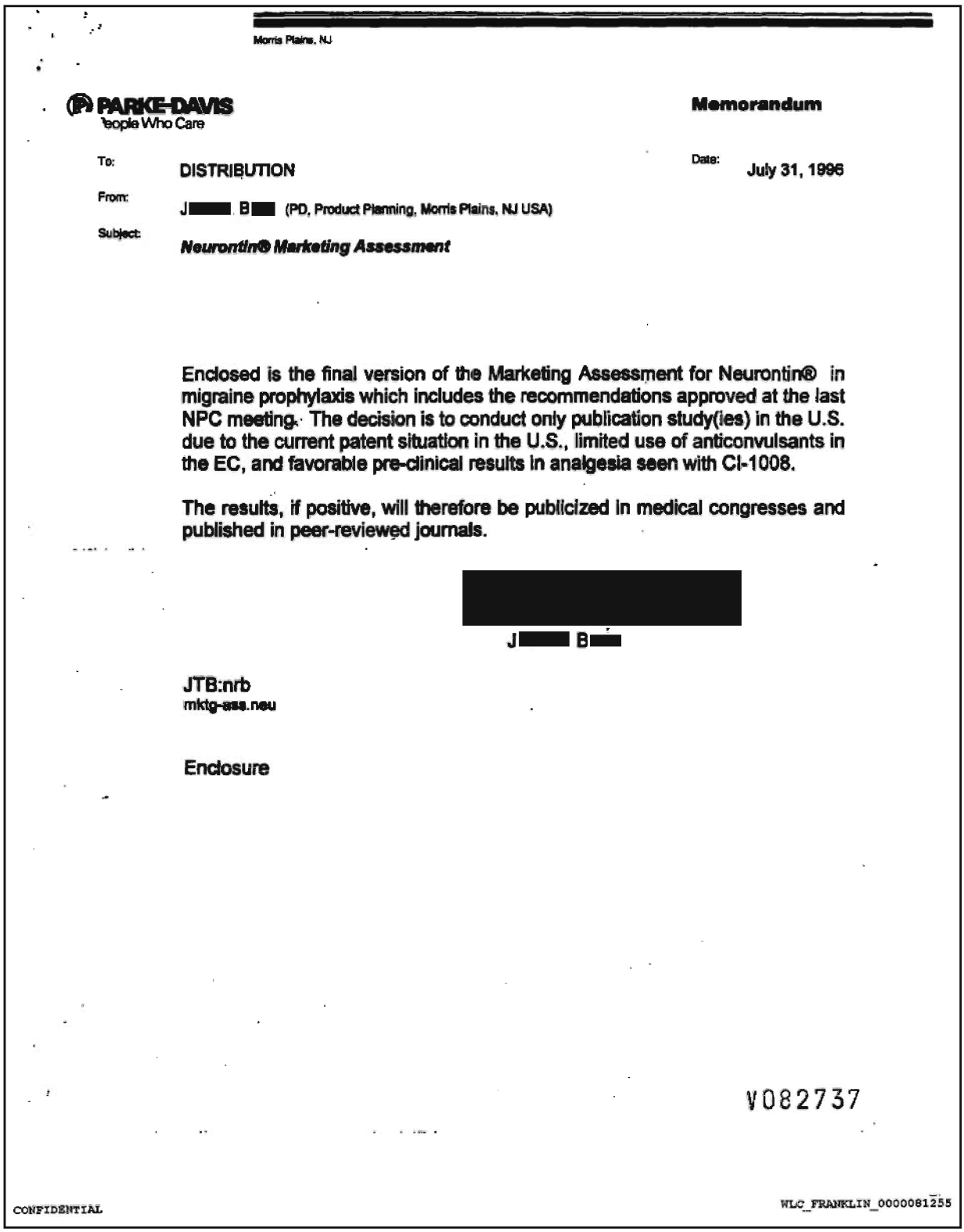
This Additional file or Online Supplement is provided along with a manuscript submitted by Vedula SS, Goldman PS, Rona IJ, Greene TM, Dickersin K. Implementation of a "publication strategy" in the context of reporting biases. A case study based on new documents from Neurontin(R) litigation.

**Online Supplement Figure 1. Extract from marketing assessment for Neurontin® in migraine prophylaxis showing recommendation to conduct publication studies**.
Names, signature and contact information of individuals have been blocked out by us such that only the initials can be seen.



[redacted]
Morris Plains, NJ

PARKE-DAVIS
People Who Care

**Memorandum**

To: DISTRIBUTION

Date: July 31, 1996

From: J[redacted] B[redacted] (PD, Product Planning, Morris Plains, NJ USA)

Subject: ***Neurontin® Marketing Assessment***

Enclosed is the final version of the Marketing Assessment for Neurontin® in migraine prophylaxis which includes the recommendations approved at the last NPC meeting. 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.

[redacted]
J[redacted] B[redacted]

JTB:nrb
mktg-ass.neu

Enclosure

V082737

CONFIDENTIAL

WLC_FRANKLIN_0000081255

**Online Supplement Figure 2. Extract from marketing assessment of Neurontin® in nociceptive pain showing recommendation to use trial data for publication only**

## 1. INTRODUCTION

***Purpose***

The purpose of this document is to assess the potential of a Neurontin combination product for use in pain. While a variety of possible combination products have been discussed, this brief assessment will focus mainly on Neurontin in combination with an NSAID and narcotics.

## 2. OBJECTIVE

The concept of a Neurontin combination product was originally considered as a result of a PD US initiated working group, exploring options for patent extension. This was further supported by a number of neuropathic pain thought leaders as they have noticed a synergistic effect when gabapentin is administered concomitantly with amitriptylene. However, due to the development timelines of potential Neurontin combination products and the clinical development of pregabalin (and potentially darbufelone), the main objective is no longer Neurontin patent extension. Rather, the objective is to create a portfolio of products for the treatment of a broad spectrum of pain syndromes ranging from moderate acute to severe chronic pain.

***Preclinical Rationale***

Animal data for a gabapentin-naproxen sodium combination demonstrated a synergistic effect over gabapentin or naproxen sodium alone, in a rat model of hyperalgesia. Preclinical data also suggests that gabapentin may provide a GI protective effect when combined with indomethacin over indomethacin alone. This would provide additional benefit to the NSAID combination product beyond potential superior efficacy. Additional animal data reported in the literature (Shimoyama, 1997) also established a synergistic effect of gabapentin combined with morphine in rat pain models.

***Clinical Rationale***

A synergistic effect with morphine has also been demonstrated in a single dose 4-way crossover study in healthy human volunteers (placebo vs. gabapentin vs. morphine vs. combination gabapentin/morphine). The analgesic effect was evaluated by pain threshold time and pain tolerance time. Major findings were (1) gabapentin vs. placebo showed no significant effect difference, (2) morphine vs. placebo showed a clear significant effect difference and (3) the combination of morphine/gabapentin was significantly more effective than morphine alone.

## Online Supplement Figure 2. Continued.

A pain market segmentation strategy has previously been implemented successfully by Syntex with Naprosyn and Anaprox. Naprosyn was targeted for OA/RA, while Anaprox was targeted for sports injuries. Detailing for each compound was based on the respective physician audience (e.g., rheumatologists for Naprosyn, emergency room physicians for Anaprox).

| ~ PAIN PORTFOLIO ~ | | | |
|---|---|---|---|
| **Neurontin** | **Pregabalin** | **Neurontin + NSAID** | **Neurontin + Opioid** |
| Neuropathic Pain (Europe) | Chronic Pain | Acute Pain | Severe Pain |
| *Approval:* 2000 | *Approval:* 4Q 2001 | *Approval:* 4Q 2001 | *Approval:* 2003 |

Pregabalin combinations would be introduced starting in 2006 as line extensions to pregabalin, potentially replacing Neurontin combinations with newer, more potent or safe components.

***Clinical Development Issues***

Potential areas of concern that have been raised include:

- ***Formulation*** – There may be compatibility issues with naproxen. Furthermore, if the dose needed is relatively high, size of the tablet/capsule may become problematic. Additionally, the lactam content of Neurontin may be affected by such a combination. As well, there is a need to develop two dosing strengths. Finally, a BID dosing program is preferred.
- ***Dose ratio*** – The animal data suggest a dose ratio of 1:1 on a mg to mg basis is the optimum formulation. It is uncertain if that will hold true for human trials.
- ***Timeline*** – The combination product would require a full development effort to develop a full regulatory dossier, although it may require less toxicology work since existing data in the public domain may suffice.
- ***Choice of NSAID*** – While naproxen is a leading compound in the US, in Europe diclofenac is clearly the dominating NSAID. However, based on the fact that only the UK may represent feasible commercial potential outside the US, there may not be an issue.
- ***Patent*** – Parke-Davis has filed patents for all potential combination products for both Neurontin and pregabalin.

***Regulatory Strategy***

Although a combination pain product NDA/MAA would be unique for Parke-Davis, numerous examples of such products exist in the US, including Arthrotec and Vicoprofen, , and a plethora of combination analgesics in Europe.



Pfizer_MPierce_0000834

## Online Supplement Figure 2. Continued.

Our primary objective is to demonstrate better efficacy with a Neurontin + naproxen sodium combination product than either product alone with doses lower than what is generically available for the treatment of low back pain, sprains, and strains. Hence, clinical trials should be powered for the primary endpoint, efficacy. Secondary endpoints should include GI tolerability, etc., although not powered to make a comparative claim. Such secondary data would be for publication only.

### 6. PRIMARY MARKET RESEARCH

***Top Line Report for Combination Product***

Primary market research was conducted with primary care physicians, orthopedic surgeons, and neurologists to initiate the process of understanding the acute and chronic pain (e.g. OA) market and to obtain a preliminary assessment of interest in Neurontin combination products for pain, in particular, a Neurontin/NSAID combination.

The interest expressed in the new product concept for the NSAID/anti-convulsant combination was at a level in this study that would indicate a recommendation to continue exploring the potential of such a compound.

In general, most respondents in this study were not satisfied with the available pain products on the market. Physicians in this study were using a multitude of products to treat both acute and chronic pain. For acute pain, these products included Toradol, Cataflam, ibuprofen, Darvocet, hydrocodone, Ultram, Tylenol #3, codeine, Tylenol, Relafen and others. For chronic pain control respondents mentioned using Percocet, Darvocet, Ultram, Neurontin, Elavil, codeine, Lortab, Lorcet, Tegretol, Esgesic, and others.

Combination therapy was most frequently used for back and neck pain, and post surgery pain control. Frequent combinations mentioned included, ibuprofen/Darvocet, Advil/Vicodin, Naproxen/Daypro, ibuprofen/Toradol, Neurontin/Tegretol and others.

Combination therapy was used most frequently for acute pain in this study, but was also used in chronic therapy. The hesitancy in chronic therapy stemmed from unknown outcomes of long-term use of combination therapy, and the belief that the fewer the drugs, the better for the patient.

As could be expected, GI side effects for the NSAIDs, and addictive potential for the narcotics were the greatest concerns for the use of pain medications. CNS side effects and lack of reliable efficacy of the anti-convulsants, and the risk of tachyphylaxis with some pain meds were also mentioned as concerns.

***New Product Concept***

In general, the New Product concept was well received. Neurologists gave the least favorable review of the product based mainly on the inability to titrate the two compounds.

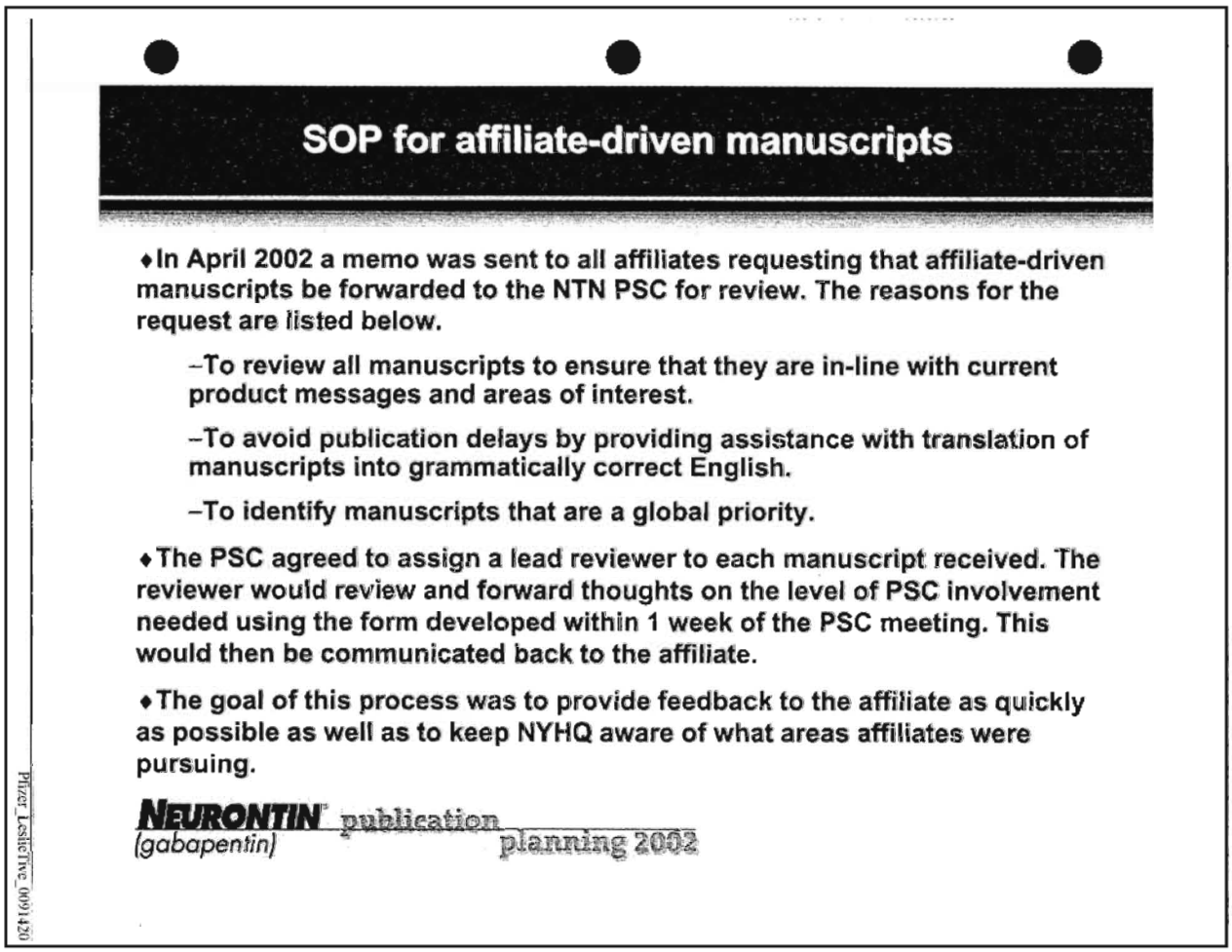
**Online Supplement Figure 3. Internal company document illustrating role of Medical Action Communications, a medical writing company, in developing key messages based on a branding guide for Neurontin**

| | | |
|---|---|---|
| | (eg, Aricept, Zoloft, Relpax) it was suggested that this may not be a global Pfizer policy but that individual teams had different approaches to this issue. It was suggested that this should be discussed in more detail internally with the Neurontin team before any policies were put in place for the Neurontin team. The general agreement is that Pfizer employees should not be 1st or last authors and a ratio of >/= 3/1 | KK |
| 4.0 | (outside to Pfizer) in authors should be maintained. | |
| | **Key Message Development Update:** 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. The team will then be asked to comment on the key | MAC PSC members |
| 5.0 | message list and provide feedback by 1-August. | |
| | **Bibliography Database search terms:** The team reviewed the draft list of key search terms that was developed. This list represents the major search categories that will be included in the database, as well as a preliminary list of searchable terms within each category. The team was asked to review this list and submit and comments or questions to SV by 30-July. | PSC members |
| | It was pointed out that one category of search term was not included in this list--key words. This category is currently being developed and will include terms from many of the other categories, as well as other terms of key relevance to the team (eg, competitor product generic and brand names). This expanded list will be submitted to the PSC for comment | MAC |
| 6.0 | by 25-July. | |
| | **Current Neurontin publications:** The status of two current publications was discussed: *1) Gabapentin vs Lamotrigine, monotherapy in epilepsy; Lancet publication.* The manuscript was discussed with the two primary authors on 18-July and there was a question regarding the statistical analysis The manuscript is awaiting submission based on Pfizer approval. | |
| | RG asked for clarification regarding the composition of the patient population for this study (number of partial vs generalized siezures). The team was informed that the study contains 20% patients with generalized seizures. RG recommended that it may be useful to consider a secondary publication that reports on a sub analysis of patients with partial seizures to demonstrate the significantly greater clinical efficacy in this area The team agreed that this might be a worthwhile pursuit and additionally suggested that there may be other sub analyses that are worthwhile considering for this study once the primary data is published. MAC agreed to work with the team to review the study and identify appropriate targets for sub analysis (eg, dosing schedule, time to exit, etc). The PSC approved the manuscript for submission. | MAC/PSC members KK |

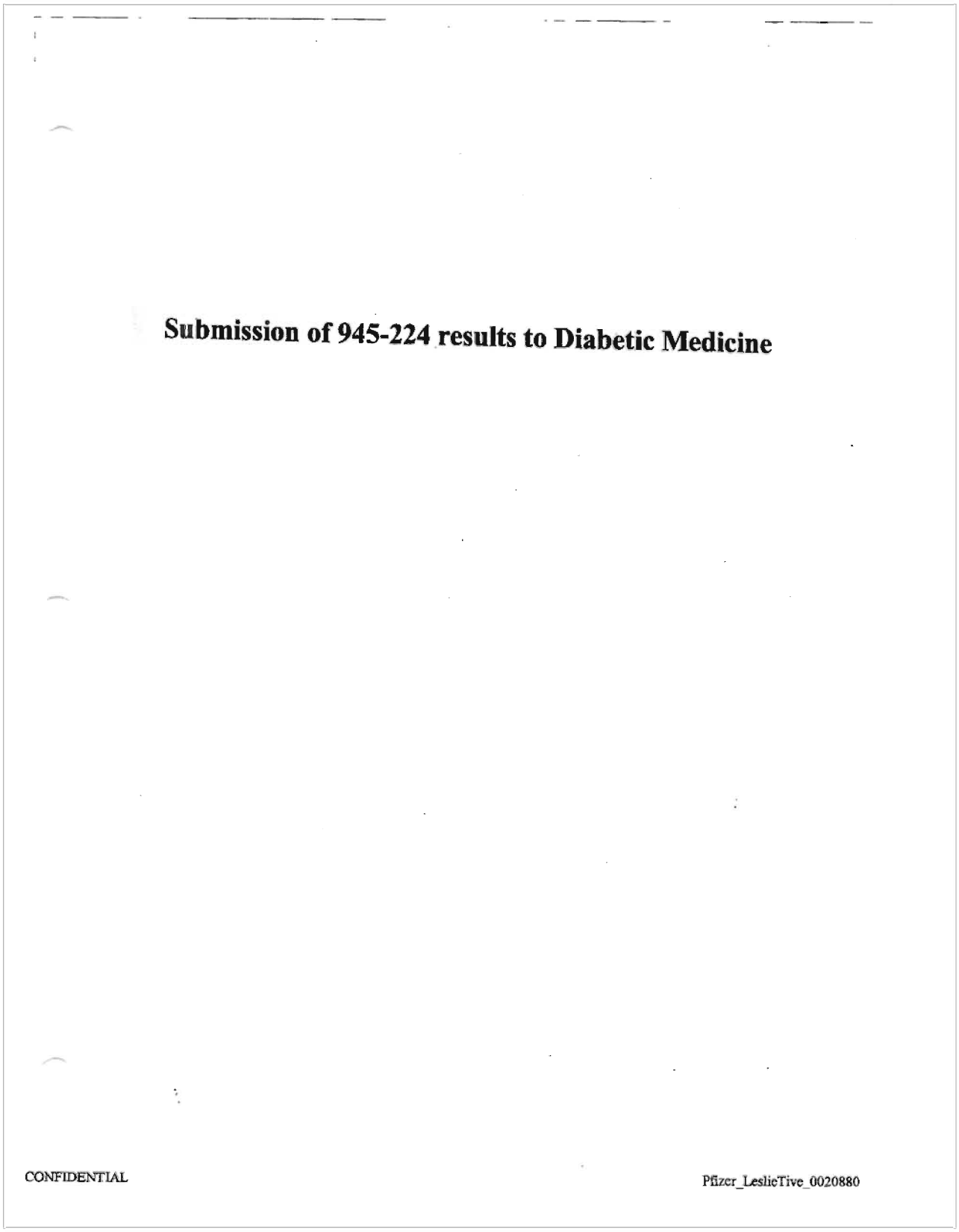
Action Report: 18-July -01 3

Pfizer_RGlanzman_0044636

**Online Supplement Figure 4. Standard operating procedure (SOP) specified that "affiliate-driven manuscripts" should be submitted for review by Neurontin Publications Sub-Committee (NTN PSC) to ensure the content is consistent with "current product messages"**



**Online Supplementary Appendix Figure 5. Peer review comments from two journals to which findings from Study 945-224 were submitted.**



Submission of 945-224 results to Diabetic Medicine

CONFIDENTIAL

Pfizer_LeslieTive_0020880

## Online Supplement Figure 5. Continued.

31.03.2003 09:46Roder, Beate

R[redacted] B[redacted]

**Von:** ScholarOneMailer@ScholarOne.com
**Gesendet:** Montag, 13. Mai 2002 14:17
**An:** b[redacted]r[redacted]@pfizer.com
**Betreff:** Diabetic Medicine DME-2002-00105

Re Gabapentin in painful diabetic neuropathy: a randomised, double-blind, placebo-controlled study

Dear Dr. R[redacted]

Thank you for submitting your paper to Diabetic Medicine. I regret that it has not been accepted for publication as it stands.

I attach the reports of the associate editor and two reviewers. You can see that they find your manuscript of interest but have raised significant concerns which would need to be addressed.

If you feel able to respond to the reviewers' comments then we will give careful consideration to a resubmitted paper. I should emphasise that we are certainly not guaranteeing acceptance at this stage. A decision will be based on whether you can meet the reviewers' concerns.

Your responses to each point made by the reviewers should be made at http://dme.manuscriptcentral.com through your Author Centre by clicking the appropriate button. Please then submit your revised manuscript by clicking its title. You will prompted to upload the file(s).

Any revised paper should be submitted to the Diabetic Medicine site within two months of your receipt of this letter.

Thank you for submitting to Diabetic Medicine.

Yours sincerely

Dr S[redacted] H[redacted]
Editor, Diabetic Medicine

Associate Editor comments:

In this multicentre controlled trial Reckless and coworkers evaluated the efficacy and safety of gabapentin (600, 1200, 2400 mg/day) compared with placebo treatment in 325 diabetic patients with painful neuropathy over 7 weeks. A subgroup of 67 patients received the drug in a subsequent 4-month open-label period. After 7 weeks the primary outcome measure (weekly mean pain score) was not improved in favor of gabapentin. In contrast, several secondary endpoints did show improvement in excess of placebo. The authors conclude that while gabapentin did not demonstrate significant effects on the primary endpoint, the improvements of some secondary endpoints indicate an overall benefit from gabapentin in painful diabetic neuropathy. This manuscript has been reviewed by two referees and a statistical advisor. Both reviewers felt that although this trial deals with an important problem in diabetic patients, they identified numerous points of critique regarding data analysis and interpretation that need to be carefully addressed. As stated by the statistical advisors, the quality of the statistics appears to be poor, and hence, the conclusions are not justified. In summary, this large controlled trial addresses an important area of patient care. However, as the present study could not demonstrate significant effects on the primary endpoint, it contrasts with the results of a previously published US trial. The authors are advised to perform an appropriate statistical analysis which should allow them to draw a less biased interpretation given the evidence indicating that gabapentin had no effect on the weekly mean pain score.

1 1

CONFIDENTIAL Pfizer_LeslieTive_0020881

## Online Supplement Figure 5. Continued.

31.03.2003 09:46R[redacted] B[redacted]
Reviewer comments:

Reviewer 1 Comments:
This is an important paper about a common problem, painful diabetic neuropathy, but needs rewritting. I have several concerns about the paper. First, I believe that the stat section should use the Bonferroni correction, given the multiple comparisons made on the same data set. This would require a final p value of $p<0.01$ or even $p<0.005$, depending on the calculation of the correction, to be considered significant. With this redo of the data, it is probable that NO statistical measures were postive. Thus, the trial would be considered a failure and the paper rewritten accordingly. Second, the issue is why this trial failed when the US trial of 3600 mg was so positive. This is an important issue esp if the hightened expectations of patients and MDs contributed to the large placebo effect. This needs more explanation along with other possible factors. Third, even with the high placebo effect the negative trial does not fit with the US trial as the mean effective dose in th!
at trial was 1800 mg. Is there no dose response curve? Luckily, the FDA is not asked to consider this in looking at Neurontin. Third, there are many areas of company bias that need elimination. For example, only carbemazipine is discussed but many other drugs have favorable trials.

Reviewer 2 Comments:
GBP in PDN by R[redacted] J et al submitted to Diabetic Medicine

This study investigated the efficacy of gabapentin (GBP) at 3 doses in relieving the pain of painful diabetic neuropathy when compared to placebo. In addition to the primary outcome of pain ratings authors used secondary outcomes such as sleep interference and quality of life (QoL) assessment tool. After 7 weeks of double-blinded treatment it was established that GBP was not different from placebo in its primary outcome. Only significant effects of GBP were: the middle 1200mg/day dose as clinical global impression of change and in some QoL measures, and at 1200mg/day and 2400mg/day dose in alleviating sleep interference due to pain. The interpretation was that the placebo effect was so high due to expectation on the part of physicians and patients.

There are many aspects of this study that need to be addressed.

The results are intriguing in many regards. The most "effective" dose, in the sense that it showed significant results in secondary outcomes was the middle dose, which was also the dose that was associated with least adverse events among GBP doses and with the lowest the dropout rate, even less than placebo, though apparently that was not statistically significant. But lower rate of adverse effects alone could not provide the explanation for middle dose to be "more effective" than the higher 2400mg/day dose since published literature (US studies) demonstrated that most patients were able to tolerate higher, 3600mg/day dose with clearly superior pain relief. Is there a president in the literature where the middle dose was more effective than the higher dose? I am not aware of any.

The issue of the highest dose selected for this study brings us to the statement on page 11, second paragraph, last sentence: "The underlying assumption was that pain relief obtained from at least 1 of the doses used in this study (600, 1200 and 2400mg/day) would be in the same order of magnitude as that seen with 3600mg/day gabapentin in the United States study" - this statement defies logic since only one dose, 2400mg/day, was the only one that was higher than what was suggested by US study to be effective dose of 1800mg/day or higher. Were the authors looking for the least effective dose? If so, that should be stated as such. Also, what was the reason that authors did not use 3600mg/day when that was shown to be safe and effective dose, even if they were looking for least effective dose? Please explain.

Most puzzling of all was the effect of the lowest dose of 600mg/day fared much worse in all outcomes including adverse events, even worse than placebo. Authors did not provide information whether any of that was significant? Did these patients experience all the adverse effects without any benefits so that is why they came out worse than any other group? Is small dose GBP pro-nociceptive? Please explain.

Authors are requested to present the pain rating (means) data over the duration of the study as line graph. It should be instructive.

It is unlikely that adverse events were the cause for such a high placebo response rate. However, one way to monitor the possible influence of unmasking investigators

## Online Supplement Figure 5. Continued.

31.03.2003 09:46R [redacted] B[redacted]

are advised to ask each of their patient at the conclusion about their impression what treatment they thought they received. Was this done in this study?

In the Patients and Method section under Safety Evaluation it is stated that physical examination, including sensory neurological examination was performed but symptoms and signs which define any neuropathic pain, including painful diabetic neuropathy was not analyzed and discussed as one of the outcomes. That is most surprising since a few of the participating authors are recognized experts in the area of neuropathic pain. Please provide the information about neurological sensory examination. This may especially be important for the group that did the worst, 600mg/day.

Statistical Advisor Comments:

On page 13 it is not correct to report both endpoint scores and change in pain score. The same applies to sleep interference scores. Repeated measures analysis of variance should be used to analyse data collected sequentially.

What was compliance? Were table counts done?

In sleep interference score were 1200 and 2400 mg groups combined? Should reported measures ANOVA of 4 groups have been done and then a predetermined tend test across 3 levels of medication?

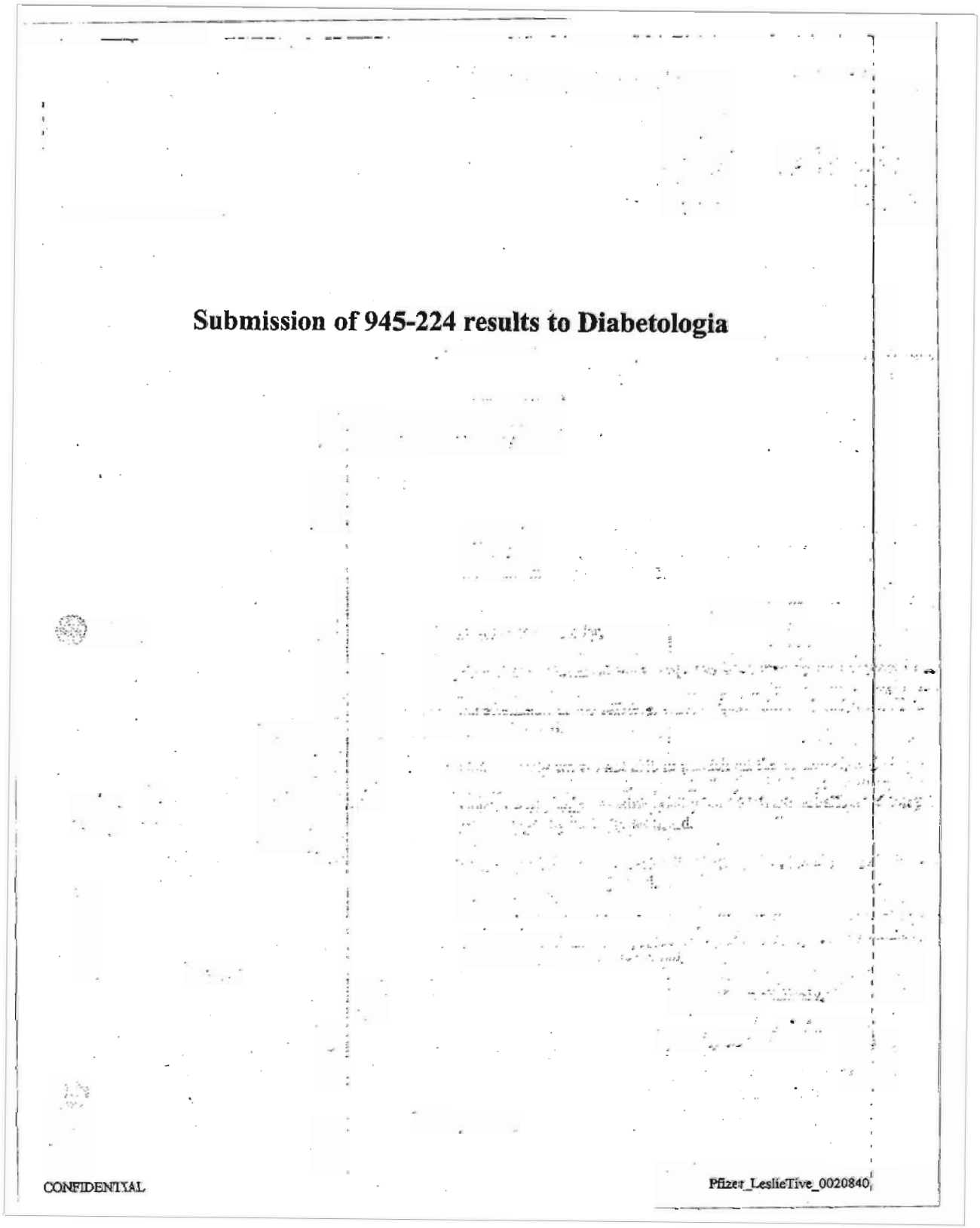
Figure 3 should be cumulative block charts. Why were 'very much' and 'much improved' groups combined? A chi-squared test for trend should have been done, not ANOVA, this is ranked categorical data, not continuous data.

p = 0.0414 (page 15) cannot really be considered significant in the light of the number of tests performed. Was a Bonferronni correction discussed?

Tests for trend should be done on data in table 5.

What were the nervous system adverse events?

**Online Supplement Figure 5. Continued.**



**Online Supplement Figure 5. Continued.**



# Diabetologia

Journal of the European Association for the Study of Diabetes (EASD)
Editor-in-Chief
W[redacted] W[redacted] M.D, Vienna
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Dr. B[redacted] R[redacted]
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14th November 2002

**Re:Diabet/2002/000754 J[redacted] R[redacted] et al.,** *' Gabapentin in painful diabetic neuropathy: a randomised, double-blind, placebo-controlled study '*
**Received: 22nd October 2002**

Dear Dr. B[redacted] R[redacted]

Your above-referenced manuscript has been read by two experts in the field but I regret to inform you that we are not able to offer publication in *Diabetologia*. This decision is based on the evaluation of the referees, whose reports are enclosed, as well as on priorities set by the Editorial Board.

Unfortunately we are not able to publish all the manuscripts that receive positive comments. The severe competition for space in the journal forces us to reject quite a few manuscripts which are of sound scientific quality but which are not allocated top priority for publication in *Diabetologia* by the editorial board.

I hope that the referees' evaluations will be helpful if you plan to revise the manuscript for submission to another journal.

I am sorry that I could not be more positive on this occasion but hope we can look forward to other contributions from you in the future. Thank you very much for allowing us to review your manuscript for *Diabetologia*.

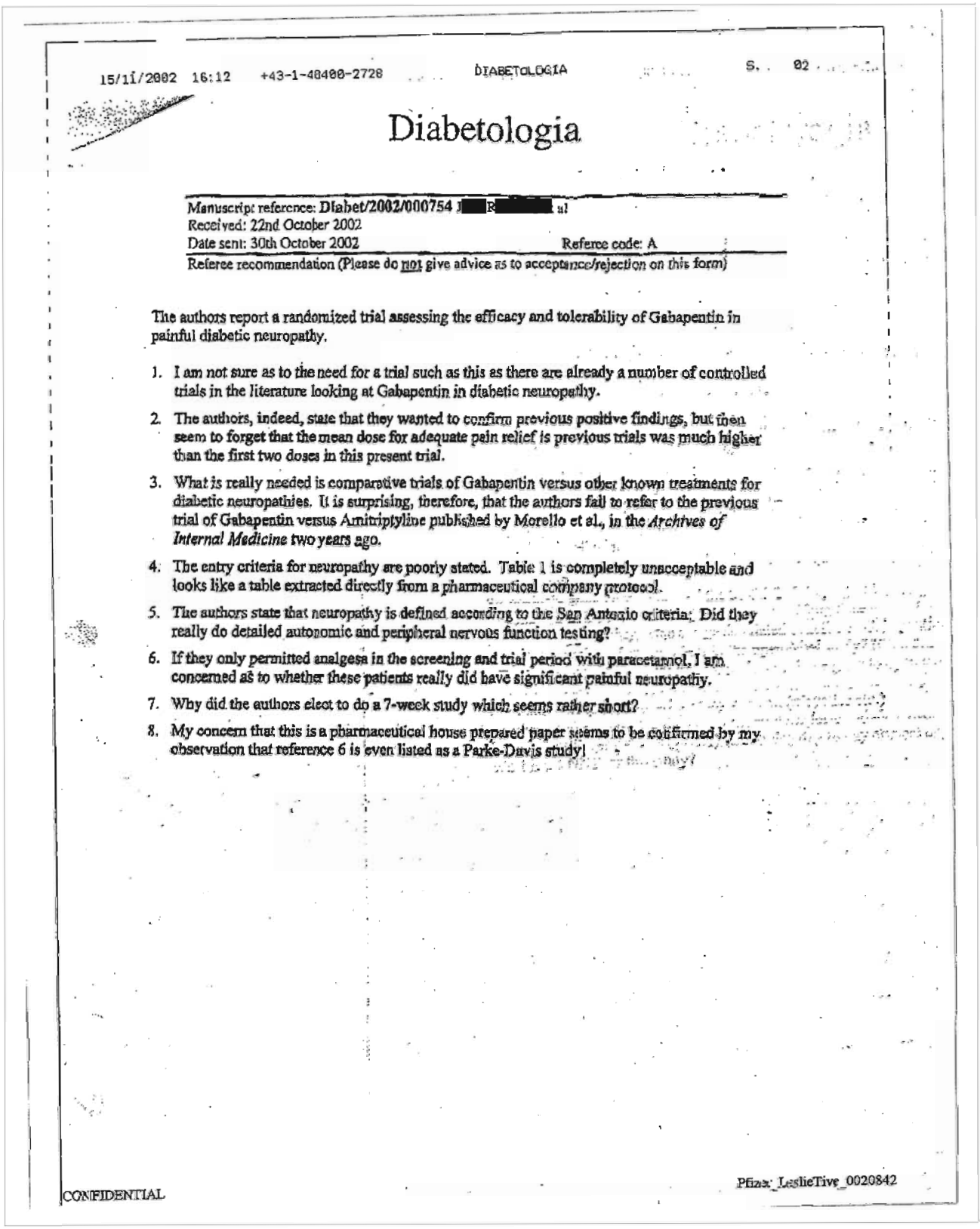
Yours sincerely,

W[redacted] W[redacted] M.D
Editor-in-Chief

CONFIDENTIAL

Pfizer_LesleTwo_0020841

## Online Supplement Figure 5. Continued.



15/11/2002 16:12 +43-1-40400-2728 DIABETOLOGIA S. 02

# Diabetologia

Manuscript reference: Diabet/2002/000754 J [redacted] al
Received: 22nd October 2002
Date sent: 30th October 2002 Reference code: A
Referee recommendation (Please do not give advice as to acceptance/rejection on this form)

The authors report a randomized trial assessing the efficacy and tolerability of Gabapentin in painful diabetic neuropathy.

1. I am not sure as to the need for a trial such as this as there are already a number of controlled trials in the literature looking at Gabapentin in diabetic neuropathy.
2. The authors, indeed, state that they wanted to confirm previous positive findings, but then seem to forget that the mean dose for adequate pain relief is previous trials was much higher than the first two doses in this present trial.
3. What is really needed is comparative trials of Gabapentin versus other known treatments for diabetic neuropathies. It is surprising, therefore, that the authors fail to refer to the previous trial of Gabapentin versus Amitriptyline published by Morello et al., in the *Archives of Internal Medicine* two years ago.
4. The entry criteria for neuropathy are poorly stated. Table 1 is completely unacceptable and looks like a table extracted directly from a pharmaceutical company protocol.
5. The authors state that neuropathy is defined according to the San Antonio criteria. Did they really do detailed autonomic and peripheral nervous function testing?
6. If they only permitted analgesa in the screening and trial period with paracetamol, I am concerned as to whether these patients really did have significant painful neuropathy.
7. Why did the authors elect to do a 7-week study which seems rather short?
8. My concern that this is a pharmaceutical house prepared paper seems to be confirmed by my observation that reference 6 is even listed as a Parke-Davis study!

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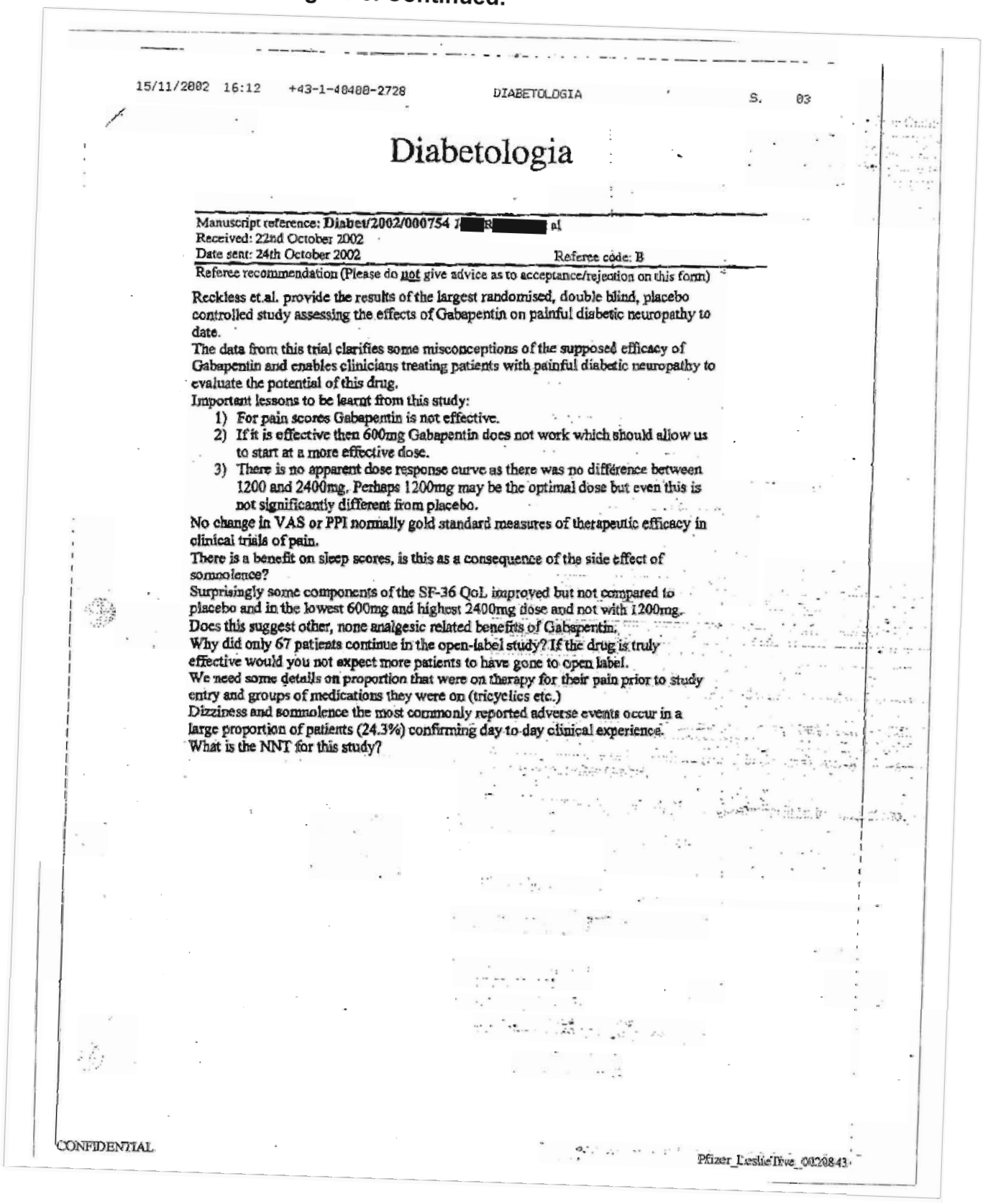
Pfizer_LeslieTive_0020842

## Online Supplement Figure 5. Continued.



15/11/2002 16:12 +43-1-40400-2728 DIABETOLOGIA S. 03

# Diabetologia

Manuscript reference: Diabet/2002/000754 [redacted] al
Received: 22nd October 2002
Date sent: 24th October 2002 Referee code: B

Referee recommendation (Please do not give advice as to acceptance/rejection on this form)

Reckless et.al. provide the results of the largest randomised, double blind, placebo controlled study assessing the effects of Gabapentin on painful diabetic neuropathy to date.

The data from this trial clarifies some misconceptions of the supposed efficacy of Gabapentin and enables clinicians treating patients with painful diabetic neuropathy to evaluate the potential of this drug.

Important lessons to be learnt from this study:

1) For pain scores Gabapentin is not effective.
2) If it is effective then 600mg Gabapentin does not work which should allow us to start at a more effective dose.
3) There is no apparent dose response curve as there was no difference between 1200 and 2400mg. Perhaps 1200mg may be the optimal dose but even this is not significantly different from placebo.

No change in VAS or PPI normally gold standard measures of therapeutic efficacy in clinical trials of pain.

There is a benefit on sleep scores, is this as a consequence of the side effect of somnolence?

Surprisingly some components of the SF-36 QoL improved but not compared to placebo and in the lowest 600mg and highest 2400mg dose and not with 1200mg. Does this suggest other, none analgesic related benefits of Gabapentin.

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.

We need some details on proportion that were on therapy for their pain prior to study entry and groups of medications they were on (tricyclics etc.)

Dizziness and somnolence the most commonly reported adverse events occur in a large proportion of patients (24.3%) confirming day to day clinical experience.

What is the NNT for this study?

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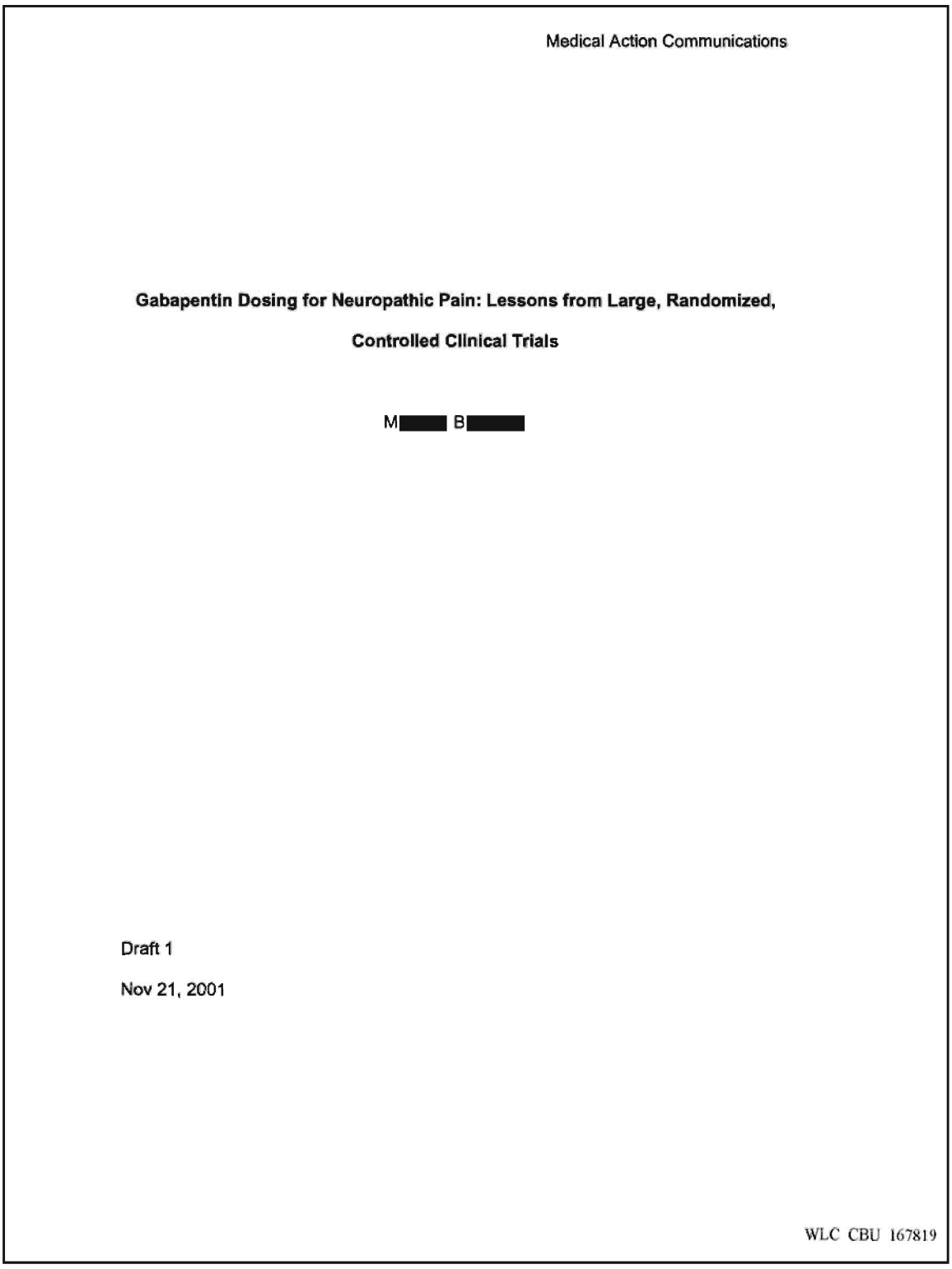
Pfizer_LeslieTive_0020843

**Online Supplement Figure 6. Internal company draft of abstract of a review written by the medical writing company and the key messages included in the review draft**



Medical Action Communications

**Gabapentin Dosing for Neuropathic Pain: Lessons from Large, Randomized, Controlled Clinical Trials**

M[redacted] B[redacted]

Draft 1

Nov 21, 2001

WLC CBU 167819

## Online Supplement Figure 6. Continued.

Medical Action Communications

**Key messages included in this manuscript:**

Market

- Neuropathic pain is underrecognized and undertreated despite being one of the most common reasons to seek medical care.

Therapeutic area

- A broad range of neuropathic states exist.
- Neuropathic pain is associated with many comorbid conditions, including mood and anxiety disorders, sleep disorders, and diseases responsible for the neuropathy, such as cancer, HIV, and diabetes.
- Neuropathic pain is often refractory to treatment.
- Tricyclic antidepressants are the standard of treatment for neuropathic pain; these are often poorly tolerated and contraindicated for patients with cardiovascular disease.
- Neuropathic pain typically responds poorly to opioids and NSAIDs.

Product specific

- Gabapentin is an anticonvulsant that has proven effective in the treatment of neuropathic pain.
- Gabapentin is a GABA derivative with a not yet fully understood mechanism of action. However, gabapentin is known to modulate calcium channels, which play an important role in chronic neuropathic pain.
- Gabapentin has been available since 1994 in the United States for the treatment of partial seizures. Vast experience in this patient population has established the excellent safety and tolerability record of gabapentin.

WLC CBU 167820

## Online Supplement Figure 6. Continued.

Medical Action Communications

- Gabapentin has a favorable pharmacokinetic profile, including no significant drug interactions.
- The recommended initial titration schedule for gabapentin in the treatment of neuropathic pain is 900 mg/d titrated over 3 days and given as three divided doses. This titration schedule is simple, well-tolerated, and achieves therapeutic benefit quickly, key factors in patient compliance.
- 1800 mg/d is the recommended dose for patients with neuropathic pain [600 mg tablet 3 times daily]; however, some patients may require doses as high as 3600 mg/d
- Gabapentin doses up to 3600 mg/d have been proven well tolerated and effective in clinical studies.

WLC CBU 167821

## Online Supplement Figure 6. Continued.



**Abstract**

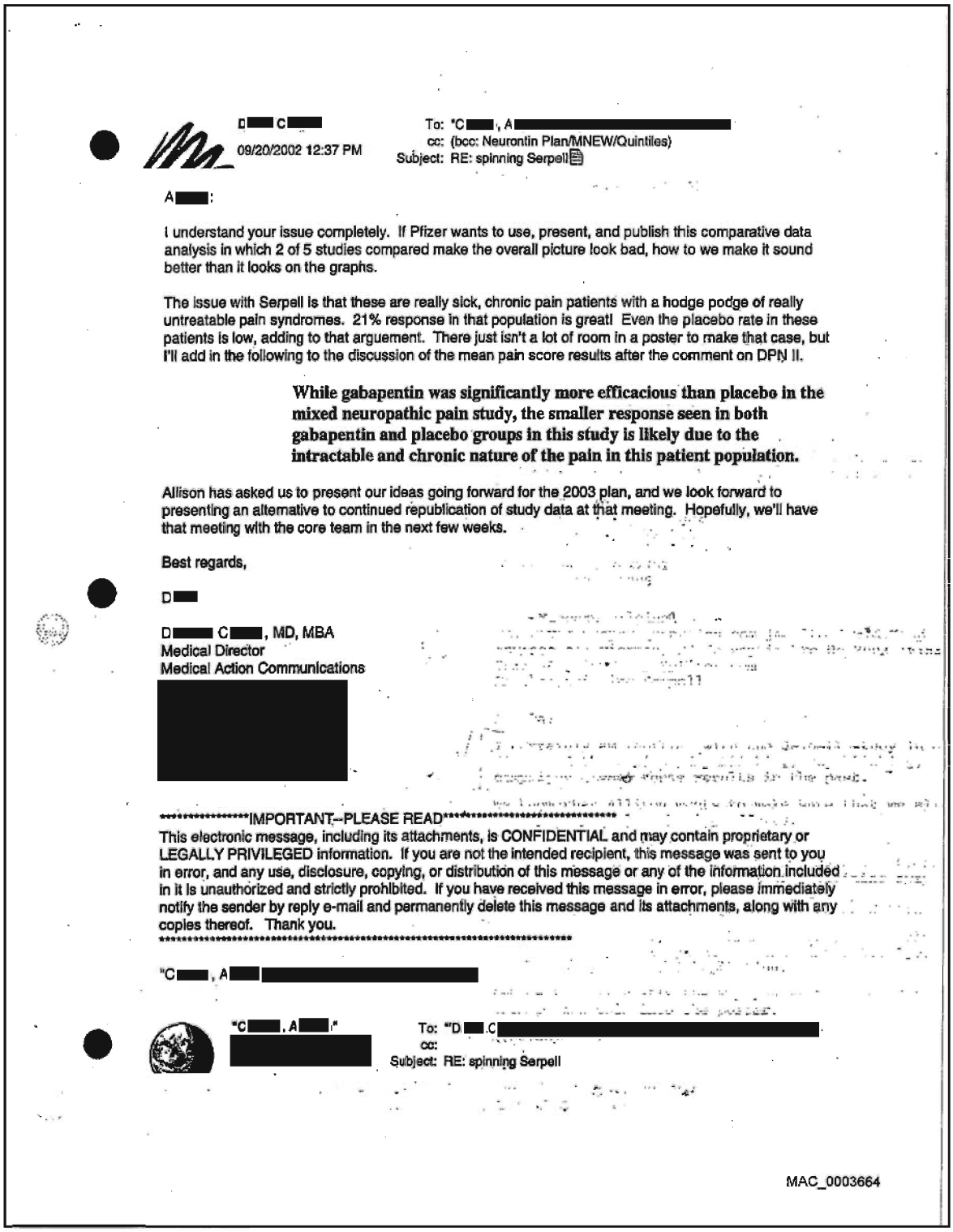
Introduction: Neuropathic pain is one of the most common reasons for seeking medical attention. However, in spite of this widespread prevalence, it is under-recognized and often inadequately treated largely because many cases are refractory to the medications used for treatment – opioids, NSAIDs, sodium-channel blockers. Currently, TCAs are first-line agents but their use is limited because they increase cardiovascular disease and mortality, particularly in patients with preexisting disease. New effective treatments are needed for the safe treatment of neuropathic pain.

Materials and Methods: Data from four large, randomized, placebo-controlled trials were reviewed to explore the efficacy and safety of gabapentin and to determine the best titration and dosing schedule.

Results: Gabapentin is effective for the treatment of painful diabetic neuropathy, postherpetic neuralgia, and other neuropathic pain syndromes. It can relieve symptoms of allodynia, burning pain, shooting pain, and hyperesthesia. Treatment should be initiated at a dose of 900 mg/d titrated over a period of three days and administered in divided doses. Additional titration to 1800 mg/d is recommended for best results. In some patients, doses up to 3600 mg/d may be needed. This titration should be based on patient response and tolerability. All doses are well tolerated, with drowsiness and somnolence being the most common side effects. Side effects are mild to moderate, are more prevalent during titration, and often subside within about 10 days of treatment initiation.

Conclusions: Gabapentin 1800 mg/d is recommended for most patients with neuropathic pain. Doses up to 3600 mg/d may be necessary for analgesia in some patients. Such doses can be safe and well tolerated.

**Online Supplement Figure 7. Internal company emails with subject "spinning Serpell" illustrating decisions by marketing personnel to spin the content in a poster to explain away unfavorable findings**



D C
09/20/2002 12:37 PM

To: "C , A
cc: (bcc: Neurontin Plan/MNEW/Quintiles)
Subject: RE: spinning Serpell

A :

I understand your issue completely. 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 to we make it sound better than it looks on the graphs.

The issue with Serpell is that these are really sick, chronic pain patients with a hodge podge of really untreatable pain syndromes. 21% response in that population is great! Even the placebo rate in these patients is low, adding to that arguement. 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 this study is likely due to the intractable and chronic nature of the pain in this patient 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. Hopefully, we'll have that meeting with the core team in the next few weeks.

Best regards,

D

D C , MD, MBA
Medical Director
Medical Action Communications

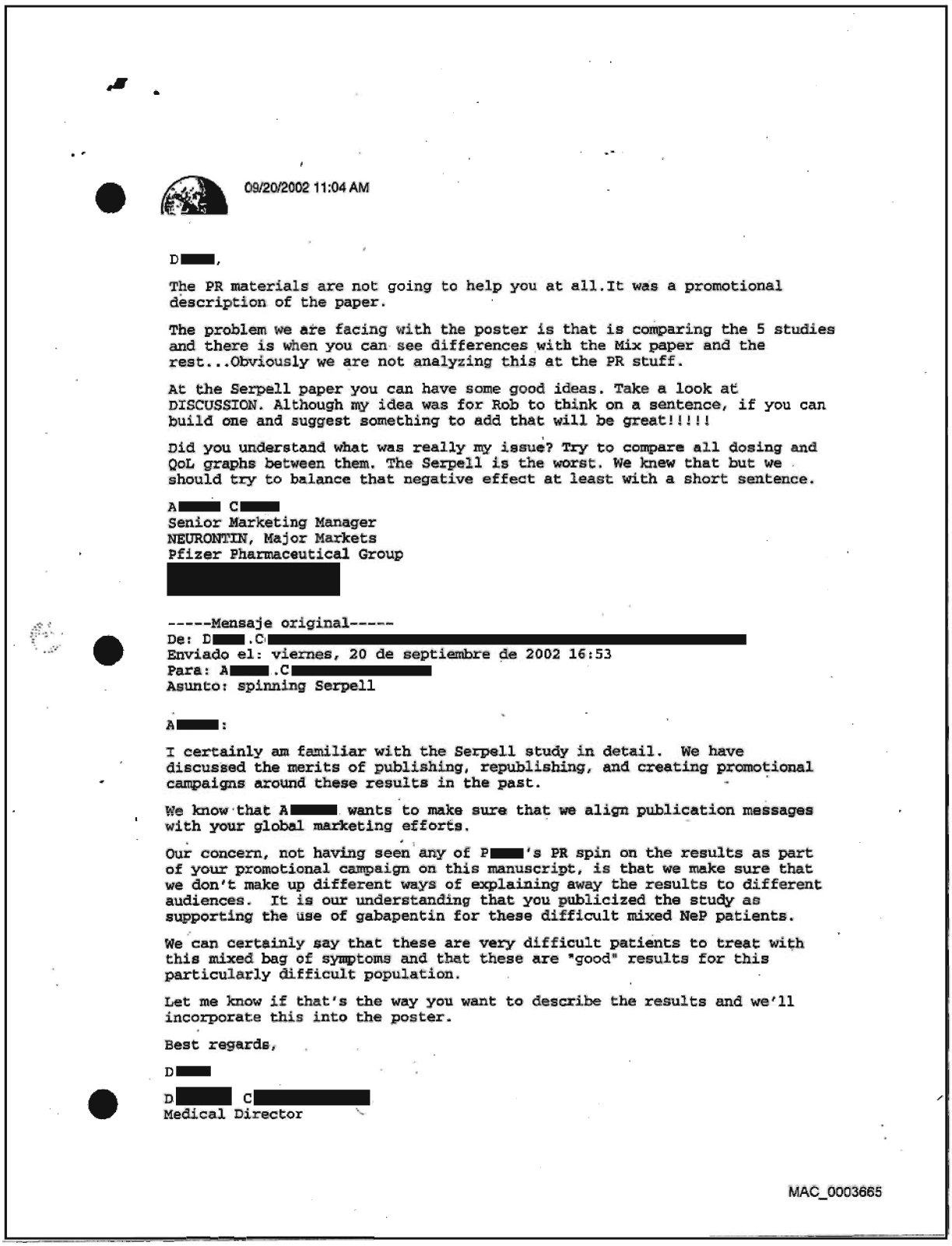
**********IMPORTANT--PLEASE READ**********
This electronic message, including its attachments, is CONFIDENTIAL and may contain proprietary or LEGALLY PRIVILEGED information. If you are not the intended recipient, this message was sent to you in error, and any use, disclosure, copying, or distribution of this message or any of the information included in it is unauthorized and strictly prohibited. If you have received this message in error, please immediately notify the sender by reply e-mail and permanently delete this message and its attachments, along with any copies thereof. Thank you.
**********

"C , A

"C , A ," To: "D C
cc:
Subject: RE: spinning Serpell

MAC_0003664

## Online Supplement Figure 7. Continued.



09/20/2002 11:04 AM

D[redacted],

The PR materials are not going to help you at all.It was a promotional description of the paper.

The problem we are facing with the poster is that is comparing the 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.

At the Serpell paper you can have some good ideas. Take a look at DISCUSSION. Although my idea was for Rob to think on a sentence, if you can build one and suggest something to add that will be great!!!!!

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.

A[redacted] C[redacted]
Senior Marketing Manager
NEURONTIN, Major Markets
Pfizer Pharmaceutical Group
[redacted]

-----Mensaje original-----
De: D[redacted].C[redacted]
Enviado el: viernes, 20 de septiembre de 2002 16:53
Para: A[redacted].C[redacted]
Asunto: spinning Serpell

A[redacted]:

I certainly am 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 that A[redacted] wants to make sure that we align publication messages with your global marketing efforts.

Our concern, not having seen any of P[redacted]'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.

We can certainly say that these are very difficult patients to treat with this mixed bag of symptoms and that these are "good" results for this particularly difficult population.

Let me know if that's the way you want to describe the results and we'll incorporate this into the poster.

Best regards,

D[redacted]

D[redacted] C[redacted]
Medical Director

MAC_0003665

**Online Supplement. Table 1. Verbatim excerpts from manuscripts and our assessment for spin in description of findings from trials included in our study.**

| Study ID | Reasons for assessment of published study reports as having included a "spin" of findings |
|---|---|
| Migraine prophylaxis | |
| 879-201[1] | • Emphasis on efficacy of gabapentin in published report based on a variety of outcomes (all of which were not specified in the protocol);<br>• Failure to report any estimates of effect and findings from statistical testing;<br>• Presentation of findings in a manner that could mislead readers on the efficacy of gabapentin (e.g., plot of a cumulative distribution of percent change in migraine attacks, an analysis that was not pre-specified in the study protocol). |
| 945-220[2] | • Conclusions of effectiveness of gabapentin in internal company research report, based on the protocol-specified primary analysis, do not match conclusions in published report.<br>Excerpt from internal company research report:<br>"*This study demonstrated the following results in patients treated with Neurontin® for up to 12 weeks:*<br>• *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;*"<br>Excerpt from published report:<br>"*Gabapentin is an effective prophylactic agent for patients with migraine.*"<br>"*This controlled clinical trial demonstrated that gabapentin was effective as a prophylactic agent in reducing the frequency of headaches in patients with migraine.*" |
| Bipolar disorders | |
| 945-209[3] | • Extensive rationale to "explain away" statistically non-significant findings.<br>Excerpt from published report:<br>"*Given the uncontrolled clinical observations of the utility of gabapentin in bipolar disorder, it is possible that gabapentin may have some clinically beneficial effects such as anxiolysis that were not adequately captured in this study. Recent reports have demonstrated that gabapentin is efficacious for the treatment of social phobia* |

| Study ID | Reasons for assessment of published study reports as having included a "spin" of findings |
|---|---|
| | *(17) and may be efficacious for some patients with panic disorder (18). Although gabapentin was not superior to placebo in this study, there was no evidence of patients on gabapentin showing a worsening of symptoms either.*"<br><br>"*We chose the study population based on perceived clinical need (i.e., patients who are treated yet remain symptomatic). Because we had no hint that gabapentin would have significant antidepressant effects, we excluded those patients whose 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.*"<br><br>"*With the current level of activity in treatment research in bipolar illness, we believe that many of these issues of methodology will take center stage and demand resolution before significant breakthroughs are possible.*" |
| 945-250[4] | • Conclusions of treatment efficacy did not account for lack of a control group in this study.<br>Excerpt from published report:<br>"*These data suggest that adjunctive GBP* [gabapentin] *is effective in bipolar disorder.*" |
| 945-291[5] | • Failure to consider lack of statistical significance for any of the secondary outcomes in drawing conclusions of efficacy of gabapentin based on findings from this trial;<br>• Extensive rationale to "explain away" unfavorable findings, for example, interpreting a failure to achieve statistical significance for any of the secondary outcomes as evidence supporting a claim of gabapentin's effectiveness in the long-term based on statistical significance observed for the primary outcome.<br>Excerpt from published report:<br>"*As expected, because patients had to be in remission at baseline, no significant differences between groups were found in YMRS, HAM-D, HAM-A and PSQI scores. However, for the PSQI-6 subscale (use of sleeping medication), the score change at month 12 in the gabapentin group -1.1 and the change in the placebo* |

| Study ID | Reasons for assessment of published study reports as having included a “spin” of findings |
|---|---|
| | *group was -0.6 (p = .0267).*”<br><br>“*Whereas there is no indication that gabapentin may have acute antimanic or antidepressant effects,9,29 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 long-term outcome subscale (primary outcome measure) and the PSQI-6 subscale.*”<br><br>“*Improvement in the CGI-BP-M, as in this study, indicates that the clinician, who was blinded to the drug, had a significant perception of improvement in the long-term outcome of gabapentin-treated patients. However, owing to the experimental nature of the design, and limited sample size, the number of secondary outcomes was very limited and we could not correlate the findings on the CGI-BP-M with a significant increase of time to relapse, which would have provided more consistency to the findings. 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. Interestingly enough, looking into the Kaplan-Meier curves in Figure 2, all relapses in the gabapentin arm occurred during the first 3 months, whereas placebo-treated patients experienced recurrence regularly throughout 1 year. This might suggest some carry-over effects of the high frequency of relapse in the gabapentin arm at baseline. This is, however, mere speculation, and only a larger sample size or a longer follow-up would have likely provided a better balance during randomization and perhaps confirmed this hypothesis.*<br><br>*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* |

| Study ID | Reasons for assessment of published study reports as having included a "spin" of findings |
|---|---|
| | *studies have suggested before. The nature of the benefit is, however, not completely clear, except for significant improvement in some items related to the quality of sleep and less need of benzodiazepines.*" |
| Neuropathic pain | |
| 945-271[6] | • Emphasis on statistically significant secondary outcomes in the discussion section and less focus on statistically non-significant findings including the primary outcome.<br>Excerpt from published report:<br>"*There was no significant difference between gabapentin and placebo on the primary outcome measure which was the change in the mean pain intensity score from baseline to the last week of treatment. However, a number of secondary outcomes improved significantly during gabapentin treatment compared with placebo. Gabapentin was superior to placebo in providing pain relief, including reduction of pain with at least by half and improving the overall status of the patient, both according to the clinician and the patient. In addition, the mean sleep interference score was reduced and certain dimensions of SF-36 improved significantly during gabapentin compared with placebo treatment.*"<br><br>"*Although the results of the present study were negative for the primary outcome measure several secondary outcomes indicated efficacy for gabapentin over placebo. More patients had improved, both according to the physician's and the patient's own opinion, during gabapentin compared with placebo treatment. One possible explanation to the findings that the mean pain intensity did not change significantly during gabapentin treatment in spite of improvement in pain relief and quality of life is that gabapentin had a more general effect on mood and well being that was reflected in the global impression of efficacy. Both gabapentin [12, 24] and pregabalin [25,27] have been shown to be effective in anxiety disorders. The possible effects of gabapentin and related drugs on the emotional aspects of pain offer an interesting field for future research.*<br><br>*This study shows that patients with neuropathic pain have* |

| Study ID | Reasons for assessment of published study reports as having included a "spin" of findings |
|---|---|
| | *a considerably lower health related quality of life compared with the general population. This is in accordance with previous studies [21]. The improvement during the five weeks of gabapentin treatment was statistically greater compared with the placebo treatment, but the absolute improvement was small. However, five weeks is a short period of time and a longer study might be necessary to demonstrate a more pronounced beneficial effect.*"<br><br>"*It is possible that the effect of gabapentin could have been greater had the maximum dose been higher. A maximum dose of 2400 mg was chosen based on results from two previous studies in diabetic neuropathy [1] and post-herpetic neuralgia [29]. In these studies forced titration was performed up to a maximum of 2600 mg. Only about 65% of the patients reached the 3600 mg dose level mainly because of AEs and little was gained in efficacy between 2400 and 3600 mg. The study [26] showed similar efficacy with gabapentin 1800 and 2400 mg in diabetic neuropathy. Both doses were significantly better than placebo.*" |
| 945-306[7] | • Explicit description in email conversations regarding "spinning" findings from this study (see Online Supplementary Appendix). |
| No study number - Gorson[8] | • Extensive rationale to "explain away" statistically non-significant findings.<br>Excerpt from published report:<br>"*We used a crossover design because of its statistical efficiency, but the MPQ and VAS scores did not return to baseline after crossover in patients who received gabapentin in phase I (the washout period was inadequate); therefore, we may have underestimated improvement with gabapentin in the VAS scale that may have been detected using a parallel group design. Furthermore, a limitation of our study was that quantitative measures (for example, nerve conduction studies, quantitative sensory thresholds) were not used to further characterise the type of neuropathy. Because of the heterogeneous nature of neuropathic pain in our study patients, we may not have identified a subset of patients who improved with gabapentin. Alternatively, the dosage of gabapentin may have been too low to induce analgesia* |

| Study ID | Reasons for assessment of published study reports as having included a “spin” of findings |
|---|---|
| | *in patients with painful diabetic neuropathy, although similar regimens have been reported to be effective in patients with other painful conditions.*”<br><br>“*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.*” |

## References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2. Mathew NT, Rapoport A, Saper J, Magnus L, Klapper J, Ramadan N, et al. Efficacy of gabapentin in migraine prophylaxis. Headache 2001;41(2):119-28.
3. Pande AC, Crockatt JG, Janney CA, Werth JL, Tsaroucha G. Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. Gabapentin Bipolar Disorder Study Group. Bipolar Disord 2000;2(3 Pt 2):249-55.
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5. Vieta E, Manuel Goikolea J, Martinez-Aran A, Comes M, Verger K, Masramon X, et al. A double-blind, randomized, placebo-controlled, prophylaxis study of adjunctive gabapentin for bipolar disorder. J Clin Psychiatry 2006;67(3):473-7.
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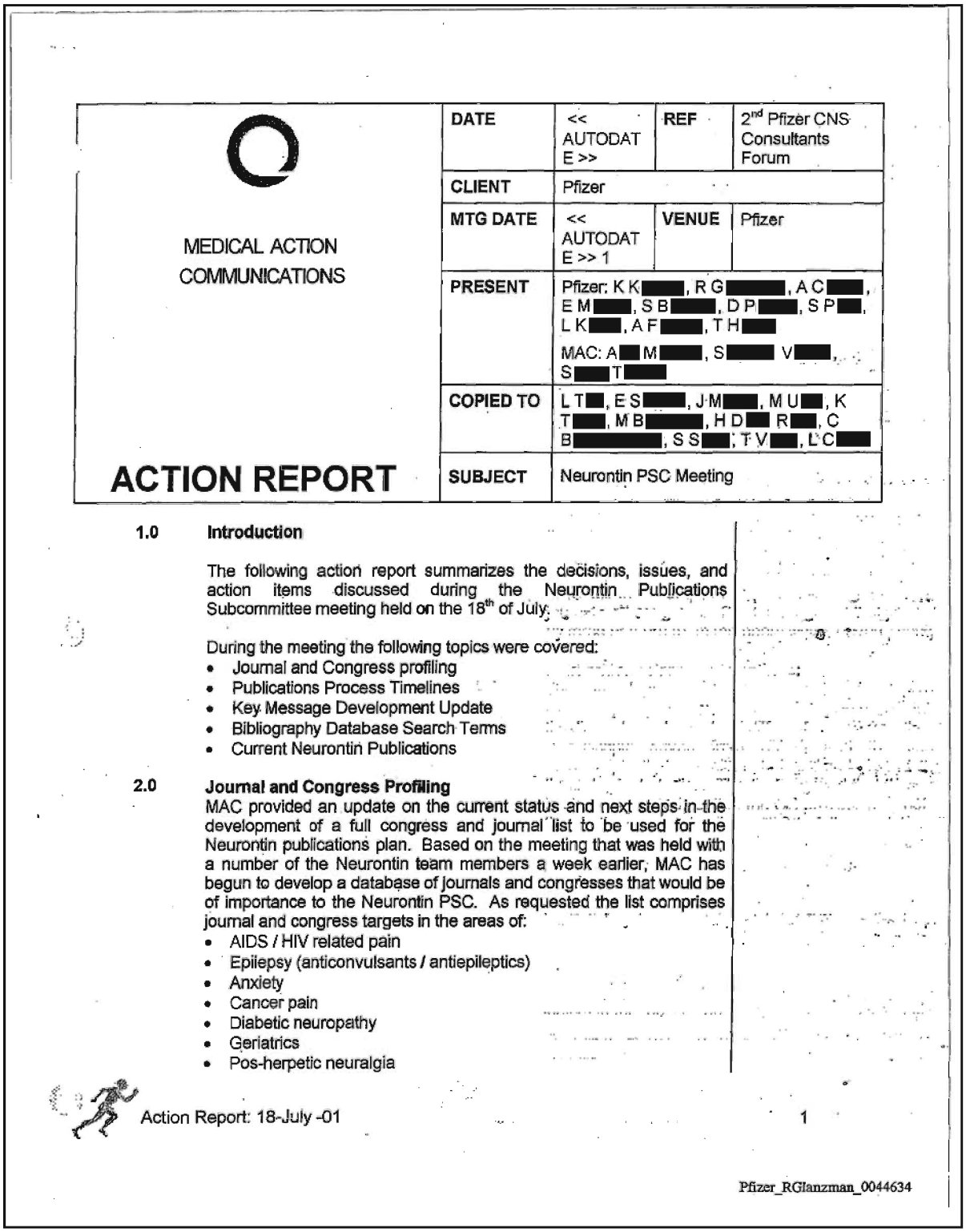
7. Serpell MG. Gabapentin in neuropathic pain syndromes: a randomised, double-blind, placebo-controlled trial. Pain 2002;99(3):557-66.
8. Gorson KC, Schott C, Herman R, Ropper AH, Rand WM. Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. J Neurol Neurosurg Psychiatry 1999;66(2):251-2.

**Online Supplement Figure 8. Medical Action Communications (MAC), a medical writing company, developed extensive profiles of journals and congresses "to be used for the Neurontin publications plan" by Neurontin team members.**



MEDICAL ACTION COMMUNICATIONS

| | | | |
|---|---|---|---|
| DATE | << AUTODATE >> | REF | 2nd Pfizer CNS Consultants Forum |
| CLIENT | Pfizer | | |
| MTG DATE | << AUTODATE >> 1 | VENUE | Pfizer |
| PRESENT | Pfizer: K K[redacted], R G[redacted], A C[redacted], E M[redacted], S B[redacted], D P[redacted], S P[redacted], L K[redacted], A F[redacted], T H[redacted]<br>MAC: A[redacted] M[redacted], S[redacted] V[redacted], S[redacted] T[redacted] | | |
| COPIED TO | L T[redacted], E S[redacted], J M[redacted], M U[redacted], K T[redacted], M B[redacted], H D[redacted] R[redacted], C B[redacted], S S[redacted], T V[redacted], L C[redacted] | | |
| SUBJECT | Neurontin PSC Meeting | | |

# ACTION REPORT

**1.0 Introduction**

The following action report summarizes the decisions, issues, and action items discussed during the Neurontin Publications Subcommittee meeting held on the 18th of July.

During the meeting the following topics were covered:

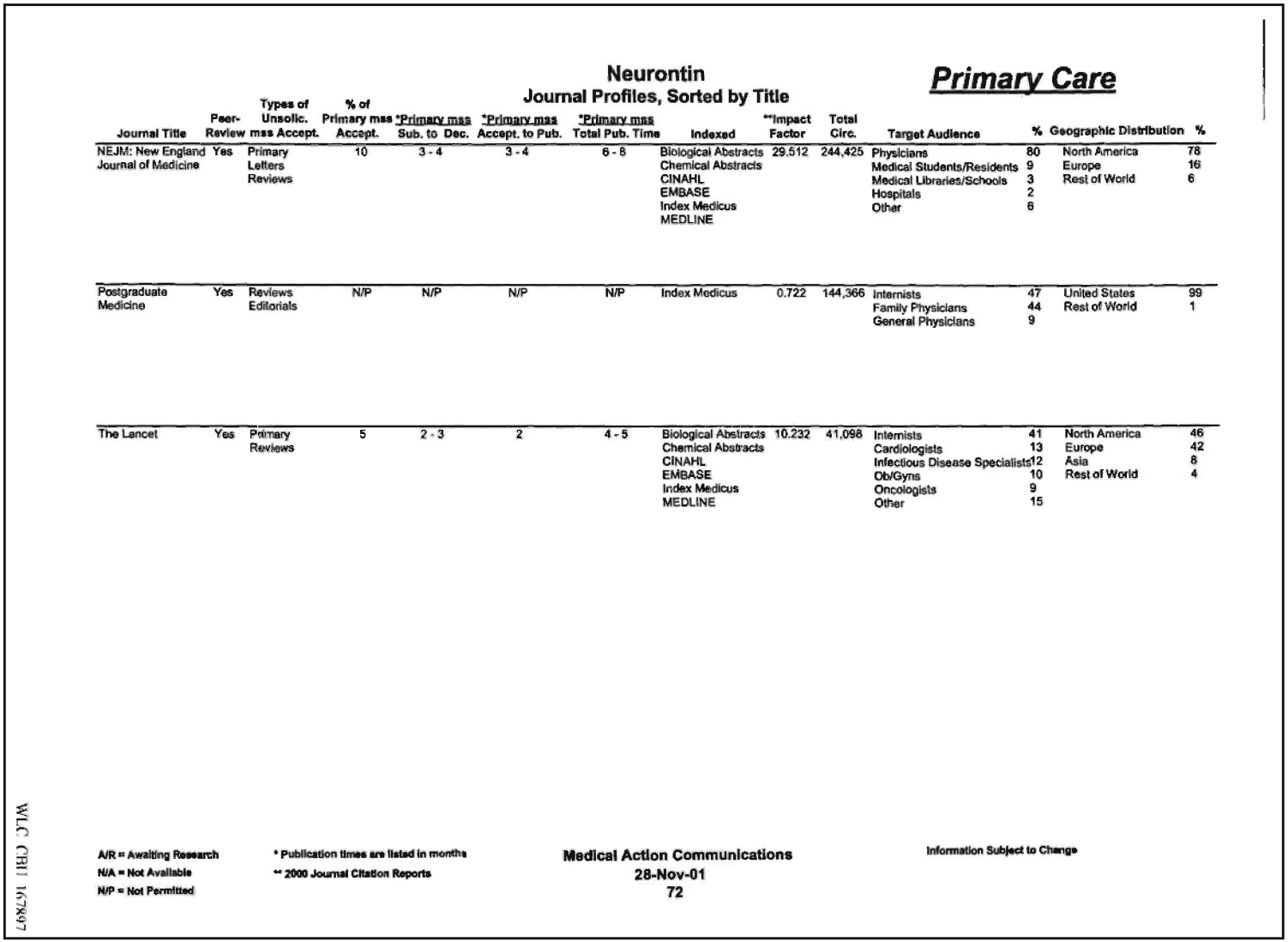
- Journal and Congress profiling
- Publications Process Timelines
- Key Message Development Update
- Bibliography Database Search Terms
- Current Neurontin Publications

**2.0 Journal and Congress Profiling**

MAC provided an update on the current status and next steps in the development of a full congress and journal list to be used for the Neurontin publications plan. Based on the meeting that was held with a number of the Neurontin team members a week earlier, MAC has begun to develop a database of journals and congresses that would be of importance to the Neurontin PSC. As requested the list comprises journal and congress targets in the areas of:

- AIDS / HIV related pain
- Epilepsy (anticonvulsants / antiepileptics)
- Anxiety
- Cancer pain
- Diabetic neuropathy
- Geriatrics
- Pos-herpetic neuralgia

**Online Supplement Figure 9. Internal company document illustrating an example of profiles for primary care journals developed for the Neurontin Publications Subcommittee**



**Neurontin**

**Journal Profiles, Sorted by Title**

***Primary Care***

| Journal Title | Peer-Review | Types of Unsolic. mss Accept. | % of Primary mss Accept. | *Primary mss Sub. to Dec. | *Primary mss Accept. to Pub. | *Primary mss Total Pub. Time | Indexed | **Impact Factor | Total Circ. | Target Audience | % | Geographic Distribution | % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NEJM: New England Journal of Medicine | Yes | Primary<br>Letters<br>Reviews | 10 | 3 - 4 | 3 - 4 | 6 - 8 | Biological Abstracts<br>Chemical Abstracts<br>CINAHL<br>EMBASE<br>Index Medicus<br>MEDLINE | 29.512 | 244,425 | Physicians<br>Medical Students/Residents<br>Medical Libraries/Schools<br>Hospitals<br>Other | 80<br>9<br>3<br>2<br>6 | North America<br>Europe<br>Rest of World | 78<br>16<br>6 |
| Postgraduate Medicine | Yes | Reviews<br>Editorials | N/P | N/P | N/P | N/P | Index Medicus | 0.722 | 144,366 | Internists<br>Family Physicians<br>General Physicians | 47<br>44<br>9 | United States<br>Rest of World | 99<br>1 |
| The Lancet | Yes | Primary<br>Reviews | 5 | 2 - 3 | 2 | 4 - 5 | Biological Abstracts<br>Chemical Abstracts<br>CINAHL<br>EMBASE<br>Index Medicus<br>MEDLINE | 10.232 | 41,098 | Internists<br>Cardiologists<br>Infectious Disease Specialists<br>Ob/Gyns<br>Oncologists<br>Other | 41<br>13<br>12<br>10<br>9<br>15 | North America<br>Europe<br>Asia<br>Rest of World | 46<br>42<br>8<br>4 |

A/R = Awaiting Research
N/A = Not Available
N/P = Not Permitted

* Publication times are listed in months
** 2000 Journal Citation Reports

**Medical Action Communications**
**28-Nov-01**
**72**

Information Subject to Change

WLC CH11 167897

**Online Supplement Figure 10. Internal company document illustrating an example of profiles for different congresses developed for the Neurontin Publications Subcommittee**

**Neurontin**
**Critical Dates List**
**Congresses, Sorted by Congress Specialty and Dates**

| Specialty | Congress | Acronym | Start | End | Location | Paper Abstract Deadline | Electronic Abstract Deadline | Late Breaker Deadline | Satellite Symposia Deadline |
|---|---|---|---|---|---|---|---|---|---|
| AIDS/HIV | National HIV/AIDS Update Conference. Annual. | NAUC | 19-Mar-02 | 22-Mar-02 | San Francisco, CA | 15-Nov-01 | 15-Nov-01 | A/R | First-come, first-served. |
| | International AIDS Conference. Biennial. | IAIDSC | 07-Jul-02 | 12-Jul-02 | Barcelona, Spain | 14-Jan-02 | 21-Jan-02 | 01-Jun-02 | 01-Feb-02 |
| | United States Conference on AIDS. Annual. | USCA | 19-Sep-02 | 22-Sep-02 | Anaheim, CA | 08-Apr-02 | 08-Apr-02 | N/P | 08-Apr-02 |
| | National HIV/AIDS Update Conference. Annual. | NAUC | Mar-03 | Mar-03 | TBD | Nov-02 | Nov-02 | A/R | First-come, first-served. |
| | United States Conference on AIDS. Annual. | USCA | Sep-03 | Sep-03 | TBD | Apr-03 | Apr-03 | N/P | Apr-03 |
| | European Conference on Clinical Aspects and Treatment of HIV Infection. Biennial. | ECCATH | Oct-03 | Oct-03 | Warsaw, Poland | Jun-03 | Jun-03 | Sep-03 | Jul-03 |
| | National HIV/AIDS Update Conference. Annual. | NAUC | Mar-04 | Mar-04 | TBD | Nov-03 | Nov-03 | A/R | First-come, first-served. |
| | International AIDS Conference. Biennial. | IAIDSC | 04-Jul-04 | 09-Jul-04 | Bangkok, Thailand | Jan-04 | Jan-04 | May-04 | Feb-04 |
| | United States Conference on AIDS. Annual. | USCA | Sep-04 | Sep-04 | TBD | Apr-04 | Apr-04 | N/P | Apr-04 |
| | European Conference on Clinical Aspects and Treatment of HIV Infection. Biennial. | ECCATH | Oct-05 | Oct-05 | TBD | Jun-05 | Jun-05 | Sep-05 | Jul-05 |
| | International AIDS Conference. Biennial. | IAIDSC | Jul-06 | Jul-06 | Paris, France | Jan-06 | Jan-06 | May-06 | Feb-06 |
| Diabetes/Endocrinology | American Diabetes Association. Annual Meeting. | ADA | 14-Jun-02 | 18-Jun-02 | San Francisco, CA | 11-Jan-02 | 11-Jan-02 | 12-Apr-02 | 15-Jan-02 |
| | European Association for the Study of Diabetes. Annual Meeting. | EASD | 01-Sep-02 | 05-Sep-02 | Budapest, Hungary | 01-Apr-02 | 01-Apr-02 | N/P | First-come, first-served. |
| | International Society of Pediatric and Adolescent Diabetes. Annual Scientific Meeting. | ISPAD | 18-Sep-02 | 21-Sep-02 | Graz, Austria | N/P | 15-Apr-02 | N/P | 15-Apr-02 |
| | American Diabetes Association. Annual Meeting. | ADA | 13-Jun-03 | 17-Jun-03 | New Orleans, LA | Jan-03 | Jan-03 | Apr-03 | Jan-03 |
| | International Diabetes Federation. Triennial Congress. | IDF | 24-Aug-03 | 29-Aug-03 | Paris, France | 01-Jan-03 | 01-Jan-03 | N/P | first-come, first-serve |
| | European Association for the Study of Diabetes. Annual Meeting. | EASD | Sep-03 | Sep-03 | TBD | Apr-03 | Apr-03 | N/P | First-come, first-served. |
| | International Society of Pediatric and Adolescent Diabetes. Annual Scientific Meeting. | ISPAD | Sep-03 | Sep-03 | Paris, France | N/P | Apr-03 | N/P | Apr-03 |
| | American Diabetes Association. Annual Meeting. | ADA | Jun-04 | Jun-04 | TBD | Jan-04 | Jan-04 | Apr-04 | Jan-04 |
| | European Association for the Study of Diabetes. Annual Meeting. | EASD | Sep-04 | Sep-04 | TBD | Apr-04 | Apr-04 | N/P | First-come, first-served. |
| | International Society of Pediatric and Adolescent Diabetes. Annual Scientific Meeting. | ISPAD | Sep-04 | Sep-04 | TBD | N/P | Apr-04 | N/P | Apr-04 |
| | International Diabetes Federation. Triennial Congress. | IDF | Aug-06 | Aug-06 | Korea | TBD | TBD | TBD | TBD |
| | International Diabetes Federation. Triennial Congress. | IDF | Aug-09 | Aug-09 | TBD | TBD | TBD | TBD | TBD |
| Epilepsy | American Epilepsy Society. Annual Meeting. | AES | 30-Nov-01 | 05-Dec-01 | Philadelphia, PA | Past | Past | N/P | Past |
| | Eilat Conference on New Antiepileptic Drugs. Biennial. | AEDS | 07-Apr-02 | 11-Apr-02 | Sicily, Italy | 01-Feb-02 | 01-Feb-02 | N/P | Past |
| | Latin American Congress on Epilepsy. Biennial. | LACE | 30-May-02 | 02-Jun-02 | Foz de Iguazú, Brazil | 01-Jan-02 | A/R | A/R | A/R |
| | Epilepsy Foundation. Annual Conference. | EFA | 12-Sep-02 | 14-Sep-02 | New Orleans, LA | N/P | N/P | N/P | Mar-02 |
| | American Epilepsy Society. Annual Meeting. | AES | 06-Dec-02 | 11-Dec-02 | Seattle, WA | Apr-02 | May-02 | N/P | Past |
| | Epilepsy Foundation. Annual Conference. | EFA | Sep-03 | Sep-03 | Washington, DC | N/P | N/P | N/P | Mar-03 |
| | International Epilepsy Congress. Biennial. | IEC | 12-Oct-03 | 16-Oct-03 | Tunis, Tunisia | Feb-03 | Feb-03 | N/P | A/R |

**TBD= To Be Determined**
**A/R= Awaiting Research**
**N/P= Not Permitted**
**Information Subject to Change**

**Medical Action Communications**
**28-Nov-01**
**79**

WLC CBU 167904

**Online Supplement Table 2. Details described in internal company documents related to journal circulation, impact factor and statistical significance for published trials included in this study[1, 2]**

| Publication | | Information from internal company documents[3] | | Statistical significance[1] | |
|---|---|---|---|---|---|
| **Citation (study number)** | **Journal** | **Total circulation[3]** | **Impact factor[3]** | **Protocol-specified primary outcome per internal company research report** | **Publication-specified primary outcome** |
| **Migraine prophylaxis** | | | | | |
| Wessely 1989[17] (879-201) | Cephalalgia | 455 | 2.391 | Not statistically significant | No P value reported |
| Mathew 2001[25] (945-220) | Headache | 2,800 | 2.699 | Not statistically significant | Statistically significant favoring gabapentin |
| **Bipolar disorders** | | | | | |
| Pande 2000[12] (945-209) | Bipolar Disorders | 455 | "Not available" | Statistically significant favoring placebo for baseline to end point change in YMRS score; not statistically significant for end point change in HAM-D score | Statistically significant favoring placebo for YMRS change scores from baseline to endpoint; not statistically significant for HAM-D score |
| Wang 2002[14] (945-250) | Bipolar Disorders | 455 | "Not available" | Internal company research report not available | Statistically significant favoring gabapentin |
| Vieta 2006[13] (945-291) | Journal of Clinical Psychiatry | 32,500 | 4.454 | Not statistically significant | Statistically significant favoring gabapentin |

**Online Supplement. Table 2. Continued.**

| Publication | | Information from internal company documents[3] | | Statistical significance[1] | |
|---|---|---|---|---|---|
| **Citation (study number)** | **Journal** | **Total circulation[3]** | **Impact factor[3]** | **Protocol-specified primary outcome per internal company research report** | **Publication-specified primary outcome** |
| **Neuropathic pain** | | | | | |
| Backonja 1998[18] (945-210) | Journal of the American Medical Association | 326,791 | 15.402 | Statistically significant favoring gabapentin | Statistically significant favoring gabapentin |
| Backonja 2002[15] (945-224) | Clinical Therapeutics | Not described | Not described | Not statistically significant | Not statistically significant |
| Gordh 2008[19] (945-271) | Pain | 7,660 | 3.853 | Not statistically significant | Not statistically significant |
| Caraceni 2004[20] (945-276) | Journal of Clinical Oncology | 24,750 | 8.773 | Not statistically significant | Statistically significant favoring gabapentin |
| Serpell 2002[21] (945-306) | Pain | 7,660 | 3.853 | Statistically significant favoring gabapentin | Statistically significant favoring gabapentin |
| Gomez-Perez 2004[22] (945-411) | The British Journal of Diabetes and Vascular Disease | Not described | Not described | Statistically significant favoring gabapentin | Statistically significant favoring gabapentin |
| Gorson 1999[16] (No study number) | Journal of Neurology, Neurosurgery, and Psychiatry | 3,870 | 2.846 | Research report not available | Statistically significant favoring gabapentin |

**Online Supplement. Table 2. Continued.**

**Legend**

HAM-D Hamilton Depression Rating Scale
YMRS Young Mania Rating Scale

**Note**:

1 Data on statistical significance for each trial have previously been presented in detail in Vedula, et.al. N Engl J Med. 2009; 361 (20): 1963-1971.
2. The publications for some of the trials pre-date the documents profiling the journals and congresses.
3. Sources of these data are internal company documents, WLC_CBU_167872 to WLC_CBU_167903, dated November 28, 2001.

**Online Supplement Figure 11. Internal company documents showing peer review comments to a submission of findings from Study 945-206 to the *BMJ*. Study 945-306 is referred to as "NN026" in this document.**

**Gabapentin in Postherpetic Neuralgia: A randomised, double blind, placebo controlled study (NN025)**
**Gabapentin in neuropathic pain syndromes:a randomised, double blind, placebo controlled trial (NN026)**

The above two studies were submitted to the British Medical Journal (BMJ) for peer review.
Unfortunately these studies were rejected for publication.
The BMJ has an open peer review system. Only one referee reviews the item and if that individual feels it is unsuitable for publication it is rejected. With the pressure of volume of papers reviewed by the BMJ their policy is that after rejection an article cannot be resubmitted for reconsideration for publication. The authors are made aware of who refereed the papers.

The comments from the referee were as follows

**NN0225**
- 'Badging' of the trial. The referee felt that two of the three named authors are from the sponsoring company and this put an overtly company favourable spin on the paper.
- 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.
- The study in its present format cannot justify gabapentin as first line treatment for neuropathic pain
- A failure to show efficacy dose response

**NN0226**
- Exclusion criteria-as above
- Analysis of gabapentin group as a whole rather than the three separate doses
- 'Badging' of trial- as above

I am confident that the vast majority of the referees concerns can be addressed in a satisfactory manner. The referee was Prof Henry McQuay from the Oxford Pain Research Group, UK

The following have been actioned

- Meeting with Synergy medical (the medical writers) undertaken and referees comments discussed
- Alternative journals and time lines for publication discussed
- Costing of further write up requested.
- Authors have made suggestions as how to address the concerns of the referee

**Proposed Strategy.**
- Aim for publication in PAIN (the journal of the IASP).

This journal is the official publication of the International Association for the Study of Pain and it publishes original research on the nature, mechanisms and treatment of pain. The journal provides a forum for the dissemination of research in the basic and clinical sciences of multidisciplinary interest.
All articles are peer-reviewed. The authors will generally be advised within 6 weeks whether the article has been accepted, rejected or requires revisions. This process may however take slightly longer as it does depend on the reviewers being able to

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## Online Supplement Figure 11. Continued.

review the articles within 2 weeks as asked. If the manuscript requires major revisions that need to be seen by the reviewers a second time, a further 4 weeks will generally lapse before final acceptance. Following acceptance, it takes 3-4 months for the paper to be published.
The acceptance rate of this journal is 35%.

- Contact H[redacted] McQ[redacted]-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
- Provide Synergy with suggestions for change in style and incorporate where possible the referees changes.

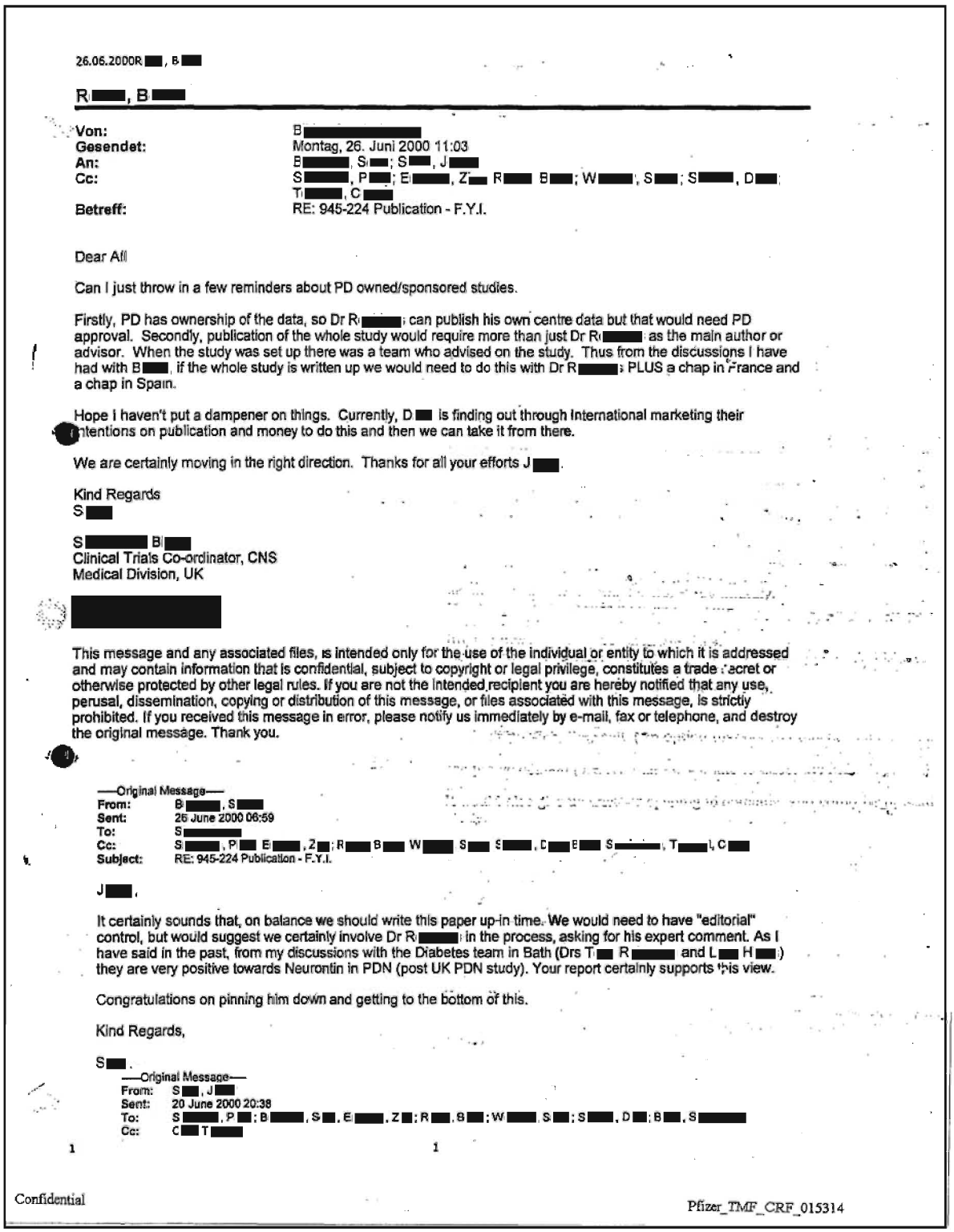
There is also the option (although not desirable) to opt for data on file.
Both Synergy and the Neurontin team feel that a publication is possible and not an unrealistic goal.

We realise that the publication of these studies and NN226 (International Diabetic study) are inextricably linked and this must also be borne in mind.

[redacted]NFIDENTIAL

Pfizer_LeslieTive_0020632

**Online Supplement Figure 12. Internal company emails illustrate that publication of statistically non-significant findings from Study 945-224 was delayed**



26.06.2000R , B

R , B

**Von:** B
**Gesendet:** Montag, 26. Juni 2000 11:03
**An:** B , S ; S , J
**Cc:** S , P ; E , Z R B ; W , S ; S , D ; T , C
**Betreff:** RE: 945-224 Publication - F.Y.I.

Dear All

Can I just throw in a few reminders about PD owned/sponsored studies.

Firstly, PD has ownership of the data, so Dr R can publish his own centre data but that would need PD approval. Secondly, publication of the whole study would require more than just Dr R as the main author or advisor. When the study was set up there was a team who advised on the study. Thus from the discussions I have had with B , if the whole study is written up we would need to do this with Dr R PLUS a chap in France and a chap in Spain.

Hope I haven't put a dampener on things. Currently, D is finding out through International marketing their intentions on publication and money to do this and then we can take it from there.

We are certainly moving in the right direction. Thanks for all your efforts J .

Kind Regards
S

S B
Clinical Trials Co-ordinator, CNS
Medical Division, UK

This message and any associated files, is intended only for the use of the individual or entity to which it is addressed and may contain information that is confidential, subject to copyright or legal privilege, constitutes a trade secret or otherwise protected by other legal rules. If you are not the intended recipient you are hereby notified that any use, perusal, dissemination, copying or distribution of this message, or files associated with this message, is strictly prohibited. If you received this message in error, please notify us immediately by e-mail, fax or telephone, and destroy the original message. Thank you.

—Original Message—
**From:** B , S
**Sent:** 26 June 2000 06:59
**To:** S
**Cc:** S , P E , Z ; R B W S S , D E S , T , C
**Subject:** RE: 945-224 Publication - F.Y.I.

J ,

It certainly sounds that, on balance we should write this paper up-in time. We would need to have "editorial" control, but would suggest we certainly involve Dr R in the process, asking for his expert comment. As I have said in the past, from my discussions with the Diabetes team in Bath (Drs T R and L H ) they are very positive towards Neurontin in PDN (post UK PDN study). Your report certainly supports this view.

Congratulations on pinning him down and getting to the bottom of this.

Kind Regards,

S .

—Original Message—
**From:** S , J
**Sent:** 20 June 2000 20:38
**To:** S , P ; B , S , E , Z ; R , B ; W , S ; S , D ; B , S
**Cc:** C T

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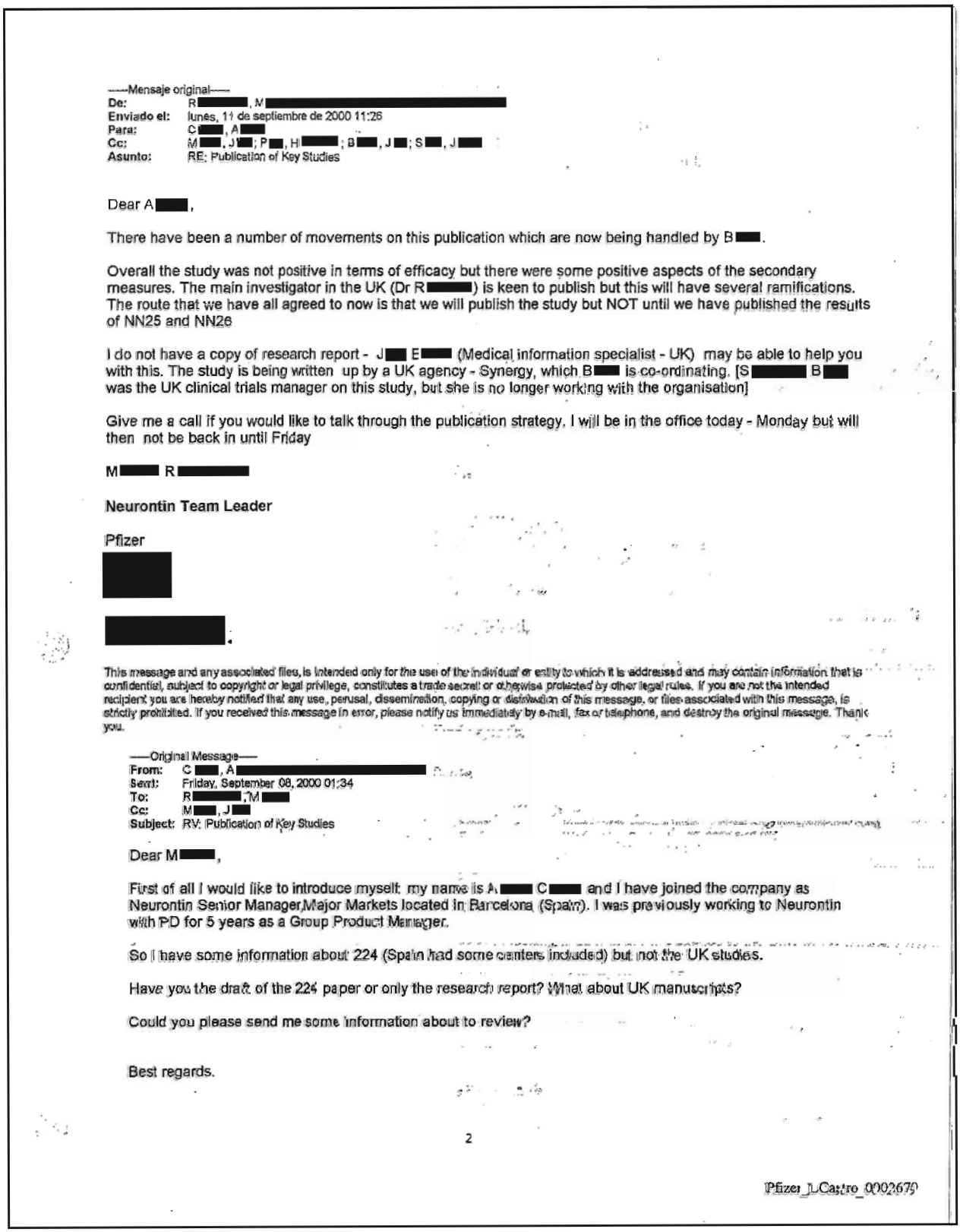
## Online Supplement Figure 12. Continued.



-----Mensaje original-----
**De:** R[redacted], M[redacted]
**Enviado el:** lunes, 11 de septiembre de 2000 11:26
**Para:** C[redacted], A[redacted]
**Cc:** M[redacted], J[redacted]; P[redacted], H[redacted]; B[redacted], J[redacted]; S[redacted], J[redacted]
**Asunto:** RE: Publication of Key Studies

Dear A[redacted],

There have been a number of movements on this publication which are now being handled by B[redacted].

Overall the study was not positive in terms of efficacy but there were some positive aspects of the secondary measures. The main investigator in the UK (Dr R[redacted]) is keen to publish but this will have several ramifications. The route that we have all agreed to now is that we will publish the study but NOT until we have published the results of NN25 and NN26

I do not have a copy of research report - J[redacted] E[redacted] (Medical information specialist - UK) may be able to help you with this. The study is being written up by a UK agency - Synergy, which B[redacted] is co-ordinating. [S[redacted] B[redacted] was the UK clinical trials manager on this study, but she is no longer working with the organisation]

Give me a call if you would like to talk through the publication strategy. I will be in the office today - Monday but will then not be back in until Friday

M[redacted] R[redacted]

**Neurontin Team Leader**

Pfizer

[redacted]

[redacted].



----Original Message----
**From:** C[redacted], A[redacted]
**Sent:** Friday, September 08, 2000 01:34
**To:** R[redacted], M[redacted]
**Cc:** M[redacted], J[redacted]
**Subject:** RV: Publication of Key Studies

Dear M[redacted],

First of all I would like to introduce myself: my name is A[redacted] C[redacted] and I have joined the company as Neurontin Senior Manager,Major Markets located in Barcelona (Spain). I was previously working to Neurontin with PD for 5 years as a Group Product Manager.

So I have some information about 224 (Spain had some centers included) but not the UK studies.

Have you the draft of the 224 paper or only the research report? What about UK manuscripts?

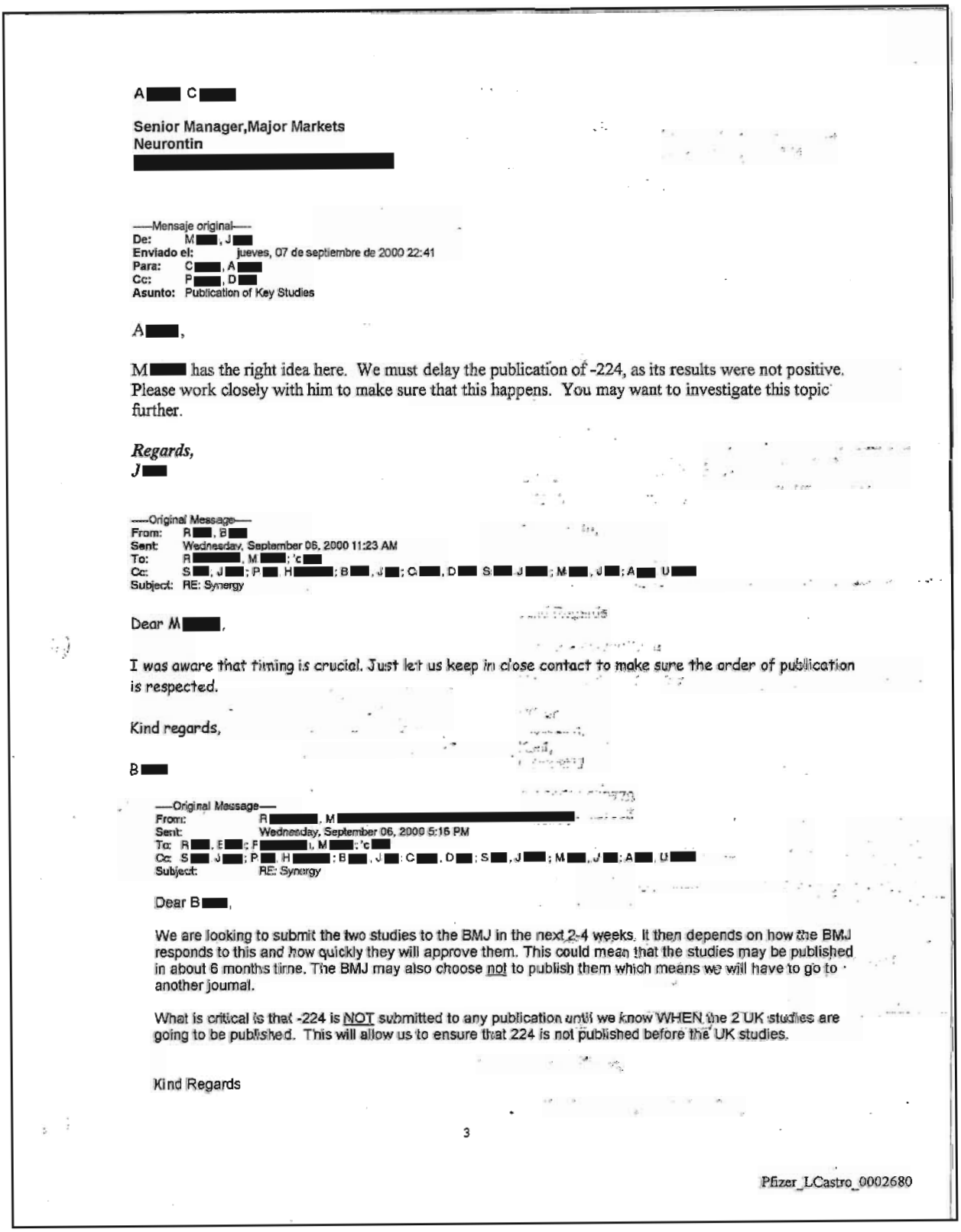
Could you please send me some information about to review?

Best regards.

2

Pfizer_LCastro_0002679

## Online Supplement Figure 12. Continued.



A [redacted] C [redacted]

**Senior Manager,Major Markets**
**Neurontin**
[redacted]

—Mensaje original—
**De:** M [redacted], J [redacted]
**Enviado el:** jueves, 07 de septiembre de 2000 22:41
**Para:** C [redacted], A [redacted]
**Cc:** P [redacted], D [redacted]
**Asunto:** Publication of Key Studies

A [redacted],

M [redacted] has the right idea here. We must delay the publication of -224, as its results were not positive. Please work closely with him to make sure that this happens. You may want to investigate this topic further.

***Regards,***
***J*** [redacted]

—Original Message—
**From:** R [redacted], B [redacted]
**Sent:** Wednesday, September 06, 2000 11:23 AM
**To:** R [redacted], M [redacted]; 'c [redacted]
**Cc:** S [redacted], J [redacted]; P [redacted], H [redacted]; B [redacted], J [redacted]; C [redacted], D [redacted]; S [redacted], J [redacted]; M [redacted], J [redacted]; A [redacted], U [redacted]
**Subject:** RE: Synergy

Dear M [redacted],

I was aware that timing is crucial. Just let us keep in close contact to make sure the order of publication is respected.

Kind regards,

B [redacted]

—Original Message—
**From:** R [redacted], M [redacted]
**Sent:** Wednesday, September 06, 2000 5:16 PM
**To:** R [redacted], E [redacted]; F [redacted], M [redacted]; 'c [redacted]
**Cc:** S [redacted], J [redacted]; P [redacted], H [redacted]; B [redacted], J [redacted]; C [redacted], D [redacted]; S [redacted], J [redacted]; M [redacted], J [redacted]; A [redacted], U [redacted]
**Subject:** RE: Synergy

Dear B [redacted],

We are looking to submit the two studies to the BMJ in the next 2-4 weeks. It then depends on how the BMJ responds to this and how quickly they will approve them. This could mean that the studies may be published in about 6 months time. The BMJ may also choose not to publish them which means we will have to go to another journal.

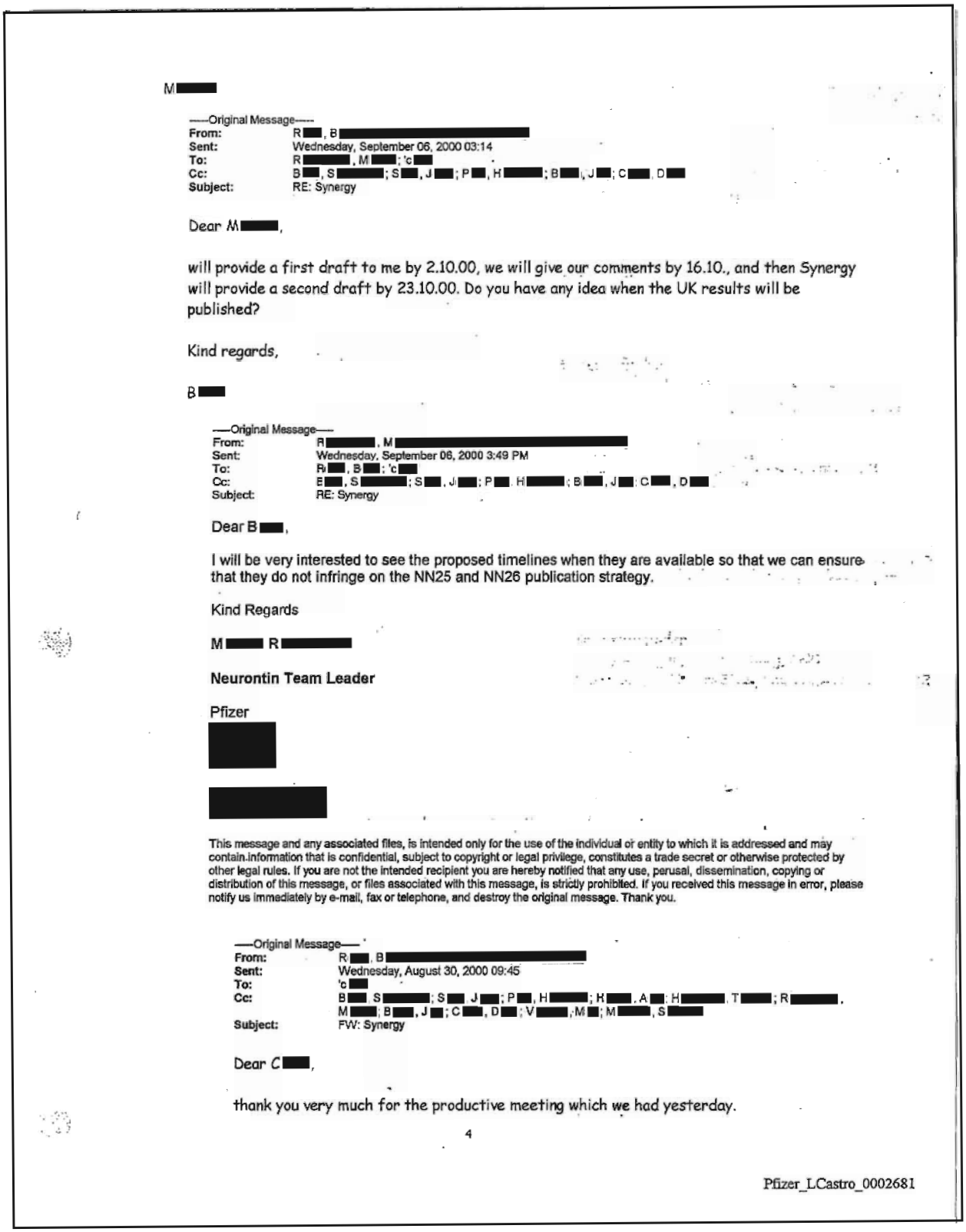
What is critical is that -224 is NOT submitted to any publication until we know WHEN the 2 UK studies are going to be published. This will allow us to ensure that 224 is not published before the UK studies.

Kind Regards

3

Pfizer_LCastro_0002680

## Online Supplement Figure 12. Continued.



M[redacted]

-----Original Message-----
**From:** R[redacted], B[redacted]
**Sent:** Wednesday, September 06, 2000 03:14
**To:** R[redacted], M[redacted]; 'c[redacted]
**Cc:** B[redacted], S[redacted]; S[redacted], J[redacted]; P[redacted], H[redacted]; B[redacted], J[redacted]; C[redacted], D[redacted]
**Subject:** RE: Synergy

Dear M[redacted],

will provide a first draft to me by 2.10.00, we will give our comments by 16.10., and then Synergy will provide a second draft by 23.10.00. Do you have any idea when the UK results will be published?

Kind regards,

B[redacted]

-----Original Message-----
**From:** R[redacted], M[redacted]
**Sent:** Wednesday, September 06, 2000 3:49 PM
**To:** R[redacted], B[redacted]; 'c[redacted]
**Cc:** B[redacted], S[redacted]; S[redacted], J[redacted]; P[redacted], H[redacted]; B[redacted], J[redacted]; C[redacted], D[redacted]
**Subject:** RE: Synergy

Dear B[redacted],

I will be very interested to see the proposed timelines when they are available so that we can ensure that they do not infringe on the NN25 and NN26 publication strategy.

Kind Regards

M[redacted] R[redacted]

**Neurontin Team Leader**

Pfizer

[redacted]

[redacted]



-----Original Message-----
**From:** R[redacted], B[redacted]
**Sent:** Wednesday, August 30, 2000 09:45
**To:** 'c[redacted]
**Cc:** B[redacted], S[redacted]; S[redacted], J[redacted]; P[redacted], H[redacted]; H[redacted], A[redacted]; H[redacted], T[redacted]; R[redacted], M[redacted]; B[redacted], J[redacted]; C[redacted], D[redacted]; V[redacted]; M[redacted]; M[redacted], S[redacted]
**Subject:** FW: Synergy

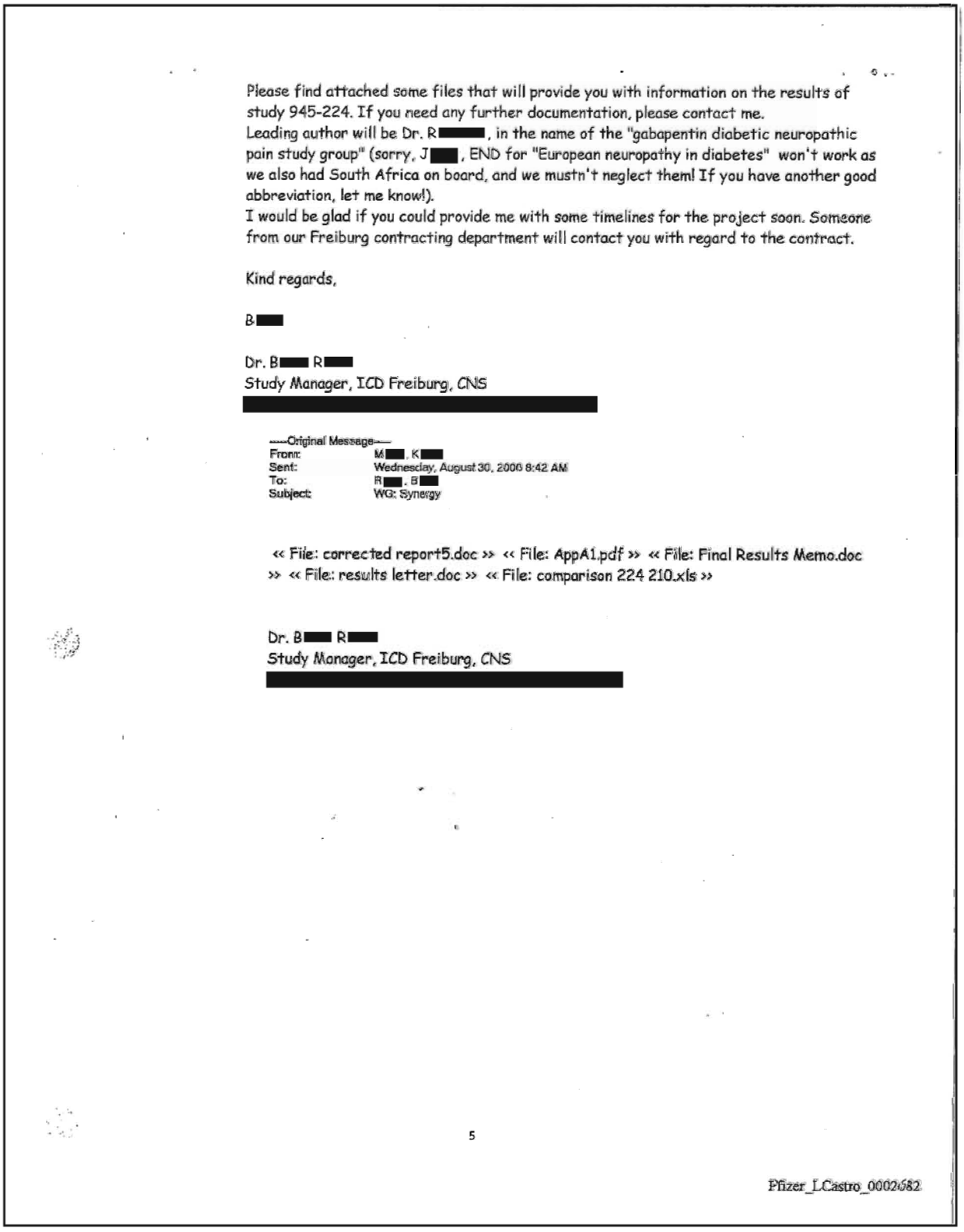
Dear C[redacted],

thank you very much for the productive meeting which we had yesterday.

4

Pfizer_LCastro_0002681

## Online Supplement Figure 12. Continued.



Please find attached some files that will provide you with information on the results of study 945-224. If you need any further documentation, please contact me.
Leading author will be Dr. R[redacted], in the name of the "gabapentin diabetic neuropathic pain study group" (sorry, J[redacted], END for "European neuropathy in diabetes" won't work as we also had South Africa on board, and we mustn't neglect them! If you have another good abbreviation, let me know!).
I would be glad if you could provide me with some timelines for the project soon. Someone from our Freiburg contracting department will contact you with regard to the contract.

Kind regards,

B[redacted]

Dr. B[redacted] R[redacted]
Study Manager, ICD Freiburg, CNS
[redacted]

-----Original Message-----
From: M[redacted], K[redacted]
Sent: Wednesday, August 30, 2006 8:42 AM
To: R[redacted], B[redacted]
Subject: WG: Synergy

<< File: corrected report5.doc >> << File: AppA1.pdf >> << File: Final Results Memo.doc >> << File: results letter.doc >> << File: comparison 224 210.xls >>

Dr. B[redacted] R[redacted]
Study Manager, ICD Freiburg, CNS
[redacted]

5

Pfizer_LCastro_0002682

## Online Supplement Figure 12. Continued.

From: M[redacted], J[redacted]
Sent: Thursday, September 13, 2001 6:48 PM
To: M[redacted], E[redacted]
Subject: RE: POPP Study

E[redacted],

Your assumptions are correct. I try to attend the pub meetings, but that is sometimes tough to do. I think that the team now can handle most of these issues, and appreciates the overall plan. 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.

Regards,

*J[redacted] M[redacted]*
*NEURONTIN WWTL*
[redacted]

—Original Message—
From: M[redacted], E[redacted]
Sent: Thursday, September 13, 2001 9:57 AM
To: M[redacted], J[redacted]
Subject: RE: POPP Study

J[redacted],

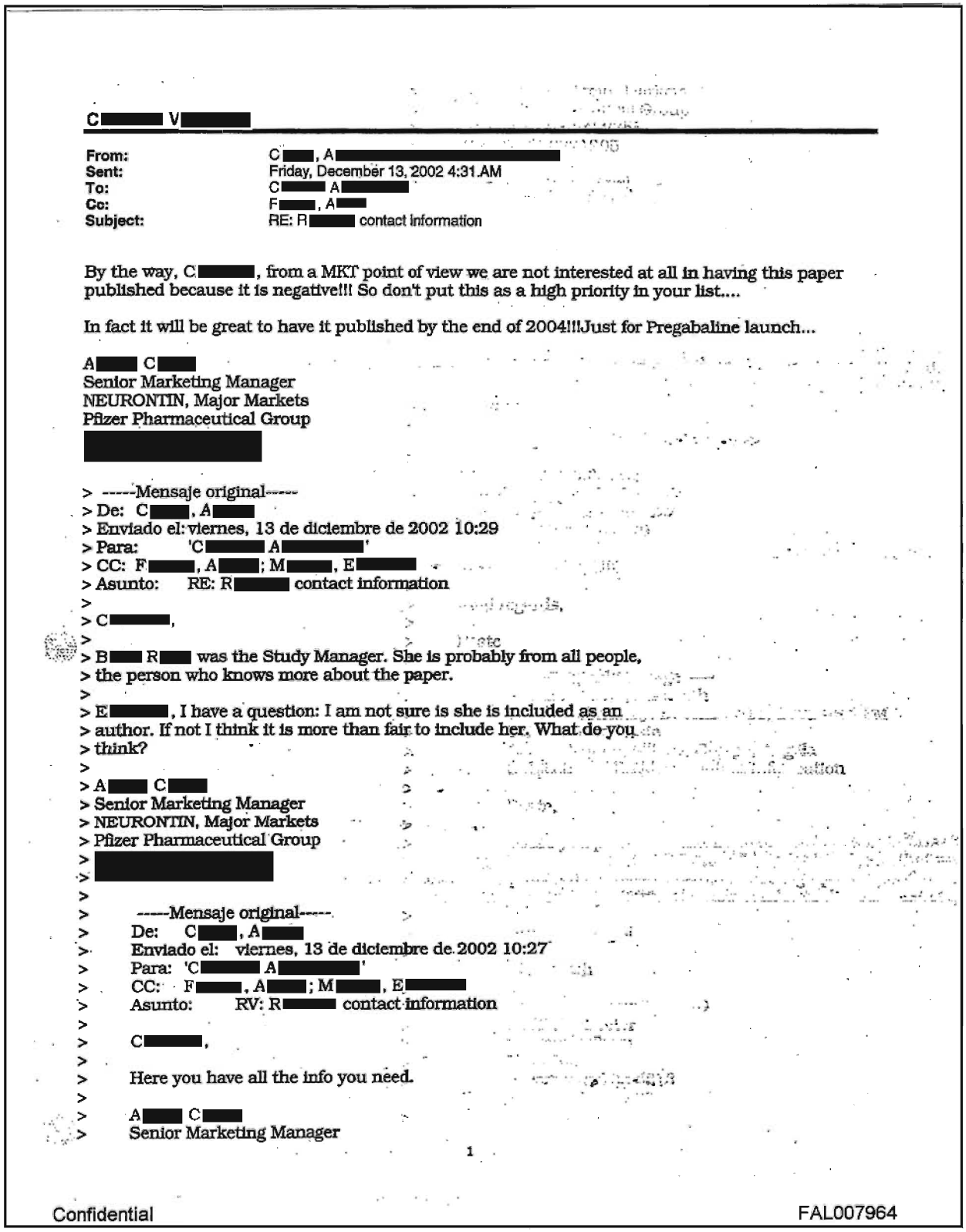
If you aren't able to attend the next publications subcommittee, please let us know your thoughts on timing abstracts/publications. The UK PHN paper will likely be published in October. The UK MNP paper is still under review and has not yet been accepted. If all goes well it would likely publish in late 2001/early 2002. The manuscript for the negative DPN paper is complete, and the first author is eager to see it submitted. I assume that we would like to maximize the time interval between the R[redacted] paper and the POPP study.

–E[redacted]

1

Pfizer_JMarino_0000809

## Online Supplement Figure 12. Continued.



C[redacted] V[redacted]

**From:** C[redacted], A[redacted]
**Sent:** Friday, December 13, 2002 4:31 AM
**To:** C[redacted] A[redacted]
**Cc:** F[redacted], A[redacted]
**Subject:** RE: R[redacted] contact information

By the way, C[redacted], 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 in your list....

In fact it will be great to have it published by the end of 2004!!!Just for Pregabaline launch...

A[redacted] C[redacted]
Senior Marketing Manager
NEURONTIN, Major Markets
Pfizer Pharmaceutical Group
[redacted]

> -----Mensaje original-----
> De: C[redacted], A[redacted]
> Enviado el: viernes, 13 de diciembre de 2002 10:29
> Para: 'C[redacted] A[redacted]'
> CC: F[redacted], A[redacted]; M[redacted], E[redacted]
> Asunto: RE: R[redacted] contact information
>
> C[redacted],
>
> B[redacted] R[redacted] was the Study Manager. She is probably from all people,
> the person who knows more about the paper.
>
> E[redacted], I have a question: I am not sure is she is included as an
> author. If not I think it is more than fair to include her. What do you
> think?
>
> A[redacted] C[redacted]
> Senior Marketing Manager
> NEURONTIN, Major Markets
> Pfizer Pharmaceutical Group
> [redacted]
>
> -----Mensaje original-----
> De: C[redacted], A[redacted]
> Enviado el: viernes, 13 de diciembre de 2002 10:27
> Para: 'C[redacted] A[redacted]'
> CC: F[redacted], A[redacted]; M[redacted], E[redacted]
> Asunto: RV: R[redacted] contact information
>
> C[redacted],
>
> Here you have all the info you need.
>
> A[redacted] C[redacted]
> Senior Marketing Manager

1

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## Online Supplement Figure 12. Continued.

T[redacted], L[redacted]

**From:** C[redacted], A[redacted]
**Sent:** Monday, November 13, 2000 10:15 AM
**To:** T[redacted], L[redacted]
**Subject:** RV: Revised draft of publication for 945-224

L[redacted],

This is the negative study that we were talking about.

I will inform B[redacted] that you will contact her.

As you can imagine, I am not in a hurry to publish it.

**A[redacted] C[redacted]**
Neurontin Senior Manager, Major Markets
Worldwide Marketing
Pfizer Pharmaceutical Group
[redacted]

-----Mensaje original-----
De: R[redacted], B[redacted]
Enviado el: lunes, 13 de noviembre de 2000 12:14
Para: 'C[redacted]'
Cc: A[redacted], U[redacted]; R[redacted], M[redacted]; B[redacted], J[redacted]; M[redacted], P[redacted]; C[redacted], A[redacted]; P[redacted], H[redacted]
Asunto: Revised draft of publication for 945-224

Dear C[redacted],

please find attached some minor changes we would like to make to the revised draft you have forwarded to me on 24-Oct-2000. These changes mainly concern wording in the statistical section, and we have tried to clarify which results refer to the double-blind phase and which to the open-label phase of this study.

comments all study 945 23 10 0...

Would you please return the revised draft to me after you have integrated our comments? I will then forward a copy of the draft publication to Dr. R[redacted] for review (in close co-operation with Dr. U[redacted] A[redacted]).

Kind regards,

B[redacted]

**B[redacted] R[redacted], PhD**
*Study Manager / Senior Clinical Scientist, CNS*
*Pfizer Pharmaceuticals Group*
*Freiburg / Germany*
[redacted]

1

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## Online Supplement Figure 12. Continued.

T[redacted], L[redacted]

**From:** B[redacted], J[redacted]
**Sent:** Monday, October 16, 2000 1:01 PM
**To:** C[redacted], A[redacted]
**Cc:** T[redacted], L[redacted]; M[redacted], J[redacted]; R[redacted], M[redacted]; A[redacted], U[redacted]
**Subject:** RE: 25 and 26 studies

Dear A[redacted]
I'm sorry to miss you in Florence as well
With regard to your question below about a dose response in N026 - it is not possible to assess one because the design of the study was similar to that of the JAMA studies in which there was a "forced titration" to 2400mg/day. As you can see from the chart below most patients progressed through to 2400mg gabapentin/day. The number of patients who stopped at the lower doses are insufficient to analyse separately.

| | Placebo | Gabapentin |
|---|---|---|
| **Dosage prescribed at visit 2** | | |
| 900mg | 6 | 12 |
| 1800mg | 127 | 122 |
| **Dosage prescribed at visit 3** | | |
| 900mg | 4 | 6 |
| 1800mg | 15 | 19 |
| 2400mg | 101 | 101 |

Hope this answers your question - if you want to discuss anything further contact me again

Regards

J[redacted]

Mrs J[redacted] B[redacted]
Medical Information Specialist
Neurontin Team
Pfizer UK

-----Original Message-----
**From:** R[redacted], M[redacted]
**Sent:** 29 September 2000 12:58
**To:** C[redacted], A[redacted]; B[redacted], J[redacted]
**Cc:** T[redacted], L[redacted]; M[redacted], J[redacted]; P[redacted], H[redacted]
**Subject:** RE: 25 and 26 studies

Dear A[redacted],
It was a pity to miss you at the Nice meeting which on the whole was very successful.

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 R[redacted]. We are not allowing him to write it up himself. J[redacted] is familiar with the data, and will update you in Florence. I will not be at the meeting.

H[redacted] P[redacted], the previous medical advisor for the pain group, has had a very good relationship with Dr R[redacted] in the past - if you want more information, he would be the best person to contact

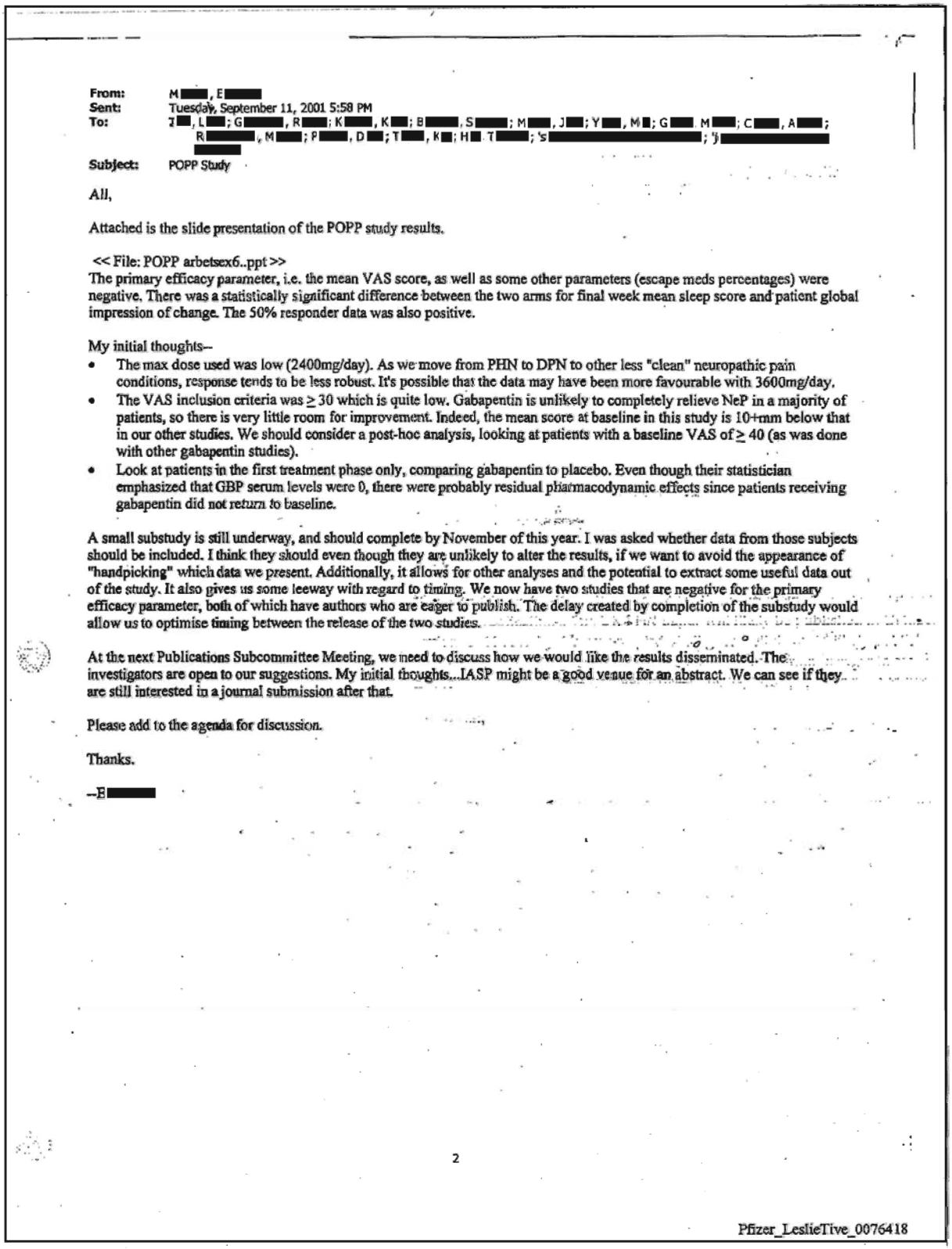
regards

M[redacted]

1

Pfizer LeslieTive 0020985

**Online Supplement Figure 13. Internal company emails illustrate that publication of statistically non-significant findings from Study 945-271 was delayed**



**From:** M[redacted], E[redacted]
**Sent:** Tuesday, September 11, 2001 5:58 PM
**To:** J[redacted], L[redacted]; G[redacted], R[redacted]; K[redacted], K[redacted]; B[redacted], S[redacted]; M[redacted], J[redacted]; Y[redacted], M[redacted]; G[redacted], M[redacted]; C[redacted], A[redacted]; R[redacted], M[redacted]; P[redacted], D[redacted]; T[redacted], K[redacted]; H[redacted], T[redacted]; S[redacted]; J[redacted]
**Subject:** POPP Study

All,

Attached is the slide presentation of the POPP study results.

<< File: POPP arbetsex6..ppt >>
The primary efficacy parameter, i.e. the mean VAS score, as well as some other parameters (escape meds percentages) were negative. There was a statistically significant difference between the two arms for final week mean sleep score and patient global impression of change. The 50% responder data was also positive.

My initial thoughts--

- The max dose used was low (2400mg/day). As we move from PHN to DPN to other less "clean" neuropathic pain conditions, response tends to be less robust. It's possible that the data may have been more favourable with 3600mg/day.
- The VAS inclusion criteria was ≥ 30 which is quite low. Gabapentin is unlikely to completely relieve NeP in a majority of patients, so there is very little room for improvement. Indeed, the mean score at baseline in this study is 10+mm below that in our other studies. We should consider a post-hoc analysis, looking at patients with a baseline VAS of ≥ 40 (as was done with other gabapentin studies).
- Look at patients in the first treatment phase only, comparing gabapentin to placebo. Even though their statistician emphasized that GBP serum levels were 0, there were probably residual pharmacodynamic effects since patients receiving gabapentin did not return to baseline.

A small substudy is still underway, and should complete by November of this year. I was asked whether data from those subjects should be included. I think they should even though they are unlikely to alter the results, if we want to avoid the appearance of "handpicking" which data we present. Additionally, it allows for other analyses and the potential to extract some useful data out of the study. It also gives us some leeway with regard to timing. We now have two studies that are negative for the primary efficacy parameter, both of which have authors who are eager to publish. 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 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.

Please add to the agenda for discusssion.

Thanks.

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