane Bias Methods Group (eds). Chapter 10. Addressing Reporting Biases. In: Higgins JPT, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions.* Version 5.0.0 [updated February 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Timmer A, Hilsden RJ, Cole J, Hailey D, Sutherland LR. Publication bias in gastroenterological research – a retrospective cohort study based on abstracts submitted to a scientific meeting. *BMC Med Res Methodol* 2002; 2: 7

Toma M, McAlister FA, Bialy L, Adams D, Vandermeer B, Armstrong PW. Transition from meeting abstract to full-length journal article for randomized controlled trials. *JAMA* 2006; 295:1281-7.

Tramèr M, Reynolds DJ, Moore RA, McQuay HJ. Impact of covert duplicate publication on meta-analysis: A case study. *BMJ* 1997; 315:635-40.

Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med* 2008; 358:252-60.

Von Elm E, Poglia G, Walder B, Tramèr MR. Different patterns of duplicate publication. An analysis of articles used in systematic reviews. *JAMA* 2004; 291:974-980.

The World Association of Medical Editors (WAME) Publication Ethics Policies for Medical Journals (http://www.wame.org/resources/publication-ethics-policies-for-medical-journals#orig Accessed June, 29 2008).

World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, Helsinki, Finland: World Medical Association, 1964, 2004. (available at: http://www.wma.net/e/policy/b3.htm)

Yank V, Rennie D, Bero LA. Financial ties and concordance between results and conclusions in meta-analyses: retrospective cohort study. *BMJ* 2007; 1202-05.

Please note that the foregoing is based on my experience, training, education and the information I have reviewed or am generally aware of. I reserve the right to supplement this report if additional information is made available.

Kay Dickersin

Kay Dickersin, MA, PhD

Date: August 11, 2008

Appendix A

Tables Describing Information in Neurontin Study Protocols and Reports

Migraine
Table 1 - Table of Citations

Study Number	Publication code	Type of report	Citation (Report)
879-201			
	879-201.RR	Research report	Research report number RR 4301-00066.
	Wessely 1987	Full-paper	Wessely P, Baumgartner Ch, Klingler D, Kreczi J, Meyerson N, Sailer L, Saltuari L, Schutt P. Preliminary results of a double-blind study with the new migraine prophylactic drug gabapentin. Cephalalgia. 1987; 7 (Supplement 6): 477-478.
945-217			
	945-217.RR	Research report	Research report number RR 995-00085.
945-220			
	945-220.RR	Research report	Research report number RR 995-00074.
	Mathew 1998	Conference abstract	Mathew NT. Efficacy and safety of gabapentin (Neurontin) in migraine prophylaxis. Presented as an abstract at the 17th Annual Meeting of the American Pain Society, 1998.
	Mathew 1999	Conference abstract	Mathew NT, Magnus-Miller L, Saper J, Podolnick P, Klapper J, Tepper S, Stacey B, Rapoport A, Ramadan N. Efficacy and safety of gabapentin (Neurontin) in migraine prophylaxis. Cephalalgia. 1999; 19: 380. Presented as an abstract at the 9th Congress of the International Headache Society, 1999.
	Mathew 2001	Full-paper	Mathew NT, Rapoport A, Saper J, Magnus L, Klapper J, Ramadan N, Stacey B, Tepper S. Efficacy of gabapentin in migraine prophylaxis. Headache. 2001; 41: 119-128.

Migraine
Table -2 Summary of Reporting Biases

Study number	Publication code	Protocol available	Date of research report (internal)	Date of last enrollment or end date for "Period(s) covered" per research report	Type of results	Location of publication	Results of primary analysis per research report	Secondary outcome (protocol) reported as primary outcome (report)	Reported analyses on selective populations as primary analysis	Publication bias (negative results and no publication final result)	Conclusions of efficacy consistent with primary analysis result (Conclusions section - report)	Conclusions of safety consistent with analysis of adverse events (Conclusions section - report)
879-201	Wessely 1987	☑	June 25, 1990	May 24, 1988	Preliminary results	Journal article	"Negative"	Yes	Yes	☑	NA[1]	NA[1]
945-217	No publication	☑	January 20, 2000.	January 25, 1999	No publication	No publication	"Negative"	NA[1]	NA[1]	☑	NA[1]	NA[1]
945-220	Mathew 1998	☑	August 24, 1999.	March 10, 1998	Preliminary results	Conference abstract	"Negative"	Yes	Unclear[2]	☐	Yes	Yes
945-220	Mathew 1999	☑	August 24, 1999.	March 10, 1998	Preliminary results	Conference abstract	"Negative"	Yes	Unclear[2]	☐	Yes	Yes
945-220	Mathew 2001	☑	August 24, 1999.	March 10, 1998	Final results	Journal article	"Negative"	No	Yes	☐	Yes	Yes

1 NA = Not Applicable

2 Unclear: Analysis population not mentioned or was unclear

Migraine
Table 3 - Comparison of Study Reports by Authors and Funding Source

Study number	Publication code	Year	Type of report	Citation	Authors/ investigators (Protocol)	Authors/ investigators (Report)	Authors/ investigators locations (Report)	Funding source (Report)
879-201	879-201.RR	June 25, 1990	Research report	Research report number RR 4301-00066.	Investigator: Prof. Dr. med. Franz Gerstenbrand Dr. L. Saltuari Monitor: Nancy Meyerson, M. Phil. Substitute: Dr. med. Bernd Schmidt Biometrics: Klaus Stern, Dipl. Math.	GOE [Godecke] Investigator(s): Feuerstein T Quebe-Fehling E Outside investigator(s): 1. Saltuari L 2. Klingler D 3. Wessely P 4. Schutt P 5. Kepplinger B	1. Neurologische Universitats-Klinik, Innsbruck, Austria. 2. Allg. Off. Krankenhaus, Linz, Austria. 3. Neurologische Universitats-Klinik, Wien, Austria. 4. Neurologische Abtlg. Fach-klin k Rhein/Rhur, Essen, West Germany. 5. LHK Mauer, Mauer, Austria.	Not applicable. Research report
879-201	Wessely 1987	1987	Full-paper	Wessely P, Baumgartner Ch, Klingler D, Kreczi J, Meyerson N, Sailer L, Saltuari L, Schutt P. Preliminary results of a double-blind study with the new migraine prophylactic drug gabapentin. Cephalalgia. 1987; 7 (Supplement 6): 477-478.	Investigator: Prof. Dr. med. Franz Gerstenbrand Dr. L. Saltuari Monitor: Nancy Meyerson, M. Phil. Substitute: Dr. med. Bernd Schmidt Biometrics: Klaus Stern, Dipl. Math.	1. Wessely P 2. Baumgartner Ch 3. Klingler D 4. Kreczi J 5. Meyerson N 6. Sailer L 7. Saltuari L 8. Schutt P	1 & 2. Neurologic University Clinic, Vienna, Austria. 3. General Hospital, Linz, Austria 4. Not mentioned. 5. Godecke, Freiburg, FRG. 6 & 7. Neurologic University Clinic, Innsbruck, Austria. 8. Fachklinik, Essen, FRG.	No funding source mentioned.

Study number	Publication code	Year	Type of report	Citation	Authors/ investigators (Protocol)	Authors/ investigators (Report)	Authors/ investigators locations (Report)	Funding source (Report)
945-217	945-217.RR	2000	Research report	Research report number RR 995-00085.	Amended protocol approval page signed by: Leslie Magnus-Miller. Parke-Davis Clinical/Medical Colleagues: Kim C. Caswell (Unsigned). Leslie Magnus-Miller (Unsigned). Parke-Davis Statistician: Paula J. Beitler (Unsigned). Principal Investigator: Unsigned. Co-investigator: Unsigned.	PD Author(s): Magnus-Miller L Bernstein P Caswell K Investigator(s): 1. Goldstein J 2. Sadowsky C 3. Hendin B 4. Kunkel R 5. Kudrow D 6. Silberstein S 7. Newman L 8. Couch J 9. Saper J 10. Rowbotham M 11. Rapoport A	1. San Francisco Headache Clinic, USA. 2. Palm Beach Neurological Group, USA. 3. Phoenix Neurological Associates, USA. 4. Cleveland Clinic Foundation, USA. 5. California Medical Clinic for Headache, USA. 6. Jefferson Headache Center, USA. 7. Montefiore Headache Unit, Albert Einstein College of Medicine, USA. 8. Oregon University of Health Sciences, USA. 9. Micihigan Head, Pain & Neurological Institute, USA. 10. UCSF Pain Clin. Research Ctr., USA. 11. New England Headache Center, USA.	Not applicable. Research report.

Study number	Publication code	Year	Type of report	Citation	Authors/ investigators (Protocol)	Authors/ investigators (Report)	Authors/ investigators locations (Report)	Funding source (Report)
945-220	945-220.RR	1999	Research report	Research report number RR 995-00074.	Parke-Davis Monitors: Leslie Magnus-Miller. Parke-Davis Statistician: Paula B. Podolnick. Parke-Davis Clinical Trials Manager: Kim C. Caswell.	PD Author(s): Magnus-Miller L Bernstein P Caswell K Investigator(s): 1. Mathew N 2. Saper J 3. Rapoport A 4. Klapper J 5. Tepper S 6. Stacey B 7. Ramadan N	1. Houston Headache Clinic, USA. 2. Michigan Head, Pain & Neurological Institute, USA. 3. New England Headache Center, USA. 4. Denver, CO, USA. No institute affiliation mentioned. 5. Seattle, WA, USA. No institute affiliation mentioned. 6. OHSU Pain Management Center, USA. 7. University of Cincinnati Headache Center, USA.	Not applicable. Research report.
945-220	Mathew 1998	1998	Conference abstract	Mathew NT. Efficacy and safety of gabapentin (Neurontin) in migraine prophylaxis. Presented as an abstract at the 17th Annual Meeting of the American Pain Society, 1998.	Parke-Davis Monitors: Leslie Magnus-Miller. Parke-Davis Statistician: Paula B. Podolnick. Parke-Davis Clinical Trials Manager: Kim C. Caswell.	Mathew NT	Not mentioned.	No funding source mentioned.

Study number	Publication code	Year	Type of report	Citation	Authors/ investigators (Protocol)	Authors/ investigators (Report)	Authors/ investigators locations (Report)	Funding source (Report)
945-220	Mathew 1999	1999	Conference abstract	Mathew NT, Magnus-Miller L, Saper J, Podolnick P, Klapper J, Tepper S, Stacey B, Rapoport A, Ramadan N. Efficacy and safety of gabapentin (Neurontin) in migraine prophylaxis. Cephalalgia. 1999; 19: 380. Presented as an abstract at the 9th Congress of the International Headache Society, 1999.	Parke-Davis Monitors: Leslie Magnus-Miller. Parke-Davis Statistician: Paula B. Podolnick. Parke-Davis Clinical Trials Manager: Kim C. Caswell.	1. Mathew NT 2. Magnus-Miller L 3. Saper J 4. Podolnick P 5. Klapper J 6. Tepper S 7. Stacey B 8. Rapoport A 9. Ramadan N	1 to 9. Not mentioned.	No funding source mentioned.
945-220	Mathew 2001	2001	Full-paper	Mathew NT, Rapoport A, Saper J, Magnus L, Klapper J, Ramadan N, Stacey B, Tepper S. Efficacy of gabapentin in migraine prophylaxis. Headache. 2001; 41: 119-128.	Parke-Davis Monitors: Leslie Magnus-Miller. Parke-Davis Statistician: Paula B. Podolnick. Parke-Davis Clinical Trials Manager: Kim C. Caswell.	1. Mathew NT 2. Rapoport A 3. Saper J 4. Magnus L 5. Klapper J 6. Ramadan N 7. Stacey B 8. Tepper S	1. Houston Headache Clinic, Texas, USA. 2. New England Headache Center, Stamford, USA. 3. Michigan Head Pain and Neurological Institute, Ann Arbor, USA. 4. Parke-Davis Medical Research, NJ, USA. 5. Colorado Neurology and Headache Center, Denver, USA. 6. University of Cincinnati, Ohio, USA. 7. Oregon Health Sciences University, Portland, USA. 8. The Polyclinic, Seattle, USA.	No funding source mentioned.

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Table 4 - Comparison of Study Reports by Participant Inclusion/Exclusion Criteria

Study number	Publication code	Type of report	Participant inclusion criteria (Protocol)	Participant inclusion criteria (Report)	Enrollment start date	Enrollment end date	Number of sites
879-201	879-201.RR	Research report	"Patients will have at least 8 migraine attacks per month." Common migraine. Resistant to prophylactic interval therapy. On no other prophylactic interval therapy. Case history and prior treatment records available. Amubulatory or hospitalized. Over 18 years of age. Female patients of child-bearing potential must use adequate contraception.	"Patients from Center 201 had to have at least 8 attacks per month to be included. For the patients of the other centers the minimum number of attacks was two attacks per month."	November 26, 1985	May 24, 1988	5
879-201	Wessely 1987	Full-paper	"Patients will have at least 8 migraine attacks per month." Common migraine. Resistant to prophylactic interval therapy. On no other prophylactic interval therapy. Case history and prior treatment records available. Amubulatory or hospitalized. Over 18 years of age. Female patients of child-bearing potential must use adequate contraception.	No inclusion criteria reported.	Not mentioned.	Not mentioned.	"multicenter trial"

Study number	Publication code	Type of report	Participant inclusion criteria (Protocol)	Participant inclusion criteria (Report)	Enrollment start date	Enrollment end date	Number of sites
945-217	945-217.RR	Research report	Male and female patients aged 16 to 75 years. Meet International Headache Society criteria for migraine 1.1 and 1.2. Female patients should not be pregnant or nursing. If sexually active, must use reliable method of contraception. Initial onset of migraine at least 6 months prior to screening. Three to eight migraine episodes per month for each of 3 months prior to screening. No prior prophylaxis for migraine or failed a trial for 1 month on no more than 2 prophylaxis regimes. No migraine prophylaxis at baseline for at least 5 half-lives of that medication. Able to comply with treatment and provide informed consent.	No deviations from protocol.	March 19, 1997	January 25, 1999	11
945-220	945-220.RR	Research report	Male and female patients aged 16 to 75 years. Meet International Headache Society criteria for migraine 1.1 and 1.2. Female patients should not be pregnant or nursing. If sexually active, must use reliable method of contraception. Initial onset of migraine at least 6 months prior to screening. Three to eight migraine episodes per month for each of 3 months prior to screening. No prior prophylaxis for migraine or failed a trial for 1 month on no more than 2 prophylaxis regimes. No migraine prophylaxis at baseline for at least 5 half-lives of that medication. Able to comply with treatment and provide informed consent.	No deviations from protocol.	November 5, 1996	March 10, 1998	7

Study number	Publication code	Type of report	Participant inclusion criteria (Protocol)	Participant inclusion criteria (Report)	Enrollment start date	Enrollment end date	Number of sites
945-220	Mathew 1998	Conference abstract	Male and female patients aged 16 to 75 years. Meet International Headache Society criteria for migraine 1.1 and 1.2. Female patients should not be pregnant or nursing. If sexually active, must use reliable method of contraception. Initial onset of migraine at least 6 months prior to screening. Three to eight migraine episodes per month for each of 3 months prior to screening. No prior prophylaxis for migraine or failed a trial for 1 month on no more than 2 prophylaxis regimes. No migraine prophylaxis at baseline for at least 5 half-lives of that medication. Able to comply with treatment and provide informed consent.	"Following screening 145 subjects (81% women) who experienced 3 - 8 migraine episodes per month and had failed no more than two prophylactic anti-migraine regimes were randomized"	Not mentioned.	Not mentioned.	"multi-center".
945-220	Mathew 1999	Conference abstract	Male and female patients aged 16 to 75 years. Meet International Headache Society criteria for migraine 1.1 and 1.2. Female patients should not be pregnant or nursing. If sexually active, must use reliable method of contraception. Initial onset of migraine at least 6 months prior to screening. Three to eight migraine episodes per month for each of 3 months prior to screening. No prior prophylaxis for migraine or failed a trial for 1 month on no more than 2 prophylaxis regimes. No migraine prophylaxis at baseline for at least 5 half-lives of that medication. Able to comply with treatment and provide informed consent.	"Following screening 145 subjects (81% women) who experienced 3 - 8 migraine episodes per month and had failed no more than two prophylactic anti-migraine regimes were randomized"	Not mentioned.	Not mentioned.	"multi-center".

Study number	Publication code	Type of report	Participant inclusion criteria (Protocol)	Participant inclusion criteria (Report)	Enrollment start date	Enrollment end date	Number of sites
945-220	Mathew 2001	Full-paper	Male and female patients aged 16 to 75 years. Meet International Headache Society criteria for migraine 1.1 and 1.2. Female patients should not be pregnant or nursing. If sexually active, must use reliable method of contraception. Initial onset of migraine at least 6 months prior to screening. Three to eight migraine episodes per month for each of 3 months prior to screening. No prior prophylaxis for migraine or failed a trial for 1 month on no more than 2 prophylaxis regimes. No migraine prophylaxis at baseline for at least 5 half-lives of that medication. Able to comply with treatment and provide informed consent.	No differences from protocol.	Not mentioned.	Not mentioned.	7

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Table 5 - Interventions and Run-in Phase

Study number	Publication code	Run-in phase (Protocol)	Run-in phase (Report)	Trial design	Total length of follow-up	Description of intervention	Treatment (gabapentin dose, duration, frequency) different from protocol
879-201	879-201.RR	No run-in phase mentioned.	No run-in phase mentioned. "At the first visit the patient was questioned concerning the number of attacks during the last three months. These retrospective data are referred to as "baseline" throughout this report."	Parallel-groups	12 weeks (Table 2 of the research report)	"Patients received placebo or 300 mg gabapentin capsules three times daily (7 a.m., 3 p.m., and 10 p.m.)."	☐
879-201	Wessely 1987	No run-in phase mentioned.	"After an initial washout period of 3 months all patients received either placebo or 3 x 300 mg gabapentin daily for another 3 months."	Parallel-groups	"3 months"	"After an initial wash-out period of 3 months all patients received either placebo or 3x300 mg Gabapentin daily for another 3 months."	☐
945-217	945-217.RR	"This study will consist of a 4-week single-blind baseline period, and a 12-week double-blind treatment period. During the 4-week baseline period, the patient will receive placebo in a single-blind manner (only the patient is blinded to the fact that the first 4 weeks of treatment are with placebo)."	"The 16-week study consisted of a 4-week single-blind baseline period and a 12-week double-blind treatment period." "Patients began the 4-week baseline period and were to have been given study medication (placebo) in a single-blinded manner."	Parallel-groups	"The 16-week study consisted of a 4-week single-blind baseline period and a 12-week double-blind treatment period."	"All patients were to have received placebo in a single-blinded manner during the 4-week basaeline period, which began following Visit 2 (Week -4)." "Each patient was to have been instructed to begin treatment with the nighttime dose of study medication on the night of Visit 3." "Study medication was to have been titrated up to 1800 mg/day during the following 4-week titration period." "Visit 4 began the stabilization period and no titration in study medication was to have been permitted between Visit 4 and study completion or dropout."	☐

Study number	Publication code	Run-in phase (Protocol)	Run-in phase (Report)	Trial design	Total length of follow-up	Description of intervention	Treatment (gabapentin dose, duration, frequency) different from protocol
945-220	945-220.RR	"This study will consist of a 4-week single-blind baseline period, and a 12-week double-blind treatment period. During the 4-week baseline period, the patient will receive placebo in a single-blind manner (only the patient is blinded to the fact that the first 4 weeks of treatment are with placebo)."	"The 16-week study consisted of a 4-week single-blind baseline period and a 12-week double-blind treatment period." "Patients began the 4-week baseline perido and were to have been given study medication (placebo) in a single-blinded manner."	Parallel-groups	"The 16-week study consisted of a 4-week single-blind baseline period and a 12-week double-blind treatment period."	"All patients were to have received placebo in a single-blinded manner during the 4-week baseline period, which began following Visit 2 (Week -4)." "Patients were to have been instructed to begin treatment with their nighttime dose of study medication on the night of Visit 3." "Study medication was to have been titrated up to 2400 mg/day during the following 4-week titration period." "Patients who could not tolerate 2400 mg/day were permitted to reduce their dose to 1800 mg/day, but no other dosage was to have been allowed." "Visit 4 began the stabilization period and no titration in study medication was permitted between Visit 4 and study completion or dropout." Differences: Table 4 lists 2 patients in gabapentin group as having received 2700 mg/day as "Final Stable Dose".	☑
945-220	Mathew 1998	"This study will consist of a 4-week single-blind baseline period, and a 12-week double-blind treatment period. During the 4-week baseline period, the patient will receive placebo in a single-blind manner (only the patient is blinded to the fact that the first 4 weeks of treatment are with placebo)."	"The study consisted of a 1-week screening phase a 4-week single-blind placebo baseline phase a 4-week titration phase and an 8-week stable dosing phase."	Parallel-groups	16 weeks. "The study consisted of a 1-week screening phasea 4-week single-blind placebo baseline phasea 4-week titration phase and an 8-week stable dosing phase."	"During the titration phasea dose-escalation of gabapentin up to 2400mg daily or matching placebo was administered."	☐

Study number	Publication code	Run-in phase (Protocol)	Run-in phase (Report)	Trial design	Total length of follow-up	Description of intervention	Treatment (gabapentin dose, duration, frequency) different from protocol
945-220	Mathew 1999	"This study will consist of a 4-week single-blind baseline period, and a 12-week double-blind treatment period. During the 4-week baseline period, the patient will receive placebo in a single-blind manner (only the patient is blinded to the fact that the first 4 weeks of treatment are with placebo)."	"The study consisted of a 1-week screening phase, a 4-week single-blind placebo baseline phase, a 4-week titration phase and an 8-week stable dosing phase."	Parallel-groups	16 weeks. "The study consisted of a 1-week screening phase, a 4-week single-blind placebo baseline phase, a 4-week titration phase and an 8-week stable dosing phase."	"During the titration phase, a dose-escalation of gabapentin up to 2400mg daily or matching placebo was administered."	☐
945-220	Mathew 2001	"This study will consist of a 4-week single-blind baseline period, and a 12-week double-blind treatment period. During the 4-week baseline period, the patient will receive placebo in a single-blind manner (only the patient is blinded to the fact that the first 4 weeks of treatment are with placebo)."	"Because of this high placebo response, a single-blind placebo phase was included in the study in an attempt to diminish the placebo response rate. During the single-blind phase, patients received one placebo capsule, taken in the evening for 4 weeks."	Parallel-groups	16 weeks. "After screening, there was a 4-week, single-blind, placebo baseline period followed by a 12-week, double-blind, treatment period."	"During the single-blind phase, patients received one placebo capsule, taken in the evening for 4 weeks." "During the 4-week titration phase, patients were started on one 300-mg capsule of gabapentin or matching placebo." "Patients were titrated to three capsules per day (end of week 1), five capsules per day (end of week 2), seven capsules per day (end of week 3), and eight capsules per day (end of week 4) in order to achieve the 2400 mg/day dose by the completion of the titration phase." "If a patient was unable to tolerate the 2400 mg/day dose, the dose was reduced to 1800 mg/day." "However, the patient had to be receiving a stable dose of study medication by the end of the titration period." "Study medication was to be given on a three-times-a-day dosing regimen."	☐

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Table 6 - Risk of Bias

Study number	Publication code	Random allocation (Protocol)	Random allocation (Report)	Method of allocation (Protocol)	Method of allocation (Report)	Concealment of allocation (Protocol)	Concealment of allocation (Report)	Method of allocation concealment (Report)	Double-blind (Protocol)	Double-blind (Report)	Blinding: Notes (Protocol)	Blinding: Notes (Report)
879-201	879-201.RR	☐	☑	"The patient number is assigned in numerical sequence corresponding to the temporal recruitment of the patient in the treatment phase. The first patient is assigned No. 1, the next patient recruited is assigned No. 2, etc." "Drop-outs are to be replaced until 40 evaluable cases have been completed."	"Patients were randomized to treatment (method: permuted blocks) with a blocking factor of 10. Each center was randomized separately."	☐	☐	No description of any attempt to conceal allocation.	☑	☑	No description on who was blinded.	No description on who was blinded.

Study number	Publication code	Random allocation (Protocol)	Random allocation (Report)	Method of allocation (Protocol)	Method of allocation (Report)	Concealment of allocation (Protocol)	Concealment of allocation (Report)	Method of allocation concealment (Report)	Double-blind (Protocol)	Double-blind (Report)	Blinding: Notes (Protocol)	Blinding: Notes (Report)
879-201	Wessely 1987	☐	☐	"The patient number is assigned in numerical sequence corresponding to the temporal recruitment of the patient in the treatment phase. The first patient is assigned No. 1, the next patient recruited is assigned No. 2, etc." "Drop-outs are to be replaced until 40 evaluable cases have been completed."	Not mentioned.	☐	☐	No description of any attempt to conceal allocation.	☑	☑	No description on who was blinded.	No description on who was blinded.
945-217	945-217.RR	☑	☑	Not mentioned.	Not mentioned.	☐	☐	No description of any attempt to conceal allocation.	☑	☑	No description on who was blinded in double-blind study phase.	No description on who was blinded in double-blind study phase.
945-220	945-220.RR	☑	☑	Not mentioned.	Not mentioned.	☐	☐	No description of any attempt to conceal allocation.	☑	☑	No description on who was blinded in double-blind study phase.	No description on who was blinded in double-blind study phase.
945-220	Mathew 1998	☑	☑	Not mentioned.	Not mentioned.	☐	☐	No description of any attempt to conceal allocation.	☑	☑	No description on who was blinded in double-blind study phase.	No description on who was blinded in double-blind study phase.

Study number	Publication code	Random allocation (Protocol)	Random allocation (Report)	Method of allocation (Protocol)	Method of allocation (Report)	Concealment of allocation (Protocol)	Concealment of allocation (Report)	Method of allocation concealment (Report)	Double-blind (Protocol)	Double-blind (Report)	Blinding: Notes (Protocol)	Blinding: Notes (Report)
945-220	Mathew 1999	☑	☑	Not mentioned.	Not mentioned.	☐	☐	No description of any attempt to conceal allocation.	☑	☑	No description on who was blinded in double-blind study phase.	No description on who was blinded in double-blind study phase.
945-220	Mathew 2001	☑	☑	Not mentioned.	"Each investigator was provided with "blinded" medication, according to a computer-generated randomization schedule prepared by Parke-Davis before the beginning of the trial." "Patients were randomized in a 2:1 ratio using a block size of six stratified by center."	☐	☐	No description of any attempt to conceal allocation.	☑	☑	No description on who was blinded in double-blind study phase.	"During the double-blind phase, investigators, patients, study monitors, and observers were blinded to codes until after the clinical database was locked."

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Table 7 - Primary Outcome and Number of Patients Assessed

Study number	Publication code	Primary outcome (protocol)	Primary outcome (Report)	Number randomized per group (Report)	Number analyzed per group - Primary outcome (Report)	Number analyzed per group for safety (Report)	Definitions for study population for analysis (Report)
879-201	879-201.RR	"The arithmetic mean of the difference between attack frequency at the start of treatment and the end of treatment is different in the two groups." [Appendix E]	"The primary efficacy criterion was the reduction of the number of migraine attacks from the retrospective 3-month baseline to treatment. To take into account the patients' varying length of treatment, the number of attacks was calculated on a 28-day basis."	44 Gabapentin / 43 Placebo. [Two patients not randomized but treated with gabapentin in an open-label fashion were included for a reported number of 46 in gabapentin group.] "All data collected are presented in the patient listings and summary tables, even if the patient had not been randomized to treatment but was given gabapentin on an open label basis (Patients 92 (879-205) and 93 (879-207))."	Efficacy analysis: 22 Gabapentin / 31 Placebo Intention to treat analysis: 42 Gabapentin / 41 Placebo	46 Gabapentin / 43 Placebo.	Eligibility for "Efficacy analysis" or "Evaluable Patients": "Patients were excluded from efficacy if they continued taking prophylactic migraine medication or did not stop it at least one month before start of treatment." "According to the protocol, treatment should have lasted 12 weeks, but no minimum duration was prescribed. The adopted limit of 28 days is somewhat arbitrary, but judged sufficient to shown an effect if it was present. (1)" Intention to treat analysis patients: "In the intent-to-treat analysis all patients were included who had received at least a single dose of study medication." "Two patients in each group were excluded from the intent-to-treat analysis because no data on the number of attacks are available or because they had never taken the test medication which had been handed out to them." Safety analysis: "All patient data were used for safety evaluations regardless of length of treatment and whether or not randomized."

Study number	Publication code	Primary outcome (protocol)	Primary outcome (Report)	Number randomized per group (Report)	Number analyzed per group - Primary outcome (Report)	Number analyzed per group for safety (Report)	Definitions for study population for analysis (Report)
879-201	Wessely 1987	"The arithmetic mean of the difference between attack frequency at the start of treatment and the end of treatment is different in the two groups." [Appendix E]	"The frequency of migraine attacks was reduced from 6.5 to 4.1 per month in the Gabapentin-group. Especially the cumulative distribution of percent reduction of migraine attacks showed a marked trend in favour of the Gabapentin group (see fig. 1)."	22 Gabapentin / 23 Placebo. "Up to February 1987 45 patients (5 males, 40 females, aged 43±10 years) have been investigated."	14 Gabapentin / 19 Placebo	Not mentioned.	Drop-outs: "..the other patients were drop-outs because of either non-compliance (n=6 for Gabapentin, n=3 for placebo) or side effects (nausea, tiredness, dizziness) (n=2 for Gabapentin, n=1 for placebo)."

Study number	Publication code	Primary outcome (protocol)	Primary outcome (Report)	Number randomized per group (Report)	Number analyzed per group - Primary outcome (Report)	Number analyzed per group for safety (Report)	Definitions for study population for analysis (Report)
945-217	945-217.RR	"Four week migraine headache rate during Stabilization Period 2 calculated as [(headache count during Stabilization period) / (# of Stabilization Period days) - (number of days in unreliable intervals)] X 28 Unreliable intervals are those for which the patient did not return a diary." "The primary analysis will be performed using the evaluable patient population."	"The primary efficacy endpoints were the 4-week migraine headache rate during stabilization period 2 and change from baseline to stabilization period 2 in the 4-week migraine headache rate in efficacy evaluable patients."	102 Gabapentin / 55 Placebo	Modified Intention to Treat: 76 Gabapentin / 46 Placebo Efficacy Evaluable: 65 Gabapentin / 37 Placebo	95 Gabapentin / 55 Placebo.	"Modified Intention to Treat Population": - "Randomized into the trial," - "Completed the titration period," - "Took at least one dose of study medication during stabilization period 2," - "Provided complete diary data for at least one day during the baseline period (i.e., the 28 days prior to baseline visit), and" - "Provided complete diary data for at least one day during stabilization period 2. "Efficacy Evaluable Population": - "Included in the MITT population," - "Took at least 75% of study medication during participatin in stabilization period 2 or discontinued the study during stabilization period 2 due to treatment failure," - "Took at least 50% of study medication during stabilization period 1," - Did not use concomitant migraine prophylactic medication," - "Provided complete diary data for at least four days/week during the baseline period (i.e., the 28 days prior to baseline visit)," - "Provided complete diary data for at least four days/week during stabilization period 2 or discontinued due to treatment failure," - "Achieved a stable dose of 1800 mg/day during stabilization periods 1 and 2," - "Had a baseline period of at least 25 days on placebo, and" - "Had at least 25 days in stabilization period 2 or discontinued due to treatment failure." "Safety Evaluable Population": - "Took at least one dose of study medication, and" - "Provided at least one post-baseline assessment."

Study number	Publication code	Primary outcome (protocol)	Primary outcome (Report)	Number randomized per group (Report)	Number analyzed per group - Primary outcome (Report)	Number analyzed per group for safety (Report)	Definitions for study population for analysis (Report)
945-220	945-220.RR	"Four week migraine headache rate during Stabilization Period 2 calculated as [(headache count during Stabilization period) / (# of Stabilization Period days) - (number of days in unreliable intervals)] X 28 Unreliable intervals are those for which the patient did not return a diary." "The primary analysis will be performed using the evaluable patient population."	"The primary efficacy endpoints were the 4-week migraine headache rate during stabilization period 2 and change from baseline to stabilization period 2 in the 4-week migraine headache rate in efficacy evaluable patients."	99 Gabapentin / 46 Placebo	Modified Intention to Treat: 77 Gabapentin / 36 Placebo Efficacy Evaluable: 62 Gabapentin / 33 Placebo	98 Gabapentin / 45 Placebo.	"Modified Intention to Treat Population": - "Randomized into the trial," - "Completed the titration period," - "Took at least one dose of study medication during stabilization period 2," - "Provided complete diary data for at least one day during the baseline period (i.e., the 28 days prior to baseline visit), and" - "Provided complete diary data for at least one day during stabilization period 2." "Efficacy Evaluable Population": - "Included in the MITT population," - "Took at least 75% of study medication during participatin in stabilization period 2 or discontinued the study during stabilization period 2 due to treatment failure," - "Took at least 50% of study medication during stabilization period 1," - Did not use concomitant migraine prophylactic medication," - "Provided complete diary data for at least four days/week during the baseline period (i.e., the 28 days prior to baseline visit)," - Provided complete diary data for at least four days/week during stabilization period 2 or discontinued due to treatment failure," - Achieved a stable dose of 1800-2400 mg/day during stabilization periods 1 and 2," - Had a baseline period of at least 25 days on placebo, and" - Had at least 25 days in stabilization period 2 or discontinued due to treatment failure." "Safety Evaluable Population": "Patients who met all the following criteria were included in the safety evaluable population": - "Took at least one dose of study medication, and" - "Provided at least one post-baseline assessment."

Study number	Publication code	Primary outcome (protocol)	Primary outcome (Report)	Number randomized per group (Report)	Number analyzed per group - Primary outcome (Report)	Number analyzed per group for safety (Report)	Definitions for study population for analysis (Report)
945-220	Mathew 1998	"Four week migraine headache rate during Stabilization Period 2 calculated as [(headache count during Stabilization period) / (# of Stabilization Period days) - (number of days in unreliable intervals)] X 28 Unreliable intervals are those for which the patient did not return a diary." "The primary analysis will be performed using the evaluable patient population."	"The primary efficacy measurement was the migraine headache rate during the fnal 4-week stabilization phase (S2)."	99 Gabapentin / 46 Placebo	Not mentioned.	Not mentioned.	No definitions mentioned.
945-220	Mathew 1999	"Four week migraine headache rate during Stabilization Period 2 calculated as [(headache count during Stabilization period) / (# of Stabilization Period days) - (number of days in unreliable intervals)] X 28 Unreliable intervals are those for which the patient did not return a diary." "The primary analysis will be performed using the evaluable patient population."	"The primary efficacy measurement was the migraine headache rate during the fnal 4-week stabilization phase (S2)."	99 Gabapentin / 46 Placebo	Not mentioned.	Not mentioned.	No definitions mentioned.

Study number	Publication code	Primary outcome (protocol)	Primary outcome (Report)	Number randomized per group (Report)	Number analyzed per group - Primary outcome (Report)	Number analyzed per group for safety (Report)	Definitions for study population for analysis (Report)
945-220	Mathew 2001	"Four week migraine headache rate during Stabilization Period 2 calculated as [(headache count during Stabilization period) / (# of Stabilization Period days) - (number of days in unreliable intervals)] X 28 Unreliable intervals are those for which the patient did not return a diary." "The primary analysis will be performed using the evaluable patient population."	"The primary outcome measure was the 4-week migraine rate during stabilization period 2 ([SP2] the last 4 weeks of the stable-dosing period) for patients who had received a stable dose of 2400 mg/day."	99 Gabapentin / 46 Placebo	Modified Intention to Treat: 56 Gabapentin / 31 Placebo	98 Gabapentin / 45 Placebo.	Modified Intent to Treat: "This population included any patient who was randomized, took at least one dose of study medication during SP2, maintained a stable dose of 2400 mg/day during SP2, had baseline migraine headache data and at least 1 day of migraine headache evaluations during SP2."

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Table 8 - Comparison of Study Reports by Results and Conclusions

Study number	Publication code	Results of primary analysis (Report)	Adverse events (Results section of Report)	Conclusions in abstract & discussion sections (Report)	Conclusions in discussion consistent with results (Report)	Conclusions in abstract consistent with results (Report)
879-201	879-201.RR	Results section of report (Section 6.2.2.1. Reduction in migraine attacks from baseline to treatment): "The reduction in attacks is significantly dependent on baseline values (p = 0.004). Treatment is not significant (p = 0.72)." (Section 6.2.4. Intent-to-treat Analysis): "In an intent-to-treat analysis the mean response ratio was -0.109 for the placebo group and -0.242 in the gabapentin group which was statistically significant (p=0.04)." "The mean of the placebo group is close to the mean of the efficacy sample (-0.093), while there is some difference between the two means in the gabapentin group (efficacy: mean -0.170). The difference is due to the exclusion of gabapentin patients whose reduction in the number of attacks was above average (see 6.2.2.4)." Abstract of report: "There was no statistically significant difference in the adjusted mean reduction in migraine attack frequency between the placebo (0.7) and gabapentin (1.4) treatment groups, or in the response ratio (difference in attack frequency from a retrospective three-month baseline to treatment divided by the sum of attacks during baseline and treatment) between the placebo (-0.093) and gabapentin (-0.170) groups."	"The percentages of patients with adverse events are comparable in both treatment groups (20.9% for placebo, 23.9% for gabapentin)." "The four patients who had severe adverse events and two other patients were withdrawn from the study are discussed in section 6.3.1.7., Withdrawals Due to Adverse Events." [This section descr bed each of the 6 patients with the following adverse events (treatment group): "moderate nausea" (placebo); "mild headache" (gabapentin); "modest gastric pain" (gabapentin); "mild nausea, but severe gait problems, dizziness, concentration impairment and tinnitus" (gabapentin); "severe muscle spasm and muscle twitching" (gabapentin); "severe gastric pain" (gabapentin); "severe hyperthyroid state" (gabapentin). Table 14 lists adverse events (percentages in parentheses for gabapentin / placebo): "Weight Increase" (0/2.3); "Fatigue" (2.2/4.7); "Headache" (2.2/2.3); "Dyspepsia" (0/2.3); Nausea &/or Vomiting (8.7/7.0); "Flatulence" (2.2/0); "Abdominal Pain" (4.3/2.3); "Hyperthyroid" (2.2/0); "Hypertonia" (2.2/0); "Ataxia" (2.2/0); "Confusion" (2.2/0); "Dizziness" (13/4.7); "Tremor" (2.2/0); "Hyperkinesia" (0/2.3); "Twitching" (2.2/0); "Paresthesia" (0/2.3); "Thinking Abnormal" (4.3/0); "Rash" (0/2.3); "Tinnitus" (2.2/0).	Abstract of report: "Gabapentin is well tolerated in patients with common migraine, but these data are not sufficient to permit conclusions regarding efficacy." Discussion section of report: "In conclusion, gabapentin showed marginal efficacy at best as prophylactic therapy in the treatment of common migraine in this study." Conclusions section of report: "Gabapentin is well tolerated in patients with common migraine, but these data are not sufficient to permit conclusions regarding efficacy."	☑	☑

Study number	Publication code	Results of primary analysis (Report)	Adverse events (Results section of Report)	Conclusions in abstract & discussion sections (Report)	Conclusions in discussion consistent with results (Report)	Conclusions in abstract consistent with results (Report)
879-201	Wessely 1987	"The frequency of migraine attacks was reduced from 6.5 to 4.1 per month in the Gabapentin-group and from 4.3 to 4.0 in the placebo group."	"33 patients were analysed (n= 14 for Gabapentin, n= 19 for placebo), the other patients were drop-outs because of either non-compliance (n=6 for Gabapentin, n=3 for placebo) or side effects (nausea, tiredness, dizziness) (n=2 for Gabapentin, n=1 for placebo)."	Abstract of report: The report had no abstract. Text of report [There was no distinction between results, discussion and conclusions sections]: "Further investigations are needed to get more conclusive results."	☐	☐

Study number	Publication code	Results of primary analysis (Report)	Adverse events (Results section of Report)	Conclusions in abstract & discussion sections (Report)	Conclusions in discussion consistent with results (Report)	Conclusions in abstract consistent with results (Report)
945-217	945-217.RR	Results section of report (Section 6.1.1. Four-Week Migraine Headache Rate): "As shown in Table 11, the median 4-week migraine headache rate at baseline was 5.0 for the efficacy evaluable patients in both the placebo group and the Neurontin® group (p=0.579)." "At stabilization period 2, the median rates were 3.0 and 3.7 (p=0.432) and the median changes from baseline were -1.7 and -1.4 for the placebo and the Neurontin® groups, respectively (p=0.583)." "No statistically significant treatment differences were observed at any study period (p≥0.081)."	"Treatment-emergent adverse events led to premature discontinuation in 13% (7/55) of patients in the placebo group and 17% (16/95) of patients in the Neurontin® group (p=0.64)." "The most frequently reported adverse events were asthenia, somnolence, infection and dizziness. Asthenia was reported by 11% (6/55) and 8% (8/95) of patients in the placebo and Neurontin® groups, respectively (p=0.772)." "Somnolence was reported by 5% (3/55) of placebo patients and 15% (14/95) of Neurontin® patients (p=0.110)." "Thirteen percent (7/55) of patients in the placebo group and no patients in the Neurontin® group reported infection (p<0.001)." "Dizziness occurred in a significantly (p=0.001) higher proportion of patients treated with Neurontin® (24%; 23/95) than in those treated with placebo (4%; 2/55)." "Thinking abnormal was reported for 7% (7/95) of patients in the Neurontin® group and no patient in the placebo group (p=0.048)." There were no other significant differences between the two treatment groups with respect to the frequency of the occurrence of individual adverse events." "Significantly (p<0.001) more patients in the Neurontin® group (47% [45/95]) experienced adverse events affecting the nervous system compared with placebo patients (20% [11/55])."	Abstract of report: The report had no abstract. Discussion section of report: "This study did not conclusively show improvements in migraine headache rate or in the quality of life with Neurontin treatment among the efficacy evaluable patients." Conclusions section of report: "In the efficacy evaluable population, no statistically significant differences were seen at any study period between the placebo and Neurontin® groups with respect to 4-week migraine headache rates;" "In the MITT population, a statistically significant difference favoring the Neurontin® group was seen during the stabilization period 1 for median and median change from baseline with respect to 4-week migraine headache rates (p≤0.034);"	☐	☑

Study number	Publication code	Results of primary analysis (Report)	Adverse events (Results section of Report)	Conclusions in abstract & discussion sections (Report)	Conclusions in discussion consistent with results (Report)	Conclusions in abstract consistent with results (Report)
945-220	945-220.RR	Results section of report (Section 6.1.1. Four-Week Migraine Headache Rate): "Pooling of centers was performed for Centers 5 and 7 for the efficacy evaluable analysis and the MITT [Modified Intention to Treat] analysis." "As shown in Table 11, the median baseline 4-week migraine headache rates were 4.3 and 4.6, respectively, for the efficacy evaluable patients in the placebo and the Neurontin® groups (p=0.277)." "At stabilization period 2, the median rates were 3.4 and 2.7 (p=0.171) and the median changes from baseline were -1.0 and -1.6 (p=0.332), respectively for the placebo and the Neurontin® groups." "No statistically significant treatment differences were observed at any study period (p≥0.171)." "As shown in Table 12, among the MITT patients, the median baseline rates were 4.3 and 4.1, respectively, for the placebo and the Neurontin® groups (p=0.474). At stabilization period 2, the median rates were statistically significantly lower for the Neurontin® group (2.7) compared to the placebo group (3.4, p=0.045). "The median changes from baseline at stabilization period 2 were -0.9 and -1.7 (p=0.113), respectively, for the placebo and Neurontin® groups."	"The most frequently reported adverse events were asthenia, infection, dizziness, and somnolence. Asthenia was reported for 27% (12/45) and 22% (22/98) of patients in the placebo and Neurontin® groups, respectively (p=0.673); infection was reported for 24% (p=0.049)." "Both dizziness and somnolence occurred more frequently in patients treated with Neurontin®: dizziness was reported for 11% (5/45) of placebo patients and 26% placebo patients and 24% (24/98) of Neurontin® patients (p=0.075)." "No adverse event occurred in a statistically significantly higher proportion of patients in the Neurontin® group than in the placebo group." "A significantly (p=0.043) higher percentage of patients in the Neurontin® group (67%; 66/98) experienced treatment-emergent associated adverse events than in the placebo group (49%; 22/45)." "The percentage of patients who experienced associated adverse events within the nervous system was significantly higher (p=0.031) in the Neurontin® group (51%; 50/98) than in the placebo group (31%; 14/45)."	Abstract of report: The report had no abstract. Discussion section of report: "This study did not conclusively show improvements in migraine headache rate or in the quality of life with Neurontin treatment among the efficacy evaluable patients." Conclusions section of report: "In the efficacy evaluable population, no statistically significant differences were seen at any study period between the placebo and Neurontin® groups with respect to 4-week migraine headache rates;" "A statistically significant (p=0.045) lower median migraine headache rate was seen in the Neurontin® group compared to the placebo group in the MITT [Modified Intention to Treat] population during stabilization period 2."	☑	☑
945-220	Mathew 1998	Conference abstract: "Preliminary results indicate that during S2subjects receiving gabapentin had a median headache rate of 2.7 versus 3.3 in the placebo group (P=0.03)."	"The two treatment groups were comparable with respect to treatment-limiting adverse events."	Conference abstract: "Thusgabapentin [sic] is demonstrated to be an effective and safe prophylactic treatment for migraine headaches."	☐	☐

Study number	Publication code	Results of primary analysis (Report)	Adverse events (Results section of Report)	Conclusions in abstract & discussion sections (Report)	Conclusions in discussion consistent with results (Report)	Conclusions in abstract consistent with results (Report)
945-220	Mathew 1999	Conference abstract: Preliminary results indicate that during S2, subjects receiving gabapentin had a median headache rate of 3.1 versus 3.6 in the placebo group (p<0.05)."	"The two treatment groups were comparable with respect to treatment-limiting adverse events."	Conference abstract: "Thus, gabapentin is demonstrated to be an effective and safe prophylactic treatment for migraine headaches."	☐	☐
945-220	Mathew 2001	Results section of report: "The migraine headache rate during the second 4 weeks of the SP2 [stabilization phase 2] for patients maintaining a stable dose of 2400 mg/day gabapentin is presented in Table 3 for the placebo- and gabapentin-treated groups." "There was a statistically significant difference (P = 0.006) between treatment groups at the end of the SP2 for the primary efficacy parameter." Abstract of report: "At the end of the 12-week treatment phase, the median 4-week migraine rate was 2.7 for the gabapentin-treated patients maintained on a stable dose of 2400 mg/day and 3.5 for placebo-treated patients (P=0.006), compared with 4.2 and 4.1, respectively, during the baseline period." "The median change in 4-week headache rate was statistically significant as well (P=0.013)."	"Adverse events occurring in more than 10% of the gabapentin-treated patients are presented in Table 4." Table 4 lists (percentages in parentheses for Gabapentin / Placebo): dizziness (25.5/11.1); somnolence (24.5/11.1); asthenia (22.4/26.7); infection (11.2/24.4). "Adverse events considered to be associated with drug treatment resulted in patient withdrawal in 13 of 98 (13.3%) gabapentin-treated patients and 3 of 45 (6.7%) placebo-treated patients." "Among gabapentin-treated patients, asthenia, dizziness, and somnolence were the only adverse events that resulted in study withdrawal in more than one patient."	Abstract of report: "Gabapentin is an effective prophylactic agent for patients with migraine." "In addition, gabapentin appears generally well tolerated with mild to moderate somnolence and dizziness." "Comments" section of report: "This controlled clinical trial demonstrated that gabapentin was effective as a prophylactic agent in reducing the frequency of headaches in patients with migraine." "Given the efficacy of gabapentin in migraine prophylaxis and its good tolerability profile, it should be considered an important addition in the management of patients who are candidates for migraine prophylaxis."	☐	☐

Psychiatric Disorders
Table 1 - Table of Citations

Study Number	Publication code	Type of report	Citation (Report)
945-209			
	945-209.RR	Research report	Research report number RR 720-04174.
	Pande 2000b	Full-paper	Pande AC, Crockatt JG, Janney CA, Werth JL, Tsaroucha G., Gabapentin Bipolar Disorder Study Group. Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. Bipolar Disorders. 2000; 2: 249-255.
945-250			
	Wang 2002	Full-paper	Wang PW, Santosa C, Schumacher M, Winsberg ME, Strong C, Ketter TA. Gabapentin augmentation therapy in bipolar depression. Bipolar Disorders. 2002; 4: 296-301.
945-291			
	945-291.Final Study Report	Research report	Final Study Report 945-291.
	Vieta 2006	Full-paper	Vieta E, Goikolea JM, Martinez-Aran A, Comes M, Verger K, Masramon X, Sanchez-Moreno J, Colom F. A double-blind, randomized, placebo-controlled, prophylaxis study of adjunctive gabapentin for bipolar disorder. Journal of Clinical Psychiatry. 2006; 67(3): 473-477.

Psychiatric Disorders
Table 2 - Summary of Reporting Biases

Study number	Publication code	Protocol available	Date of research report (internal)	Date of last enrollment or end date for "Period(s) covered" per research report	Type of results	Location of publication	Results of primary analysis per research report	Secondary outcome (protocol) reported as primary outcome (report)	Reported analyses on selective populations as primary analysis	Publication bias (negative results and no publication final result)	Conclusions of efficacy consistent with primary analysis result (Conclusions section - report)	Conclusions of safety consistent with analysis of adverse events (Conclusions section - report)
945-209	Pande 2000b	☑	March 26, 1999.	July 1997.	Final results	Journal article	"Negative"	No	Yes	☐	Yes	Yes
945-250	Wang 2002	☑	Not available.	Not available.	Final results	Journal article	"Positive"	No	No	☐	Yes	Yes
945-291	Vieta 2006	☐	June 22, 2004.	February 2004.	Final results	Journal article	"Negative"	NA[1]	Unclear[2]	☐	No	Yes

1 NA = Not Applicable; no protocol available

2 Unclear: Analysis population not mentioned or was unclear

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Table 3 - Comparison of Study Reports by Authors and Funding Source

Study number	Publication code	Year	Type of report	Citation	Authors/ investigators (Protocol)	Authors/ investigators (Report)	Authors/ investigators locations (Report)	Funding source (Report)
945-209	945-209.RR	1999	Research report	Research report number RR 720-04174.	Principal Investigator: Lori Altshuler Coinvestigator: Robert Gerner Parke-Davis Clinical Monitors: Atul C. Pande Jerri G. Crockatt Lisa Greek-Donnellan Parke-Davis Biometrician: Noel Mohberg	PD Authors: Crockatt J Janney C Pande AC Werth JL Investigators [listed on the title page of report]: 1. L. Altshuler 2. G. B. Kaplan 3. C. L. Bowden 4. J. R. Calabrese 5. D. L. Dunner 6. L. Gyulai 7. R. Hirschfeld 8. S. L. McElroy 9. T. Ketter 10. G. Sachs 11. P. Suppes 12. C. Zarate 13. J. Zajecka 14. R. B. Lydiard [Additional investigators listed in Appendix A.1 but not the title page of report]: 15. Gerner R 16. Rhodes L 17. Shelton M 18. Hendrickson H 19. Keck PE	Appendix A.1 lists the following: 1 & 15. "VA Med Ctr, West LA, Los Angeles, CA". 2. VA Medical Center, Providence RI. 3 & 16. "Univ of Texas Health Science Center", San Antonio, TX. 4 & 17. "Mood Disorder Program", Cleveland, OH. 5 & 18. University of Washington Medical Center, Seattle, WA. 6. University of Pennsylvania Medical Center, Philadelphia, PA. 7. University of Texas Medical Branch, Galveston, TX. 8 & 19. Biological Psychiatry Program, College of Medicine, Cincinnati, OH. 9. Stanford School of Medicine, Stanford, CA. 10. Massachusetts General Hospital, Boston, MA. 11. UT Southwest Medical Center, Dallas TX. 12. McLean Hospital, Belmont, MA. 13. Women's Board Depression Treatment & Research Center, Chicago, IL. 14. Department of Psychiatry & Behavioral Sciences, Clinical Research Section, Charleston, SC.	Not applicable. Research report.

Study number	Publication code	Year	Type of report	Citation	Authors/ investigators (Protocol)	Authors/ investigators (Report)	Authors/ investigators locations (Report)	Funding source (Report)
945-209	Pande 2000b	2000	Full-paper	Pande AC, Crockatt JG, Janney CA, Werth JL, Tsaroucha G., Gabapentin Bipolar Disorder Study Group. Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. Bipolar Disorders. 2000; 2: 249-255.	Principal Investigator: Lori Altshuler Coinvestigator: Robert Gerner Parke-Davis Clinical Monitors: Atul C. Pande Jerri G. Crockatt Lisa Greek-Donnellan Parke-Davis Biometrician: Noel Mohberg	1. Atul C Pande 2. Jerri G Crockatt 3. Carol A Janney 4. John L Werth 5. Georgia Tsaroucha 6. Gabapentin Bipolar Disorder Study Group [Footnote]: "The following are members of the Gabapentin Bipolar Disorder Study Group: 7. L. Altshuler 8. R. Gerner 9. C.L. Bowden 10. L. Rhodes 11. J.R. Calabrese 12. M. Shelton 13. D.L. Dunner 14. H. Hendrickson 15. L. Gyulai 16. R. Hirschfeld 17. G.B. Kaplan 18. T. Ketter 19. R.B. Lydiard 20. S.L. McElroy 21. P.E. Keck, Jr 22. G. Sachs 23. P. Suppes 24. J. Zajecka 25. C. Zarate	"Atul C Pande, Jerri G Crockatt, Carol A Janney, John L Werth, Georgia Tsaroucha and Gabapentin Bipolar Disorder Study Group2[superscript] Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, MI 48105, USA" 7 & 8. Los Angeles, CA 9 & 10. San Antonio, TX 11 & 12. Cleveland, OH 13 & 14. Seattle, WA 15. Philadelphia, PA 16. Galveston, TX 17. Providence, RI 18. Stanford, CA 19. Charleston, SC 20 & 21. Cincinnati, OH 22. Boston, MA 23. Dallas, TX 24. Chicago, IL 25. Belmont, MA	"This study was funded by the Parke-Davis Research Division of Warner-Lambert Company."

Study number	Publication code	Year	Type of report	Citation	Authors/ investigators (Protocol)	Authors/ investigators (Report)	Authors/ investigators locations (Report)	Funding source (Report)
945-250	Wang 2002	2002	Full-paper	Wang PW, Santosa C, Schumacher M, Winsberg ME, Strong C, Ketter TA. Gabapentin augmentation therapy in bipolar depression. Bipolar Disorders. 2002; 4: 296-301.	Principal Investigator: 1. Terence A. Ketter Co-investigator(s): 2. Mirene E. Winsberg 3. Sallie G. DeGolia 4. Magdolna Dunai 5. Colleen O'Meara 6. Debbie L. Tate 7. Connie M. Strong Parke-Davis Contact: 8. Diana Ryan	1. Wang PW 2. Santosa C 3. Schumacher M 4. Winsberg ME 5. Strong C 6. Ketter TA	All authors: Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA	"This study was supported by a research grant from Pfizer, Inc."
945-291	945-291.Final Study Report	Not mentio-ned.	Research report	Final Study Report 945-291.	Protocol not available.	Not mentioned in available documents.	Not mentioned in available documents.	Not applicable. Research report (Final Study Report).

Study number	Publication code	Year	Type of report	Citation	Authors/ investigators (Protocol)	Authors/ investigators (Report)	Authors/ investigators locations (Report)	Funding source (Report)
945-291	Vieta 2006	2006	Full-paper	Vieta E, Go kolea JM, Martinez-Aran A, Comes M, Verger K, Masramon X, Sanchez-Moreno J, Colom F. A double-blind, randomized, placebo-controlled, prophylaxis study of adjunctive gabapentin for bipolar disorder. Journal of Clinical Psychiatry. 2006; 67(3): 473-477.	Protocol not available.	1. Eduard Vieta 2. Jose Manuel Goikolea 3. Anabel Martinez-Aran 4. Merce Comes 5. Katia Verger 6. Xavier Masramon 7. Jose Sanchez-Moreno 8. Francesc Colom	1, 2, 3, 4, 7 & 8. Bipolar Disorders Program, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, Barcelona, Spain 5. Investigation, Development, and Innovation Department, Pfizer S.A. 6. Euroclin Institute, Barcelona, Spain. 7. Department of Psychiatry, Autonomous University of Madrid, Madrid, Spain. 8. Department of Psychological Medicine, Institute of Psychiatry, London, England.	"This study was supported by Pfizer S.A., Madrid, Spain." "we thank the Spanish collaborative group of the Pfizer S.A. study #0945-421-291."

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Table 4 - Comparison of Study Reports by Participant Inclusion/Exclusion Criteria

Study number	Publication code	Type of report	Participant inclusion criteria (Protocol)	Participant inclusion criteria (Report)	Enrollment start date	Enrollment end date	Number of sites
945-209	945-209.RR	Research report	"Participants will meet the following criteria to be eligible to participate in the study: - Diagnosis of Bipolar I disorder (DSM-IV) with manic/hypomanic or mixed symptomatology despite adequate ongoing therapy with lithium, valproate, or lithium plus valproate in combination; - YMRS score ≥8 at B1, B2, and DBR; - Aged 16 years or older; - Males; or nonpregnant, nonlactating females who are postmenopausal, surgically sterilized, or using a barrier or hormonal method of contraception and have a negative pregnancy test; - Able to understand and cooperate with study procedures; and - Have signed a written informed consent prior to entering the study."	[Synopsis of report]: "patients must have scored ≥12 on the Young Mania Rating Scale (YMRS) at visit V1 and must have scored ≥8 at V2 and V3." The research report consisted of a synopsis, letter to investigators and appendices.	March 1996.	July 1997.	"14 Centers in the US"

Study number	Publication code	Type of report	Participant inclusion criteria (Protocol)	Participant inclusion criteria (Report)	Enrollment start date	Enrollment end date	Number of sites
945-209	Pande 2000b	Full-paper	"Participants will meet the following criteria to be eligible to participate in the study: - Diagnosis of Bipolar I disorder (DSM-IV) with manic/hypomanic or mixed symptomatology despite adequate ongoing therapy with lithium, valproate, or lithium plus valproate in combination; - YMRS score ≥8 at B1, B2, and DBR; - Aged 16 years or older; - Males; or nonpregnant, nonlactating females who are postmenopausal, surgically sterilized, or using a barrier or hormonal method of contraception and have a negative pregnancy test; - Able to understand and cooperate with study procedures; and - Have signed a written informed consent prior to entering the study."	"The study sample consisted of outpatients (n = 117) of either gender, aged 16 years or older. Patients were required to have a diagnosis of bipolar I disorder based on DSM-IV criteria with manic/hypomanic or mixed symptoms. A structured clinical interveiw was not required for diagnosis." "To be included in this study, patients had to meet criteria for a lifetime diagnosis of bipolar disorder (type I) and score ≥ 12 on the Young Mania Rating Scale at the initial clinic visit, despite ongoing therapy with lithium, valproate or lithium and valproate in combination." "Patients were required to have a plasma lithium level of ≥ 0.5 mEq/L, or a plasma valproate concentration of ≥ 50 µg/mL."	Not mentioned.	Not mentioned.	"..14 centers in the USA."
945-250	Wang 2002	Full-paper	"1. Males or nonpregnant, nonlactating females who are postmenopausal, surgically sterilized, or using a barrier or hormonal method of contraception and have a negative pregnancy test, age 16 years or older, no weight restriction 2. A verified diagnosis of Bipolar Disorders (BPI, BPII, or BPNOS by DSM-IV) with depressed symptomatology despite ongoing therapy with mood stabilizer(s). 3. HAM-D score of at least 16 at B1 and OTC (Open Treatment Commencement); Able to understand and cooperate with study procedures; and prior to participation in this study, each subject must sign an informed consent."	"Twenty-three outpatients meeting DSM-IV criteria for bipolar I or II disorder by semistructured clinical interview were seen in the Bipolar Disorders Clinic at Stanford University." "All met DSM-IV criteria for major depressive episode with a 28-item HDRS [Hamilton Depression Rating Scale] > 18 at screening, and at baseline, 1 week later."	Not mentioned.	Not mentioned.	1

Study number	Publication code	Type of report	Participant inclusion criteria (Protocol)	Participant inclusion criteria (Report)	Enrollment start date	Enrollment end date	Number of sites
945-291	945-291.Final Study Report	Research report	Protocol not available.	Not mentioned in available documents.	May 14, 1999.	February 26, 2004.	Not mentioned.
945-291	Vieta 2006	Full-paper	Protocol not available.	"Twenty-five subjects aged from 18 to 75 years with a diagnosis of bipolar I or II disorder (according to DSM-IV criteria) treated with any standard mood stabilizer like lithium, valproate, carbamazepine, or any combination during the last year were recruited." "Other inclusion criteria were as follows: 2 bipolar episodes or more during the last year, Clinical Global Impressions scale for Bipolar Illness, Modified (CGI-BP-M) score ≥ 4, last episode having occurred within 6 months prior to randomization, and, if the subject was treated with thyroxine, stable treatment during the last year." "Importantly, the patients had to be euthymic at randomization, defined as a score of 8 or less on the Hamilton Rating Scale for Depression (HAM-D) and 4 or less on the Young Mania Rating Scale (YMRS)." "Therefore, patients had to be in clinical remission at study entry, allowing the assessment of the actual prophylactic effects of the therapy. Indeed, this rather unusual design caused a number of protocol violations, as some patients who were initially enrolled had to be excluded because they were not in remission at study entry."	May 1999.	February 2004.	7

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Table 5 - Interventions and Run-in Phase

Study number	Publication code	Run-in phase (Protocol)	Run-in phase (Report)	Trial design	Total length of follow-up	Description of intervention (Report)	Treatment (gabapentin dose, duration, frequency) different from protocol
945-209	945-209.RR	"Following the 2-week, single-blind, placebo baseline period, double-blind study drug is added-on to patients' existing therapy as gabapentin 600 to 3600 mg/day or matching placebo administered orally BID or TID for 10 weeks."	[Synopsis of report]: "Following a 2-week, single-blind placebo lead-in and stabilization phase, patients were randomized to receive either placebo or gabapentin in a 10-week, double-blind, flexible-dose, parallel group, multicenter study."	Parallel-groups	10 weeks. [Synopsis of report]: "Following a 2-week, single-blind placebo lead-in and stabilization phase, patients were randomized to receive either placebo or gabapentin in a 10-week, double-blind, flexible-dose, parallel group, multicenter study."	[Synopsis of report]: "Gabapentin (or matching placebo) was given at a dose of 600 to 3600 mg/day divided into 3 times daily (TID) dosing. The design called for study medication dosing to increase in up to 600-mg increments (≤2 capsules) per day to a maximum daily dosage of 3600 mg/day." "Dosing adjustments were made at the discretion of the investigator according to the clinical status of the patient." "At the end of the 10-week double-blind treatment phase, study medication dose was decrease by 2 capsules/day."	☐
945-209	Pande 2000b	"Following the 2-week, single-blind, placebo baseline period, double-blind study drug is added-on to patients' existing therapy as gabapentin 600 to 3600 mg/day or matching placebo administered orally BID or TID for 10 weeks."	"The study began with a 2-week, single-blind, placebo lead-in, during which the doses of lithium and/or valproate could be adjusted to the clinician's satisfaction and the minimum threshold concentrations mentioned above could be obtained."	Parallel-groups	10 weeks. "Patients were evaluated at weekly visits for the first 4 weeks after randomization, and biweekly for the next 6 weeks."	"If patients continued to meet entry criteria at the end of the placebo lead-in, they were randomized to double-blind treatment with either gabapentin (dosed flexibly between 600 and 3600 mg/day, given t.i.d) or placebo for 10 weeks." "After randomization, the doses of lithium and valproate were required to be held steady unless dose changes were required to ensure patient safety."	☐

Study number	Publication code	Run-in phase (Protocol)	Run-in phase (Report)	Trial design	Total length of follow-up	Description of intervention (Report)	Treatment (gabapentin dose, duration, frequency) different from protocol
945-250	Wang 2002	"This study comprises 2 periods: open baseline evaluation and open treatment (Appendix C)."	Not mentioned.	Not applicable	"12-week open trial"	Gabapentin. "Patients received a 12-week open trial of GBP [gabapentin] added to current stable psychotropic regimen." "GBP was initiated at 300 mg at bedtime and increased by 300 mg every four nights until symptom relief or adverse effects were noted." "Final GBP dose was clinically determined, but did not exceed 3600 mg per day in divided doses (range 600-3300 mg)." "GBP was given as a single evening dose up to 1200 mg; and above this in divided doses, as a result of saturable gastrointestinal absorption."	☐
945-291	945-291.Final Study Report	Protocol not available.	Not mentioned in available documents.	Parallel-groups	Not mentioned in available documents.	"The patients were randomized to 2 parallels groups, inititated the titration during 1 week received Gabapentin or Placebo added to previous treatment (Lithium, Valproate, Carbamazepine or any combination) and no treatment with antipsychotics and antidepressants." "The patients who received Gabapentin were taken an initial dosage of 1200 mg/ day, this dosage was maintained until the end of the study. In the presence of a new episode, the dosage could was increased until 2400 mg/ day and in the presence of drug related adverse event, the dosage could was reduced until 900 mg/ day."	☐

Study number	Publication code	Run-in phase (Protocol)	Run-in phase (Report)	Trial design	Total length of follow-up	Description of intervention (Report)	Treatment (gabapentin dose, duration, frequency) different from protocol
945-291	Vieta 2006	Protocol not available.	"Randomly assigned patients were titrated during 1 week, and they received gabapentin or placebo added to the previous treatment..."	Parallel-groups	"The trial duration was 1 year."	Gabapentin. "Randomly assigned patients were titrated during 1 week, and they received gabapentin or placebo added to the previous treatment (lithium, valproate, carbamazepine, or any combination) and no treatment with antipsychotics and antidepressants." "Patients who received gabapentin started with an initial dosage of 1200 mg/day; this dosage was maintained until the end of the study." "In the presence of emerging symptoms, the dosage could be increased up to 2400 mg/day in either arm, and, in the presence of a drug-related adverse event, the dosage could be reduced to 900 mg/day." "The drug was taken 3 times a day."	☐

Psychiatric Disorders
Table 6 - Risk of Bias

Study number	Publication code	Random allocation (Protocol)	Random allocation (Report)	Method of allocation (Protocol)	Method of allocation (Report)	Concealment of allocation (Protocol)	Concealment of allocation (Report)	Method of allocation concealment (Report)	Double-blind (Protocol)	Double-blind (Report)	Blinding: Notes (Protocol)	Blinding: Notes (Report)
945-209	945-209.RR	☑	☑	"To ensure a balance in study treatment assignment within these ongoing therapy categories, the study medication will be randomly assigned within the lithium, valproate, or lithium plus valproate strata in each center."	[Synopsis of report]: "Following a 2-week, single-blind placebo lead-in and stabilization phase, patients were randomized to receive either placebo or gabapentin in a 10-week, double-blind, flexible-dose, parallel group, multicenter study."	☐	☐	No description of any attempt to conceal allocation.	☑	☑	No description on who was blinded in single-blind and double-blind phases of the study.	No description on who was blinded in single-blind and double-blind phases of the study.
945-209	Pande 2000b	☑	☑	"To ensure a balance in study treatment assignment within these ongoing therapy categories, the study medication will be randomly assigned within the lithium, valproate, or lithium plus valproate strata in each center."	"If patients continued to meet entry criteria at the end of the placebo lead-in, they were randomized to double-blind treatment with either gabapentin (dosed flexibly between 600 and 3600 mg/day, given t.i.d) or placebo for 10 weeks."	☐	☐	No description of any attempt to conceal allocation.	☑	☑	No description on who was blinded in single-blind and double-blind phases of the study.	No description on who was blinded in single-blind and double-blind phases of the study.

Study number	Publication code	Random allocation (Protocol)	Random allocation (Report)	Method of allocation (Protocol)	Method of allocation (Report)	Concealment of allocation (Protocol)	Concealment of allocation (Report)	Method of allocation concealment (Report)	Double-blind (Protocol)	Double-blind (Report)	Blinding: Notes (Protocol)	Blinding: Notes (Report)
945-250	Wang 2002	☐	☐	"This study will have an open, uncontrolled design."	"Twenty-three outpatients meeting DSM-IV criteria for bipolar I or II disorder by semistructured clinical interview were seen in the Bipolar Disorders Clinic at Stanford University."	☐	☐	Not applicable.	☐	☐	Not applicable.	Not applicable.
945-291	945-291.Final Study Report	☐	☑	Protocol not available.	Not mentioned in available documents.	☐	☐	No description of any attempt to conceal allocation in available documents.	☐	☑	Protocol not available.	No description on who was blinded.
945-291	Vieta 2006	☐	☑	Protocol not available.	"The randomization was generated confidentially by the sponsor (K.V. and X.M. Pfizer S.A., Spain) prior to the study using the SAS Statistical Package (SAS Institute, Inc.; Cary, N.C.) for the computer."	☐	☐	No description of any attempt to conceal allocation.	☐	☑	Protocol not available.	"Both subjects and clinicians were blinded regarding gabapentin/placebo assignment."

Pscyhiatric Disorders
Table 7 - Primary Outcome and Number of Patients Assessed

Study number	Publication code	Primary outcome (protocol)	Primary outcome (Report)	Number randomized per group (Report)	Number analyzed per group - Primary outcome (Report)	Number analyzed per group for safety (Report)	Definitions for study population for analysis (Report)
945-209	945-209.RR	"The primary efficacy measures will be baseline to end point change in the HAM-D [Hamilton Depression Rating Scale] total score; baseline to end point change in the YMRS [Young Mania Rating Scale] score; and percent of patients in each treatment group who are responders on the ISS [Internal States Scale]." "The primary population will be all patients randomized to treatment who complete at least 7 days of double-blind treatment at 600 or more mg/day, have assessments at baseline (visit DBR) and at Week 1 or later, and who are not excluded because of protocol violations or variations." "A secondary population will be the Intent-to-Treat population which is defined as all patients randomized to treatment and who have at least 1 postrandomization visit."	"The primary efficacy measures were the baseline to end point change in YMRS score and the baseline to end point change in HAM-D score." "The YMRS and HAM-D change scores were each analyzed using analysis of covariance (ANCOVA) for the Week 1 Completers population.	[Synopsis of report]: Not mentioned. [Letter to Investigators]: "The intent-to-treat population for this study consisted of 117 patients randomized, of whom 114 had a post-randomization observation on either placebo (n = 59) or gabapentin (n = 55)."	[Synopsis of report]: "Week 1 Completers": 52 Gabapentin / 59 Placebo "Intent to Treat (ITT) population": 58 Gabapentin / 59 Placebo	58 Gabapentin / 59 Placebo (Appendix C.45)	Intent-to-treat population (Letter to Investigators): "The intent-to-treat population for this study consisted of 117 patients randomized, of whom 114 had a post-randomization observation on either placebo (n = 59) or gabapentin (n = 55)." Week one Completers (Synopsis of report): "Week One Completers were defined as patients who completed at least 7 days of double-blind treatment at 600 or more mg/day, and had a baseline (Visit 1, 2, or 3) and at least 1 post randomization observation on or after study Day 6. Week 1 Completers were defined for each efficacy parameter."

Study number	Publication code	Primary outcome (protocol)	Primary outcome (Report)	Number randomized per group (Report)	Number analyzed per group - Primary outcome (Report)	Number analyzed per group for safety (Report)	Definitions for study population for analysis (Report)
945-209	Pande 2000b	"The primary efficacy measures will be baseline to end point change in the HAM-D [Hamilton Depression Rating Scale] total score; baseline to end point change in the YMRS [Young Mania Rating Scale] score; and percent of patients in each treatment group who are responders on the ISS [Internal States Scale]." "The primary population will be all patients randomized to treatment who complete at least 7 days of double-blind treatment at 600 or more mg/day, have assessments at baseline (visit DBR) and at Week 1 or later, and who are not excluded because of protocol violations or variations." "A secondary population will be the Intent-to-Treat population which is defined as all patients randomized to treatment and who have at least 1 postrandomization visit."	"The efficacy assessments included the YMRS (10), Hamilton Depression Rating Scale (11) (HAM-D), Hamilton Anxiety Rating Scale (12) (HAM-A), Clinical Global Impression of Severity (CGIS) and Clinical Global Impression of Change (CGIC)." "The efficacy analyses were carried out on the intent-to-treat (ITT) population that included all randomized patients who received at least one dose of study medication." "For all analyses, endpoint was defined as the week-10 (termination visit) score for patients who completed treatment or the last available post-randomization score (last observation carried forward, LOCF) for patients who withdrew from the study."	Not mentioned. "The ITT population for this study comprised of 117 patients randomized, 114 of whom had a post-randomization observation on either placebo (n = 59) or gabapentin (n = 55)."	58 Gabapentin / 59 Placebo	58 Gabapentin / 59 Placebo	Intent to treat population: "The efficacy analyses were carried out on the intent-to-treat (ITT) population that included all randomized patients who received at least one dose of study medication." Week 1 Completers: Not mentioned.
945-250	Wang 2002	"The primary efficacy measures in this analysis will be Hamilton Depression (HAM-D) total score adjusted for baseline score and the percent of patients group who are determined to be "responders" according to the criterion of the final HAM-D being at least fifty percent less than the initial HAM-D."	"The primary outcome measure was decreased in HDRS [Hamilton Depression Rating Scale] from baseline."	Open-label, uncontrolled study: 23 patients were enrolled.	22. "One patient was lost to follow-up early in the study without evaluable data, and thus was not included in subsequent analyses."	22.	No definitions mentioned.

Study number	Publication code	Primary outcome (protocol)	Primary outcome (Report)	Number randomized per group (Report)	Number analyzed per group - Primary outcome (Report)	Number analyzed per group for safety (Report)	Definitions for study population for analysis (Report)
945-291	945-291.Final Study Report	Protocol not available.	"The primary efficacy parameter main was the Clinical Global Impression of Severity (CGIS) of the disorder, was assessed at all visits ot be performed during the study by the CGIS." "The primary efficacy parameter was defined as the change at month 12 from baseline in the Clinical Global Impression of Severity (CGIS)."	20 Gabapentin / 22 Placebo.	Intent-to-treat: 20 Gabapentin / 21 Placebo. Per Protocol: 13 Gabapentin / 12 Placebo.	20 Gabapentin / 22 Placebo.	Intent-to-treat population: "Subjects were included in the Intent-to-Treat (ITT) Population if the subjects were randomized, received at least one dose of study medication, and had at least one post-baseline data for at least one of the efficacy variables." Per Protocol population: "Subjects were included in the Per Protocol (PP) population if the subjects were included in the ITT population and met the following additional criteria: - Subject between 18 and 75 years old; - With more than 1 (≥ 2) episodes in the last year and CGI score ≥ 4 at visit 1; - HAM-D score ≤ 8 or YMRS score ≤ 4 at visit 1; - Had received concomitant permitted medication only in the presence of an episode during the study (see sections 5.3 and 7.6 of the protocol); and - Had adequate treatment compliance rate of 80% and 120% during study period."

Study number	Publication code	Primary outcome (protocol)	Primary outcome (Report)	Number randomized per group (Report)	Number analyzed per group - Primary outcome (Report)	Number analyzed per group for safety (Report)	Definitions for study population for analysis (Report)
945-291	Vieta 2006	Protocol not available.	"The primary efficacy parameter was the CGI-BP-M [Clinical Global Impressions scale for Bipolar Illness, Modified], which was assessed at all study visits." "This clinician-rated instrument measures the severity of symptoms (subscales for manic and for depressive symptoms) and the severity of the disorder (primary outcome of this trial on a 7-point scale ranging from 1 [not at all] to 7 [the most extremely ill patient])."	13 Gabapentin / 12 Placebo	13 Gabapentin / 12 Placebo. "The reasons for discontinuation in the gabapentin group were as follows: 2 subjects (15%) no longer wanted to participate in the study, 2 subjects (15%) had lack of efficacy, 1 subject (8%) had adverse events, and 1 subject (8%) had other reasons." "The reasons for discontinuation in the placebo group were as follows: 3 patients (25%) no longer wanted to participate in the study 1 subject (8%) had lack of efficacy, 1 subject (8%) had adverse events, and 1 subject (8%) had other reasons."	13 Gabapentin / 12 Placebo.	No definitions mentioned. "All statistical analyses were done by intention to treat and last observation carried forward."

Psychiatric Disorders
Table 8 - Comparison of Study Reports by Results and Conclusions

Study number	Publication code	Results of primary analysis (Report)	Adverse events (Report)	Conclusions in abstract & discussion sections (Report)	Conclusions consistent with results in discussion (Report)	Conclusions consistent with results in abstract (Report)
945-209	945-209.RR	Synopsis of report: "Baseline to endpoint change in YMRS and HAM-D scores did not favor the gabapentin group." Letter to Investigators: "Table 1 shows the baseline to end point changes by treatment in the YMRS and HAM-D. Neither scale favored gabapentin. To the contrary, placebo patients showed a greater decrease in the total YMRS score than the gabapentin patients." [Table 1 of the letter provides the following values for "Change" in YMRS and HAM-D scores. For YMRS scores, the change values reported were: -5.8 for gabapentin and -8.9 for placebo with an asterisk indicating "p<.05" in a footnote. For HAM-D scores, the change values reported were: -0.1 for gabapentin and -1.5 for placebo."] "When all patients who had a change in lithium doses (n = 16) are removed from the efficacy analysis, the YMRS treatment difference still favors placebo but is no longer statistically significant." "Another potential confound may have been treatment non-compliance. Several patients in the gabapentin group had plasma drug levels below the limit of detection, suggesting some of them may not have taken the drug as prescribed."	"Most adverse events were consistent with known side-effects of gabapentin, the most common being somnolence and dizziness." "Thirteen patients (6 of whom were receiving gabapentin) experienced a serious adverse event." "Five placebo-treated patients and 7 gabapentin-treated patients withdrew due to adverse events." "There were no deaths during the study. One patient died 10 months after discontinuing from the study."	Synopsis of report: "The results from this study do not indicate that gabapentin is effective as adjunctive therapy. However, there was no evidence that gabapentin caused a worsening of symptoms. A lack of patient compliance may have biased the outcome as gabapentin plasma concentrations suggested that several patients had not taken study drug as prescribed." Letter to Investigators: "Given that gabapentin is being used by many clinicians with apparent success, it seems likely the results of study 945-209 are not entirely reliable. While it cannot be asserted that gabapentin is effective in bipolar disorder, the results of this study also do not permit the conclusion that it is not. There was no evidence of patients on gabapentin showing a worsening of symptoms either."	☑	☑

Study number	Publication code	Results of primary analysis (Report)	Adverse events (Report)	Conclusions in abstract & discussion sections (Report)	Conclusions consistent with results in discussion (Report)	Conclusions consistent with results in abstract (Report)
945-209	Pande 2000b	Results section of report: "However, comparison of YMRS change scores from baseline to endpoint (LOCF) by ANCOVA revealed a significant difference that favored placebo treatment." [Table 2 of the report provides the following values for "Adjusted means" for YMRS and HAM-D scores. For YMRS scores, the "Adjusted means" reported were -6.5 for gabapentin and -9.9 for placebo. For HAM-D scores, the "Adjusted means" reported were 0.01 for gabapentin and -1.3 for placebo.]	Table 5 lists adverse events and percentages (Gabapentin / Placebo): Somnolence (24.1/11.9); dizziness (19/5.1); diarrhea (15.5/11.9); headache (10.3/11.9); amnesia (10.3/3.4). Table 6 lists "serious adverse events": Pericarditis; manic depressive reaction; manic reaction; cervix carcinoma; psychosis.	Discussion section of report: "The findings of this study did not demonstrate that gabapentin is an effective adjunctive treatment when adminsitered to patients with bipolar disorder who have moderate to severe symptoms that are persisting despite treatment with lithium and/or valproate." "When all patients who had a change in lithium doses are removed from the efficacy analysis, the YMRS treatment difference numerically favors placebo, but is no longer statistically significant. This suggests that the patients whose lithium dose was adjusted during the baseline period have a disproportionately large influence on the overall results." "Another potential factor that may influence outcome in patients with bipolar disorder is treatment non-compliance. No gabapentin was detected in the plasma of some patients assigned to that treatment arm, suggesting poor compliance." "This study included a heterogeneous patient population who, despite being 'refractory' to mood-stabilizing treatments, showed a robust response to placebo." "Although gabapentin was not superior to placebo in this study, there was no evidence of patients on gabapentin showing a worsening of symptoms earlier." "Because we had no hint that gabapentin would have significant antidepressant effects, we excluded those patients whose	☑	☑

Study number	Publication code	Results of primary analysis (Report)	Adverse events (Report)	Conclusions in abstract & discussion sections (Report)	Conclusions consistent with results in discussion (Report)	Conclusions consistent with results in abstract (Report)
				symptoms consisted only of depression at the time of entry into the study. This may have been an erroneous assumption and we may have excluded patients who could potentially be treatment responders." Abstract of report: "The findings of this study did not demonstrate that gabapentin is an effective adjunctive treatment when administered to outpatients with bipolar disorder."		

Study number	Publication code	Results of primary analysis (Report)	Adverse events (Report)	Conclusions in abstract & discussion sections (Report)	Conclusions consistent with results in discussion (Report)	Conclusions consistent with results in abstract (Report)
945-250	Wang 2002	Results section of report: "In the entire group of 22 patients, GBP [gabapentin] augmentation (mean final dose = 1725 ± 726 mg, range = 600-3300 mg) yielded a 53% mean decrease in HDRS [Hamilton Depression Rating Scale] ratings from 32.5 ± 7.7-16.5 ± 12.8 (t = 8.1, df = 21, p < 0.0001) (Table 2, Fig. 1)."	"Mild sedation was the most common adverse effect, noted in seven of 22 patients (32%)." "Mean weight gain was 2.0 ± 6.9 pounds (p = ns [non-significant]), and was not related to GBP [gabapentin] dose." "One patient, concurrently on DVPX [divalproex] (dose = 500 mg per day), discontinued GBP because of impaired cognition, despite being a responder and remitter." "Two subjects (one female BP II subject, with history of rapid cycling and antidepressant-induced hypomania and one male BP I subject, without history of rapid cycling or antidepressant-induced hypomania) developed 3 days of hypomanic symptoms, which spontaneously remitted." "One female BP II subject, with history of rapid cycling and antidepressant-induced hypomania, became hypomanic, necessitating study discontinuation."	Discussion section of the report: "These data suggest that adjunctive GBP [gabapentin] is effective in bipolar depression." "Thus, adjunctive GBP may be an important option for bipolar patients with suboptimal antidepressant responses to standard mood stabilizers." "However, the significance and generalizability of our findings to other patients are limited by the small sample size, open treatment design, and lack of a randomized, parallel control group." "However, such open designs suggest the need for formal, controlled studies." "Further studies with larger samples and blinded, randomized controlled methodology are required to further assess the efficacy of this treatment strategy." Abstract of the report: "Open adjunctive GBP was effective and well tolerated in patients with mild to moderate bipolar depression." "This open pilot study must be viewed with caution, and randomized controlled studies are warranted."	☑	☑

Study number	Publication code	Results of primary analysis (Report)	Adverse events (Report)	Conclusions in abstract & discussion sections (Report)	Conclusions consistent with results in discussion (Report)	Conclusions consistent with results in abstract (Report)
945-291	945-291.Final Study Report	"Primary efficacy results of the CGIS in the ITT population were not statistically significant (p=0,3952). Statistical Power of the difference (0,4) was 14%." "Change at month 12 vs baseline in Gabapentin group was -1,9 (±1,3) statistically significant (p<0,05) and in Placebo group -0,8 (±1,4) was not statistically significant. Change at month 12 of Gabapentin vs Placebo was statically significant (p < 0,05)."	"The most frequent adverse events in Gabapentin group were: Constipation, 4 subjects, 20%; insomnia, 3 subjects, 15%; headache, 3 subjects, 15 %; nausea 3 subjects, 15 %." "The most frequent adverse events in placebo group were: Insomnia, 4 subjects, 18%; headache, 2 subjects, 9%; Diarrhea, 2 subject, 9%." "One subject, who received Gabapentin, discontinued due to a serious adverse event, it was a myocardial infarction, 5,0% No subjects of the placebo group discontinued due to a serious adverse event."	"SUMMARY The adverse events profile of Gabapentin in the study was consistent with the labeled adverse events for this product. This trial demonstrate that gabapentin is well tolerated as add-on treatment in patients with bipolar disorder. The results of the primary and secondary efficacy parameter did not show statistically differences between Gabapentin and Placebo."	☑	☐

Study number	Publication code	Results of primary analysis (Report)	Adverse events (Report)	Conclusions in abstract & discussion sections (Report)	Conclusions consistent with results in discussion (Report)	Conclusions consistent with results in abstract (Report)
945-291	Vieta 2006	Results section of report: "The change in CGI-BP-M [Clinical Global Impressions scale for Bipolar Illness, Modified] score between groups was statistically significant (gabapentin -2.1, placebo -0.6, p = 0.0046)."	"Ten patients (77%) in the gabapentin group and 7 taking placebo (58%) reported adverse events, mostly mild." "The most frequent ones, involving more than 10% of patients in the gabapentin group were constipation, N = 4 (31%); headache, N = 3 (23%); nausea, N = 3 (23%); dizziness, N = 2 (15%); insomnia, N = 2 (15%); and tremor, N = 2 (15%)." "Only 1 patient in each group discontinued the study owing to an adverse event, including a patient who was randomly assigned to gabapentin and suffered a myocardial infarction that was not considered to be related to the treatment."	Discussion section of the report: "Whereas there is no indication that gabapentin may have acute antimanic or antidepressant effects, this trial suggests that gabapentin may still carry some benefits on the long-term outcome." "Besides, in this trial, there was no sign of destabilization of mood and there were few side effects." "However, the specific nature of the long-term benefits is a bit unclear, because improvements were only significant in the CGI-BP-M [Clinical Global Impressions scale for Bipolar Illness, Modified] long-term outcome subscale (primary outcome measure) and the PSQI-6 subscale." "The main reason for the absence of positive findings in survival analysis is likely to be the extremely high number of previous episodes in the gabapentin arm. It seems that randomization failed to balance such variables, particularly the number of previous depressive episodes, which was 19 in the gabapentin arm as compared to 8 in the placebo arm at baseline." "In conclusion, despite the apparent lack of acute efficacy of gabapentin, this study suggests that this drug is likely to provide some benefits on the long-term outcome of the disorder, confirming what some clinicians and open-label studies have suggested	☑	☑

Study number	Publication code	Results of primary analysis (Report)	Adverse events (Report)	Conclusions in abstract & discussion sections (Report)	Conclusions consistent with results in discussion (Report)	Conclusions consistent with results in abstract (Report)
				before." "Despite some limitations, this study also provides some indirect support to the notion that some drugs might possess mood-stabilizing properties regardless of their lack of efficacy for the acute treatment of manic or depressive episodes." Abstract of the report: "This small, randomized clinical trial comparing the prophylactic efficacy of adjunctive gabapentin to placebo suggests that, despite lack of acute efficacy, treatment with gabapentin might provide some benefit on the long-term outcome of bipolar disorder."		

Nociceptive Pain
Table 1 - Table of Citations

Study Number	Publication code	Type of report	Citation (Report)
1032-001			
	1032-001.RR	Research report	Research report number RR 720-04378
1032-002			
	1032-002.RR	Research report	Research report number RR 720-04479.
1032-003			
	1032-003.RR	Research report	Research report number RR 720-30044.
1032-004			
	1032-004.RR	Research report	Research report number RR 720-04481.
1035-001			
	1035-001.RR	Research report	Research report number RR 720-04455.
1035-001. Addndm-B			
	1035-001. Addndm-B.RR	Research report	Research report number RR 720-04483.
1035-002			
	1035-002.RR	Research report	Research report number RR 720-04471.

Nociceptive Pain
Table 2 - Summary of Reporting Biases

Study number	Publication code	Protocol available	Date of research report (internal)	Date of last enrollment or end date for "Period(s) covered" per research report	Type of results	Location of publication	Results of primary analysis	Secondary outcome (protocol) reported as primary outcome (report)	Reported analyses on selective populations as primary analysis	Publication bias (negative results and no publication final result)	Conclusions of efficacy consistent with primary analysis result (Conclusions section - report)	Conclusions of safety consistent with analysis of adverse events (Conclusions section - report)
1032-001	No publication	☑	February 17, 2000.	August 2, 1999.	No publication	No publication	"Negative"	NA[1]	NA[1]	☑	NA[1]	NA[1]
1032-002	No publication	☑	October 31, 2000.	June 19, 2000.	No publication	No publication	"Negative"	NA[1]	NA[1]	☑	NA[1]	NA[1]
1032-003	No publication	☑	September 27, 2001.	September 22, 2000.	No publication	No publication	"Negative"	NA[1]	NA[1]	☑	NA[1]	NA[1]
1032-004	No publication	☑	August 16, 2000.	April 12, 2000.	No publication	No publication	"Negative"	NA[1]	NA[1]	☑	NA[1]	NA[1]
1035-001	No publication	☑	June 28, 2000.	February 23, 2000.	No publication	No publication	"Negative"	NA[1]	NA[1]	☑	NA[1]	NA[1]
1035-001. Addndm-B	No publication	☑	October 31, 2000.	March 15, 2000.	No publication	No publication	"Negative"	NA[1]	NA[1]	☑	NA[1]	NA[1]
1035-002	No publication	☑	December 20, 2000.	August 25, 2000.	No publication	No publication	"Negative"	NA[1]	NA[1]	☑	NA[1]	NA[1]

* NA = Not Applicable

Nociceptive Pain
Table 3 - Comparison of Study Reports by Authors and Funding Source

Study number	Publication code	Year	Type of report	Citation	Authors/ investigators (Protocol)	Authors/ investigators (Report)	Authors/ investigators locations (Report)	Funding source (Report)
1032-001	1032-001.RR	April 4, 2000	Research report	Research report number RR 720-04378	Principal Investigator: Paul Desjardins Coinvestigator: Stephen Daniels Parke-Davis Clinical/Medical Colleagues: Michelle Buroker Kilgore Trevor Mundel Parke-Davis Statistician: Noel Mohberg Subinvestigator(s): R. Dean Jasper Steven J. Perkins Franklin Bonnasso Donald Steed	PD Author(s): Giordani AB Buroker Kilgore M Mundel T Yan C Investigator(s): Daniels S Desjardins P	"Study 1032-001 was conducted under the direction of the Principal Investigators, Stephen Daniels, DO, and Paul Desjardins, DMD, PhD, at the Austin, Texas, Clinical Research Center of Scirex Corporation and monitored by Parke-Davis personnel."	Not applicable. Research report.

Study number	Publication code	Year	Type of report	Citation	Authors/ investigators (Protocol)	Authors/ investigators (Report)	Authors/ investigators locations (Report)	Funding source (Report)
1032-002	1032-002.RR	October 31, 2000	Research report	Research report number RR 720-04479.	Parke-Davis Clinical/Medical Colleagues: Michelle Buroker Kilgore Trevor Mundel Parke-Davis Statistician: Chongqing Yan	PGRD [Pfizer Global Research & Development] Author(s): 1. Buroker Kilgore M 2. Diaz F 3. Giordani AB 4. Mundel T 5. Sesti AM 6. Ventura AY Investigator(s): 7. Roland Moskowitz 8. Abraham Sunshine 9. Thomas Schnitzer 10. James Taborn 11. Alan Kivitz 12. David Coval 13. Bobon Beningno 14. Maria Greenwald 15. Jaques Caldwell 16. Stanley Cohen 17. Roy Fleischmann 18. John Ervin 19. Robert Levin 20. Walter Chase 21. Charles Birbara	7. University of Cleveland, Cleveland, OH 8. Analgesic Development, Ltd, New York, NY 9. Northwestern University, Chicago, IL 10. Midwest Arthritis Center, Kalamazoo, MI 11. Altoona Center for Clinical Research, Duncansville, PA 12 & 13. NTouch Research Corporation, Decatur, GA 14. Advances in Medicine, Rancho Mirage, CA 15. Halifax Clinical Research Institute, Daytona Beach, FL 16 & 17. Metroplex Clinical Research Center, Dallas, TX 18. Center for Pharmaceutical Research, Kansas City, MO 19. Tampa Bay Medical Research Inc, Clearwater, FL 20. Private Practice, Austin, TX 21. Clinical Pharmacology Study Group, Worcester, MA	Not applicable. Research report.

Study number	Publication code	Year	Type of report	Citation	Authors/ investigators (Protocol)	Authors/ investigators (Report)	Authors/ investigators locations (Report)	Funding source (Report)
1032-003	1032-003.RR	September 27, 2001	Research report	Research report number RR 720-30044.	Parke-Davis Clinical/Medical Colleagues: Michelle Buroker Kilgore Trevor Mundel Parke-Davis Statistician: Chongqing Yan	PGRD [Pfizer Global Research & Development] Author(s): 1. Buroker Kilgore M 2. Giordani AB 3. Mundel T 4. Sesti AM 5. Ventura AY 6. Yan C Investigator(s); 7. Roland Moskowitz 8. Thomas Schnitzer 9. James Taborn 10. Alan Kivitz 11. David Coval 12. Bobon Beningno 13. Maria Greenwald 14. Jacques Caldwell 15. Stanley Cohen 16. Roy Fleischmann 17. John Ervin 18. Walter Chase 19. Charles Birbara	7. University of Cleveland, Cleveland, OH 8. Northwestern University, Chicago, IL 9. Midwest Arthritis Center, Kalamazoo, MI 10. Altoona Center for Clinical Research, Duncansville, PA 11 & 12. NTouch Research Corporation 13. Advances in Medicine, Rancho Mirage, CA 14. Halifax Clinical Research Institute, Daytona Beach, FL 15 & 16. Metroplex Clinical Research Center, Dallas, TX 17. Center for Pharmaceutical Research, Kansas City, MO 18. Ractice, Austin, TX 19. Clinical Pharmacology Study Group, Worcester, MA	Not applicable. Research report.
1032-004	1032-004.RR	August 16, 2000	Research report	Research report number RR 720-04481.	Parke-Davis Clinical/Medical Colleagues: Marykay Hes Michael Jaffe Jean-Louis Abitbol R. Michael Poole Parke-Davis Statistician: Chongqing Yan	PD Authors: 1. Giordani AB 2. Hotary L 3. Jaffe M 4. Nelson D 5. Sesti AM Investigator(s): 6. Lanza FL	6. Houston Institute for Clinical Research, Houston, Texas.	Not applicable. Research report.

Study number	Publication code	Year	Type of report	Citation	Authors/ investigators (Protocol)	Authors/ investigators (Report)	Authors/ investigators locations (Report)	Funding source (Report)
1035-001	1035-001.RR	June 28, 2000	Research report	Research report number RR 720-04455.	Parke-Davis Clinical/Medical Colleagues: Author: Michelle Buroker Kilgore Study Manager: Gregory C. Henry Drug Director/Therapy Head: Trevor Mundel Statistician: Chongqing Yan Principal Investigator: Paul Desjardins Subinvestigator(s): Stephen Daniels R. Dean Jasper Franklin S. Bonasso Donald L. Steed	PD Author(s): 1. Diaz F 2. Dougherty KM 3. Henry GC 4. Mundel T Investigator(s): 5. Desjardins P	5. SCIREX Corporation, Austin, TX.	Not applicable. Research report.

Study number	Publication code	Year	Type of report	Citation	Authors/ investigators (Protocol)	Authors/ investigators (Report)	Authors/ investigators locations (Report)	Funding source (Report)
1035-001. Addndm-B	1035-001. Add	October 31, 2000	Research report	Research report number RR 720-04483.	Protocol 1035-001: Parke-Davis Clinical/Medical Colleagues: Author: Michelle Buroker Kilgore Study Manager: Gregory C. Henry Drug Director/Therapy Head: Trevor Mundel Statistician: Chongqing Yan Principal Investigator: Paul Desjardins Subinvestigator(s): Stephen Daniels R. Dean Jasper Franklin S. Bonasso Donald L. Steed Protocol 1035-001 Addendum-B: Investigator: Paul Desjardins Parke-Davis Approval Signatures: Study Manager: Greg Henry Drug Manager: Trevor Mundel Statistician: Chongqing Yan Therapeutic Head: Michael Poole	PD Author(s): 1. Diaz F 2. Dougherty KM 3. Henry GC 4. Mundel T Investigator(s): 5. Desjardins P	5. SCIREX Corporation, Austin Texas.	Not applicable. Research report.

Study number	Publication code	Year	Type of report	Citation	Authors/ investigators (Protocol)	Authors/ investigators (Report)	Authors/ investigators locations (Report)	Funding source (Report)
1035-002	1035-002.RR	December 20, 2000	Research report	Research report number RR 720-04471.	Parke-Davis Clinical/Medical Colleagues: Gregory Henry Trevor Mundel Chongqing Yan	PGRD [Pfizer Global Development & Research] Author(s): 1. Dougherty KM 2. Henry GC 3. Mundel T 4. Yan C Investigator(s): 5. Sunshine A 6. Katz JA	5. Analgesic Development, Ltd., New York, NY 6. Tucson Orthopedic Institute, Tucson, AZ	Not applicable. Research report.

Nociceptive Pain
Table 4 - Comparison of Study Reports by Participant Inclusion/Exclusion Criteria

Study number	Publication code	Type of report	Participant inclusion criteria (Protocol)	Participant inclusion criteria (Report)	Enrollment start date	Enrollment end date	Number of sites
1032-001	1032-001.RR	Research report	"- Men or women. Women must have a negative pregnancy test and must be using a reliable form of contraception; - Age between 18 and 65 years (inclusive); - Scheduled for an outpatient oral surgical procedure to remove 1 to 2 ipsilateral third molars, at least 1 of which is mandibular and fully or partially impacted in bone; - Good health as determined by medical history and physical examination; - Negative alcohol breath test on day of surgery prior to surgery; - Must understand the nature of the study and provide a written informed consent as descr bed in Appendix E; and - Must be reliable, cooperative, and in the opinion of the investigator, able to understand the information required in the pain questionnaire/analgesia diary." "These criteria are mandatory and must be met to provide evaluable data."	No differences from protocol.	May 14, 1999	August 2, 1999	1

Study number	Publication code	Type of report	Participant inclusion criteria (Protocol)	Participant inclusion criteria (Report)	Enrollment start date	Enrollment end date	Number of sites
1032-002	1032-002.RR	Research report	"Screening (maximum of 2 weeks) Patients must meet the following mandatory inclusion criteria at the time of screening to be eligible to enter the washout phase: - OA of the knee [per Amendment 1], specificially: - Knee pain; and - Grade 2, 3, or 4 OA by x-ray criteria as defined by the Kellgren and Lawrence Grading System of OA. This must be documented with a report from an x-ray of the study joint taken either at screening or within 1 year prior to screening; - Pain should be: - MILD, MODERATE, or SEVERE on a 4-point categorical scale when walking on a flat surface (ie, patients with EXTREME pain or NONE are excluded); and - Present for at least 15 of the preceding 30 days when walking on a flat surface - Men or women of any race or ethnic group (women must be postmenopausal, surgically sterilized, or using a method of contraception acceptable to the investigator); - At least 45 years of age; - Able to complete the required assessment questionnaires, tests, and evaluations. Visual and auditory acuity (with glasses or hearing aid, if required) must be sufficient to complete the protocol-specified procedures; - Other than the signs and symptoms associated with diagnosed OA, patients must be in good health and capable of ambulating continuously without assistance (a cane is the only allowable ambulation aid) for at least 5 minutes; any concurrent diseases (eg, coronary artery disease, diabetes, hypertension) should be under good control as determined by the investigator. Patients may also have generalized OA affecting other joints in addition to the study joint, but the symptoms in joints other than the signal knee joint must clearly be of lesser severity. Each patient's health will be verified by history, screening physical examination, electrocardiogram, and clinical laboratory tests; and - Provide written informed consent. Patients must give voluntary and informed consent to participate in the study. Patients unable to provide written informed consent must demonstrate assent to the procedures and must have written consent from their legal representatives."	No differences from protocol and amendments to protocol in inclusion criteria described. "Twenty patients who did not satisfy the entry criteria in some respect were entered into the study."	December 20, 1999	June 19, 2000	13

Study number	Publication code	Type of report	Participant inclusion criteria (Protocol)	Participant inclusion criteria (Report)	Enrollment start date	Enrollment end date	Number of sites
			"Washout (3-14 days) Upon entry into the washout phase, NSAID and/or analgesic therapy will be discontinued. Patients will be asked to complete daily pain diaries and must have completed them for 75% of the possible washout days. Within the 3- to 14-day washout phase, patients must: - Rate knee pain intensity on wa king on a flat surface as at least MODERATE for at least the day prior to randomization [per Amendment 1]; - Have refrained from using any prior analgesic medication (except acetaminophen but mo more than 4 g/day [per Amendment 1]) for at least 5 half lives of the particular medication (see Appendix A.5); - Have refrained from taking acetaminophen 12 hours prior to randomization; and - Be randomized to study medication."				

Study number	Publication code	Type of report	Participant inclusion criteria (Protocol)	Participant inclusion criteria (Report)	Enrollment start date	Enrollment end date	Number of sites
1032-003	1032-003.RR	Research report	"Eligible patients include men or women who have completed 4 weeks of treatment in Study 1032-002 (4-week, randomized, double-blind, placebo- and positive-controlled, multicenter study of gabapentin in combination with naproxen sodium in patients with acute osteoarthritis [OA] pain the knee), a subset of screen failures for that protocol, and patients that have completed Addendum A to Study 1032-002." "The inclusion criteria applied to patients in protocol 1032-002 will also apply to this open-label extension. Briefly, elig ble patients are men or women at least 45 years of age with a diagnosis of OA of the knee. In addition, patients must meet the following inclusion criteria: - Completion of 4 weeks of treatment and all Visit 6 assessments in Protocol 1032-002, or completion of 1 week of treatment and all Visit 4 assessments in Addendum A to Protocol 1032-002. Addendum A patients must also complete all Visit 6 assessments in Protocol 1032-002; - Patients that enroll from Protocol 1032-002 or Addendum A to Protocol 1032-002 must have been compliant, in the opinion of the investigator, with the study medication regimen and procedural requirements of those protocols; - Patients who are Screen failures in Protocol 1032-002 but who met all of the inclusion/exclusion criteria except one of the following will be allowed to enter the open-label study: - Able to ambulate continuously without assistance (a cane is the only allowable ambulation aid) for at least 5 minutes; - Patient has generalized OA affecting other joints in addition to the study joint, but symptoms in joints other than the signal knee joint must clearly be of lesser severity; - Presence of any prosthesis, implanted device, or brace of the study joint; or - Other screen failures may be allowed but only with prior approval from the Parke-Davis study manager. - Women must be postmenopausal, surgically sterilized, using oral contraceptives, or using another method of contraception acceptable to the investigator; and - Able to supply voluntary and informed consent to participate in the study. Patients unable to provide written informed consent must demonstrate assent to the procedures and must have written consent from their legal representative(s)."	No differences from protocol.	February 9, 2000	September 22, 2000	"Eleven centers in the United States"

Study number	Publication code	Type of report	Participant inclusion criteria (Protocol)	Participant inclusion criteria (Report)	Enrollment start date	Enrollment end date	Number of sites
1032-004	1032-004.RR	Research report	"Subjects must be: - In good health as determined by medical history, physical examination, ECG, and clinical laboratory measurement or if they have any concurrent diseases, the investigator must consider them under good control; - Volunteers of any race or ethnic group (women must be postmenopausal, surgically sterilized, or using a method of contraception acceptable to the investigator) - Between the age of 18 to 60 years; - No mucosal injury (except traumatic petechiae or erythema of the esophagus) as determined by the baseline endoscopy [Omitted citation to footnotes in original text]; - In the opinion of the investigator, able and willing to comply with study requirements, tests, evaluation, and to complete the required diary; and - Subjects must give voluntary informed consent to participate in the study."	No differences from protocol.	January 18, 2000	April 12, 2000	1

Study number	Publication code	Type of report	Participant inclusion criteria (Protocol)	Participant inclusion criteria (Report)	Enrollment start date	Enrollment end date	Number of sites
1035-001	1035-001.RR	Research report	"Healthy patients scheduled for elective oral surgery for removal of 1 or 2 ipsilateral third molars, at least 1 of which is mandibular and fully or partially impacted in bone, will be eligible to enroll in the study. Those willing to enter and participate will undergo surgery and receive a single dose of blinded medication, stratified by baseline pain intensity, postsurgery when patient-rated pain intensity on a 4-point categorical scale is moderate or severe and patient-rated pain intensity on a VAS [visual analog scale] is ≥45 mm." "- Men or women. Women must have a negative pregnancy test and must be using a reliable form of contraception; - Age between 18 and 40 years (inclusive); - Scheduled for an outpatient oral surgical procedure to remove 1 to 2 ipsilateral third molars, at least 1 of which is mandibular and fully or partially impacted in bone; - Good health as determined by medical history and physical examination; - Negative alcohol breath test on day of surgery prior to surgery; - Must understand the nature of the study and provide a written informed consent as descr bed in Appendix E; and - Must be reliable, cooperative, and in the opinion of the investigator, able to understand the information required in the pain questionnaire."	No differences from protocol.	12/28/99	February 23, 2000	1

Study number	Publication code	Type of report	Participant inclusion criteria (Protocol)	Participant inclusion criteria (Report)	Enrollment start date	Enrollment end date	Number of sites
1035-001. Addndm-B	1035-001. Addndm-B.RR	Research report	Protocol 1035-001: "Healthy patients scheduled for elective oral surgery for removal of 1 or 2 ipsilateral third molars, at least 1 of which is mandibular and fully or partially impacted in bone, will be eligible to enroll in the study. Those willing to enter and participate will undergo surgery and receive a single dose of blinded medication, stratified by baseline pain intensity, postsurgery when patient-rated pain intensity on a 4-point categorical scale is moderate or severe and patient-rated pain intensity on a VAS [visual analog scale] is ≥45 mm." "- Men or women. Women must have a negative pregnancy test and must be using a reliable form of contraception; - Age between 18 and 40 years (inclusive); - Scheduled for an outpatient oral surgical procedure to remove 1 to 2 ipsilateral third molars, at least 1 of which is mandibular and fully or partially impacted in bone; - Good health as determined by medical history and physical examination; - Negative alcohol breath test on day of surgery prior to surgery; - Must understand the nature of the study and provide a written informed consent as descr bed in Appendix E; and - Must be reliable, cooperative, and in the opinion of the investigator, able to understand the information required in the pain questionnaire."	No differences from protocol.	February 25, 2000	March 15, 2000	1

Study number	Publication code	Type of report	Participant inclusion criteria (Protocol)	Participant inclusion criteria (Report)	Enrollment start date	Enrollment end date	Number of sites
1035-002	1035-002.RR	Research report	"Those willing to enter and participate will receive a single dose of blinded medication, stratified by baseline pain intensity, postsurgery when patient-rated pain intensity on a 4-point categorical scale is moderate or severe." "Men or women. Women of childbearing potential must have a negative pregnancy test prior to receiving study medication and must be using a reliable form of contraception; - Must be 18 years of age or older; - Must have undergone one of the following major inpatient orthopedic surgical procedures: - Total knee replacement; - Total hip replacement; - Hip hemiarthroplasty (replacement of femoral head); - Total shoulder replacement; - Major rotator cuff tear repair (acute complete tears); - Osteotomy (major lower extremities only; - Open reduction internal fixation (isolated lower extremities without other coexisting major trauma); - Spinal fusions. - Must have no clinically significant illness which would contraindicate the patient's participation in the trial as determined by medical history, physical examination, or laboratory findings as recorded in their hospital chart; - Must understand the nature of the study and provide a written informed consent as descr bed in Appendix E; - Must be reliable, cooperative, and in the opinion of the investigator, able to understand the information required in the pain questionnaire/analgesia diary; - Must be experiencing self-rated postoperative pain secondary to orthopedic surgery; - Must be able to take oral medication; These criteria are mandatory and must be met to provide evaluable data."	No differences from protocol.	12/03/99	August 25, 2000	2

Nociceptive Pain
Table 5 - Interventions and Run-in Phase

Study number	Publication code	Run-in phase (Protocol)	Run-in phase (Report)	Trial design	Total length of follow-up	Description of intervention	Treatment (gabapentin dose, duration, frequency) different from protocol
1032-001	1032-001.RR	Not mentioned.	Not mentioned.	Parallel-groups	"One dose"	"The Parke-Davis Clinical Pharmacy Operations Department provided study medication in bottles of 3 identical capsules containing NPN [naproxen], GBP [gabapentin], or placebo." Table 2 lists the treatment groups: PBO: 3 capsules of placebo; GBP250mg: 2 capsules placebo plus 1 capsule gabapentin 250 mg; GBP125/NPN125: 1 capsule placebo plus 1 capsule gabapentin 125 mg plus naproxen sodium 125 mg; GBP125/NPN250: 1 capsule placebo plus 1 capsule gabapentin 125 mg plus 1 capsule naproxen sodium 250 mg; GBP250/NPN125: 1 capsule placebo plus 1 capsule gabapentin 250 mg plus 1 capsule naproxen sodium 125 mg; GBP250/NPN250: 1 capsule placebo plus 1 capsule gabapentin 250 mg plus 1 capsule naproxen sodium 250 mg; NPN125 mg: 2 capsules placebo plus 1 capsule naproxen sodium 125 mg; NPN250 mg: 2 capsules placebo plus 1 capsule naproxen sodium 250 mg; NPN550 mg: 2 capsules placebo plus 1 capsule naproxen sodium 550 mg. "Each oral dose was administered with at least 4 ounces of water and all capsules were swallowed intact within 1 minute of swallowing the first capsule." "Patients were encouraged to avoid additional analgesic medication for at	☐

Study number	Publication code	Run-in phase (Protocol)	Run-in phase (Report)	Trial design	Total length of follow-up	Description of intervention	Treatment (gabapentin dose, duration, frequency) different from protocol
						least 90 minutes after study drug administration. At any time patients could choose to receive "resuce medication," either acetaminophen 1000 mg or acetaminophen/hydrocodone combination, ordered by the physician."	

Study number	Publication code	Run-in phase (Protocol)	Run-in phase (Report)	Trial design	Total length of follow-up	Description of intervention	Treatment (gabapentin dose, duration, frequency) different from protocol
1032-002	1032-002.RR	"The study consists of 3 phases: a screening phase, a washout phase, and a 4-week double-blind treatment phase." "The first day on which a patient discontinues his/her NSAID [non-steroidal anti-inflammatory drug] and/or analgesic therapy will be considered the first day of the washout phase. The purpose of the washout phase is to precipitate an increase in OA [osteoarthritis] pain, and to ensure a minimum level of OA pain in the study." "Upon entry into the washout phase, NSAID and/or analgesic therapy (other than acetaminophen rescue) will be discontinued. Patients wil be asked to complete daily pain diaries and must have completed them for 75%of the possible washout days." "Within the 3- to 14-day washout phase, patients must: - Rate knee pain intensity on walking on a flat surface as MODERATE, SEVERE, or EXTREME; - Have refrained from using any prior analgesic medication (except acetaminophen) for at least 5 half lives of the particular medication; and - Be randomized to study medication."	"The study consisted of Screening (2 weeks maximum), Washout (from 3 to 14 days in duration), and a 2-phase double-blind treatment period (of 4 weeks total duration)." "Washout was used to precipitate an increase in, and ensure a minimum level of OA pain."	Parallel-groups	Unclear. "This was a 4-week, randomized, double-blind, placebo- and positive-controlled, parallel-group, multicenter study (Figure 1). The study consisted of Screening (2 weeks maximum), Washout (from 3 to 14 days in duration), and a 2-phase double-blind treatment period (of 4 weeks total duration).	"Table 3 shows the dose design used to maintain blinding." [Table 3 shows the following groups: Placebo (3 capsules), GBP125 (2 capsules placebo and 1 capsule 125 mg gabapentin), GBP125/NPN250 (1 capsule each of placebo, 125 mg gabapentin and 250 mg naproxen sodium), NPN250 (2 capsules placebo and 1 capsule 250 mg naproxen sodium), NPN550 (2 capsules placebo and 1 capsule 550 mg naproxen sodium). "Patients were treated with study medication twice a day (BID) for the 28 days of the study. Patients who received GBP125 or NPN250 for their first dose of study medication were treated with GBP125/NPN250 in Study Phase 2." [Figure 1 indicates: "Study Phase 1" lasted for 12 hours after "Dose 1" and "Study Phase 2" lasted from "Hour 12 to Study Day 28".] "Patients took their first dose of study medication on the morning of Day 1 in the clinic after being randomized. Patients took an evening dose at home on Day 1 after completing 12 hours of efficacy assessments. The BID-dosing regimen continued throughout the 4-week double-blind treatment period."	☐

Study number	Publication code	Run-in phase (Protocol)	Run-in phase (Report)	Trial design	Total length of follow-up	Description of intervention	Treatment (gabapentin dose, duration, frequency) different from protocol
1032-003	1032-003.RR	Not mentioned.	Not mentioned.	Open-label, uncontrolled	"No minimum time on open-label treatment was required."	"Study medication consisted of 125-mg gabapentin capsules and 250-mg naproxen sodium capsules and market-image (combination) capsules (Table 2)." "All patients began open-label treatment with GBP125/NPN250. If the investigator determined a lack of efficacy and this dose was well-tolerated after at least 4 weeks of dosing, patients could titrate to GBP250/NPN500. Patients who did not tolerate the higher dose could titrate back to GBP125/NPN250."	☐

Study number	Publication code	Run-in phase (Protocol)	Run-in phase (Report)	Trial design	Total length of follow-up	Description of intervention	Treatment (gabapentin dose, duration, frequency) different from protocol
1032-004	1032-004.RR	"The study consists of 3 phases: screening, baseline, and a 1-week double-blind dosing phase." "Screening Phase - Subjects will be assessed for study eligibility during the screening phase, which may be up to a maximum period of 2 weeks." "Baseline Phase - Subjects will undergo a predose endoscopy."	"The study consisted of 3 phases: Screening (2-week maximum duration), Baseline (1 day), and a 1-week double-blind dosing phase (Figure 1)."	Parallel-groups	"The study consisted of 3 phases: Screening (2-week maximum duration), Baseline (1 day), and a 1-week double-blind dosing phase (Figure 1)."	"Subjects satisfying the inclusion/exclusion criteria (specified in Sections 4.2.1 and 4.2.2) entered the double-blind phase and were randomly assigned to 1 of 5 study drug groups: 1. Placebo (PBO) 2. Gabapentin 125 mg with Naproxen Sodium 250 mg (GBP125/NPN250) 3. Gabapentin 250 mg with Naproxen Sodium 500 mg (GBP250/NPN500) 4. Naproxen Sodium 250 mg (NPN250) 5. Naproxen Sodium 500 mg (NPN500)" "Each subject received 3 capsules BID, except for Study Days 1 and 8 (Table 2). All but the last dose were to be taken with food and at the same times each morning and evening." "The last dose (Day 8) was to be taken without food, 2 to 4 hours prior to the postdose endoscopy. Subjects were paged, morning and evening through Day 7, to remind them to take their doses of study drug."	☐

Study number	Publication code	Run-in phase (Protocol)	Run-in phase (Report)	Trial design	Total length of follow-up	Description of intervention	Treatment (gabapentin dose, duration, frequency) different from protocol
1035-001	1035-001.RR	Not mentioned.	Not mentioned.	Parallel-groups	8 hours. "A nurse observer queried patients regarding pain intensity at the following target time points: immediately before administration of study medication (Time 0), and 0.33 (20 minutes), 0.66 (40 minutes), 1, 2, 3, 4, 5, 6, 7, and 8 hours postdose." "Patients were encouraged to remain in the clinic for observation for a total of 8 hours after the initial dose of study medication. Further treatment was at the discretion of the investigator."	"Patients who experienced postsurgery pain that was rated moderate or severe in intensity on a 4-point categorical scale and ≥45 mm on a 100 mm visual assessment scale (VAS) were stratified by pain intensity and randomly assigned to 1 of 5 treatment groups (Figure 1): 1. Placebo 2. Gabapentin 250 mg and Hydrocodone 10 mg (GBP250/HC10) 3. Gabapentin 250 mg (GBP250) 4. Hydrocodone 10 mg (HC10) 5. Acetaminophen 1000 mg and Hydrocodone 10 mg (APAP1000/HC10)" "Patient received a single dose of study medication." "Each patient received 2 capsules and 2 caplets (Table 2). Each dose was administered with at least 4 ounces of water and all doses were swallowed intact within 1 minute of swallowing the first dose." "Patients were encouraged to avoid additional analgesic medication for at least 90 minutes after study drug administration. If at anytime thereafter self-rated pain was at least moderate, patients could receive "rescue medication" (an NSAID such as buprofen), as ordered by the physician. Prior to rescue medication, patients had a final assessment and blood draw."	☐

Study number	Publication code	Run-in phase (Protocol)	Run-in phase (Report)	Trial design	Total length of follow-up	Description of intervention	Treatment (gabapentin dose, duration, frequency) different from protocol
1035-001. Addndm-B	1035-001. Addndm-B.RR	Protocol 1035-001: Not mentioned.	Not mentioned.	Parallel-groups	8 hours. "A nurse observer queried patients regarding pain intensity at the following target time points: immediately before administration of study medication (Time 0), and 0.33 (20 minutes), 0.66 (40 minutes), 1, 2, 3, 4, 5, 6, 7, and 8 hours postdose." "Patients were encouraged to remain in the clinic for observation for a total of 8 hours after the initial dose of study medication. Further treatment was at the discretion of the investigator."	"Patients who experienced postsurgery pain that was rated moderate or severe in intensity on a 4-point categorical scale and ≥45 mm on a 100-mm visual analog scale (VAS) were stratified by pain intensity and randomly assigned to 1 of 5 treatment groups (Figure 2): 1. Placebo (PBO); 2. Gabapentin 250 mg and Hydrocodone 5 mg (GBP250/HC5); 3. Gabapentin 125 mg and Hydrocodone 10 mg (GBP250/HC10); 4. Gabapentin 500 mg and Hydrocodone 10 mg (GBP500/HC10); and 5. Gabapentin 500 mg (GBP500)." "Each patient received 3 capsules (Table 2)." "Each dose was administered with at least 4 ounces of water and all capsules were swallowed intact within 1 minute of swallowing the first capsule." "Patients were encouraged to avoid additional analgesic medication for at least 90 minutes after study drug administration. If at anytime thereafter self-rated pain was at least moderate, patients could receive "rescue medication" (an NSAID such as buprofen), as ordered by the physician. Prior to rescue medication, patients had a final assessment and blood draw."	☐

Study number	Publication code	Run-in phase (Protocol)	Run-in phase (Report)	Trial design	Total length of follow-up	Description of intervention	Treatment (gabapentin dose, duration, frequency) different from protocol
1035-002	1035-002.RR	"All short-acting analgesics must be last used 2 hours prior to the baseline assessments and administration of study medication." "At 24 hours postsurgery, patients must be able to tolerate a minimum of 4 hours with their epidural suspended. Parenteral short-acting opioid can be delivered as a bolus or via PCA during this 4-hour period. However, if administered, there must be a minimum wait of 2 hours prior to the baseline assessments and administration of the study medication."	"Washout of Analgesic Medications - Use of short-acting opioids, delivered as a bolus or via Patient Controlled Analgesia (PCA), was permitted following surgery. This analgesic use must have ceased at least 2 hours prior to study medication dosing. - Use of epidural analgesia was permitted for 24 hours following surgery. At 24 hours, patients were required to suspend epidural use for at least 4 hours. During these 4 hours, patients could receive short-acting opioids as described above. - Use of any analgesic, centrally acting, of anti-inflammatory medications within 2 hours prior to study drug administration was prohibited."	Parallel-groups	8 hours. "Patients were encouraged to remain in the hospital for observation for a total of 8 hours after their initial dose of study medication."	"Patients who experienced postoperative pain that was self-rated as moderate (2 points) or severe (3 points) in intensity on a 4-point categorical scale and satisfied an analgesic washout of at least 2 hours were randomly assigned to 1 of 4 treatment groups: 1. Placebo 2. Gabapentin 250 mg and Hydrocodone 10 mg (GBP250/HC10) 3. Gabapentin 250 mg (GBP250) 4. Hydrocodone 10 mg (HC10)" "Patients received a single dose of study medication." "Each patient received 2 capsules (Table 3) to be swallowed intact within a 1-minute period." "Patients were encouraged to avoid additional analgesic medication for at least 90 minutes after study drug administration. If at anytime thereafter self-rated pain was at least moderate, patients could receive rescue medication (including reinitiation of epidural), as ordered by the investigator. Prior to rescue medication, patients had a final assessment."	☐

Nociceptive Pain
Table 6 - Risk of Bias

Study number	Publication code	Random allocation (Protocol)	Random allocation (Report)	Method of allocation (Protocol)	Method of allocation (Report)	Concealment of allocation (Protocol)	Concealment of allocation (Report)	Method of allocation concealment (Report)	Double-blind (Protocol)	Double-blind (Report)	Blinding: Notes (Protocol)	Blinding: Notes (Report)
1032-001	1032-001.RR	☑	☑	"The identity of medication will be randomized in blocks according to procedures conducted by the Biometrics Department of Parke-Davis. Patients will be assigned to prenumbered study medication provided by Parke-Davis." "Blinded capsules containing placebo, gabapentin or naproxen sodium will be available and supplied by Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, CPO. All participants will remain blinded until after all patients have completed the study and all data issues have been resolved." "Study medication will be assembled	"Patient randomization was stratified by baseline pain intensity. Patients with baseline pain intensity scores of 2 (moderate) were randomized to a single stratum and patients with baseline pain intensity scores of 3 (severe) were randomized to a second stratum." "This was accomplished by randomization number assignment- patients who fell into the first stratum were assigned sequentially increasing randomization numbers starting from the lowest number (1). Patients who fell into the second stratum were assigned sequentially decreasing numbers starting from the highest randomization number (576)."	☐	☐	No description of any attempt to conceal allocation.	☑	☑	"In order to maintain blinding all capsules will appear identical." "All participants will remain blinded until after all patients have completed the study and all data issues have been resolved."	No description on who was blinded.

Study number	Publication code	Random allocation (Protocol)	Random allocation (Report)	Method of allocation (Protocol)	Method of allocation (Report)	Concealment of allocation (Protocol)	Concealment of allocation (Report)	Method of allocation concealment (Report)	Double-blind (Protocol)	Double-blind (Report)	Blinding: Notes (Protocol)	Blinding: Notes (Report)
				by CPO, USA, according to a randomizataion code provided by the Biometrics Department."								

Study number	Publication code	Random allocation (Protocol)	Random allocation (Report)	Method of allocation (Protocol)	Method of allocation (Report)	Concealment of allocation (Protocol)	Concealment of allocation (Report)	Method of allocation concealment (Report)	Double-blind (Protocol)	Double-blind (Report)	Blinding: Notes (Protocol)	Blinding: Notes (Report)
1032-002	1032-002.RR	☑	☑	"Randomization will be stratified by center and baseline pain intensity. Patients with a baseline pain intensity score of moderate (2) will be in 1 stratum and patients with a score of severe (3) [or extreme (4) deleted per Amendment 1] will be in the other stratum. Centers with low enrollment will be randomly pooled together to form new centers for analysis." [per Amendment 1]: "Patients in 2A and B treatment arms will be switched to the treatment group 2A+B after their first dose of treatments. These patients will only be used for collecting safety data. At Stage 2 and 3, any comparisons involving 2A+B in efficacy analyses will only include the patients who are originally	"PGRD [Pfizer Global Research & Development] Biometrics Department generated the randomization code. The block size was 5." "Randomization was stratified by center and baseline pain intensity." "Patients who rated their pain after their first 1-minute wa k as moderate (2) were randomized to 1 stratum and patients with a score of severe (3) were randomized to a second stratum." "Patients were randomly assigned to treatment and the blinded medication sequentially dispensed. All study medication was prepackaged in trays for each patient, identified by randomization number and a control number, and contained detailed instructions for daily administration." "It was planned to randomly pool together centers with low enrollment and	☐	☐	No description of any attempt to conceal allocation.	☑	☑	No description on who was blinded.	No description on who was blinded.

Study number	Publication code	Random allocation (Protocol)	Random allocation (Report)	Method of allocation (Protocol)	Method of allocation (Report)	Concealment of allocation (Protocol)	Concealment of allocation (Report)	Method of allocation concealment (Report)	Double-blind (Protocol)	Double-blind (Report)	Blinding: Notes (Protocol)	Blinding: Notes (Report)
				randomized in this treatment groups." "Let "A" be naproxen sodium 125 mg, "B" be gabapentin 125 mg, and "C" be naproxen sodium 550 mg; the 6 treatment groups in the order of anticipated potency are: Placebo, 2B, A+B, 2A, 2A+2B, and C." "The medication will be individually assembled for each patient and identified by the patient study number and a control number, according to a randomization code prepared by the Parke-Davis CPO Department. Patients will be randomly assigned to treatment and the blinded medication sequentially dispensed."	use the pooled centers for analysis." [Omitted citation to reference in original text]. "Because the lowest enrollment was 8 patients in Center 4, it was decided, prior to breaking the blind, that no pooling was necessary."						

Study number	Publication code	Random allocation (Protocol)	Random allocation (Report)	Method of allocation (Protocol)	Method of allocation (Report)	Concealment of allocation (Protocol)	Concealment of allocation (Report)	Method of allocation concealment (Report)	Double-blind (Protocol)	Double-blind (Report)	Blinding: Notes (Protocol)	Blinding: Notes (Report)
1032-003	1032-003.RR	☐	☐	Not applicable. Open-label, uncontrolled trial.	Not applicable.	☐	☐	Not applicable.	☐	☐	Not applicable.	Not applicable.
1032-004	1032-004.RR	☑	☑	"A simple fixed block size randomization will be applied." "The study drug will be packaged in subject-specific, nonchildproof trays, according to the randomization code prepared by the Parke-Davis CPO department. Subjects will be randomly assigned to study drug and will be dispensed sequentially."	"A simple fixed block size randomization was used with a block size of 5."	☐	☐	No description of any attempt to conceal allocation.	☑	☑	No description on who was blinded.	"All data remained blinded until all subjects completed the study and all data issues were resolved. The randomization code was broken on May 31, 2000"

Study number	Publication code	Random allocation (Protocol)	Random allocation (Report)	Method of allocation (Protocol)	Method of allocation (Report)	Concealment of allocation (Protocol)	Concealment of allocation (Report)	Method of allocation concealment (Report)	Double-blind (Protocol)	Double-blind (Report)	Blinding: Notes (Protocol)	Blinding: Notes (Report)
1035-001	1035-001.RR	☑	☑	"The identity of medication will be randomized in blocks according to procedures conducted by the Biometrics Department and Clinical Pharmaceutical Operations Department (CPO) of the Parke-Davis." "Patients will be assigned to prenumbered study medication provided by Parke-Davis." "Patients will be randomized by their pain status. Patients with Moderate pain will receive medication labeled with ascending numbers beginning with 157. Those with Severe pain will receive descending numbers beginning with 468." "Randomization will be stratified by baseline pain	"At the request of the Biometrics Department, Parke-Davis Clinical Pharmacy Operations generated the randomization code for 468 patients with a block size of 13." "Patient randomization was stratified by baseline pain intensity. Patient number was assigned based on baseline pain intensity and by participation in the serial pharmacokinetic (PK) analysis (Addendum A)." "Patients with moderate pain (baseline pain intensity score of 2) and participants in Addendum A were assigned sequentially increasing numbers from 1." "Nonparticipants experiencing moderate pain were assigned sequentially increasing numbers from 157." "Patients with severe pain (baseline pain intensity score of 3) and participants in Addendum A were	☐	☐	No description of any attempt to conceal allocation.	☑	☑	"Blinded capsules containing placebo, gabapentin, or hydrocodone will be available and supplied by Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company CPO. All participants will remain blinded until after all patients have completed the study and all data issues have been resolved."	"All participants remained blinded until after all patients completed the study and all data issues were resolved."

Study number	Publication code	Random allocation (Protocol)	Random allocation (Report)	Method of allocation (Protocol)	Method of allocation (Report)	Concealment of allocation (Protocol)	Concealment of allocation (Report)	Method of allocation concealment (Report)	Double-blind (Protocol)	Double-blind (Report)	Blinding: Notes (Protocol)	Blinding: Notes (Report)
				intensity. Patients with a baseline pain intensity score of moderate (2) will be in one stratum, and patients with a score of severe (3) will be in another stratum. Patients participating in the Addendum A will be randomized to a separate block of study medication. They will also be stratified according to baseline pain intensity."	assigned sequentially decreasing numbers from 156." "Nonparticipants experiencing severe pain were assigned sequentially decreasing numbers from 648."							

Study number	Publication code	Random allocation (Protocol)	Random allocation (Report)	Method of allocation (Protocol)	Method of allocation (Report)	Concealment of allocation (Protocol)	Concealment of allocation (Report)	Method of allocation concealment (Report)	Double-blind (Protocol)	Double-blind (Report)	Blinding: Notes (Protocol)	Blinding: Notes (Report)
1035-001. Addndm-B	1035-001. Addndm-B.RR	☑	☑	Protocol 1035-001: "The identity of medication will be randomized in blocks according to procedures conducted by the Biometrics Department and Clinical Pharmaceutical Operations Department (CPO) of the Parke-Davis." "Patients will be assigned to prenumbered study medication provided by Parke-Davis." "Patients will be randomized by their pain status.Patients with Moderate pain will receive medication labeled with ascending numbers beginning with 157. Those with Severe pain will receive descending numbers beginning with 468." "Randomization	"At the request of the Biometrics Department, Parke-Davis Clinical Pharmacy Operations generated the randomization code for 150 patients with a block size of 5." "Patients were randomized by their baseline pain intensity. Patients in moderate pain (baseline pain intensity score of 2) were assigned sequentially increasing numbers beginning with Number 501. Patients with severe pain (baseline pain intensity score of 3) were assigned sequentially decreasing numbers from Number 650."	☐	☐	No description of any attempt to conceal allocation.	☑	☑	Protocol 1035-001: "Blinded capsules containing placebo, gabapentin, or hydrocodone will be available and supplied by Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company CPO. All participants will remain blinded until after all patients have completed the study and all data issues have been resolved."	"All participants remained blinded until after all patients completed the study and all data issues were resolved."

Study number	Publication code	Random allocation (Protocol)	Random allocation (Report)	Method of allocation (Protocol)	Method of allocation (Report)	Concealment of allocation (Protocol)	Concealment of allocation (Report)	Method of allocation concealment (Report)	Double-blind (Protocol)	Double-blind (Report)	Blinding: Notes (Protocol)	Blinding: Notes (Report)
				will be stratified by baseline pain intensity. Patients with a baseline pain intensity score of moderate (2) will be in one stratum, and patients with a score of severe (3) will be in another stratum. Patients participating in the Addendum A will be randomized to a separate block of study medication. They will also be stratified according to baseline pain intensity."								

Study number	Publication code	Random allocation (Protocol)	Random allocation (Report)	Method of allocation (Protocol)	Method of allocation (Report)	Concealment of allocation (Protocol)	Concealment of allocation (Report)	Method of allocation concealment (Report)	Double-blind (Protocol)	Double-blind (Report)	Blinding: Notes (Protocol)	Blinding: Notes (Report)
1035-002	1035-002.RR	☑	☑	"The identity of medication will be randomized in blocks according to procedures conducted by the Biometrics Department of Parke-Davis. Patients will be assigned to prenumbered study medication provided by Parke-Davis." "Randomization will be stratified by center and baseline pain intensity. Patients with a baseline pain intensity score of moderate (2) will be in one stratum and patients with a score of severe (3) will be in another stratum."	"The Pfizer Global Research & Development (PGRD) Biometrics Department generated the randomization code for 384 patients with a block size of 4." "Patient randomization was stratified by center and by baseline pain intensity." "Patients with moderate pain were assigned sequentially increasing numbers from 1 to 192." "Patients in severe pain were assigned sequentially increasing numbers from 501 to 692."	☐	☐	No description of any attempt to conceal allocation.	☑	☑	"In order to maintain blinding all capsules will appear identical." "All participants will remain blinded untill after all patients have completed the study and all data issues have been resolved."	"All participants' data remained blinded until after all patients completed the study and all data issues were resolved."

Nociceptive Pain
Table 7 - Primary Outcome and Number of Patients Assessed

Study number	Publication code	Primary outcome (protocol)	Primary outcome (Report)	Number randomized per group (Report)	Number analyzed per group - Primary outcome (Report)	Number analyzed per group for safety (Report)	Definitions for study population for analysis (Report)
1032-001	1032-001.RR	"Primary efficacy measures include PR [Pain Relief], PID ["..difference between the baseline pain intensity and the pain intensity at another time point"], PRID ["..is the sum of the pain relief and the pain intensity difference at a given time point"], time to onset and duration of analgeisa." "Scores are derived from the pain assessments." "A nurse observer will query the patients regarding pain intensity at the following target time points: immediately before administration of study medication (Time 0) and 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 postdose." "A nurse observer will query the patients regarding pain relief at the target times of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours postdose." "If rescue medication is administered, final assessment is made immediately before rescue medication is taken."	"The primary efficacy endpoint was the summed pain-intensity difference over the first 6 hours postdose (SPID6)."	"Of these, 483 were randomly assigned to treatment: 50 patients to each of the GBP250, GBP125/NPN125, GBP125/NPN250, GBP250/NPN250, NPN125, and NPN250 groups, 52 patients each to the placebo and GBP250/NPN125 groups, and 79 patients to the NPN550 group."	[per Figure 4, Page 37: 50 patients in each of the GBP250, GBP125/NPN125, GBP125/NPN250, GBP250/NPN250, NPN125, and NPN250 groups, 52 patients each to the placebo and GBP250/NPN125 groups, and 79 patients to the NPN550 group.]	All patients randomized (483) were analyzed for safety evident from adding numbers provided in Figure 12 on page 51 of the research report.	"The population analyzed was the intent-to-treat (ITT) population, defined as all patients randomized to treatment who received study medication, and who had a baseline and post baseline scores as defined in the FDA guidance." [Omitted citation to reference mentioned in original text].

Study number	Publication code	Primary outcome (protocol)	Primary outcome (Report)	Number randomized per group (Report)	Number analyzed per group - Primary outcome (Report)	Number analyzed per group for safety (Report)	Definitions for study population for analysis (Report)
1032-002	1032-002.RR	"The primary efficacy parameter is SPID6, the sum of pain intensity difference over the first 6 hours."	[per Inferential Analysis Plan, Appendix D.1]: "Summed pain intensity difference over the first 6 hours (SPID6)"	Table 8 indicates the number of patients randomized as follows: 53 to placebo, 52 to GBP125/NPN250, 51 to GBP125, 54 to NPN250, and 52 to NPN550. Table 8 lists number of patients who "Entered Study Phase 2": 53 in placebo group, 155 in GBP125/NPN250 group and 51 in the NPN550 group.	Figure 2 indicates number of patients analyzed at the end of "Study Phase 1": 53 in placebo group, 52 in GBP125/NPN250 group, 51 in GBP125 group, 54 in NPN250 group, 52 in NPN550 group. Number of patients analyzed in "Study Phase 2" is not clear.	Appendix C.2.01 indicates number of patients analyzed for adverse events: 53 in placebo group, 157 in GBP125/NPN250 group, and 52 in NPN550 group.	Intent-to-treat population: "The analysis set was the intent-to-treat (ITT) population, defined as all patients randomized to treatment who received at least one dose of study medication." "All Study Phase 2 efficacy analyses and comparisons included only the patients who were originally randomized to GBP125/NPN250, placebo, or NPN550. Patients in the NPN250 and GBP125 treatment arms for Study Phase 1 received GBP125/NPN250 treatment for Study Phase 2. Only safety data were used for these patients from Study Phase 2."

Study number	Publication code	Primary outcome (protocol)	Primary outcome (Report)	Number randomized per group (Report)	Number analyzed per group - Primary outcome (Report)	Number analyzed per group for safety (Report)	Definitions for study population for analysis (Report)
1032-003	1032-003.RR	"The following efficacy assessments will be performed, unless otherwise noted,at baseline, 1, 3, 6, 9, and 12 months and every 6 months thereafter; - Pain subscale of the WOMAC LK 3.1 Scale; - Stiffness subscale of the WOMAC LK 3.1 Scale; - Physical Function subscale of the WOMAC LK 3.1 Scale; - Patient assessment of pain walking on a flat surface from WOMAC LK 3.1 Scale; - Patient Global Assessment of OA (assessed on 5-point L kert Scale); - Clinician Global Assessment of OA (assessed on 5-point L kert Scale); - HUI Mark 2 and Mark 3; and - SF-36 (this instrument will only be administered every 6 months)."	"Although this was primarily a safety study, select efficacy assessments were scheduled during the clinic visits. Instruments used were: - The Western Ontario and McMaster Universities Likert Version 3.1 (WOMAC LK3.1) OA Index questionnaire, - Patient and clinician global assessments of OA, - The Health Utilities Index (HUI) Mark 2 and 3, and -The Short Form Health Survey (SF-36)." "However, because the study was terminated early, efficacy data were not summarized."	Per Table 4, 212 "Patients Entered in Open-Label Study"	Not applicable. "However, because the study was terminated early, efficacy data were not summarized."	212 patients.	"The analysis set was all patients who received at least one dose of study medication."

Study number	Publication code	Primary outcome (protocol)	Primary outcome (Report)	Number randomized per group (Report)	Number analyzed per group - Primary outcome (Report)	Number analyzed per group for safety (Report)	Definitions for study population for analysis (Report)
1032-004	1032-004.RR	"The primary efficacy parameter is the ulcer and erosion incidence, defined as a gastric mucosal score ≥3 according the modified Lanza 8-point scale, after 1 week of study drug dosing." [Omitted citation to reference in original text].	"The primary efficacy parameter was the ulcer and erosion incidence, defined as gastric mucosal score ≥3 according to the modified Lanza 8-point scale, after 1 week of study drug dosing." [Omitted citation to reference in original text].	"Of these, 206 (73%) were randomly assigned to 1 of the 5 study drug groups (42 to placebo, and 41 each to GBP125/NPN250, GBP250/NPN500, NPN250, and NPN500)."	Placebo: 42; GBP125/NPN250: 41; GBP250/NPN500: 41; NPN250: 41; NPN500: 40. [Data extracted from Figure 2.]	Placebo: 42; GBP125/NPN250: 41; GBP250/NPN500: 41; NPN250: 41; NPN500: 41. [Data extracted from Table 17.]	Intent-to-treat (ITT): "The primary sample was intent-to-treat (ITT) subjects, defined as all subjects randomized who received at least one dose of study drug, and who had a postdose measurement (endoscopy or UGI symptom score). All efficacy analyses were performed on this sample." Completers: "The secondary sample was Completers, defined as randomized subjects who took at least 36 capsules of study drug and had a postdose measurement." "Analyses of the primary parameter and the UGI symptom scores, other than the exploratory UGI symptom correlation analyses to aid in development of the UGI symptom questionnaire, was planned originally for this sample. However, because the ITT and Completers samples were identical, the Inferential Analysis Plan was amended and the separate Completers analyses and summaries were not performed."
1035-001	1035-001.RR	"The primary efficacy parameter is SPID6, the sum of pain intensity difference over the first 6 hours."	"The primary efficacy endpoint was the summed pain-intensity difference over the first 6 hours postdose (SPID6)."	"Of these 325 were randomly assigned to treatment: 51 to the placebo group, 75 to the GBP250/HC10 group, 77 to the GBP250 group, 76 to the HC10 group, and 46 to the APAP1000/HC10 group."	Table 6 mentions Intent-to-Treat population as 51 in placebo group, 75 in the GBP250/HC10 group, 77 in the GBP250 group, 76 in the HC10 group, 46 in the APAP1000/HC10 group	Table 16 mentions numbers analyzed for adverse events: 51 in placebo group, 75 in GBP250/HC10 group, 77 in GBP250 group, 76 in HC10 group, 46 in APAP1000/HC10 group.	Intent-to-treat population: "The population was the intent-to-treat (ITT) population, defined as all patients randomized to treatment who received study medication, and who had a baseline and postbaseline score as defined in the FDA 1997 guidance." [Omitted citation to reference in original text].

Study number	Publication code	Primary outcome (protocol)	Primary outcome (Report)	Number randomized per group (Report)	Number analyzed per group - Primary outcome (Report)	Number analyzed per group for safety (Report)	Definitions for study population for analysis (Report)
1035-001. Addndm-B	1035-001. Addndm-B.RR	Protocol 1035-001: "The primary efficacy parameter is SPID6, the sum of pain intensity difference over the first 6 hours."	"The following efficacy measures were summarized: - Summed pain-intensity difference over the first 6 hours postdose (SPID6); - Summed pain-intensity difference over the first 8 hours postdose (SPID8); - Total pain relief over the first 6 hours (TOTPAR6) and 8 hours (TOTPAR8), - Summed pain relief intensity difference over the first 6 hours (SPRID6) and 8 hours (SPRID8); - Pain-intensity difference from baseline (PID); - Pain relief (PR); - Summed pain relief and pain-intensity difference (PRID); - Time-to-onset by 1-stopwatch method; - Time-to-rescue medication; and - Patient Global Assessment of Study Medication." "A nurse observer queried patients regarding pain intensity at the following target time points: immediately before administration of study medication (Time 0), and 0.33 (20 minutes), 0.66 (40 minutes), 1, 2, 3, 4, 5, 6, 7, and 8 hours postdose." "If rescue medication was administered, final assessment was made immediately before the dose was taken."	"Of these, 101 were randomly assigned to treatment: 20 to each of the placebo, GBP250/HC5, GBP125/HC10, and GBP500/HC10 groups, and 21 to the GBP500 group."	Table 4: 20 each in placebo group, GBP250/HC5 group, GBP125/HC10 group, GBP500/HC10 group, and 21 in GBP500 group	Table 8: 20 each in placebo group, GBP250/HC5 group, GBP125/HC10 group, GBP500/HC10 group, and 21 in GBP500 group	Intent-to-treat population: "The population was the intent-to-treat (ITT) population, defined as all patients randomized to treatment who received study medication, and who had a baseline and postbaseline score as defined in the FDA 1997 guidance." [Omitted citation to reference in original text].

Study number	Publication code	Primary outcome (protocol)	Primary outcome (Report)	Number randomized per group (Report)	Number analyzed per group - Primary outcome (Report)	Number analyzed per group for safety (Report)	Definitions for study population for analysis (Report)
1035-002	1035-002.RR	"The primary efficacy parameter is SPID6, the sum of pain intensity difference over the first 6 hours." "A nurse observer will query the patients regarding pain relief at the target times of 20 and 40 minutes and at 1,2, 3, 4, 5, 6, 7, and 8 hours postdoese."	"The primary efficacy endpoint was the summed pain intensity difference over the first 6 hours postdose (SPID6)." "A nurse observer queried patients regarding pain intensity at the following target time points: immediately before administration of study medication (Time 0), and 0.33 (20 minutes), 0.66 (40 minutes), 1, 2, 3, 4, 5, 6, 7, and 8 hours postdose. If rescue medication was administered, final assessment was made immediately before the dose was taken."	"Of these, 200 were randomly assigned to treatment: 49 to the placebo group, 51 to the GBP250/HC10 group, 50 to the GBP250 group, and 50 to the HC10 group."	"Primary ANCOVA Model": Not mentioned. "Alternative ANCOVA Models": "Baseline opiate concentration and metabolizer status data were available for only 116 and 109 patients, respectively; therefore, these analyses were not as well-powered as the primary ANCOVA." "Eleven patients did not complete the study."	Table 18 indicates the following number of patients analyzed for safety: 49 in placebo group, 51 in GBP250/HC10 group and 50 each in GBP250 and HC10 groups. "A total of 47 patients (24%) in this study experienced at least 1 adverse event (Table 18)." [However, if we calculate using the numbers in the above statement from the text in section 6.7.1.1, the number of patients analyzed seem to be 195.833 (47/0.24). This is inconsistent with the numbers analyzed as depicted in Table 18].	Intent-to-treat population: "The population was the intent-to-treat (ITT) population, defined as all patients randomized to treatment who received study medication and who had a baseline and postbaseline scores as defined in the FDA 1997 guidance." [Omitted citation to reference in original text].

Nociceptive Pain
Table 8 - Comparison of Study Reports by Results and Conclusions

Study number	Publication code	Results of primary analysis (Report)	Adverse events (Results section of Report)	Conclusions in abstract & discussion sections (Report)	Conclusions in discussion consistent with results (Report)	Conclusions in abstract consistent with results (Report)
1032-001	1032-001.RR	"The GBP250 [gabapentin 250 mg]/NPN250 [naproxen sodium 250 mg] combination was statistically significantly different from placebo (p = 0.0001) and from GBP250 (p = 0.0001), as well as numerically superior to NPN250 (p = 0.0946), on the SPID6 [summed pain-intensity difference over the first 6 hours postdose] efficacy measure." "The GBP125/NPN250 combination was also statistically significantly different from placebo (p = 0.0001) and from GBP250 (p = 0.0001), as well as numerically superior to NPN250 (p = 0.0646) on the SPID6 efficacy measure." "The remaining 2 GBP/NPN combinations were significantly different from placebo (p = 0.001) and from GBP250 (p = 0.0196 for GBP125/NPN125 compared to GBP250 and p = 0.0052 for GBP250/NPN125 compared to GBP250) on the SPID6 endpoint." "The min-test as defined in the method section was negative in these cases (Table 11)." "Both GBP/NPN combinations that contain 250 mg of NPN were not statistically different from NPN550 in analgesic effect, although NPN550 was significantly better than NPN250 by itself (Table 12)."	"A total of 206 patients (43%) in this study experienced at least 1 adverse event (Table 17)." "Across treatment groups, the percentage of patients who experienced adverse events ranged from 34% of the GBP250 [gabapentin 250 mg]/NPN250 [naproxen sodium 250 mg] to 50% of the GBP250 group (Appendix C.16.1)." "Adverse events considered associated with study medications were experienced by 24% of all patients." "The incidence of frequently occurring adverse events in this study (experienced by more than 5% of patients in any single treatment group) ranged from 6% for somnolence in the placebo group to 22% for nausea in both the NPN125 [naproxen sodium 125 mg] and GBP125 [gabapentin 125 mg] /NPN125 groups." "Adverse events of particular note are pain (14% of the GBP125/NPN125 group), vomiting (14% of the NPN125 group), and headache (20% of the GBP group)."	Synposis of report: "In patients with pain resulting from dental surgery, this study demonstrated statistically significantly better analgesic effects of the GBP250/NPN250 and GBP125/NPN250 combinations compared with placebo, GBP250, and NPN250." "Efficacy was detected on PI [pain intensity], PIR [no abbreviation mentioned], and PRID [summed pain relief and pain-intensity difference] scales at times ranging between 3 and 6 hours postdose." Conclusions section of report: 'In patients with pain resulting from dental surgery, this study demonstrated statistically significantly better analgesic effects (SPID6) [summed pain-intensity difference over the first 6 hours postdose] of the GBP250/NPN250 and GBP125/NPN250 combinations compared with placebo and GBP250, and numerically superior effects compared with NPN250." "In addition, efficacy was detecteed on PI, PIR, and PRID scales at times ranging between 3 and 6 hours postdose."	☑	☑

Study number	Publication code	Results of primary analysis (Report)	Adverse events (Results section of Report)	Conclusions in abstract & discussion sections (Report)	Conclusions in discussion consistent with results (Report)	Conclusions in abstract consistent with results (Report)
1032-002	1032-002.RR	"No significant difference between GBP125/NPN250 and placebo, GBP125, or NPN250 was observed on the SPID6 (p = 0.788, 0.392, and 0.815, respectively) (Table 9)." "GBP125/NPN250 was significantly better than placebo on most Study Phase 2 measures at most time points and was not significantly different from NPN550 at almost every time point." "No differences between any treatment groups, including between the NPN550 active control and placebo, were observed on the SPID6 (Table 9)."	"Fifteen patients experienced adverse events during Study Phase 1 (Table 16)." "Three patients (including one who withdrew from the study) treated with GBP125 (either alone or in combination with NPN250) and one treated with NPN550 experienced dizziness." "One patient in each of the placebo, GBP125/NPN250, NPN550 groups reported headaches." "The most frequent adverse event during Study Phase 2 was peripheral edema, experienced by nearly 6% of the GBP125/NPN250 group compared with about 2% of the placebo and NPN550 groups (Table 17)." "The incidence of GI-related adverse events (diarrhea, constipation, dyspepsia, and nausea) ranged from about 2% to 6% of patients for the GBP125/NPN250 and NPN550 groups, compared with almost 0% for the placebo group." "Dizziness, somnolence, and asthenia occurred more frequently among GBP125/NPN250-treated patients than among patients in the placebo or NPN550 groups (about 3% compared with almost 0%)." "More complaints of pain and crams (abdominal pain, back pain, leg pain, shoulder pain, leg cramps, back spasms) were reported for patients in the GBP125/NPN250 group." "Two male patients in the GBP125/NPN250 group, aged 74 and 73 years, experienced serious adverse events during the study (Table 18)." "Patient 007003 was hospitalized and found to have a duodenal ulcer with gastric erosion (duodenal ulcer) considered associated with treatment. Patient 008009 was diagnosed with a stenosis of the carotid artery (peripheral vascular disorder) considered unrelated to treatment and underwent a carotid endarterectomy during the study." "A total of 7 patients withdrew from the study due to adverse events."	Synopsis of report: "For patients with OA of the knee, GBP125/NPN250 (CI-1032) provided pain relief and performed on other outcome measures significantly better than placebo and not substantially differently from NPN550 during the 4-week portion of this study." "No conclusions regarding the performance of CI-1032 as an acute analgesic were possible due to the failure of the OA flare pain model to separate active treatments from placebo in this multicenter implementation." "CI-1032 was well-tolerated over a 4-week course of treatment." Discussion section of report: "The data from the second (4 week) phase of this study demonstrate that gabapentin in combination with naproxen sodium has potential for subacute or chronic treatment of OA." "Statistical separation of GBP125/NPN250 from placebo was also observed during most of Study Phase 2, however significance levels in comparisons with placebo were generally higher for NPN550 than for GBP125/NPN250. GBP125/NPN250 was not statistically different from NPN550 on most Study Phase 2 measures." No separation of active treatments from placebo was demonstrated during the single-dose evaluation, Study Phase 1."	☐	☑

Study number	Publication code	Results of primary analysis (Report)	Adverse events (Results section of Report)	Conclusions in abstract & discussion sections (Report)	Conclusions in discussion consistent with results (Report)	Conclusions in abstract consistent with results (Report)
1032-003	1032-003.RR	"A total of 206 patients (43%) in this study experienced at least 1 adverse event (Table 17)." "Across treatment groups, the percentage of patients who experienced adverse events ranged from 34% of the GBP250 [gabapentin 250 mg]/NPN250 [naproxen sodium 250 mg] to 50% of the GBP250 group (Appendix C.16.1)." "Adverse events considered associated with study medications were experienced by 24% of all patients." "The incidence of frequently occurring adverse events in this study (experienced by more than 5% of patients in any single treatment group) ranged from 6% for somnolence in the placebo group to 22% for nausea in both the NPN125 [naproxen sodium 125 mg] and GBP125 [gabapentin 125 mg] /NPN125 groups." "Adverse events of particular note are pain (14% of the GBP125/NPN125 group), vomiting (14% of the NPN125 group), and headache (20% of the GBP group)."	"The body systems most frequently effected by adverse events were the body as a whole (53 patients, 25%), the digestive system (39 patients, 18%), and the nervous system (26 patients, 12%)." "The most frequently occurring adverse events during open-label treatment were peripheral edema (15 patients, 7%), pain, dyspepsia, and infection (12 to 13 patients each, 6%), and constipation and dizziness (10 patients each, 5%) (Table 5). Peripheral edema was also the most frequently occurring adverse event among patients treated with GBP125/NPN250 during 1032-002 Study Phase 2 (9 of 157 patients, 6%)." "A larger percentage of patients withdrew from open-label treatment during Study 1032-003 due to adverse events compared with GBP125/NPN250-treated patients during double-blind treatment in Study 1032-002 (30 of 212 patients, 14% compared with 3 of 157 patients, 2%, respectively)." "Dyspepsia, peripheral edema, and somnolence each led to the withdrawal of 3 patients (1.4%). Asthenia, diarrhea, and gastrointestinal disorder each led to the withdrawal of 2 patients (0.9%)."	Synopsis of report: "GBP125/NPN250 and GBP250/NPN500 were well-tolerated under longer term, open-label conditions." Discussion section of report: "Because earlier double-blind trials showed no strong superiority of GBP125/NPN250 over NPN550, the study was terminated prior to completion." "Efficacy data and all other data were not summarized." "The percentage of patients who experienced adverse events was higher during open-label treatment (56% compared with 37%). Likewise, the percentage of patients who withdrew due to an adverse event was higher during open-label treatment (14% compared with 2%)." "No serious adverse events were attributed to treatment, nor were there any adverse events of concern that emerged during longer term treatment with GBP/NPN."	☑	☑

Study number	Publication code	Results of primary analysis (Report)	Adverse events (Results section of Report)	Conclusions in abstract & discussion sections (Report)	Conclusions in discussion consistent with results (Report)	Conclusions in abstract consistent with results (Report)
1032-004	1032-004.RR	"According to Fisher's Exact Test, the incidence of gastric ulcers and erosions in the NPN500 [naproxen sodium 500 mg] group was not statistically significantly different from that in the GBP [gabapentin]125/NPN250 (p = 0.121) or the GBP250/NPN500 (p = 0.656) study drug groups (Table 9)." "Twenty-four (60%) subjects who took NPN500 had a gastric mucosal score ≥3 after 1 week of study drug dosing, compared with 17 (42%) subjects in the GBP125/NPN250 group and with 22 (54%) subjects in the GBP250/NPN500 group (Figure 2)."	"The most frequently occurring adverse events were gastrointestinal system-related in every study drug group." "For the higher dose combination group, GBP250/NPN500, 7 (17%) of subjects experienced flatulence, compared with 3 to 4 subjects (7% to 10%) in the other active study drug groups and 1 subject (<3%) in the placebo group." "Dyspepsia was more frequent among subjects in the NPN500 group: 8 subjects, almost 20%, compared with 3 subjects (7%) in the NPN250 group and 1 subject (<3%) of the placebo group (Table 18)." "There was no treatment difference with respect to anorexia, constipation, diarrhea, nausea, abdominal pain, vomiting, or withdrawals due to GI-related AEs [adverse events] per Fisher's Exact tests." "Also, the odds of experiencing flatulence were 8.4 times greater in the GBP250/NPN500 group than in the placebo group (p = 0.029)." [Omitted citation to footnotes in original text]. "Somnolence was the only nervous system adverse event reported by 2 or more subjects in any study group: 3 subjects (7%) in the GBP250/NPN500 group and 1 subject (<3%) in the GBP125/NPN250 group (Table 18)."	Synopsis section of report: "The specific combination doses under investigation in Study 1032-04 (GBP125/NPN250 BID and GBP250/NPN500 BID) do not provide cytoprotection against NPN-induced gastric injury. The downward trend in gastric injury for NPN250 and GBP125/NPN250 compared with NPN500 and GBP250/NPN500, and the similarity between the groups with the same NPN doses, suggest that halving the dose of NPN, with or without GBP, results in less gastric mucosal injury." Discussion section of report: "The primary results of this study in humans did not show any evidence of cytoprotection against NPN-induced gastric injury at the doses studied (GBP125/NPN250 BID and GBP250/NPN500 BID)." "Study 1032-004 did suggest that the lower dose of NPN (250 mg BID) may be less injurious to the gastric mucosa than NPN500 BID. However, the differences between the doses may not be clinically relevant."	☑	☑

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1035-001	1035-001.RR	"The GBP250/HC10 group was statistically significantly different from the placebo (p = 0.0044) and the GBP250 groups (p = 0.0155), and numerically better than HC10 (p = 0.0771), on the SPID6 efficacy measure (Table 7). The min-test, as defined in the methods (Section 4.5.4.1), was negative." "In other planned comparisons, APAP1000/HC10 was significantly better than all other treatment groups, including the GBP250/HC10 group (Table 8). The SPID6 efficacy measures for the GBP250 group and the HC10 group did not separate from the placebo group (p >0.05)."	"The incidence of frequently occurring adverse events (experienced by more than 4% of patients in any treatment group) ranged from 4% for somnolence in the HC10 group to 28% dizziness in the GBP250/HC10 (Table 16)." "The frequency of dizziness in the GBP250/HC10 group appeared to be additive of the effects seen with either GBP250 or HC10 alone, and was statistically significantly higher in the GBP250/HC10 group than in the placebo group (Odds Ratio = 4.57, 95% CI = 1.35-17.02)." "The frequency of nausea in the GBP250/HC10 group (9%) was almost 2-fold less than that of the HC10 group (17%). Despite this difference, the vomiting frequency was about the same between the 2 groups." "Dizziness was the most common adverse event associated with GBP250/HC10 treatment (27% of patients). The dizziness frequencies reported for the groups treated with the individual components of the combination were 9% for GBP250 and 17% for HC10." "The remaining adverse events most frequently associated with GBP250/HC10 treatment were headache (12%), nausea (9%), vomiting (8%), and somnolence (7%)."	Discussion section of report: "This study was the first clinical study to assess the efficacy and safety of gabapentin used in combination with hydrocodone for the treatment of acute pain." "The APAP1000 [acetaminophen 1000mg]/HC10 [hydrocodone 10 mg] group consistently outperformed the placebo group on all efficacy measures, demonstrating the validity of this study." "The GBP250 [gabapentin 250 mg]/HC10 [hydrocodone 10 mg] group provided significantly better pain relief than the placebo and GBP250 groups on most efficacy measures." "In addition, the GBP250/HC10 significantly outperformed the HC10 group on the 3- and 4-hour PRID, giving positive min-test results for the combination at these time points." "The PR, PID, and PRID curves suggest that gabapentin potentiates the analgesic effects of HC10. The GBP250/HC10 and HC10 curves are comparable for the first 2 hours. After this time, HC10 begins losing potency, but GBP250/HC10 retains its potency through 8 hours." "The GBP250/HC10 combination provided analgesic relief more quickly than either of its components." "In patients with pain resulting from dental surgery, this study demonstrated statistically significantly better analgesic effects (SPID6) of the GBP250/HC10 group compared with the placebo and GBP250 groups, and numerically better than the HC10	☑	☑

Study number	Publication code	Results of primary analysis (Report)	Adverse events (Results section of Report)	Conclusions in abstract & discussion sections (Report)	Conclusions in discussion consistent with results (Report)	Conclusions in abstract consistent with results (Report)
				group." Synopsis of report: "In patients with pain resulting from dental surgery, this study demonstrated statistically better analgesic effects (SPID6) of the GBP250/HC10 combination compared with placebo and GBP250, and numerically superior effects compared with HC10." "In addition, efficacy was detected by positive min-test results on the PID at 3 and 4 hours postdose and PRID 3 hours postdose."		

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1035-001. Addndm-B	1035-001. Addndm-B.RR	"Based on summary statistics, the GBP/HC combination groups tended to have greater pain relief than either the placebo group or the GBP500 group." "The GBP125/HC10 treatment group showed a maximal effect on the PI, PR, PID, and PRID measures at 2 hours postdose." "The effects seen for the GBP500/HC10 group were better overall than for the GBP250/HC5 group. The placebo and GBP500 groups had the smallest effect." "By 1 hour, 60% of patients in the GBP125/HC10 group experienced meaningful pain relief." "For comparison, the frequencies of meaningful pain relief for the other treatment groups at 1 hour postdose were 35% for placebo, 40% for GBP250/HC5, 25% for GBP500/HC10, and 29% for GBP500." "The percentage of responders was highest for the GBP125/HC10 group (40%), follwed by the GBP250/HC5 and GBP500/HC10 groups (35% each). The GBP500 and placebo treatment groups had responder rates of 24% and 10%, respectively."	"Dizziness was the most frequent adverse event experienced by patients receiving the GBP/HC combinations. For the combination treatment groups containing HC10, the incidence of dizziness increased with the amount of GBP in the combination. The frequency of dizziness was 30% for the GBP125/HC10 group compared with 45% for the GBP500/HC10 group." "The frequency of dizziness for patients treated with GBP125/HC10 was similar to that of patients treated with GBP250/HC10 (28%)."	Synopsis section of report: "Based on summary statistics, GBP/HC combination groups tended to have greater pain relief than placebo. The greatest relief was seen in the GBP125/HC10 treatment group. The GBP/HC combinations were well-tolerated with no remarkable side effects." Discussion section of report: "The small number of patients in each treatment group precluded inferential analyses of these data; however, trends were detected in the summary statistics. The GBP125/HC10 combination performed numerically better than the GBP250/HC5 and GBP500/HC10 combinations on all efficacy measures, and the GBP500/HC10 combination performed numerically better than the GBP250/HC5 combination." "The SPID6 results obtained with GBP125/HC10 treatment appear consistent with those obtained with GBP250/HC10 treatment, suggesting that GBP doses of 125 or 250 mg in combination with HC10 provide comparable pain relief (Table 9)." [Omitted citation to reference in original text]. "Also, no apparent analgesic benefit was obtained by increasing GBP to 500 mg in the combination (Figure 4), and increased side effects occurred with the GBP500/HC10 combination."	☑	☑

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1035-002	1035-002.RR	"Primary ANCOVA Model The GBO250/HC10 group was statistically significantly better than the placebo (p = 0.0001) and GBP250 groups (p = 0.0146) on the SPID6 primary efficacy measure (Table 8). The GBP250/HC10 group did not separate from the HC10 group (0.9187), therefore, the min-test result was negative." "The SPID6 efficacy measure for the GBP250 group was not statistically significantly better than that of the placebo group." "Alternative ANCOVA Models" "Baseline opiate concentration and metabolizer status data were available for only 116 and 109 patients, respectively; therefore, these analyses were not as well-powered as the primary ANCOVA." "The results of the analysis performed using baseline opiate concentration (Table 10) are very similar to those in the primary model (Section 6.3.1). For the model incorporating metabolizer status, the only statistically significant comparison for the GBP250/HC10 group was against the placebo group."	"Ten patients withdrew because of the adverse event of fever. Two patients experienced a serious event, including one patient who died. Both of these patients were in the placebo group." "Overall, the body systems most frequently affected by adverse events were body as a whole (20%), nervous system (9%), and digestive system (6%). The most frequent adverse events in each of these body systems were fever, somnolence, and vomiting, respectively (Table 19)." "Of all adverse events, only somnolence and dizziness occurred at higher frequencies in the GBP250/HC10 group than the placebo group." "The frequencies of these 2 adverse events were compared between the GBP250/HC10 and placebo groups using Fisher's exact test. There were no significant differences in these comparisons (p = 0.2326 for somnolence, p = 0.2602 for dizziness)."	Synopsis of report: "The combination of GBP250/HC10 was significantly better than placebo in relieving postsurgical pain; however, 250 mg of gabapentin does not appear to substantially potentiate the analgesic efficacy of 10 mg of hydrocodone in this model. A single oral dose of GBP250/HC10 was well-tolerated with no remarkable side effects." Discussion section of report: "The GBP250/HC10 group provided significantly better pain relief than the placebo and GBP250 groups on the majority of efficacy measures." "The GBP250/HC10 group did not significantly outperform the HC10 group on any of the efficacy measures examined." "Pain relieving effects of the active treatments (GBP250/HC10 and HC10) were seen as early as 40 minutes postdose. These data suggest that 250 mg of gabapentin does not potentiate the effects of 10 mg hydrocodone in this model." "This is in contrast to the apparent potentiation effects of gabapentin with hydrocodone in a dental pain model, Protocol 1035-001." [Omitted citation to reference in original text].	☑	☑