Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Vedula SS, Bero L, Scherer RW, Dickersin K. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. N Engl J Med 2009;361:1963-71.

Outcome Reporting in Industry-Sponsored Trials of Gabapentin for Off-label Use

Supplement to: Vedula SS, Bero L, Scherer RW, Dickersin K. Outcome Reporting in Industry-Sponsored Trials of Gabapentin for Off-Label Use. N Engl J Med 2009; 361:1963-71.

Table of Contents

Table 1 - Trials Conducted, Documents Available and Publication Status by Indication

Trial ID	Protocol	Research report	Publication status	
			Other reports	Full length published article
Migraine prophylaxis				
879-201[a]	√	√	Wessely 1987[b,16]	No full length publication
945-217[a]	√	√	None	No publication
945-220[a]	√	√	Mathew 1998[17] (Abstract) Mathew 1999[18] (Abstract)	Mathew 2001[19]
Bipolar disorders				
945-209[a]	√	√[c]	None	Pande 2000[20]
945-250[d]	√	Not available	None	Wang 2002[21]
945-291[a]	Not available	√[e]	None	Vieta 2006[22]
Neuropathic pain				
945-210[a]	√	√	Backonja 1997[b, 23] (Abstract)	Backonja 1998[24]
945-224[a]	√	√	Backonja 2002[25] (Poster) Backonja 2003[26] (Review with pooled analyses)	No full length publication
945-271[f, g]	√	√	Gordh 2002[27] (Abstract)	Gordh 2008[28]
945-276[a]	Not available	√	None	Caraceni 2004[29]
945-306[a]	√	√	Serpell 2002[30] (Poster)	Serpell 2002[31]
945-411[a]	√	√	Gomez-Perez 2002[32] (Abstract)	Gomez-Perez 2004[33]
A945-1008[a]	√	√[e]	None	No publication
No Trial ID - Dallocchio[a]	Not available	Not available	None	Dallocchio 2000[34]
No Trial ID – Gorson[f]	√	Not Available	Gorson 1998[35] (Abstract) Gorson 1999[36] (Letter to editor)	No full length publication
Nociceptive pain				
1032-001[a]	√	√	None	No publication
1032-002[a]	√	√	None	No publication
1032-003[d]	√	√	None	No publication
1032-004[a]	√	√	None	No publication
1035-001[g]	√	√	None	No publication
1035-002[a]	√	√	None	No publication

Table 1 Legend:

a	Randomized, parallel group trial
b	Preliminary results
c	Synopsis of research report plus letter to investigators reporting trial results
d	Open-label uncontrolled trial
e	"Final Study Report" (an abridged version of research report)
f	Randomized, crossover trial
g	Includes main trial plus ancillary study

Table 2 - All Primary Outcomes Examined in 20 Clinical Trials of Gabapentin, as Described in the Protocol and Main Study Publication

	Migraine					Bipolar disorders						Neuropathic pain															Nociceptive pain					
Primary outcomes described in protocols & publications	**879-201**		**945-217**	**945-220**		**945-209**		**945-250**		**945-291**		**945-210**		**945-224**		**945-271**		**945-276**		**945-306**		**945-411**		**A945-1008**	**No Trial ID - Gorson**		**1032-001**	**1032-002**	**1032-003**	**1032-004**	**1035-001**	**1035-002**
	Protocol	**Wessely 1987[a]**	**Protocol**	**Protocol**	**Mathew 2001**	**Protocol**	**Pande 2000[a]**	**Protocol**	**Wang 2002**	**–[b]**	**Vieta 2006**	**Protocol**	**Backonja 1998**	**Protocol**	**Backonja 2003**	**Protocol**	**Gordh 2008**	**–[b]**	**Caraceni 2006**	**Protocol**	**Serpell 2002**	**Protocol**	**Gomez-Perez 2004**	**Protocol**	**Protocol[a]**	**Gorson 1999[a]**	**Protocol**	**Protocol**	**Protocol[a]**	**Protocol**	**Protocol**	**Protocol**
Mean of difference between attack frequency at start and end of treatment	√																														
Frequency of migraine attacks in the gabapentin group		√																													
Cumulative distribution of percent reduction in migraine attacks		√																													
Proportion of patients with mild worsening of their initial status		√																													
Proportion with a decrease in frequency of migraine attacks		√																													
Four week migraine headache rate during stabilization period 2			√[c]	√[c]																											
Four week migraine headache rate during stabilization period 2 for patients who received a stable dose of 2400 mg/day					√																										
Hamilton Depression Rating Scale (HAM-D)						√	√	√	√																						
Percent responders according to criterion of final HAM-D score at least 50% of baseline score								√																							

Table 2 - All Primary Outcomes Examined in 20 Clinical Trials of Gabapentin, as Described in the Protocol and Main Study Publication

	Migraine					Bipolar disorders						Neuropathic pain															Nociceptive pain					
Primary outcomes described in protocols & publications	**879-201**		**945-217**	**945-220**		**945-209**		**945-250**		**945-291**		**945-210**		**945-224**		**945-271**		**945-276**		**945-306**		**945-411**		**A945-1008**	**No Trial ID - Gorson**		**1032-001**	**1032-002**	**1032-003**	**1032-004**	**1035-001**	**1035-002**
	Protocol	**Wessely 1987[a]**	**Protocol**	**Protocol**	**Mathew 2001**	**Protocol**	**Pande 2000[a]**	**Protocol**	**Wang 2002**	**–[b]**	**Vieta 2006**	**Protocol**	**Backonja 1998**	**Protocol**	**Backonja 2003**	**Protocol**	**Gordh 2008**	**–[b]**	**Caraceni 2006**	**Protocol**	**Serpell 2002**	**Protocol**	**Gomez-Perez 2004**	**Protocol**	**Protocol[a]**	**Gorson 1999[a]**	**Protocol**	**Protocol**	**Protocol[a]**	**Protocol**	**Protocol**	**Protocol**
Hamilton Anxiety Rating Scale (HAM-A)							√[d,e]																									
Young Mania Rating Scale (YMRS)						√	√																									
Responders on the Internal States Scale						√	√																									
Clinical Global Impression of Severity (CGIS)							√[d]			√																						
Clinical Global Impression of Change (CGIC)							√[d]																									
Life chart for recurrent affective illness							√[d]																									
Short Form-36 (SF-36)							√[d]																									
Clinical Global Impression scale for Bipolar Illness, Modified (CGI-BP-M)											√																					
Weekly mean pain score (Likert scale)												√	√	√	√					√	√			√								
Mean pain intensity score (Visual Analog Scale; VAS) during last week of each treatment period (two treatment periods)																√																

Table 2 - All Primary Outcomes Examined in 20 Clinical Trials of Gabapentin, as Described in the Protocol and Main Study Publication

	Migraine					Bipolar disorders						Neuropathic pain															Nociceptive pain					
Primary outcomes described in protocols & publications	879-201		945-217	945-220		945-209		945-250		945-291		945-210		945-224		945-271		945-276		945-306		945-411		A945-1008	No Trial ID - Gorson		1032-001	1032-002	1032-003	1032-004	1035-001	1035-002
	Protocol	Wessely 1987[a]	Protocol	Protocol	Mathew 2001	Protocol	Pande 2000[a]	Protocol	Wang 2002	–[b]	Vieta 2006	Protocol	Backonja 1998	Protocol	Backonja 2003	Protocol	Gordh 2008	–[b]	Caraceni 2006	Protocol	Serpell 2002	Protocol	Gomez-Perez 2004	Protocol	Protocol[a]	Gorson 1999[a]	Protocol	Protocol	Protocol[a]	Protocol	Protocol	Protocol
Mean pain intensity score (VAS) for each of the following periods: run-in, treatment period 1, washout, treatment period 2																	√															
Tactile allodynia																√[f]																
Cold allodynia																√[f]																
Pin-prick hyperalgesia																√[f]																
Global pain score registered in CRF																		√														
Average follow-up pain score																			√													
Percent reduction from baseline in final weekly mean pain score																						√	√									
Weekly mean score for each VAS for each week of the treatment period																									√							
Visual analog scale (VAS) – difference in mean change																										√						
Global assessment of pain																									√	√						
Quality of life questionnaires																									√							
McGill Pain Questionnaire (MPQ)																										√						
Present Pain Intensity scale																										√						

Table 2 - All Primary Outcomes Examined in 20 Clinical Trials of Gabapentin, as Described in the Protocol and Main Study Publication

	Migraine					Bipolar disorders						Neuropathic pain															Nociceptive pain					
Primary outcomes described in protocols & publications	**879-201**		**945-217**	**945-220**		**945-209**		**945-250**		**945-291**		**945-210**		**945-224**		**945-271**		**945-276**		**945-306**		**945-411**		**A945-1008**	**No Trial ID - Gorson**		**1032-001**	**1032-002**	**1032-003**	**1032-004**	**1035-001**	**1035-002**
	Protocol	**Wessely 1987[a]**	**Protocol**	**Protocol**	**Mathew 2001**	**Protocol**	**Pande 2000[a]**	**Protocol**	**Wang 2002**	**–[b]**	**Vieta 2006**	**Protocol**	**Backonja 1998**	**Protocol**	**Backonja 2003**	**Protocol**	**Gordh 2008**	**–[b]**	**Caraceni 2006**	**Protocol**	**Serpell 2002**	**Protocol**	**Gomez-Perez 2004**	**Protocol**	**Protocol[a]**	**Gorson 1999[a]**	**Protocol**	**Protocol**	**Protocol[a]**	**Protocol**	**Protocol**	**Protocol**
Pain relief (PR)																										√[c]					
Pain intensity difference (PID)																										√[c]					
Pain relief intensity difference (PRID)																										√[c]					
Time to onset of analgesia																										√[c]					
Duration of analgesia																										√[c]					
Sum of pain intensity difference over the first 6 hours (SPID6)																											√		√	√
Pain subscale of the Western Ontario and McMaster Universities Likert Version 3.1 (WOMAC LK 3.1)																												√			
Stiffness subscale of the Western Ontario and McMaster Universities Likert Version 3.1 (WOMAC LK 3.1)																												√			
Physical Function subscale of the Western Ontario and McMaster Universities Likert Version 3.1 (WOMAC LK 3.1)																												√			

Table 2 - All Primary Outcomes Examined in 20 Clinical Trials of Gabapentin, as Described in the Protocol and Main Study Publication

	Migraine					Bipolar disorders						Neuropathic pain															Nociceptive pain					
Primary outcomes described in protocols & publications	**879-201**		**945-217**	**945-220**		**945-209**		**945-250**		**945-291**		**945-210**		**945-224**		**945-271**		**945-276**		**945-306**		**945-411**		**A945-1008**	**No Trial ID - Gorson**		**1032-001**	**1032-002**	**1032-003**	**1032-004**	**1035-001**	**1035-002**
	Protocol	Wessely 1987[a]	Protocol	Protocol	Mathew 2001	Protocol	Pande 2000[a]	Protocol	Wang 2002	–[b]	Vieta 2006	Protocol	Backonja 1998	Protocol	Backonja 2003	Protocol	Gordh 2008	–[b]	Caraceni 2006	Protocol	Serpell 2002	Protocol	Gomez-Perez 2004	Protocol	Protocol[a]	Gorson 1999[a]	Protocol	Protocol	Protocol[a]	Protocol	Protocol	Protocol
Patient assessment of pain walking a flat surface from Western Ontario and McMaster Universities Likert Version 3.1 (WOMAC LK 3.1)																													√			
Health Utilities Index Mark 2																													√			
Health Utilities Index Mark 3																													√			
Short form – 36 (SF-36)																													√			
Patient global assessment of osteoarthritis																													√			
Clinician global assessment of osteoarthritis																													√			
Ulcer and erosion incidence																														√		

Table 2 Legend

References to the main study publication associated with each study ID are as follows:
879-201[16], 945-220[19], 945-209[20], 945-250[21], 945-291[22], 945-210[24], 945-224[26], 945-271[28], 945-276[29], 945-306[31], 945-411[33], No Trial ID - Gorson[36].

a Did not distinguish between primary and secondary outcomes. We counted all outcomes listed as primary.

b Protocol for this trial was not available (primary outcome per internal company research report is shown in this table).

c The statistical analysis plan-defined primary outcomes are in agreement with the protocol-defined primary outcomes for 9 of 12 cases where an analysis plan is available. For the three trials where there is disagreement, the statistical analysis plan-defined primary outcomes are as follows:
945-217: "Four-week migraine headache rate (MHR) during the Stabilization Period 2" and "Change from baseline to Stabilization Period 2 in migraine headache rate."
945-220: "Four-week migraine headache rate (MHR) during the Stabilization Period 2" and "Change from baseline to Stabilization Period 2 in migraine headache rate."
1032-001: "SPID6 (Summed pain intensity difference over the first 6 hours)."

d Protocol-specified secondary outcomes reported in publication with no distinction between primary and secondary outcomes. We counted them as primary outcomes.

e Per amendment to the protocol.

f Primary outcomes for an ancillary study described in the internal company research report. The protocol for the ancillary study was not available. They were reported as secondary outcomes in the publication.

Table 3 – P values for Primary Outcome(s): Comparison between Research Report and Main Published Report

Trial ID Report ID	P value for protocol-specified primary outcome[a] Research report	 Publication	P value for publication-specified primary outcome
Migraine prophylaxis			
879-201 Wessely 1987(Abstract)	0.72	P value not reported	P value not reported
945-217 No publication	0.432	No publication	No publication
945-220 Mathew 2001	0.171	Primary outcome per protocol not reported	0.006
Bipolar disorders			
945-209 Pande 2000	• <0.05 for YMRS, favoring placebo • P value not reported for HAM-D	• 0.03 for YMRS, favoring placebo • 0.4 for HAM-D	• 0.03 for YMRS, favoring placebo • 0.40 for HAM-D
945-250 Wang 2002	Research report not available	• <0.0001 for HAM-D • <0.0001 for percent responders	<0.0001 for HAM-D
945-291 Vieta 2006	0.3952[a]	Primary outcome per research report not reported	0.0046
Neuropathic pain			
945-210 Backonja 1998	0.0004	<0.001	<0.001
945-224 Backonja 2003 (Review with pooled results)	0.12	"No significant difference"	"No significant difference"
945-271 Gordh 2008	0.20 for change in mean pain score for second treatment period adjusting for baseline pain intensity (Primary outcomes in ancillary study: 0.13 for tactile allodynia, 0.9 for cold allodynia, 0.35 for pin-prick-evoked hyperalgesia)	0.2 for change in mean pain score for second treatment period adjusting for baseline pain intensity	0.2
945-276 Caraceni 2006	"doesn't show any evident difference between drugs."[a]	Primary outcome per research report not reported	0.025
945-306 Serpell 2002	0.048	0.048	0.048
945-411 Gomez-Perez 2004	<0.001	0.009	0.009
A945-1008 No publication	0.0008	No publication	No publication

Table 3 – P values for Primary Outcome(s): Comparison between Research Report and Main Published Report (cont'd)

Trial ID Report ID	P value for protocol-specified primary outcome[a] Research report	 Publication	P value for publication-specified primary outcome
No Trial ID - Gorson Gorson 1999 (Letter to editor)	Research report not available	Primary outcome per protocol not reported	0.03 for MPQ 0.42 for VAS 0.2 for PPI 0.11 for patients reporting moderate or excellent pain relief
Nociceptive pain			
1032-001 No publication	"positive"	No publication	No publication
1032-002 No publication	"Not statistically significant[b]"	No publication	No publication
1032-003 No publication	Not reported[c]	No publication	No publication
1032-004 No publication	• 0.121 for GBP125/NPN250 vs NPN500; • 0.656 for GBP250/NPN500 vs NPN500	No publication	No publication
1035-001 No publication	"negative[b]"	No publication	No publication
1035-002 No publication	0.9187	No publication	No publication

Table 3 Legend:

References to the main publications associated with each study ID are as follows:
879-201[16], 945-220[19], 945-209[20], 945-250[21], 945-291[22], 945-210[24], 945-224[26], 945-271[28], 945-276[29], 945-306[31], 945-411[33], No Trial ID - Gorson[36].

a Primary outcome described in research report was used if protocol was not available.
b Multiple groups and comparisons, none statistically significant.
c "However, because the study was terminated early, efficacy data were not summarized."

Abbreviations:
GBP125: gabapentin 125 mg
GBP250: gabapentin 250 mg
HAM-D: Hamilton Rating Scale for Depression
MPQ: McGill Pain Questionnaire
NPN250: naproxen sodium 250 mg
NPN500: naproxen sodium 500 mg
PPI: Present Pain Intensity
YMRS: Young Mania Rating Scale
VAS: Visual Analogue Scale

Table 4
Documents Reviewed and Relationship to Litigation

Some internal company documents reviewed in our study became available in 2002 as a result of litigation initiated against Pfizer and Warner-Lambert in the mid-1990s. In 2004, Warner-Lambert, which had been acquired by Pfizer in 2000, admitted guilt for off-label marketing of its anticonvulsant drug gabapentin.[8] We also examined source documents obtained in more recent litigation against Pfizer related to trials conducted to test gabapentin's effectiveness for off-label use in migraine, bipolar disorders, neuropathic pain, and nociceptive pain. All study protocols, the internal company research reports, and published reports relating to clinical trials sponsored by Pfizer and Parke-Davis for the indications noted were obtained as part of the legal action.

KD served as the expert witness for the plaintiffs' attorneys and SV assisted her with the research for her report. She signed an agreement in August 2008 agreeing to be bound by a protective order entered in pending litigation against Pfizer, which limits disclosure of confidential discovered information unless such information is ordered unsealed by the court, or the claim of confidentiality is waived by the claiming party. Through communications with counsel involved in the litigation occurring between August and October 2008, Pfizer agreed to waive any confidentiality claims concerning documents reviewed as part of KD's expert report. As a result, all of the documents reviewed for this article have had their confidentiality claims waived. The expert report that was prepared by KD for the plaintiffs' lawyers for this litigation with the use of these internal company documents is available in a public database, the Drug Industry Documents Archive (http://dida.library.ucsf.edu/pdf/oxx18r10).

An *ad hoc* search of MEDLINE in November 2008, for an abstract referenced in the company's research report but not found as cited, identified a new full report[28] associated with study 945-271, published in August 2008. Thus, this document was retrieved outside the discovery process. We matched the publication to the protocol for this trial using information on funding source, authors, study sites, and number of participants.

Table 5
List of Documents Accessed:
Internal Company Research Reports, Protocols, Analysis Plans, and Publications

Migraine prophylaxis

- **879-201**
  - Research Report 4301-00066
  - Wessely P, Baumgartner Ch, Klingler D, et al. Preliminary results of a double-blind study with the new migraine prophylactic drug gabapentin. Cephalalgia 1987; 7 (Supplement 6): 477 - 8.
- **945-217**
  - Research Report 995-00085
  - No publication
- **945-220**
  - Research Report 995-00074
  - Mathew NT. Efficacy and safety of gabapentin (Neurontin) in migraine prophylaxis. Presented at the 17th Annual Scientific Meeting of the American Pain Society, San Diego, CA, November 5-8, 1998. Abstract.
  - Mathew NT, Magnus-Miller L, Saper J, et al. 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 NT, Rapoport A, Saper J, et al. Efficacy of gabapentin in migraine prophylaxis. Headache 2001; 41: 119 - 28.

Bipolar disorders

- **945-209**
  - Research Report 720-04174
  - 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 Disord 2000; 2: 249 - 55.
- **945-250**
  - Research report was not available.
  - Protocol for 945-250 (PFIZER_MDL_0000460)
  - Wang PW, Santosa C, Schumacher M, Winsberg ME, Strong C, Ketter TA. Gabapentin augmentation therapy in bipolar depression. Bipolar Disord 2002; 4: 296 - 301.
- **945-291**
  - Final Study Report 945-291
  - Vieta E, Goikolea JM, Martinez-Aran A, et al. A double-blind, randomized, placebo-controlled, prophylaxis study of adjunctive gabapentin for bipolar disorder. J Clin Psychiatry 2006; 67(3): 473 - 7.

Table 5 - List of Documents Accessed (cont'd)

Neuropathic pain

- **945-210**
  - Research Report 720-03908
  - Backonja M, Hes MS, LaMoreaux LK, Garofalo EA, Koto EM, and the US Gabapentin Study Group 210. Gabapentin reduces pain in diabetics with painful peripheral neuropathy: results of a double-blind, placebo-controlled trial (945-210). Presented at the 16th Annual Scientific Meeting of the American Pain Society, New Orleans, October 23-26, 1997. Abstract.
  - Backonja M, Beydoun A, Edwards KR, et al for the Gabapentin Diabetic Neuropathy Study Group. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus. A randomized controlled trial. JAMA 1998; 280 (21): 1831 - 6.
- **945-224**
  - Research Report 720-04130
  - Backonja M, Mutisya EM. Review of gabapentin dosing in five placebo-controlled clinical trials for neuropathic pain. Eur J Neurol 2002;9:Suppl 2:191. Abstract. (Citation for poster for this abstract: Backonja M-M, Mutisya EM. Gabapentin demonstrates a nonlinear dose-response across five multicenter trials for neuropathic pain. Presented at the European Federation of Neurological Societies Annual Congress, Vienna, October 26-29, 2002.)
  - Backonja M, Glanzman RL. Gabapentin dosing for neuropathic pain: evidence from randomized, placebo-controlled clinical trials. Clin Ther 2003; 25 (1): 81 - 104.
- **945-271**
  - Final Report of Study 945-271 (PFIZER_LCASTRO_0043325) and Final Report of Sub-Study to 945-271 (PFIZER_LCASTRO_0027113)
  - Gordh T, Stubhaug A, Jensen TS, et al. Gabapentin in chronic peripheral postoperative and posttraumatic neuropathic pain. Presented at the 10th World Congress on Pain, San Diego, CA, August 17-22, 2002. Abstract.
  - Gordh TE, Stubhaug A, Jensen TS, et al. Gabapentin in traumatic nerve injury pain: A randomized, double-blind, placebo-controlled, cross-over, multi-center study. Pain 2008; 138: 255 - 66.
- **945-276**
  - Final Report of Study 945-276 (PFIZER_LCASTRO_0026332)
  - Caraceni A, Zecca E, Bonezzi C, et al.. Gabapentin for neuropathic cancer pain: a randomised controlled trial from the Gabapentin Cancer Pain Study Group. J Clin Oncol 2004; 22(14): 2909 - 17.
- **945-306**
  - Research Report 430-00125
  - Serpell MG and the Neuropathic Pain Study Group. Gabapentin in neuropathic pain syndromes: a randomised, double-blind, placebo-controlled trial. Presented at the Fifth International Conference on Mechanisms and Treatment of Neuropathic Pain Annual Meeting, Hamilton, Bermuda, November 21-23, 2002. Poster.
  - Serpell MG, Neuropathic Pain Study Group. Gabapentin in neuropathic pain syndromes: a randomised, double-blind, placebo-controlled trial. Pain. 2002; 99:557 - 66.
- **945-411**
  - Research Report 720-30154
  - Gómez-Pérez FJ, Perez-Monteverde A, Nascimento O, Aschner P, Tagle M, Fichtner, for the Latin American Diabetic Neuropathy Study Group. Gabapentin for the treatment of painful diabetic peripheral neuropathy: titration to efficacy is superior to lower fixed dose. Presented at the Fifth International Conference on Mechanisms and Treatment of Neuropathic Pain Annual Meeting, Hamilton, Bermuda, November 21-23, 2002. Poster.

Table 5 - List of Documents Accessed (cont'd)

  - Gómez-Pérez FJ, Perez-Monteverde A, Nascimento O, et al for the Latin American Diabetic Neuropathy Study Group. Gabapentin for the treatment of painful diabetic neuropathy: dosing to achieve optimal clinical response. Br J Diabetes Vasc Dis 2004; 4(3): 173 - 8.
- **A945-1008**
  - Final Study Report for A945-1008 (PFIZER_LKNAPP_0062214)
  - No publication
- **No ID – Gorson**
  - Research report and SAP were not available.
  - Protocol for trial (WLC_FRANKLIN_000010239)
  - Gorson KC, Schott C, Rand WM, Herman R, Ropper AH. Gabapentin in the treatment of painful diabetic neuropathy: a placebo-controlled, double-blind, crossover trial. Neurology 1998; 50 (Suppl 4): A103.
  - 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: 251 - 2.
- **No ID – Dallocchio**
  - Research report, protocol, and SAP were not available.
  - Dallocchio C, Buffa C, Mazzarello P, Chiroli S. Gabapentin vs. amitryptiline in painful diabetic neuropathy: an open-label pilot study. Journal of Pain and Symptom Management. 2000; 20(4): 280-285.

Nociceptive pain

- **1032-001**
  - Research Report 720-04378
  - No publication
- **1032-002**
  - Research Report 720-04479
  - No publication
- **1032-003**
  - Research Report 720-30044
  - No publication
- **1032-004**
  - Research Report 720-04481
  - No publication
- **1035-001**
  - Research Report 720-004455 and Research Report 720-004483
  - No publication
- **1035-002**
  - Research Report 720-004471
  - No publication

Box - Examples of Practices Resulting in Disagreement between Protocol and Publication for Definition of the Primary Outcome

Introduced new primary outcome in the publication

- 945-220
  - Protocol:
    - "Four week migraine headache rate during stabilization period 2"
  - Publication:
    - "4-week migraine rate during stabilization period 2 for patients who had received a stable dose of 2400 mg/day." (ie, outcome reported only for subgroup of population that received an acceptable dose)

Did not distinguish between primary and secondary outcomes in the publication, although they were distinctly specified in the protocol

- 945-209
  - Protocol-specified primary outcomes:
    - "baseline to end point change in the HAM-D total score"
    - "baseline to end point change in the YMRS score"
    - "percent of patients in each treatment group who are responders on the ISS"
  - Protocol-specified secondary outcomes:
    - "baseline to end point change in CGIS scores"
    - "percent of patients in each treatment group who are responders on the Life Chart, CGIC, and SF-36"
  - Publication ("efficacy assessments"):
    - "YMRS"
    - "Hamilton Depression Rating Scale (HAM-D)"
    - "Hamilton Anxiety Rating Scale (HAM-A)"
    - "Clinical Global Impression of Severity (CGIS)"
    - "Clinical Global Impression of Change (CGIC)"
    - Internal state scale (ISS)
    - Life chart for recurrent affective illness (Life chart)
    - SF-36 quality of life questionnaire

Relegated one or more protocol-specified primary outcomes to a secondary outcome in the publication

- 945-250
  - Protocol:
    - "…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."
  - Publication:
    - "The primary outcome was decreased in HDRS from baseline" [sic]. One of the secondary outcomes in publication: "Patients were deemed responders if they had at least a 50% decrease on final HDRS ratings compared with baseline."

Did not describe one or more protocol-specified primary outcomes in the publication

- 879-201
  - Protocol:
    - "The arithmetic mean of the difference between attack frequency at the start of treatment and the end of treatment"
  - Publication:
    - "frequency of migraine attacks" in each group
    - "cumulative distribution of percent reduction of migraine attacks"
    - Proportion of patients with worsening of their initial status
    - Proportion of patients in each group showing "a decrease of the frequency of migraine attacks"

Sensitivity Analysis

Description of our Findings using the Statistical Analysis Plan-Defined Primary Outcomes Instead of Protocol-Defined Primary Outcomes, When the Two Disagreed

Methods

When it was available, a "statistical analysis plan" (various names were used) was typically located as an appendix to the internal company research report and was not included as part of the study protocol. The one exception was Study 879-201, in which the section "Statistical Planning and Evaluation of the Study" was included as an appendix to the protocol.

In the analyses presented in our article, we compared the primary outcome described in the study protocol with the primary outcomes described in the research report and publication. Thus, in our article, we considered the protocol-defined primary outcome to be that described in the "statistical analysis plan" for only Study 879-201.

We conducted a sensitivity analysis to examine whether we would obtain different results, from those in the article, if we compared the primary outcome described in the "statistical analysis plan" with the primary outcomes described in the research report and publication.

Findings

Twelve of the 18 trials with protocols had an associated statistical analysis plan (see article text, Results section). In 9/12 cases, the primary outcome(s) specified in the protocol agreed with the primary outcome specified in the statistical analysis plans.

For the three trials where the protocol-described and statistical analysis plan-described primary outcomes disagreed, we compared the P values reported for the two outcomes in the research report (see table below). For 2/3 trials (Studies 945-217 and 945-220), the P values in the research report would not be considered statistically significant for either the protocol-defined or the two statistical analysis plan-defined primary outcomes. For the third trial (Study 1032-001), the P value reported in the research report for the protocol-defined primary outcomes was described as "positive" and the P value reported for the statistical analysis plan-defined primary outcome was "negative".

Comment

There was only one case of disagreement in the reported statistical significance, depending on whether one considered the protocol-defined or statistical analysis plan-defined primary outcome. In this one case, the trial results we report in the article (for the protocol-defined primary outcome) indicated evidence of effectiveness in the internal company research report, while the results for the statistical analysis plan-defined primary outcome indicated no evidence of effectiveness in the internal company research report. Thus, we believe that use of the protocol-defined outcome for the analysis presented in our article (as opposed to the statistical analysis plan-defined primary outcome) is conservative.

Table. P-values for protocol-specified and statistical analysis plan-specified primary outcomes

	Research report		Publication
Study ID	Protocol-defined primary outcome	SAP-defined primary outcome	
945-217	P = 0.432	P = 0.583	No publication
945-220	P = 0.171	P = 0.332	P = 0.006 (new primary outcome)
1032-001	"positive"	"negative"	No publication

Figure - Number of Secondary Outcomes in Protocols and Publications of Included Trials

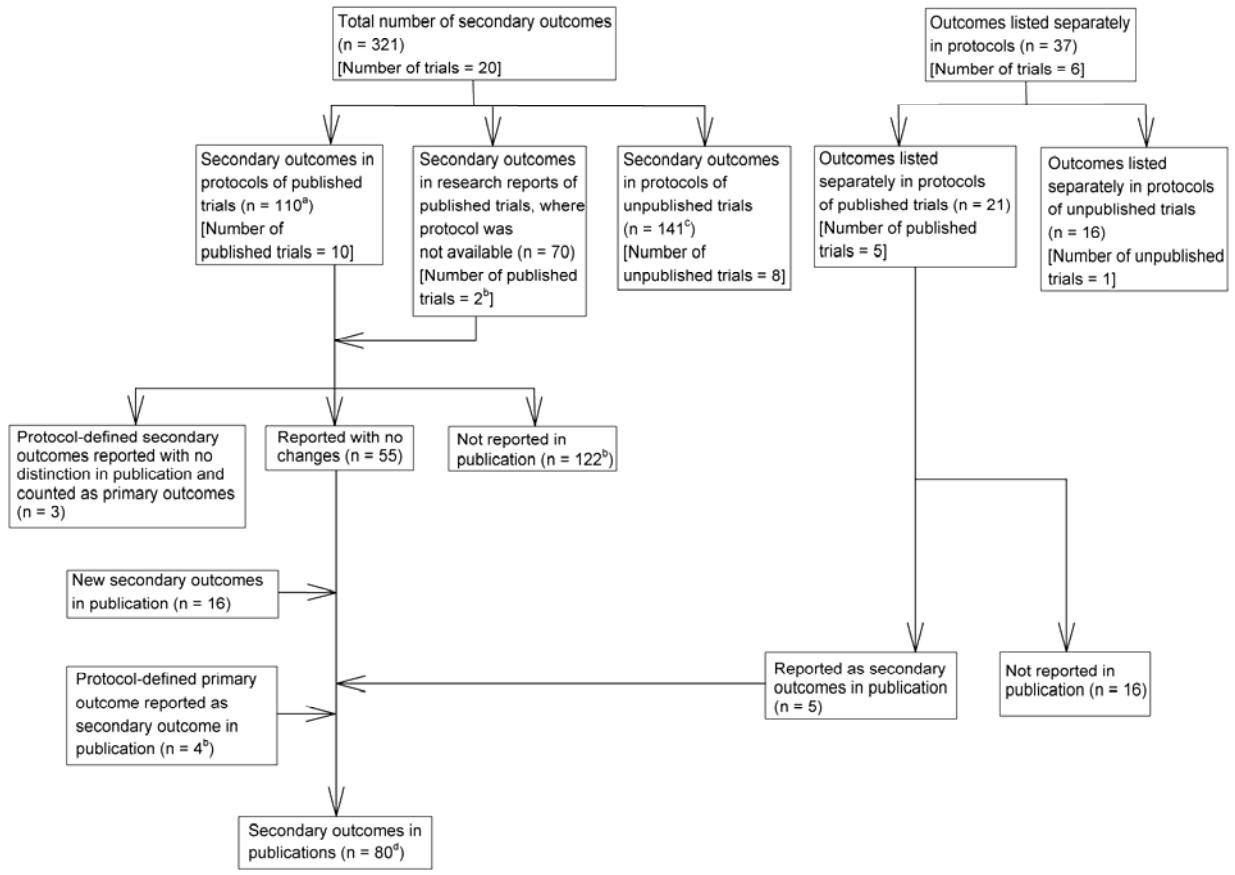

Figure Legend

a Does not include three outcomes reported in protocol for one trial with no distinction between primary and secondary outcomes. We counted them as primary outcomes and they are shown in Figure 1.

b The research report for a sub-study under an additional trial included three primary outcomes and five secondary outcomes. The protocol for this sub-study was not available. We counted the sub-study as part of the main trial. All three primary outcomes from the sub-study were reported as secondary outcomes in the publication. None of the secondary outcomes in the research report for the sub-study were mentioned in the publication.

c Does not include nine outcomes reported in protocol with no distinction between primary and secondary outcomes for one trial. We counted them as primary outcomes and they are shown in Figure 1.

d Does not include seven new outcomes in publications that were reported with no distinction between primary and secondary outcomes. We counted them as primary outcomes and they are shown in Figure 1.