CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-397
21-423
21-424

MEDICAL REVIEW(S)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 (301) 827-7410

REVIEW AND EVALUATION OF CLINICAL DATA

NDA #	**21-397** **21-423** **21-424**
Sponsor	Parke-Davis Pharmaceuticals Limited
Generic Name	Gabapentin
Proprietary Name	Neurontin
Pharmacologic Class	Anti-epileptic
Proposed Indication	For the management of postherpetic neuralgia in adults
Submission Date	August 6, 2001
Clinical Reviewer	Sharon Hertz, M.D.
Completion Date	May 24, 2002

EXECUTIVE SUMMARY

A. Overview Of Clinical Program

Established name:	Gabapentin
Trade Name:	Neurontin
Drug Class:	Anti-epileptic
Proposed Indication:	For the management of postherpetic neuralgia
Dose:	Capsules 100, 300, 400 mg; Tablets 600 and 800 mg; Oral Solution 50 mg/ml
Route:	Oral
Regimen:	A single 300-mg dose on Day 1, 600 mg/day on Day 2 (divided BID), and 900 mg/day on Day 3 (divided TID), followed by titration to a maximum of 3600 mg/d (divided TID).

Gabapentin was studied in two trials in patients with postherpetic neuralgia. A total of 563 patients were enrolled, 336 of whom received gabapentin. Additional safety information was obtained from three clinical trials in other neuropathic pain trials enrolling patients with painful diabetic peripheral neuropathy and neuropathy of mixed etiologies. An additional 794 patients were enrolled in these trials, 484 of whom received gabapentin. Safety data from non-neuropathic pain trials in studies evaluating the efficacy and pharmacokinetics of gabapentin in combination with naproxen sodium or hydrocodone were added to the evaluation of deaths, SAEs and discontinuations due to AEs.

B. Efficacy

Study 945-211 was a double-blind, randomized, placebo-controlled trial of gabapentin in patients with post-herpetic neuralgia. Patients were titrated to a dose of 3600 mg over a 4-week period and maintained on the final stable dose for four more weeks. A total of 229 patients were enrolled and 184 (80.3%) completed the study. The most common reason for early study discontinuation was adverse event, occurring in 21 of the 113 gabapentin patients (18.6%) and in 14 of the 116 placebo patients (12.1%.) Only 64.6% of the gabapentin treated patients reached a final stable dose of 3600 mg/d. The remainder of patients reached final stable doses from 1200 mg/d to 3000 mg/d.

Study 945-295 was a double-blind, randomized, placebo-controlled trial of gabapentin in patients with post-herpetic neuralgia. Patients were titrated to either 1800 mg/day or 2400 mg/day over a 3-week period and maintained on the final stable dose for four weeks. A total of 334 patients were enrolled and 272 (81.4%) completed the study. One hundred and fifteen patients received gabapentin 1800 mg/day, 108 patients received gabapentin 2400 mg/day, and 111 patients received placebo. All patients were successfully titrated to the intended treatment dose. One patient from each of the gabapentin groups required a dose reduction during the study.

The planned primary outcome measure in both studies was the change in mean weekly Pain Rating Scale score from the patient diary. The gabapentin treatment groups all

demonstrated statistically significant improvement in pain compared with placebo. The treatment effect was similar in size across all gabapentin treatment arms. Separation from placebo was seen as early as one week after titration was begun. The percent of patients with a 50% reduction in pain was also similar across all treatment groups. The secondary efficacy outcome measures reflecting pain measurements were supportive of the primary efficacy measure. Additional secondary efficacy measures of sleep interference, global impression of change by patient and investigator, all favored gabapentin over placebo.

These results demonstrate that gabapentin doses of 1800 mg/day, 2400 mg/day, and 3600 mg/day were effective for post-herpetic neuralgia. Patients should undergo a gradual titration from 300 mg/day to 1800 mg/day. Although there does not appear to be additional benefit from higher doses, safety data support the use of doses up to 3600 mg/day.

C. Safety

The safety database presented an adequate assessment of the adverse event profile of gabapentin in the postherpetic neuralgia patient population, with confirmatory safety findings in other neuropathic pain conditions. The safety database consisted of 1357 patients in double-blind, placebo-controlled and open label studies of gabapentin in neuropathic pain. The postherpetic neuralgia studies enrolled 563 patients. A total of 820 patients received gabapentin, primarily over a period of six to eight weeks. Additional safety information for deaths, serious adverse events (SAEs), and discontinuations due to adverse events was obtained from four ongoing studies in diabetic neuropathy and mixed etiology neuropathic pain, and from combinations studies with naproxen and hydrocodone in non-neuropathic pain.

Patients were evenly distributed across gender, but more than 80% of patients were Caucasian. Twenty five percent of patients were over the age of 75 in the overall population, and in the postherpetic neuralgia trials, 50% of the patients were over the age of 75.

Of the 11 deaths reported, there was only one death for which there was any reason to suspect even a small contributory roll of study medication. The patient had widely metastatic prostate cancer, and died following the onset of sleepiness, 3 days after beginning gabapentin. The patient had been receiving concomitant morphine which can increase the bioavailability of gabapentin, possibly contributing to CNS depression. The investigator attributed the cause of death due to progression of the underlying cancer.

There were few serious adverse events for which a contributory role could be assigned to gabapentin. In the neuropathic pain studies, gabapentin may have played a role in one case of peripheral edema with subsequent cellulitis, and likely contributed to the somnolence seen following an intentional overdose. There was one case of angioedema in a patient on no concomitant medications, but the study drug assignment had not been unblinded at the time of the report.

Adverse events were fairly common and occurred in more gabapentin-treated patients than placebo treated patients. PHN patients who were older, had greater proportion of discontinuations due to adverse events. It may be that older patients have a greater bioavailability of gabapentin which is excreted exclusively by the kidney, and so are more susceptible to adverse events. However, other unidentified factors may also have contributed.

The nature of the adverse events were consistent with the adverse event profile known from study of gabapentin in other patient populations. The most common adverse events were dizziness and somnolence, followed by peripheral edema and dry mouth. There was less ataxia, fatigue, and nystagmus compared with the epilepsy population, consistent with the known polypharmacy with anticonvulsants in the epilepsy trials.

While drug-drug interactions were not evident in the safety findings during the clinical trials, studies with co-administration of hydrocodone and a literature report evaluating co-administration of morphine indicate the potential for interactions with opiates. These interactions, primarily reflecting increased bioavailability of gabapentin when co-administered with opioids, have the potential to be clinically meaningful. This information will need to be adequately communicated to the health-care provider community through appropriate labeling and promotional materials.

D. Dosing

The lack of a dose response relationship across the 1800 mg/day, 2400 mg/day, and 3600 mg/day suggest that for most patients, 1800 mg/day will appropriate target dose for titration. Patients should begin titration with a single 300-mg dose on Day 1, 600 mg/day on Day 2 (divided BID), and 900 mg/day on Day 3 (divided TID). Gradual titration should proceed to 1800 mg/day (divided TID). Although an acceptable safety profile has been demonstrated up to a dose of 3600 mg/day, little additional benefit is expected from titration beyond 1800 mg/day.

E. Special Populations

There was a larger treatment effect in patients $\geq$75 years. This finding may result from a greater bioavailability of gabapentin due to age-related reductions in renal function, although other unidentified factors may also be contributing to this effect.

Adverse events were overall, more frequent among patients over the age of 75. The only individual adverse events that were notably more common in this group were dizziness and peripheral edema. There were no effects of gender on the distribution of adverse events. There was too little racial diversity to evaluate the effects of race on the adverse event profile.

As gabapentin is excreted unchanged by the kidneys, dosing must be reduced in the setting of renal impairment, once creatinine clearance is less than 60 mL/min.

The incidence of postherpetic neuralgia in patients under the age of 18 is so low as to preclude the ability to study gabapentin for this indication in that population. The

sponsor has requested a waiver from the study of postherpetic neuralgia in pediatrics and this request is acceptable.

APPEARS THIS WAY
ON ORIGINAL

SECTION 1 INTRODUCTION AND BACKGROUND

SECTION 1.1 Drug Established and Proposed Trade Name, Drug Class, Proposed Indication, Dose, Regimens, Age Groups

Established name:	Gabapentin
Trade Name:	Neurontin
Drug Class:	Anti-epileptic
Proposed Indication:	For the management of postherpetic neuralgia, [redacted]
Dose:	Capsules 100, 300, 400 mg; Tablets 600 and 800 mg; Oral Solution 50 mg/ml
Route:	Oral
Regimen:	A single 300-mg dose on Day 1, 600 mg/day on Day 2 (divided BID), and 900 mg/day on Day 3 (divided TID), followed by titration to 1800 mg/d (divided TID).

SECTION 1.2 State Of Armamentarium For Indication

A pre-NDA meeting was held on May 14, 2001. The meeting package was reviewed prior to the meeting. During this meeting the Division informed the sponsor that a [redacted] indication would not be granted. Specific indications for specific conditions would be considered. Substantial evidence of efficacy from replicated adequate and well-controlled trials for specific indications such as postherpetic neuralgia (PHN) or painful diabetic peripheral neuropathy (DPN) would be required for approval. The sponsor was informed that based on the information in the meeting package, sufficient information for an indication of pain associated with DPN was not available based on the two studies synopses submitted. For PHN, dose replication had not been demonstrated as the two clinical study synopses submitted utilized different treatment arms, and this could result in a nonapproval for this indication as well. The sponsor reported that the study designs for the PHN and DPN trials had been agreed upon by Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products.

SECTION 1.3 Important Milestones In Product Development

Neurontin has been approved as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy and as adjunctive therapy in the treatment of partial seizures in pediatric patients age 3 - 12 years. The original NDA was followed by NDAs for additional formulations and for the pediatric indication. The three dosage forms are bioequivalent and have a common package insert.

1. 20-235 Neurontin Capsules 100, 300, 400 mg; Dec. 30, 1993
2. 20-882 Neurontin Tablets 600 and 800 mg; Oct 9, 1998
3. 21-129 Neurontin Oral Solution 50 mg/ml; Mar 2, 2000
4. 21-216 Neurontin Oral Solution 50 mg/ml-Pediatrics; Oct 12, 2000

There is a Phase 4 commitment associated with the approval of NDA 21-216, to conduct a repeated-dose neonatal/juvenile rat study to assess the developmental neurotoxicity of

gabapentin. A protocol submitted to [redacted] was reviewed, and concurrence with the study design was conveyed to the sponsor by the review division on July 13, 2001. The sponsor expects a study report by December, 2002.

Gabapentin has been studied under six INDs:

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]

SECTION 1.4 Other Relevant Information

Foreign Marketing History

As of June14, 2001, Neurontin has been approved for the management of neuropathic pain in 34 countries. A specific indication for neuropathic pain in diabetic neuropathy and postherpetic neuralgia has been approved in Austria, Chile, Denmark, Finland, Germany, and Switzerland, for diabetic neuropathy, PHN, and trigeminal neuralgia in Singapore, and PHN in France. Other varied neuropathic pain indications exist in 26 countries including Australia, Italy, Ireland, Spain, New Zealand, the United Kingdom, Aruba, Czech Republic, Romania, and Slovakia, and many countries in Latin America and Asia.

[redacted]

Neurontin has not been withdrawn from the market for safety or efficacy reasons in any country where it has been approved.

Neurontin has been approved for the treatment of epilepsy in many countries.

SECTION 2 CLINICALLY RELEVANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY

Gabapentin is structurally related to gamma-aminobutyric acid (GABA), a primarily inhibitory neurotransmitter. While initially intended to mimic the effects of GABA, this does not appear to be a clinically meaningful action of gabapentin. The mechanism by which gabapentin exerts its pharmacological actions is unknown for both PHN and epilepsy.

This is a Type 6 NDA and all of the information about the manufacture and controls of the drug substance and drug product is included in the approved NDA 20-235, Neurontin (gabapentin) Capsules. The inactive ingredients for the capsules are lactose, cornstarch, and talc.

An updated environmental assessment was submitted in support of this NDA. The conclusion by the CMC reviewer was that the new indication will not result in an appreciable increase in the amount of gabapentin being introduced into the environment.

SECTION 3 HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

The PK characteristics of gabapentin have been well described. Gabapentin reaches its peak plasma concentration 3 to 4 hours postdose following a single oral dose. Plasma concentrations of gabapentin are not dose-proportional over a range of 1200 to 4800 mg/day (given every 8 hours). Absolute bioavailability of gabapentin was approximately 60%, 47%, 34%, 33%, and 27% following 900, 1200, 2400, 3600, and 4800 mg/day, given in divided doses q8h, respectively. This is because the absorption of gabapentin relies on a saturable transport mechanism. Food increases the absolute bioavailability of gabapentin by a small amount (14% with a high-fat meal) that is not considered clinically significant.

Gabapentin is eliminated unchanged, by renal excretion with no significant hepatic metabolism. Less than 3% of gabapentin circulates bound to plasma protein. Gabapentin half-life is approximately 5 to 7 hours in healthy subject.

As gabapentin is not appreciably metabolized in humans, studies in hepatic impairment have not been performed. Renal impairment does require reductions in dosing, once creatinine clearance is less than 60 mL/min.

[redacted]

[redacted]

gabapentin (125 mg) were co-administered. There was no effect on naproxen by gabapentin. Co-administration of gabapentin (125 to 500 mg) and hydrocodone (10 mg) resulted in a decrease in the hydrocodone $C_{max,}$ by 3% to 21%, and AUC by 4% to 22%, based on gabapentin dose in a dose-dependent manner. Gabapentin AUC values were increased by hydrocodone 14%.

Additionally, literature reports describe a 44% increase in gabapentin AUC following administration of a 60 mg controlled-release morphine capsule 2 hours prior to a 600 mg gabapentin capsule. No effects on the PK parameters of morphine were reported.

As discussed below under Dosing, no dose-response relationship was observed in the clinical trials in support of this application. The response size was similar across the 1800 mg/d, 2400 mg/d, and 3600 mg/d dosing arms.

SECTION 4 DESCRIPTION OF CLINICAL DATA AND SOURCES

SECTION 4.1. Overall Data

The original NDA submission dated August 6, 2001 was intended to support an indication for t [redacted]. This submission included data on 1357 patients studied in 5 pivotal, double-blind, placebo-controlled, clinical studies in patients with neuropathic pain, and two clinical pharmacology studies. Additional data from ongoing foreign studies and early trials of gabapentin in combination with naproxen and in combination with hydrocodone were included in the safety analysis.

The submission dated October 4, 2001, addressed a request by the Review Division for an integrated dataset consisting of adverse event safety data from each of the studies contributing to the ISS.

The submission dated November 30, 2001 included additional safety data requested by the Division, AEs by dose at onset. This database reflected information from all completed clinical, pharmacologic, and combination studies. This was supplemented with deaths, SAEs, and discontinuations due to AEs from ongoing foreign studies.

The 120-day safety update was submitted on December 6, 2001. This submission consisted of a partial study report for open-label study 945-411 The AEs reported during this study were not integrated with prior safety data. Updated reporting of deaths, SAEs, and discontinuations due to AEs were provided.

The requested indication was changed to post herpetic neuralgia, documented in a submission dated December 20, 2001. In the same submission, the sponsor provided an efficacy analysis of the 563 patients in the two double-blind, placebo-controlled clinical studies in patients with neuropathic pain associated with postherpetic neuralgia. A total of 336 patients received gabapentin in these trials. The sponsor included 23 patients with PHN who received gabapentin during a mixed neuropathy study in the analysis. A safety dataset including only patients with postherpetic neuralgia was included in this submission at the request of the Division and the sponsor also resubmitted the data from the original submission combining the original five completed clinical trials, four ongoing studies, two clinical pharmacology studies and eight gabapentin combination therapy studies.

SECTION 4.2. Tables Listing the Clinical Trials

Clinical Pharmacology Studies

Study 945-190 was a uncontrolled, multiple dose PK study to determine steady-state, dose-proportionality study of gabapentin doses of 1200, 2400, 3600, and 4800 mg/day in healthy subjects. Multiple doses were given on Days 1, 2, 8, 9, 15, 16, 22, and 23, and single doses on Days 3, 10, 17, and 24.

Study 1032-015 was an open-label, randomized, 3-way crossover study to compare single-dose PK of gabapentin and naproxen administered separately and together. Single oral doses consisted of gabapentin 125 mg, naproxen sodium 250mg, or the 2 combined. Dosing took place on Days 1, 8, and 15.

Clinical Neuropathic Pain Studies

Table 4.1 Original Five Completed Clinical Neuropathic Pain Studies

Study	Description	Number of Patients	
		ITT	Completed
945-210 US and Canada	DPN. One-week baseline followed by an 8-week d-b phase (4 w titration; 4 w fixed dose) with placebo or a target dose of 3600 mg/day gabapentin (GBP), given in 3 equally divided doses (TID). If intolerable AEs occurred during titration, the GBP dosage was decreased one dosage level to 900, 1200, 1800, or 2400 mg/day, given TID.	165	135
945-211 US	PHN. One-week baseline followed by an 8-week d-b phase (4 w titration; 4 w fixed dose) with placebo or a target dose of 3600 mg/day GBP, given TID. If intolerable AEs occurred during titration, the GBP dosage was decreased one dosage level to 1200 (minimum), 1800, or 2400 mg/day, given TID.	229	184
945-224 Europe and South Africa	DPN. One-week baseline followed by a 7-week d-b phase (3 w titration; 4 w fixed dose) with placebo or GBP 600, 1200, or 2400 mg/day, given TID. 67 pts (14 of whom received placebo during d-b) entered a 4-month open-label phase where GBP was started at 600 mg/day and titrated over 4 w at the discretion of the investigator to a maximum of 2400 mg/day, given TID. At the end of 4 w the GBP dose remained stable for an additional 3 months.	324 DB 67 OL	276 DB 50 OL
945-295 UK	PHN. One-week baseline followed by a 7-week d-b phase (3 w titration; 4 w fixed dose) with placebo or GBP 1800 or 2400 mg/day, given TID.	334	272
945-306 UK	Various neuropathic pain syndromes. 1w baseline followed by an 8-week d-b phase (4 w titration-, 4 w fixed dose) with a maximum dose of GBP of 2400 mg/day, given TID. Based on effect, pts could remain at 900 or 1800 mg/day, given TID.	305	234
945-411	DPN. OL, 7-week, OL, half fixed-dose 900 mg/d, half titrated to ≤ 3600 mg/d (4 w titration)	339	

US = United States; UK = United Kingdom; ITT Population = All rand. pts who received at least 1 dose of study medication; DB = d-b; OL = Open-label.

Non-Neuropathic Pain/Combination Studies

Table 4.2 Original Five Completed Clinical Neuropathic Pain Studies

Study	Number of Patients	Description
1032-001 US	483	GPN/NPN 3rd molar extraction. Single dose, d-b, placebo controlled, factorial design
1032-002 US	262	GPN/NPN Osteoarthritis, d-b, placebo-controlled, factorial design
1032-003 US	212	GBP/NPN OL extension of 1032-002
1032-004 US	206	GPN/NPN D-b, placebo-controlled study evaluating protective effects of GBP against NPN induced gastric mucosal injury
1032-010 US	24	GPN/NPN Bioequivalence of combination capsule and individual components given together
1035-001 US	325	GPN/HC 3rd molar extraction. Single dose, d-b, placebo controlled, factorial design
1035-002 US	200	GPN/HC Post-op orthopedic surgery, single dose, d-b, placebo-controlled, factorial design
1035-003 US	9	GPN/HC abuse liability study

SECTION 4.3 Postmarketing Experience

Safety

The sponsor's Worldwide Safety Surveillance group reviewed their postmarketing safety databases through December 31, 2000 for adverse events in which gabapentin was a primary suspect medication. The reports are submitted by health care professionals and consumers, and obtained from AE registries, medical literature, and postmarketing clinical studies. Each case represents one patient, but a given patient may be reported in more than one case.

The sponsor segregated the reports based on the available information providing the indication for which the gabapentin had been used. These are listed below in Table 4.3, Neuropathic Pain, Other, and Unknown. This type of mostly volunteering reporting tends to underreport cases. There is also no accurate denominator available to determine how these frequencies compare with controlled clinical trials. The percentages below represent the percent of the cases for that indication heading.

Of 7655 cases reporting 20,076 events, 75% originated in the US, and neuropathic pain was identified as the indication in1294 cases. The most frequent reports were dizziness, somnolence, asthenia, and peripheral edema. The spectrum of AEs reported, and the most frequent AEs reported, are both consistent with the experience from the clinical trials.

Table 4.3 Summary of Postmarketing AEs for Gabapentin Reported in ≥2% of Neuropathic Pain Cases Compared to Cases With Other and Unknown Indications

COSTART Body System	Neuropathic	Other	Unknown

COSTART Preferred AE Term	Pain [a]		Indications		Indications [b]	
Body as a Whole	N	%	N	%	N	%
Accidental injury	27	(2.1%)	96	(2.0%)	9	(0.6%)
Asthenia	89	(6.9%)	259	(5.3%)	34	(2.3%)
Drug interaction	62	(4.8%)	203	(4.2%)	68	(4.7%)
Headache	58	(4.5%)	196	(4.0%)	25	(1.7%)
Pain	73	(5.6%)	132	(2.7%)	20	(1.4%)
Digestive System						
Diarrhea	44	(3.4%)	123	(2.5%)	23	(1.6%)
Nausea	52	(4.2%)	155	(3.2%)	27	(1.9%)
Drug, Usage						
Off-label use of drug [c]	1112	(85.9%)	1961	(40.3%)	11	(0.8%)
Metabolism and Nutrition						
Edema peripheral/peripheral edema [d]	77	(6.0%)	166	(3.4%)	53	(3.7%)
Weight gain	49	(3.8%)	201	(4.1%)	55	(3.8%)
Nervous System						
Amnesia	40	(3.1%)	119	(2.5%)	30	(2.1%)
Ataxia	33	(2.6%)	139	(2.9%)	16	(1.1%)
Confusion	31	(2.4%)	141	(2.9%)	25	(1.7%)
Dizziness	130	(10.1%)	327	(6.7%)	37	(2.6%)
Insomnia	30	(2.3%)	112	(3.1%)	16	(1.1%)
Nervousness	39	(3.0%)	115	(2.4%)	15	(1.0%)
Paresthesia	33	(2.6%)	93	(1.9%)	16	(1.1%)
Somnolence	124	(9.6%)	421	(8.7%)	68	(4.7%)
Thinking abnormal	35	(2.7%)	145	(3.0%)	28	(1.9%)
Tremor	45	(3.5%)	104	(2.1%)	26	(1.8%)
Twitching	27	(2.1%)	65	(1.3%)	12	(0.8%)
Respiratory						
Dyspnea	28	(2.2%)	60	(1.2%)	7	(0.5%)
Skin and Appendages						
Alopecia	42	(3.3%)	154	(3.2%)	39	(2.7%)
Pruritus	31	(2.4%)	75	(1.5%)	9	(0.6%)
Rash	54	(4.2%)	170	(3.5%)	50	(3.5%)
Special Senses						
Abnormal vision/vision abnormal [d]	36	(2.8%)	93	(2.0%)	16	(1.0%)
Amblyopia	56	(4.3%)	123	(2.5%)	24	(1.7%)
Total Number of Cases	**1294**		**4857**		**1440**	

a All reported indication terms were individually inspected. Indications specifically listed as neuropathic pain or considered to be a clinically equivalent term(s) upon medical review (reflex sympathetic dystrophy, herpes zoster, and diabetic neuropathy) were included.

b 64 cases in databases where no data was entered in the indication field are not included in this table.

c Coding convention dated December 7, 1999; "off-label use of drug" to be used as an adverse event when the reported indication is not listed in the US package insert. Prior to December 7, 1999 "off-label use of drug" was not uniformly captured as an adverse event.

d Two individual COSTART terms combined.

Source: Table 24, P. 62, Vol. 1.52

SECTION 4.4 Literature Review

Controlled and uncontrolled clinical trial reports, case reports, review articles, book chapters, pharmacokinetic and pharmacodynamic trial reports, and letters to the editor were provided in a literature review submitted by the sponsor. Articles on the basic

science of pain in animal models and in *in vitro* models were included. The clinical reports included trials in antineoplastic therapy included painful neuropathy, mixed etiology series, complex regional pain syndrome, trigeminal neuralgia, glossopharyngeal neuralgia, multiple sclerosis associated pain, failed back syndrome, chronic pain associated with spinal cord injury, pain following recovery from Guillian Barre syndrome, post-thoracotomy pain, phantom limb and stump pain, interstitial cystitis, and erythromelalgia. None of these reports could be considered as providing substantial evidence of efficacy due to a variety of methodological issues including open-label, uncontrolled, and retrospective designs.

SECTION 5 CLINICAL REVIEW METHODS

SECTION 5.1 Describe How Review Was Conducted

The individual study reports for Studies 945-211 and 945-295 were reviewed individually, for efficacy. The ISE submitted by the sponsor was then reviewed for information on combined analyses to evaluate effects in subpopulations. Datasets depicting patient dosing, particularly for Study 945-211 were reviewed. Independent analyses were performed to substantiate the duration on doses during titration and highest dose achieved. Primary efficacy outcome data was reviewed intermittently from the datasets to corroborate the sponsor's summary tables.

Safety was evaluated by review of the ISS submitted on August 6, 2001, including the five original competed neuropathic pain studies, followed by a review of the ISS submitted on December 20, 2001, including only the PHN subjects. All patient narratives were reviewed. Individual CRFs were reviewed intermittently to corroborate the data in the patient narratives and CRTs. The electronic datasets for all adverse events were reviewed and event frequencies were recalculated. Verbatim and preferred terms were compared for accuracy.

SECTION 5.2 Overview Of Materials Consulted In Review

Table 5.1 Materials Consulted In Review

N000	06-Aug-2001	Original NDA Submission, Vol. 2, 51-118
N000 BM	04-Oct-2001	Dataset integrating the individual safety datasets
N000 BZ	30-Nov-2001	ISS dataset with dose at onset, ISE PHN studies Pediatric waiver, Financial Disclosure
N000 PW	30-Nov-2001	Request for Waiver of Pediatric Studies
N000 SU	06-Dec-2001	120-day Safety Update
N000 BZ	19-Dec-2001	
N000 BM	20-Dec-2001	ISS text for PHN, Proposed Label, Risk/Benefit Analysis, Vol. 1-13
Response to Reviewer Questions Submitted by Email		
5/9/02		5/7/02 Question about population exposure-response relationships
5/10/02		5/7/02 Questions about background characteristics for Study 945-211, analysis of paracetamol consumption
5/10/02		5/10/02 Question about dosing in Study 945-224
5/13/02		5/9/02 Questions about number of narratives for SAEs and discontinuations due to AEs
5/17/02		5/10/02 Question about differences in listings in electronic datasets

SECTION 5.3 Overview Of Methods Used To Evaluate Data Quality And Integrity
The study protocols were compared with the study reports for the two studies submitted in support of efficacy and the results reviewed. The ISS was reviewed in detail. Data from the in-text tables was compared with the case report tabulations and data listings in the appendices. Data points from all of the deaths and serious adverse events were followed through from the ISS, appendices, narratives, CRT's, and CRFs

Discrepancies were noted in the electronic safety datasets submitted on November 30, 2001 (aelistp.xpt) and October 14, 2001 (aelist.xpt and aepref.xpt). The sponsor was queried about the different number of rows of data in these datasets. In a faxed response dated May 17, 2002, the sponsor described the use of only ITT patients with at least one AE during a study in aelist.xpt and aelistp.xpt, while aepref.xpt included all patients and all AE entries, including entries noted as "none".

The sponsor was asked to explain why there were a greater number of narratives (35) for patients with SAEs than there were patients reported in the original ISS table (Table 18, p. 50, Vol. 1.52) and the safety update. In a faxed response dated May 13, 2001, the sponsor provided a breakdown. Thirty-two of 820 gabapentin-treated patients had SAEs. Of the 35 narratives for patients assigned to receive gabapentin, two patients had events during baseline before study drug was begun. They are counted in the table under Gabapentin, but their narratives report study drug as "none". Four patients with SAEs during the open label phase of Study 945-224 have Gabapentin in the header of the narratives but were not counted in Table 18 under gabapentin. One patient with a narrative that references gabapentin, was actually off study drug following study termination when the event occurred and so was not included in Table 18.

SECTION 5.4 Were Trials Conducted In Accordance With Accepted Ethical Standards
The trials submitted appear to have been conducted in accordance with accepted ethical standards.

SECTION 5.5 Evaluation Of Financial Disclosure

APPEARS THIS WAY
ON ORIGINAL

SECTION 6.0 INTEGRATED REVIEW OF EFFICACY

SECTION 6.1 Summary of Efficacy

The two pivotal trials submitted in support of the efficacy of gabapentin for the indication of neuropathic pain associated with postherpetic neuropathy, Study 945-211 and Study 945-295, were both successful in demonstrating efficacy. Study 945-211 was a double-blind, randomized, placebo-controlled trial, which compared 3600 mg/day of gabapentin and placebo over a 4-week titration period and a 4-week stable dose period. Study 945-295, was also a double-blind, randomized, placebo-controlled trial, and compared gabapentin treatment arms of 1800 mg/day and 2400 mg/day with placebo over a 3-week titration period and a 4-week stable dose period. Two hundred and twenty nine patients were enrolled in Study 945-211, 113 of whom received gabapentin 3600 mg/day. Three hundred and thirty four patients were enrolled in Study 945-295, 115 patients were treated with gabapentin 1800 mg/day and 108 patients with gabapentin 2400 mg/day. The planned primary outcome measure for both studies was the diary based pain rating at study termination compared to baseline. There were statistically significantly greater reductions in pain when the gabapentin groups were compared to placebo. The secondary outcome measures favored the gabapentin treatment groups. The magnitude of the treatment effect was comparable across treatment arms and studies for the primary outcome measure and for responder rates.

SECTION 6.2 Individual Studies

Section 6.2.1 Study 945-211

Study Summary

Study 945-211 was a double-blind, randomized, placebo-controlled trial of gabapentin in patients with post-herpetic neuralgia. A total of 229 patients were randomized, 116 whom received placebo and 113 of whom received gabapentin. Patients were titrated to a dose of 3600 mg over a 4-week period and maintained on the final stable dose for four more weeks. The planned primary outcome measure was the pain rating scale. No inferential statistics were planned for the numerous secondary outcome measures.

A total of 229 patients were enrolled and 184 (80.3%) completed the study. The most common reason for early study discontinuation was adverse event, occurring in 21 of the 113 gabapentin patients (18.6%) and in 14 of the 116 placebo patients (12.1%.) Only 64.6% of the gabapentin treated patients reached a final stable dose of 3600 mg/d. The remainder of patients reached final stable doses from 1200 mg/d to 3000 mg/d.

Although the sponsor planned to perform the primary analyses on a defined evaluable population consisting of 51 placebo patients and 48 gabapentin patients, this reviewer considered the intent-to-treat population consisting of 116 placebo patients and 113 gabapentin patients the primary population for the evaluation of efficacy. The primary outcome measure of change in Pain Rating Scale demonstrated a statistically significantly greater reduction in pain for the gabapentin treated patients compared to the placebo treated patients (-2.1 and -0.5, respectively, $p<0.001$.) The results of the secondary

efficacy measures of Sleep Interference, Global Impression of Change by Patient and Investigator, Short-Form McGill Pain Questionnaire, VAS score, Present Pain Intensity all favored gabapentin over placebo. Seven of the nine subscales of the SF-36 Quality of Life Assessment favored gabapentin over placebo. The Total Mood Score from the Profile of Mood States strongly favored gabapentin over placebo, with the remaining subscales showing little difference.

These results demonstrate that gabapentin was effective in reducing the neuropathic pain of post-herpetic neuralgia. The effective dose demonstrated in this trial was 3600 mg/day for most of the patients.

STUDY PROTOCOL 945-211

Title:. Double-blind, Randomized Placebo-Controlled, Parallel-Group, Multi-center Trial to Determine the Efficacy and Safety of Neurontin in Subjects with Peripheral Neuropathy (Post-Herpetic Neuralgia)

Objective: To compare the efficacy and safety of gabapentin and placebo in relieving pain in subjects with post-herpetic neuralgia (PHN).

Study Duration: 9 weeks

Population: N=200 subjects (planned)

Inclusion Criteria:

1. Male, female, >18 years of age
2. Not pregnant, not nursing, on acceptable contraceptive
3. Pain for > 3 months after healing of rash
4. VAS of $\geq$ 40 mm at screening and baseline, and average score of $\geq$ 4 over prior 7 days by Pain Rating Scale
5. Completion of at least 4 diaries in 7 days prior to baseline
6. Discontinuation of muscle relaxants, anticonvulsants, mexiletine, topical analgesics and other analgesics at least 2 weeks prior to screening. (Tricyclics and narcotics are permitted, but must remain stable.)

Exclusion Criteria:

1. Prior neurolytic or neurosurgical therapy
2. Immunocompromised
3. Severe liver or kidney disease or significant hematological disease
4. Pain other than PHN that may confound results
5. History of drug or alcohol abuse within 1 year.

Study Design:

- Study Drug: gabapentin 300 mg and placebo
- Initial dose 900 mg/d (after 4-5 day titration from 300 mg/d), titration steps: 1800 mg/d and 3600 mg/d

- Subjects unable to tolerate a dose level were to be permitted to return to the next lowest level, if 1800 was not tolerated, 1200 mg/d was to be permitted.
- Titration was to be completed by the end of week 4 with patients on a stable dose through week 8.
- Subjects were to keep daily diaries and schedule 5 office visits. Patients were to have been contacted by the investigators by telephone twice a week.
- Medication compliance was to be judged by capsule count at each visit. Missing greater than 20% of scheduled doses was to be cause for removing the subject from the study. Blood levels at Visit 5 were to help confirm that placebo patients did not take marketed gabapentin during the study.

Table 6.1 Dosing Titration Schedules

	Number of Study Medication Capsules[1]							
	Day 0[2]	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Target[3]
1st Week	1	1-3	1-3	1-3	3	3	3	900mg
2nd Week	3-6	3-6	3-6	3-6	6	6	6	1800mg
3rd Week	6-8	6-9	6-8	6-8	8	8	8	2400mg
4th Week	8-12	8-12	8-12	8-12	12	12	12	3600mg
	Fixed-Dose by end of Week 4 to Week 8 Visit							

1. One capsule is equal to gabapentin 300mg or placebo.
2. First dose will be taken in the evening of Visit 2 (Day 0, Baseline Visit).
3. Targeted regimen is divided into TID dosing.

Table 6.2 Study Timetable

	Week -1	Visit 2	Visit 3	Visit 4	Visit 5
	Screening +/-2 days	Week 0 Baseline	Week 2 +/-2 days	Week 4 +/-2 days	Week 8[1] +/-2 days
Inclusion/Exclusion Criteria (Screening Questionnaire)	X				
Informed Consent	X				
Medical History	X	update			
Brief Physical & Neurological Exam	X	update			X
Labs: CBC, Chem Profile	X				X
Serum Pregnancy Test	X				
Gabapentin Plasma Conc.					X
SF-MPQ, VAS, PPI	X	X	X	X	X
SF-36, POMS		X			X
Global Impr. of Change					X
Study Med. Dispensed		X	X	X	
Patient Diaries[2]	X -------	-------X-------	--------X-------	--------X-------	X---------
Adverse Event Assessment			--------X-------	-------X--------	X---------

1. Week 8 assessments will be completed at the last study visit in the case of an early termination.
2. Investigator/coordinator will contact the subject by telephone twice weekly between clinic visits.

Outcome Measures:

Average Pain Rating Scale - A 0-10 scale from 0 = "no pain" to 10 = "worst possible pain", to be rated daily

SF-36

Short-form McGill Pain Questionnaire (SF-MPQ) - Three main components:

1. 15 pain descriptors, each rated from 0 = none, to 3 = severe

- The Total score is based on all 15 descriptors with a maximum score of 45.
- The Sensory score is based on the following descriptors: Throbbing, Shooting, Stabbing, Sharp, Cramping, Gnawing, Hot-burning, Aching, Heavy, Tender, Splitting (max score 33)
- The Affective score is based on the following descriptors: Tiring/Exhausting, Sickening, Fearful, Punishing/Cruel (max score 12)

2. A 100mm VAS
3. Present pain intensity on a 0-5 scale from 0 = no pain to 5 = excruciating

Sleep Rating Scores

A 0-10 scale from 0 = does not interfere with sleep to 10 = completely interferes with sleep, in response to the question of "how your pain has interfered with your sleep during the past 24 hours."

Global Impression of Change

A 1-7 scale from 1 = much improved to 7 = much worse

Statistical Assessment:

Primary Efficacy: Change from baseline in the average Pain Rating Scale. This was to be summarized by treatment group and evaluated for within treatment changes using the paired t-test. Between treatment comparisons were to be made using a linear regression model with treatment and site as experimental factors and baseline pain, gender and race as candidate covariates. If the residuals from the regression model were not normally distributed, the Wilcoxon signed rank test was to be used.

Secondary Efficacy: The sponsor notes that these were not to be used for inferential purposes, but only have confidence intervals and point estimates calculated for each treatment.

1. Global impression of change by subject
2. Sleep score change from baseline
3. SF McGill pain questionnaire change from baseline
4. VAS change from baseline
5. Present Pain Intensity (PPI) at each visit
6. SF-36 quality of life change from baseline
7. Profile of Mood States (POMS) change from baseline
8. Global impression of change by physician

Safety: AEs, labs, PE, neuro exam

The evaluable population was defined as those patients who:

- Complied with protocol directed concurrent medication rules
- Were at least 80% compliant with treatment medication during stable dosing phase
- Completed at least 4 out of 7 days of diaries during the week prior to baseline and the last week of stable dosing
- Were not major protocol violators.
- Drop-outs due to PHN pain anytime beyond the first week of study medication were to be classified as treatment failures and LOCF was to be utilized for efficacy analyses.

The intent-to-treat population was defined as all subjects randomized, with any follow-up data. LOCF was to be utilized for subjects missing the data from the last week of stable dosing diaries.

The safety population was defined as all subjects who had taken at least one dose of study medication and provided follow-up information.

The sponsor defined study compliance as follows:

1. The first day of stable dosing was the date of the first stable dose of study medication as reported on the Visit 4 CRF.
2. If the start day was ≤21 days after baseline, the start day was defined as 21 days. If it was > 21 days after baseline, the actual day was used.
3. The final day of stable dosing was defined as the last day of study medication, unless more than 63 day, when it was defined as 63 days.
4. A stable dose was defined as the situation in which the dose at the final study day was the same for the preceding 21 days or more.
5. At least two diaries with dosing data per week for at least 2 weeks of stable dosing period and at least 4 diaries during Week 8.
6. Study medication data was taken from diaries for the stable dosing phase. Periods or days with at least one entry for number of capsules were determined and the total number of capsules during the period calculated. Missing numbers were considered zero.
7. The total number of prescribed capsules was calculated for the period when diary data was available.
8. The percent of study medication was calculate by divided the total number of capsules by the total number prescribed At least 80% was considered compliant.

The criteria for exclusion from the efficacy analysis were presented in the study report as follows:

- Patients not randomized
- No evidence of any study medication use
- No post-baseline efficacy assessment
- Treatment for less than 21 days on a stable dose, unless dropped out due to PHN pain
- Fewer than 2 diaries with dosing data per week for at least 2 of the stable dosing weeks
- <80% or >120% of prescribed dose during the entire study based on compliance criteria
- Use of disallowed concurrent medication
- Major protocol violations
- Discontinuation early after at least 1 week of treatment and met at least one non-evaluability criteria
- Insufficient number of pain ratings in diaries, <4 within 7-day period after 6 weeks of treatment
- Week 8 office visit was <42 days and >63 days form first dose

Partial exclusions included patients without a baseline assessment for a given scale, patients with post-baseline assessments outside permitted time window (+/-7 days from scheduled week)

Protocol Amendments:
None

RESULTS
Post Hoc Analyses
In the protocol only descriptive statistics were planned for the secondary efficacy measures. However, the sponsor provided inferential statistics, citing "Additional Request Dated 25 September 1997." Additional information about this analysis was requested on 12/6/01 and received by email on 12/11/01. The sponsor reports that the inferential testing on the secondary efficacy parameters was performed as a result of an internal company request. The analysis was performed following unblinding of the study. No description of how the analysis was performed was provided other than that they were the same method used for the primary analysis. No corrections for multiple analyses were performed. The results of these analyses will be reported for informational purposes only. The post hoc nature of these analyses, following study unblinding, invalidates any conclusions based upon them, and the lack of adjustment for multiple comparisons further invalidates these results.

General Comments
The sponsor's efficacy analysis was performed in the evaluable population, with ITT analyses used as confirmatory. This population was narrowly defined, and consisted of less than half of the ITT population. For the purposes of this review, this reviewer considers the results from analyses of the ITT population primary, and the results from analyses of the evaluable population secondary.

Disposition
Investigators from 17 centers enrolled and randomized a total of 229 patients, 116 of whom received placebo and 113 of whom received gabapentin. Of the 229 randomized, 184 completed the study. The reasons for discontinuation presented in Table 6.3 , reveal that few patients discontinued from either group for lack of efficacy. The most common reason for study discontinuation from either treatment group was the occurrence of an adverse event.

Table 6.3 Patient Disposition

	Placebo N (%)	Gabapentin N (%)	Overall N (%)
Total Randomized	116	113	229
Completed Study	95 (81.9%)	89 (78.8%)	184 (80.3%)
Premature Discontinuation:	21(18.1%)	24 (21.2%)	45 (19.7%)
Reasons for Discontinuation:			
Treatment Failure	2 (1.7%)	0 (0.0%)	2 (0.9%)
Adverse Event	14 (12.1%)	21(18.6%)	35 (15.3%)
Lack of Compliance with Protocol	2 (1.7%)	1 (0.9%)	3 (1.3%)
Personal Reasons	2 (1.7%)	1 (0.9%)	3 (1.3%)
Lost to Follow-up	1 (0.9%)	0 (0.0%)	1 (0.4%)
Other	0 (0.0%)	1 (0.9%)	1 (0.4%)

Source: Sponsor's Table 9, Vol. 1.77, P. 88

All 229 patients have been included in the safety population. Four patients from the gabapentin group were excluded from the ITT population. All four of these patients discontinued from the study early, prior to the first set of assessments after beginning treatment with study drug, resulting in no pain data subsequent to starting study drug. All four patients had been assigned to the gabapentin 3600 mg/d group. The reasons for study discontinuation for these four patients are listed below.

Table 6.4 Reasons for Termination Prior To First Assessment After Treatment Begun, ITT Population

Patient	Dose at time of termination	Reason for termination
211-09-132	1800 mg/d	AE: Dizziness
211-14-159	300 mg/d	AE: Headache, Dizziness
211-16-123	600 mg/d	Non-compliance with titration/ diary entries
211-16-149	1200 mg/d	AE: Rectal bleeding

From Sponsor's Appendix A.6 (Vol. 1.77, P. 294) and Patient Profiles

For the efficacy analyses however, many patients in the ITT population were excluded from individual outcome measure analyses. The Patient's Global and Investigator's Global Impression of Change, SF-36, and POMS were assessments only made at the Week 8 or termination visit so no information was available to carry forward. However, Pain by VAS and PPI from the McGill questionnaire did have intermediate response times. It is unclear why LOCF was not applied to these analyses.

Table 6.5 Overview of the Analysis Patients: Number Excluded from each Analysis

Patients	Excluded from		Placebo	Gabapentin
	Variables	Assessment Time	(N = 116)	(N = 113)
Safety Evaluable	All	All	0 (0.0%)	0 (0.0%)
			Number of Patients Included: Safety	
			116	113
Intent-to-Treat	All	All	0 (0.0%)	4 (3.5%)
			Number of Patients included: Intent-to-Treat	
			116	109
	Diary: Pain	Week 2	0 (0.0%)	0 (0.0%)
		Week 4	0 (0.0%)	0 (0.0%)
		Week 8 (or last visit)	0 (0.0%)	0 (0.0%)
	Patient's Global	Week 8 (or last visit)	14 (12.1%)	15 (13.8%)
	Pain VAS	Week 2	5 (4.3%)	4 (3.7%)
		Week 4	3 (2.6%)	3 (2.8%)
		Week 8 (or last visit)	3 (2.6%)	3 (2.8%)
	PPI	Week 2	5 (4.3%)	4 (3.7%)
		Week 4	3 (2.6%)	3 (2.8%)
		Week 8 (or last visit)	3 (2.6%)	3 (2.8%)
	SF-36	Week 8 (or last visit)	5 (4.3%)	5 (4.6%)
	POMS	Week 8 (or last visit)	23 (19.8%)	22 (20.2%)
	Inv.'s Global	Week 8 (or last visit)	14 (12.1%)	15 (13.8%)
	Diary: Steep	Week 2	0 (0.0%)	0 (0.0%)
		Week 4	7 (6.0%)	11 (10.1%)
		Week 8 (or last visit)	0 (0.0%)	0 (0.0%)
	McGill Pain	Week 2	17 (14.7%)	15 (13.8%)
		Week 4	6 (5.2%)	7 (6.4%)
		Week 8 (or last visit)	6 (5.2%)	5 (4.6%)

NOTE: Percents for All Variables' for Safety, ITT are based on the total number of randomized patients. Percents for individual variables for ITT are based on the total number of patients within each analysis.
From Sponsor's Table 3 , Vol. 1.77, P. 44

The efficacy evaluable population consisted of 51 placebo patients and 48 patients from the gabapentin group. The reasons for the numerous exclusions are described below. Many patients had more than one reason for exclusion from this population. Protocol violations were the most common reasons for exclusion. Very few subjects from the evaluable population were excluded from individual outcome measure analyses.

Table 6.6 Reasons for Exclusion from Evaluable Population

	Placebo	Gabapentin
Total Failing to Meet Efficacy Criteria	65	65
Lack of Compliance <21 days stable dose % dosing <80%, >120% Drop out not for PHN pain) <2 diaries/2 stable weeks	22	23
Protocol Violator Most recent Zoster > 5y ago Did not meet inclusion criteria Did not reach stable dose ≥1200 mg/d Unstable concomitant meds	60	56
<4 Pain ratings for 7 days prior to baseline	5	5

Note: Patients often had more than one reason for failing to meet the criteria for the evaluable population
From Sponsor's Appendix A.5 (Vol. 1.77, P. 267)

Protocol Violation

There were numerous protocol violations by patients in both treatment groups. The most common violations are listed in Table 6.6.

Demographics and Baseline Characteristics

There were no statistically or clinically significant differences in the demographic characteristics of subjects in the two treatment groups.

Table 6.7 Summary of Demographic and Disease Characteristics at Baseline: Safety Population

	Placebo (N = 116)	Gabapentin (N = 113)	p-value [a]	overall (N = 229)
Gender [n(%)]				
Male	56 (48.3%)	63 (55.8%)	0.258	119 (52.0%)
Female	60 (51.7%)	50 (44.2%)		110 (48.0%)
Age(years)				
N	116	113	0.197	229
Mean (SD)	72.6 (10.0)	70.8 (10.5)		71.7 (10.3)
Median	74.0	72.0		74.0
Range	(39.0, 89.0)	(36.0, 90.0)		(36.0, 90.0)
Race [n(%)]				
White, Non-Hispanic	109 (94.0%)	99 (87.6%)	0.096 [a]	208 (90.8%)
Black, Non-Hispanic	3 (2.6%)	10 (8.8%)		13 (5.7%)
Hispanic (White or Black)	3 (2.6%)	2 (1.8%)		5 (2.2%)
Asian or Pacific Islander	1 (0.9%)	2 (1.8%)		3 (1.3%)
Weight (lb)				
N	115	113	0.627	228
Mean (SD)	162.6 (35.8)	160.2 (37.6)		161.4 36.7)
Median	160.0	158.0		160.0
Range	(78.0,294.0)	(81.0,268.0)		(78.0,294.0)
Height (In)				
N	115	113	0.182	228
Mean (SD)	65.5 (4.4)	66.3 (5.0)		65.9 (4.7)
Median	66.0	65.0		65.5
Range	(54.0, 74.0)	(54.0, 86.0)		(54.0, 86.0)
Months since last zoster eruption				
N	116	113	0.256	229
Mean (SD)	47.4 (45.5)	41.0 (38.7)		44.2 (42.3)
Median	29.8	27.5		29.2
Range	(2.4, 264.2)	(3.2, 217.2)		(2.4, 264.2)

@ Comparison between the two treatment groups using t-test or chi-square test.
(a) p-value is based on comparison of whites versus non-whites.
From Sponsor's Table 4, Vol. 1.77, P. 47

The baseline characteristics of patients was provided in a limited manner in the ISE. Both treatment groups had similar periods of time since the last Zoster eruption. Information on the duration of PHN, number of previous drugs tried, and drug categories tried were not collected for this study as they were for Study 945-295.

Table 6.8 Baseline PHN Characteristics

	Placebo N=116	Gabapentin 3600 mg N=113
Duration since last Zoster eruption, Years		
Mean (SD)	3.9 (3.8)	3.4 (3.2)
Median	2.6	2.3
Min, Max	0.2, 22.2	0.3,18.3

Source: Appendix E, P. 279, Vol. 10, 12-20-02,

The sponsor provided listings of medications used prior to the study which were started and/or stopped within 30 days of initiating study medication, and concomitant medication which were started during the study or if prior to the study, continued during the study. There is no listing of which medications were begun during the study, for instance to treat adverse events, so comparison of the available listings is not very informative. Overall, the prior and concomitant medications were similar between the two study groups. The most notable differences were antibiotics used by 4% of the placebo group and 11% of the gabapentin group, antihyperlipidemic drugs used by 16% of the placebo group and 11% of the gabapentin group, aspirin used by 16% of the placebo group and 21% of the gabapentin group, estrogens or progesterone used by 18% of the placebo group and 5% of the gabapentin group, thyroid drugs used by 14% of the placebo group and 8% of the gabapentin group, and vasodilators used by 22% of placebo patients and 27% of the gabapentin group. These differences most likely represent preexisting differences in the two groups.

Titration and Dosing Results

The protocol called for a titration period lasting up to 4 weeks according to a prescribed titration regimen, followed by a four week period of stable dosing. As can be seen below, there was a large variability in the number of days of titration and in the number of days of stable dosing. Only one patient failed to reach the minimum acceptable stable dose of 1200 mg/d.

Table 6.9 Summary of Extent of Exposure of Patients to Study Medication, Safety Evaluable Patients

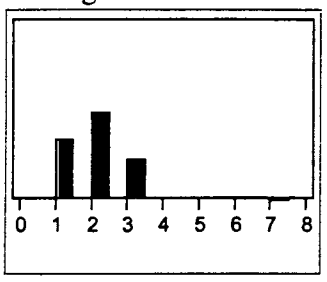
	Placebo	Gabapentin
No. of Days on Study Medication (N)	116	113
Mean (SD)	50.7 (14.39)	49.1 (16.69)
Median	56.0	56.0
Min - max	2 - 63	2 - 63
No. of Days of Titration (N)	116	113
Mean (SD)	24.7 (6.06)	23.6 (6.43)
Median	26.0	25.0
Min - Max	2 - 56	2 - 41
No. of Days of Stable Dosing (N)	103	96
Mean (SD)	30.4 (7.26)	30.9 (7.20)
Median	32.0	32.0
Min - Max	3 - 43	4 - 43
No.(%) of Patients at Maximum achieved dose (mg/day)		
900	1 (1.0%)	0
1200	0	6 (6.3%)
1500	0	1 (1.0%)
1800	3 (2.97)	8 (8.3%)
2100	0	1 (1.0%)
2400	13 (12.6%)	12 (12.5%)
2700	1 0.07)	5 (5.2%)
3000	0	1 (0.07)
3300	1 (1.07.)	0
3600	84 (81.6%)	62 (64.6%)

Source: Sponsor's Table 5, Vol. 1.77, P. 50.

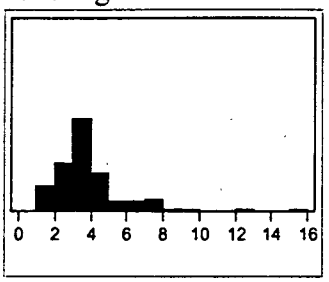
A review of the dosing during the titration period was performed. The question to be answered was whether there was a means of examining efficacy at 1800 mg/day and 2400 mg/day. According to the titration schedule, patients could have been exposed to these doses for up to one week, and all patients could have been on 1800 mg/d on study day 13 and 2400 mg/day on study day 20, had the titration schedule been followed very closely. The medication dosing data was obtained from electronic database md945211. The duration of time each subject was dosed with 300 mg/day, 1800 mg/day, and 2400 mg/day was extracted. Subjects for whom 1800 mg/days or 2400mg/day was the final titrated dose were excluded from the analysis. As can be seen from Figure 1 and Table 6.10, the duration of treatment on 1800 mg/day and 2400 mg/day varied, with most patients on these doses less than one week. The distribution of durations was skewed to the left, with a median duration of 2 days for both doses, and few patients received either dose for 7 days. A duration of treatment of less than 7 days is too short for an assessment of efficacy. Furthermore, because the interval of therapy with any given dose was shorter than the titration schedule dictated, one cannot make the assumption that on day 13 many patients were receiving 1800 mg/d or on day 20 many patients were receiving 2400 mg/d.

Figure 1 Distribution of Dosing, in Days

300 mg/d



1800 mg/d



2400 mg/d

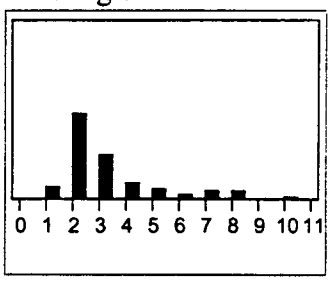


Table 6.10 Number of Days/Dose, Titration Period

		300 mg/d	1800 mg/d	2400 mg/d
100.0%	maximum	7.00	15.00	10.0
75.0%	quartile	2.00	4.00	4.00
50.0%	median	2.00	3.00	2.00
25.0%	quartile	1.00	2.00	2.00
0.0%	minimum	1.00	1.00	1.00
N		106	98	74
Mean (SD)		1.93 (0.88)	3.49 (2.20)	3.15 (1.90)

Source: Electronic Database md94521

Efficacy Results

Primary Efficacy

The planned primary efficacy outcome measure was the change from baseline in the average Pain Rating Scale. The difference from baseline to Week 8 or termination visit for this 0 to 10 scale was statistically significantly different between treatment groups. The difference was -2.1 for the gabapentin group compared with -0.5 for the placebo group ($p<0.001$). This difference occurred from the setting of comparable mean baseline scores (6.5 for the placebo group and 6.3 for the gabapentin group). Interestingly, the within group analyses were statistically significant for both groups ($p=0.005$ for placebo, $p<0.001$ for gabapentin), although the difference in scores for the placebo group was only -0.5.

Table 6.11 Summary of Pain Rating Score: Patient's Diary, Intent-to-Treat Patients

Statistics	Placebo	Gabapentin	Between Groups P-Value *
Baseline	N=116	N=109	
Mean (SD)	6.5 (1.7)	6.3 (1.7)	
95% CI	(6.1 , 6.8)	(6.0 , 6.7)	
Median [Min, Max]	6.4 [3.0, 10.0]	6.4 [0.6, 10.0]	
Week 8 (or last visit)	N=116	N=119	
Mean (SD)	6.0 (2.4)	4.2 (2.3)	
95% CI	(5.5 , 6.4)	(3.8 , 4.6)	
Median [Min, Max]	6.1 [0.6, 10.0]	3.9 [0.0, 10.0]	
Change from Baseline to Week 8	N=116	N=109	
Mean (SD)	-0.5 (1.6)	-2.1 (2.1)	< 0.001
95% CI	(-0.8 , -0.2)	(-2.5 , -1.7)	
Median [Min, Max]	-0.2 [-4.7, 3.7]	-2.0 [-7.7 , 2.4]	
Within Groups P-Values:	0.005	< 0.001	

NOTE: Included are patients with assessments at both baseline and Week 8 (or last visit). Four patients in the gabapentin group had no pain scores following baseline. The p-values are for the comparisons of

means between two treatment groups and within each treatment group on the change from baseline to Week 8 (or Last visit). The comparison between groups is based on an ANCOVA model including fixed terms of treatment, center, treatment-by-center along with the baseline value as a covariate using ranked data. The within group comparisons are based on the Wilcoxon signed rank test.
* Primary Analysis.
Source: Sponsor's Table 14, Vol. 1.77, P. 83.

The results form the evaluable population were similar to the ITT population. The mean difference within the placebo group was -0.5 and in the gabapentin group -2.7. This difference was statistically significantly different (p=0.001) (Sponsor's Table 13, Vol. 1.77, P. 82).

Although not designated as either primary or secondary efficacy measures, the change from baseline to Weeks 2 and 4 for the Pain Rating Score were provided. The change from baseline to Week 2 was -0.2 (CI -0.4, 0.0) for the placebo group and -1.6 (CI -1.9,-1.3) for the gabapentin group (ITT population). The change from baseline to Week 4 was -0.3 (CI -0.6, -0.1) for the placebo group and -2.0 (CI -2.3, -1.6) for the gabapentin group. These changes are consistent with the findings at Week 8, and suggest that for many patients, the onset of efficacy may begin as early as 2 weeks after initiating therapy with gabapentin.

Secondary Efficacy
The sponsor planned not to use the secondary efficacy analyses for between-treatment group inferential purposes, but only to calculate confidence intervals and point estimates for each treatment. However, the sponsor has performed some comparative statistics for some of the secondary efficacy analyses, as noted below. These comparisons are included in this review for completeness, but as they are post hoc analyses that do not take into account multiple comparisons, are not considered contributory toward the assessment of efficacy.

Sleep Score
Both treatment groups experienced an improvement in the rating of how pain interfered with sleep . The change from baseline was greater for the gabapentin group, but no statistical analysis comparing the two treatment groups was performed.

Table 6.12 Summary of Sleep Rating Score: Patient's Diary, Intent-to-Treat Patients

Statistics	Placebo	Gabapentin
Baseline		
N	116	109
Mean (SD)	4.1 (2.9)	4.3 (2.8)
95% CI	(3.6 , 4.6)	(3.8 , 4.8)
Week 8 (or last visit)		
N	116	109
Mean (SD)	3.6 (3.0)	2.4 (2.5)
95% CI	(3.0 , 4.1)	(0.9 , 2.8)
Change from Baseline to Week 8		
N	116	109
Mean (SD)	-0.5 (0.9)	-1.9 (2.5)
95% CI	(-0.9 , -0.2)	(-2.4 , -1.5)

NOTE: Included are patients with assessments at both baseline and Week 8 (or last visit).
Source: Sponsor's Table 16, Vol. 1.77, P. 86.

The change to Week 2 and Week 4 evaluations were similar for the ITT population. The change from baseline to Week 2 was -0.1 for the placebo group and -1.4 for the gabapentin group. The change from baseline to Week 4 was -0.4 for the placebo group and -2.1 for the gabapentin group.

Global Impression of Change

This rating was performed by the subjects and independently by the investigators. The results are fairly similar for the two sets of ratings. More subjects and investigators provided ratings of Minimally, Moderately, and Much Improved for the gabapentin-treated patients than the placebo-treated patients. There were a few more subjects rated Minimally and Moderately Worse among the placebo-treated group than the gabapentin-treated group. The biggest difference was the greater number of subjects rated No Change among the placebo-treated patients.

Table 6.13 Summary of Global Impression of Change at Week 8 (or Last Visit) by Patient and Investigator, Intent-to-Treat Patients

	Patient Rating			Investigator Rating		
	Placebo (N = 116)	Gabapentin (N = 109)	Treatment Difference	Placebo (N = 116)	Gabapentin (N = 109)	Treatment Difference
Frequency Counts [n (%)]						
(1) Much Improved	6 (5.2%)	21 (9.3%)	15 (14.1%)	3 (2.6%)	17 (15.6%)	14 (13.0%)
(2) Moderately Improved	8 (6.9%)	26 (23.9%)	18 (17.0%)	12 (0.3%)	26 (23.9%)	14 (13.6%)
(3) Minimally Improved	9 (7.8%)	19 (7.4%)	10 (9.6%)	7 (6.0%)	19 (7.4%)	12 (11.4%)
(4) No Change	69 (59.5%)	25 (22.9%)	-44 (-36.6%)	71 (61.2%)	29 (26.6%)	-42 (-34.6%)
(5) Minimally worse	5 (4.3%)	3 (2.8%)	-2 (-1.5%)	7 (6.0%)	2 (1.8%)	-5 (-4.2%)
(6) Moderately Worse	5 (4.3%)	0 (0%)	-5 (-4.3%)	2 (1.7%)	0 (0%)	-2 (-1.7%)
(7) Much worse	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	1 (0.9%)
Missing	14 (12.1%)	15 (3.8%)	1 (1.7%)	14 (2.1%)	15 (13.8%)	1 (1.7%)
Mean (SD)	3.7 (1.1)	2.6 (1.2)		3.7 (0.9)	2.8 (1.2)	
Summary of Much Improved						
95% CI	0.7%, 9.7%	11.4%, 27.2%	4.8%, 23.4%	0.0%, 5.9%	8.3%, 22.9%	4.7%, 21.3%

Treatment difference refers to Gabapentin - Placebo.
Source: Sponsor's Table 18, P. 89 and Table 20, P. 92, Vol. 1.77

SF McGill Pain Questionnaire

There were greater improvements in the change from baseline in the McGill pain questionnaire total, sensory and affective scores among the gabapentin-treated patients compared with placebo-treated patients. The post-hoc comparisons between the gabapentin and placebo treatment groups revealed statistical significance for all three scores, although the mean changes were modest for both treatment groups. As previously noted, no corrections were made for multiple comparisons. The change from baseline for the sensory score is greater than for the affective score and appears to account for much of the change from baseline to Week 8 for the total score.

Table 6.14 McGill Pain Questionnaire: Total, Sensory and Affective Scores, Intent-to-Treat Patients

Score	Assessment Time	Statistics	Placebo (N=116)	Gabapentin (N=109)	p-value [a]
Total		N	110	104	
	Baseline	Mean (SD)	18.7 (8.5)	17.2 (9.6)	
		95% CI of Mean	(17.1, 20.3)	(15.3, 19.0)	
		Median [Min, Max]	19.0 [3.0, 42.0]	15.0 [3.0, 41.0]	
	Week 8 (or Last visit)	Mean (SD)	16.8 (10.8)	11.4 (9.3)	
		95% CI of Mean	(14.8, 18.9)	(9.6, 13.1)	
		Median [Min, Max]	15.0 [0.0, 45.0]	9.0 [0.0, 45.0]	
	Change from Baseline	Mean (SD)	**-1.3 (8.9)**	**-5.8 (8.9)**	<0.001
		95% CI of Mean	(-3.5, -0.2)	(-7.5, -4.1)	
		Median [Min, Max]	0.0 [-23, 19.0]	-5.5 [-28, 18.0]	
Sensory Score		N	110	104	
	Baseline	Mean (SD)	14.5 (6.4)	13.6 (7.2)	
		95% CI of Mean	(13.4, 15.7)	(12.2, 15.0)	
		Median [Min, Max]	15.0 [2.0, 33.0]	12.0 [2.0, 32.0]	
	Week 8 (or Last visit)	Mean (SD)	13.0 (8.0)	9.3 (7.1)	
		95% CI of Mean	(11.5, 14.5)	(8.0, 10.7)	
		Median [Min, Max]	12.0 [0.0, 33.0]	8.0 [0.0, 33.0]	
	Change from Baseline	Mean (SD)	**-1.5 (6.8)**	**-4.3 (7.0)**	<0.001
		95% CI of Mean	(-2.5, -0.3)	(-5.6, -2.9)	
		Median [Min, Max]	-1.0 [-18, 15.0]	-3.5 [-20, 14.0]	
Affective Score		N	110	104	
	Baseline	Mean (SD)	4.1 (3.2)	3.6 (3.2)	
		95% CI of Mean	(3.5, 4.7)	(3.0, 4.2)	
		Median [Min, Max]	4.0 [0.0, 12.0]	3.0 [0.0, 12.0]	
	Week 8 (or Last visit)	Mean (SD)	3.8 (3.6)	2.0 (2.7)	
		95% CI of Mean	(3.2, 4.5)	(1.5, 2.5)	
		Median [Min, Max]	3.0 [0.0, 42.0]	1.0 [0.0, 12.0]	
	Change from Baseline	Mean (SD)	**-0.3 (3.0)**	**-1.5 (2.9)**	<0.001
		95% CI of Mean	(-0.9, 0.3)	(-2.1, -1.0)	
		Median [Min, Max]	0.0 [-8.0, 8.0]	-1.0 [-8.0, 7.0]	

NOTE: When the intensity value was missing for any descriptor, the subclass score which includes the descriptor was set to missing. When any one of the subclass stores was missing, the total score was set to missing.

a. The sponsor notes this analysis was from an "Additional Request, 25 September 1997."

Source: Sponsor's Table 22, Vol. 1.77, P. 95, App. D.16, Vol. 1.79, P. 698

The results of the total scores from the change from baseline to Week 2, -1.4 for the placebo group and -5.5 for the gabapentin group, and Week 4, -1.3 for the placebo group and -6.8 for the gabapentin group are similar to the results from the change to Week 8. These results also suggest that the onset of efficacy is earlier than Week 8, and as early as Week 2 for some patients. The change from baseline to Week 2 and Week 4 for the sensory score and the affective score were also comparable to the baseline to Week 8 scores (Appendices B.9, B.10, B.11, Vol. 1.78, pp. 356-362).

The results from the evaluable population are similar to the results from the ITT population and are not considered further in this review.

VAS

There was a notable decrease in the mean VAS score change from baseline for the gabapentin-treated patients over the 8 week treatment period, 23.8 mm, compared with the placebo-treated patients, 7.9 mm using the ITT population. No post hoc statistical evaluation was provided for this measure.

Table 6.15 McGill Pain Visual Analog Scale Score, Intent-to-Treat Patients

Assessment Tim	Statistics	Placebo	Gabapentin
		(N=113)	(N=106)
Baseline	Mean (SD)	68.5 (5.9)	66.4 (5.8)
	95% CI of Mean	(65.6, 71.4)	(63.4, 69.4)
	Median [Min, Max]	68.0[37,100]	67.0 [38,100]
Week 8 (or last visit)	Mean (SD)	60.6 (24.6)	42.6 (24.0)
	95% CI of Mean	(56.1, 65.2)	(38.0, 47.2)
	Median [Min, Max]	63.0 [1,100]	40.0 [0, 99]
Change from Baseline	Mean (SD)	**-7.9 (21.5)**	**-23.8 (23.3)**
	95% CI of Mean	(-12, -3.9)	(-28, -19)
	Median [Min, Max]	-2.0 [-60, 36]	-22 [-87, 28]

Source: Sponsor's Table 24, Vol. 1.77, P. 98

The changes in VAS score from baseline to Week 2 were -3.7 for the placebo group and -17.9 for the gabapentin group. From baseline to Week 4, the changes in VAS were -5.3 for the placebo group and -22.3 for the gabapentin group.

Present Pain Intensity (PPI)

The distribution of PPI results at each visit was comparable for the two groups, ITT population, at baseline. At Week 8, there were fewer patients rating their pain as Distressing and more as Mild Pain or No Pain in the gabapentin group. The post hoc comparison between the two treatment groups by the sponsor demonstrated statistical significance (p=0.006.)

Table 6.16 Summary of MPQ Present Pain Intensity (PPI) Rating for Each Category, ITT

Assessment Time	Placebo (N=116)	Gabapentin (N=109)
Baseline		
Mean (SD)*	2.4 (1.08)	2.4 (1.05)
Pain Ratings [n(%)]:		
(0) No Pain	3 (2.6%)	2 (1.8%)
(1) Mild	15 (12.9%)	15 (13.8%)
(2) Discomforting	46 (39.7%)	48 (44.0%)
(3) Distressing	34 (29.3%)	27 (24.8%)
(4) Horrible	9 (7.8%)	9 (8.3%)
(5) Excruciating	6 (5.2%)	5 (4.6%)
Missing	3 (2.6%)	3 (2.8%)
Week 8 (or last visit):		
Mean (SD)	2.0 (1.18)	1.6 (1.14)
Pain Ratings [n(%)]:		
(0) No Pain	**10 (8.6%)**	**17 (15.6%)**
(1) Mild	**29 (25.0%)**	**34 (31.2%)**

(2) Discomforting	**38 (32.8%)**	**40 (36.7%)**
(3) Distressing	**27 (23.3%)**	**8 (7.3%)**
(4) Horrible	4 (3.4%)	4 (3.7%)
(5) Excruciating	5 (4.3%)	3 (2.8%)
Missing	3 (2.6%)	3 (2.8%)

The mean and standard deviation are calculated based an the scores printed in front of the category descriptor.
Source: Sponsor's Table 26, Vol. 1.77, P. 101

The results of the PPI for the ITT population for Week 4 were very similar to Week 8 with some changes noted as early as Week 2.

Table 6.17 Summary of MPQ Present Pain Intensity (PPI) Rating for Each Category, ITT

	Week 2		Week 4	
Assessment Time	Placebo (N=116)	Gabapentin (N=109)	Placebo (N=116)	Gabapentin (N=109)
Mean (SD)*	2.3 (1.01)	1.8 (1.02)	2.1 (1.12)	1.7 (1.14)
Pain Ratings [n(%)]:				
(0) No Pain	4 (3.4%)	11 (10.1%)	6 (5.2%)	17 (15.6%)
(1) Mild	18 (15.5%)	25 (22.9%)	27 (23.39%)	24 (22.08%)
(2) Discomforting	45 (38.8%)	51 (46.8%)	42 (36.2%)	46 (42.2%)
(3) Distressing	33 (28.4%)	13 (11.9%)	27 (23.3%)	14 (12.8%)
(4) Horrible	9 (7.8%)	3 (2.8%)	7 (6.0%)	1 (0.9%)
(5) Excruciating	2 (1.7%)	2 (1.8%)	4 (3.4%)	4 (3.7%)
Missing	5 (4.3%)	4 (3.7%)	3 (2.6%)	3 (2.8%)

* The mean and standard deviation are calculated based an the scores printed in front of the category descriptor.
Source: Appendix B.15, Vol. 1.78, P. 369

SF-36 Quality Of Life

The gabapentin treated patients showed improvement in the Health Transition, Physical Function , Role-Physical, Bodily Pain, Vitality, Social Functioning, Mental Health subscale scores from baseline to Week 8. The improvements were modest for most of these subscales as seen below. All of the subscales were transformed to a 0-100 scale except Health Transition. The mean change in Physical Functioning was only 4.5, in Mental Health ,6.7, in Vitality, 8, and in Social Functioning, 8.7. The mean change in Health Transition was 0.4 on a 1-5 scale. The Role-Emotional and General Health subscales did not show improvement for the gabapentin treated patients. The placebo-treated patients demonstrated smaller changes in all subscales except General Health and Role Emotional which demonstrated small improvements that were slightly greater than for the gabapentin-treated patients.

Table 6.18 SF-36 Quality of Life Assessment: Summary of transformed Score (0-100) by Subscale Intent-to-Treat Patients

Parameter	statistics	Placebo (N=111)	Gabapentin (N=104)
Health Transition	N	99	89
Baseline	Mean (SD)	2.9 (0.9)	2.7 (0.0)

	95% CI of Mean	(2.7,3.0)	(2.5,2.9)
Change from Baseline	Mean (SD)	**0.1 (0.9)**	**0.4 (1.2)**
	95% CI of Mean	(-0.1,0.2)	(0.2,0.7)
Physical Functioning	N	101	92
Baseline	Mean (SD)	57.6 (29.3)	61.7 (24.5)
	95% CI of Mean	(51.9,63.3)	(56.7,66.7)
Change from Baseline	Mean (SD)	**-0.1 (19.5)**	**4.5 (19.4)**
	95% CI of Mean	(-3.9,3.7)	(0.5,8.5)
Role-Physical	N	101	93
Baseline	Mean (SD)	40.4 (41.4)	40.9 (40.7)
	95% CI of Mean	(32.3,46.4)	(32.6,49.1)
Change from Baseline	Mean (SD)	**2.7 (29.1)**	**14.3 (41.4)**
	95% CI of Mean	(-3.0,8.4)	(5.8,22.7)
Bodily Pain	N	100	92
Baseline	Mean (SD)	42.7 (18.8)	42.9 (20.1)
	95% CI of Mean	(39.0,46.4)	(38.8,47.0)
Change from Baseline	Mean (SD)	**4.7 (17.8)**	**14.5 (20.4)**
	95% CI of Mean	(1.2,8.2)	(10.3,18.7)
General Health	N	101	93
Baseline	Mean (SD)	62.3 (23.5)	62.5 (20.5)
	95% CI of Mean	(57.7,66.9)	(58.6,66.9)
Change from Baseline	Mean (SD)	**2.0 (13.2)**	**0.3 (14.8)**
	95% CI of Mean	(-0.6,4.6)	(-2.7,3.3)
Vitality	N	101	93
Baseline	Mean (SD)	45.8 (23.6)	46.7 (21.6)
	95% CI of Mean	(41.2,50.4)	(42.3,51.1)
Change from Baseline	Mean (SD)	**-2.2 (15.7)**	**8.4 (19.6)**
	95% CI of Mean	(-5.2,0.9)	(4.5,12.4)
Social Functioning	N	97	85
Baseline	Mean (SD)	65.5 (30.1)	65.4 (25.4)
	95% CI of Mean	(59.5,71.5)	(59.4,71.5)
Change from Baseline	Mean (SD)	**3.9 (24.1)**	**8.7 (28.9)**
	95% CI of Mean	(-0.9,8.7)	(2.5,14.8)
Role-Emotional	N	101	93
Baseline	Mean (SD)	61.1 (44.2)	70.3 (40.4)
	95% CI of Mean	(52.4,69.7)	(62.1,78.5)
Change from Baseline	Mean (SD)	**3.6 (37.1)**	**-1.8 (37.2)**
	95% CI of Mean	(-3.6,10.9)	(-9.4,5.8)
Mental Health	N	101	93
Baseline	Mean (SD)	69.2 (20.2)	67.9 (20.0)
	95% CI of Mean	(65.3,73.2)	(63.8, 72.0)
Change from Baseline	Mean (SD)	**0.7 (15.4)**	**6.7 (16.5)**
	95% CI of Mean	(-2.3,3.7)	(3.4,10.1)

Note: Included are patients with assessments at Baseline and Week 8 (or Last visit). If ≥ 50% of the items in a scale was missing, the subscale score was set to missing. Missing item scores for those with a response an at least 50% of the items were imputed as the mean item score of recorded items in the same subscale.
Source: Sponsor's Table 28, Vol. 1.77, P. 108

Profile of Mood States (POMS)

The only score of the POMS with a notable change from baseline was the Total Mood Disturbance score, with a 15.0 point change for the gabapentin-treated patients compared with a 2.9 point change for the placebo-treated patients.

Table 6.19 Profile of Mood States: Total Mood Disturbance Score and subscale Scores Intent-to-Treat Patients

Parameter Assessment Time	statistics	Placebo (N=116)	Gabapentin (M=109)
Total Mood Disturbance	N	91	84
Baseline	Mean (SD)	30.6 (36.6)	31.9 (35.7)
	95% CI of Mean	(23.1, 38.1)	(24.3, 39.6)
Change from Baseline	Mean (SD)	**-2.9 (20.5)**	**-15.0 (27.9)**
	95% CI of Mean	(-7.1, 1.4)	(-21.0, -9.1)
Tension-Anxiety	N	92	85
Baseline	Mean (SD)	10.8 (7.5)	11.8 (8.4)
	95% CI of Mean	(9.3, 12.4)	(10.0, 13.6)
Change from Baseline	Mean (SD)	**-1.2 (4.9)**	**-2.4 (6.9)**
	95% CI of Mean	(-2.2, -0.2)	(-3.9, -1.0)
Depression-Dejection	N	91	86
Baseline	Mean (SD)	10.6 (10.4)	10.7 (10.1)
	95% CI of Mean	(8.5, 12.5)	(8.6, 12.8)
Change from Baseline	Mean (SD)	**-0.8 (6.5)**	**-4.5 (7.2)**
	95% CI of Mean	(-2.1, 0.5)	(-6.0, -3.0)
Anger-hostility	N	92	86
Baseline	Mean (SD)	6.8 (7.7)	7.4 (8.4)
	95% CI of Mean	(5.2, 8.4)	(5.6, 9.2)
Change from Baseline	Mean (SD)	**-0.3 (4.6)**	**-3.0 (6.4)**
	95% CI of Mean	(-1.2, 0.7)	(-4.4, -1.7)
Vigor-Activity	N	93	86
Baseline	Mean (SD)	14.9 (6.3)	15.5 (6.1)
	95% CI of Mean	(13.6, 16.2)	(14.2, 16.8)
Change from Baseline	Mean (SD)	**0.1 (4.6)**	**0.8 (5.4)**
	95% CI of Mean	(-0.8, 1.1)	(-0.4, 1.9)
Fatigue-Inertia	N	93	87
Baseline	Mean (SD)	11.2 (7.6)	11.5 (7.6)
	95% CI of Mean	(9.6, 12.7)	(9.9, 13.2)
Change from Baseline	Mean (SD)	**-0.6 (4.9)**	**-3.8 (6.7)**
	95% CI of Mean	(-1.6, 0.4)	(-5.2, -2.3)
Confusion-Bewilderment	N	93	86
Baseline	Mean (SD)	6.5 (4.8)	6.6 (4.5)
	95% CI of Mean	(5.5, 7.5)	(5.6, 7.5)
Change from Baseline	Mean (SD)	**0.0 (3.0)**	**-1.0 (3.5)**
	95% CI of Mean	-0.5, 0.7)	(-1.7, -0.3)

NOTE: Included are patients with assessments at both baseline and Week 8 (or last visit). when more then one item per subscale was missing, the subscale score was set to missing. When a subscale contained one missing value, that score was imputed as the mean score of the remaining items of the subscale. When one or two item were missing in the entire POMS scale, the missing score (s) was imputed by the mean score of the remaining items in POMS to calculate total POMS score. The Total Mood Disturbance score was set to missing if any subscale score was missing.

Section 6.2.2 STUDY 945-295
STUDY 945-295 was performed in the UK and Ireland.

Study Summary
Study 945-295 was a double-blind, randomized, placebo-controlled trial of gabapentin in patients post-herpetic neuralgia. Patients were titrated to either 1800 mg/day or 2400 mg/day over a 3-week period and maintained on the final stable dose for four weeks. The planned primary outcome measure was the mean weekly pain score from the patient diary.

A total of 334 patients were enrolled and 272 (81.4%) completed the study. One hundred and fifteen patients received gabapentin 1800 mg/day, 108 patients received gabapentin 2400 mg/day, and 111 patients received placebo. All patients were successfully titrated to the intended treatment dose. One patient from each of the gabapentin groups required a dose reduction during the study.

The primary outcome measure of the change from baseline of the mean weekly pain score from the patient diary was evaluated as percent change due to a non-normal distribution in the sponsor's analysis. Both percent change from baseline, and absolute pain score at end of study were statistically significantly improved for each gabapentin group compared with placebo ($p<0.01$). Statistically significant differences from placebo were present for both gabapentin groups, for the secondary analysis of mean weekly pain score throughout the study, for both percent change and absolute pain score at each week of the study. An analysis of responders characterized by $\geq$ 50% reduction in pain revealed a greater number among the gabapentin treated patients (32% and 34% for the 1800 mg/day and 2400 mg/day, respectively) compared to the placebo treated patients (14%), and these were statistically significantly different ($p=0.001$ for both comparisons).

The statistical analyses did not correct for multiple comparisons. The results of the secondary efficacy measure of Sleep Interference, while achieving a p-value of 0.01 in comparison between gabapentin groups and placebo group, the actual difference was very small and of questionable clinical significance. The results of comparisons between gabapentin groups and placebo for Short-Form McGill Pain Questionnaire scores were small in size and of questionable clinical significance. All three treatment groups demonstrated improvements, with the trends favoring the gabapentin groups. The Global Impression of Change demonstrated statistically significantly greater numbers of patients rating themselves as much or very much improved in the gabapentin groups compared to placebo. The clinical ratings of Global Improvement were similar. The SF-36 Quality of Life Assessment did not demonstrate meaningful differences between the gabapentin groups and placebo.

These results demonstrate that gabapentin doses of 1800 mg/day and 2400 mg/day were comparably effective in reducing the neuropathic pain of post-herpetic neuralgia.

Study Protocol
Title:. A Double-blind, Placebo-Controlled Trial of Gabapentin for the Treatment of Post-Herpetic Neuralgia

Objective: To evaluate the efficacy and safety of gabapentin at doses of 1800 mg and 2400 mg per day in relieving pain in patients with post-herpetic neuralgia.

Study Duration: 7 weeks (including a 1 week baseline)

Population: N=402 subjects (planned)

Inclusion Criteria:
1. Male, female, >18 years of age
2. Not pregnant, not nursing, on acceptable contraceptive
3. Pain for > 3 months after healing of acute herpes zoster skin rash
4. Completion of at least 4 days of diaries with daily pain and sleep interference scores in 7 days prior to baseline
5. Average score of ≥ 4 over prior 7 days by Pain Rating Scale, ≥ 40 mm on VAS

Exclusion Criteria:
1. Failure to respond to prior treatment with gabapentin at >1200 mg/d or failure to respond at lower doses due to AEs
2. Creatinine clearance ≤ 60 mL/min, renal impairment
3. Significant neurological or psychiatric disorders that might impair assessment of pain
4. Skin conditions that could alter sensation in affected dermatome
6. Anticonvulsants, neuroleptics, or any concomitant medication within 14 to 30 days that could alter effectiveness of study medication.
5. Pain other than PHN that may confound results
6. History of drug or alcohol abuse within 1 year.
7. Use of strong opioids, capsaicin, muscle relaxants, mexiletine, lipoic acid or dextromethorphan within 30 days, NSAIDs or anticonvulsants within 14 days.

Study Design:
- Study Drug: gabapentin 300 mg, 400 mg, and placebo
- Treatment Arms:
  Placebo
  Gabapentin 600 mg TID (1800 mg/d)
  Gabapentin 800 mg TID (2400 mg/d)
- Subjects were to have clinic visits at screening, weeks 1, 2, 3, and 6 and telephone contact at weeks 4 and 5
- Subjects were to be randomized following a one week baseline period during which diaries were to be maintained
- At least 4 complete diary entries during the baseline period were to be required to qualify for randomization.
- Concomitant medications to be permitted were: paracetamol up to 4 gm/d, stable SSRI or tricyclic antidepressant for prior 30 days, minor opioids stable for prior 30

days (dihydrocodeine or compound analgesics), bedtime dose of benzodiazepine with stable dose for prior 30 days. Maximum 300 mg ASA for cardiac or stroke prophylaxis.

Table 6.20 Dosing Titration Schedules

	Daily Dosage	Day	Capsules to be taken		
		1	Morning	Midday	Evening
Week 1	300 mg	1	0	0	1x300 mg
	600 mg	2	1x300 mg	0	1x300 mg
	900 mg	3	1x300 mg	1x300 mg	1x300 mg
	1200mg	4-7	1x400 mg	1x400 mg	1x400 mg
Week 2	1500 mg	1	2x300 mg	1x300 mg	2x300 mg
	1800 mg	2-7	2x300 mg	2x300 mg	2x300 mg
Week 3	**1800 mg**	1-7	2x300 mg	2x300 mg	2x300 mg
OR	2100 mg	1	2x300 mg	1x300 mg, 1x400 mg	2x400 mg
	2400mg	2-7	2x400 mg	2x400 mg	2x400 mg
Week 4-7	**1800 mg**	All	2x300 mg	2x300 mg	2x300 mg
OR	**2400 mg**	All	2x400 mg	2x400 mg	2x400 mg

Outcome Measures:

- Daily pain diary - an 11-point Likert scale with 0 ="no pain" and 10 = "worst possible pain."
- Short-form McGill Pain Questionnaire (SF-MPQ) - Three main components:
  1. 15 pain descriptors, each rated from 0 = none, to 3 = severe
     - The Total score is based on all 15 descriptors with a maximum score of 45.
     - The Sensory score is based on the following descriptors: Throbbing, Shooting, Stabbing, Sharp, Cramping, Gnawing, Hot-burning, Aching, Heavy, Tender, Splitting (max score 33)
     - The Affective score is based on the following descriptors: Tiring/Exhausting, Sickening, Fearful, Punishing/Cruel (max score 12)
  2. A 100mm VAS
  3. Present pain intensity on a 0-5 scale from 0 = no pain to 5 = excruciating
- SF-McGill Pain Questionnaire (SF-MPQ) - pain descriptors score as total, sensory and affective scores, present pain intensity (PPI), overall pain intensity by VAS
- Mean paracetamol consumption
- Clinical and Patient Global Impression of Change (CGIC and PGIC) - 7 point scales ranging from 1 = "very much improved" to 7 = "very much worse."
- Sleep interference score - an 11 point Likert scale with 0 = "pain does not interfere with sleep" and 10 = " pain completely interferes with sleep."

Statistical Assessment:

The primary efficacy measure was to be the mean weekly pain score from the daily pain diary. Self assessment of pain during past 24 hours was to be performed daily on waking. The baseline score was to consist of the mean of the last 7 pain diary entries preceding Visit 1. The final weekly mean pain score was to be the mean of the last 7 pain diary entries preceding Visit 6 or the last 7 days on study medication for non-completers.

An ANCOVA was to be performed with treatment and cluster (centers with at least 20 patients, or centers with fewer grouped based on geographical area) in the model and screening mean pain score as covariate.

Supplemental analyses:

- Analysis of mean pain score for each week separately
- Change of weekly mean pain score from baseline at end point and at each week separately.
- The effects of age, duration of pain and use of tricyclic antidepressants will be investigated for effect
- Percentage of patients achieving 50% reduction in mean pain scores

Secondary:

- Mean weekly sleep interference score - computed for each week and last visit, analyzed the same as the primary pain analysis
- SF-MPQ - analyzed at week 7 with randomization scores as covariate.
- Sleep interference score
- CGIC and PGIC - obtained at final visit, analyzed using a modified ridit transformation with Cochran-Mantel-Haenszel procedure
- Mean paracetamol consumption - computed for each week and last visit
- SF-36 Quality of Life (QOL) questionnaire. This instrument measures responses to questions in eight domains: physical function, role limitations due to physical problems, social functions, bodily pain, general mental health, role of limitations caused by emotional problems, vitality, and general health.

No adjustments will be made for multiple comparisons. The sponsor notes that the large number of comparisons being performed may result in the occurrence of some significant statistical outcomes by chance alone. The sponsor planned to not give "undue consideration" to any particular significant difference, but look at the pattern of significant differences.

Protocol Amendments:

Amendment 1

The details of prohibited concurrent medications were amended. Originally, NSAIDs and anticonvulsants were prohibited for the 14 days prior and during the study and strong opioids, benzodiazepines, capsaicin, muscle relaxants, mexiletine and lipoic acid were prohibited for 30 days prior and during the study. The amendment called for strong opioids to remain prohibited for 30 days prior and during the study and all other prohibited medications for 14 days prior to and during the study. Homeopathic remedies and acupuncture were prohibited for 30 days prior and during the study. TENS units were prohibited during the study.

Amendment 2

The description of patient recruitment from hospital centers was changed to hospital centers and general practices.

RESULTS

Post Hoc Analyses

The sponsor states in the study report that an adjustment was to be made in the primary efficacy analysis for multiplicity involved in comparing 2 doses of gabapentin with placebo. To control the overall probability of claiming a significant advantage of gabapentin over placebo, these comparisons were to be made using Dunnet's procedure.

Disposition

Three hundred and thirty four patients of 411 screened for the study were randomized to a treatment group. One hundred fifteen patients were treated with gabapentin 1800 mg, 108 patients with gabapentin 2400 mg, and 111 patients with placebo. Disposition is detailed in Table 6.21. Patients in the gabapentin treatment groups were two to three times more likely to discontinue study participation early due to adverse events than placebo patients (13.0% and 17.6% for the 1800 mg/day and 2400 mg/day doses respectively, vs. 6.3% for placebo).

Table 6.21 Patient Disposition

	Placebo	Gabapentin 1800 mg	Gabapentin 2400 mg	Total
Screened				411
Withdrawn prior to randomization (n(%))				77 (18.7)
Did not meet entry criteria				52 (12.7)
Adverse Event				3 (0.7)
Other				22 (5.4)
Randomized (n(%))	111	115	108	334
Withdrawn from treatment (n(%))	17 (15.3)	22 (19.1)	23 (21.3)	62 (18.6)
Adverse event	7 (6.3)[a]	15 (13.0)	19 (17.6)	41 (12.2)
Lack of compliance	3 (2.7)[a]	2 (1.7)	1 (0.9)	6 (1.8)
Lack of efficacy	4 (3.6)	2 (1.7)	1 (0.9)	7 (2.1)
Other	3 (2.7)	3 (2.6)	2 (1.9)	8 (2.4)
Completed Treatment (n(%))	94 (84.7)	93 (80.9)	85 (78.7)	272 (81.4)

a One patient was reported by the investigator as withdrawing due to lack of compliance, but the adverse event pages indicated that an unrelated episode of "Back Pain" had precipitated withdrawal. For summary purposes this patient has been regarded as a withdrawal due to adverse events
Source: Sponsor's Table 5, Vol. 1.95, P. 22

Protocol Violations

Thirteen patients were randomized to treatment despite having a mean baseline pain score below the value of 4 specified in the inclusion criteria. However, 11 of these patients had scores over 3.5. There were four patients entered into the study with fewer than four days of sleep diary entries, including one patient with no baseline sleep scores, but all four of these patients had sufficient pain diary entries. Five patients from one center were administered the SF-36 after treatment was begun and were excluded from the analysis of that instrument.

Baseline Background and Demographic Characteristics

The three treatment groups were similar in demographic characteristics as detailed in Table 6.22.

Table 6.22 Patient Characteristics - Intent-to-treat Population

	Placebo	Gabapentin 1800 mg	Gabapentin 2400 mg
Sex, N (%)			
Men	46 (41.4)	46 (40.0)	46 (42.6)
Women	65 (58.6)	69 (60.0)	62 (57.4)
Age, Years			
N	111	115	108
Mean (SD)	72.8 (11.4)	73.3 (9.4)	74.1 (10.0)
Range	28.9,94.8	22.5,88.6	36.1,90.8
Weight, Kg			
N	110	112	106
Mean (SD)	68.8 (13.8)	68.9 (14.2)	73.2 (13.1)
Min - Max	34.8,115.0	42.0, 124.4	43.0,101.5

Source: Sponsor's Table 3, Vol. 1.95, P. 20

The characteristics of the patients' experiences with PHN were similar. The patients in the gabapentin 2400 mg group had a longer mean duration of PHN symptoms compared with the placebo, while the gabapentin 1800 mg group was a shorter mean duration. The prior treatment history was similar between groups with respect to the number and type of therapies tried.

Table 6.23 Background PHN Characteristics

	Placebo	Gabapentin 1800 mg	Gabapentin 2400 mg
Duration since resolution of acute infection, Years			
Mean (SD)	3.9 (4.6)	3.4 (3.8)	4.3 (5.3)
Median	2.4	2.2	2.3
Min, Max	0.1,28.4	0.2,19.4	0.1,31.6
Duration since diagnosis, Years			
Mean (SD)	3.9 (4.7)	3.3 (3.8)	4.5 (5.3)
Median	2.2	1.9	2.5
Min, Max	0.1,28.4	0.1,19.4	0.3,30.7
Number of previous drugs tried, N (%)			
Not known	1 (1)	3 (3)	1 (1)
0	1 (1)	0 (0)	0 (0)
1	17 (15)	17 (15)	14 (13)
2	23 (21)	32 (28)	20 (19)
3	38 (34)	28 (24)	40 (37)
4	13 (12)	11 (10)	14 (13)
5	6 (5)	13 (11)	10 (9)
6-10	10 (9)	10 (9)	9 (8)
>10	2 (2)	1 (1)	0 (0)
Drug categories tried, N(%)			
Anticonvulsant	62 (56)	69 (60)	72 (67)
Amitriptyline	79 (71)	83 (72)	83 (77)
Mild analgesics	102 (92)	107 (93)	100 (93)

Source: Sponsor's Table 4, Vol. 1.95, P. 21

The types of concomitant medications used during the trial were fairly similar between treatment groups. The four most frequently used concomitant medications used were amitriptyline, Aporex (dextropropoxyphene and paracetamol), Panadeine Co (codeine and paracetamol), paracetamol, and Paramol-118 (dihydrocodeine and paracetamol) as detailed in Table 6.24. Except for paracetamol, these medications were used by more patients in the gabapentin 2400 mg group than the other treatment groups with the largest between group differences occurring between gabapentin 2400 mg and placebo. The placebo group had the highest incidence of using no concurrent medications.

Table 6.24 Concomitant Medications

	Placebo	Gabapentin 1800 mg	Gabapentin 2400 mg
Amitriptyline	20.0%	27.2%	29.6%
Aporex	10.0%	12.3%	14.8%
Panadeine Co	14.5%	11.4%	13.9%
Paracetamol	40.9%	38.6%	38.0%
Paramol-118	2.7%	7.4%	7.5%
None	17.2%	15.8%	12.0%

Source: Sponsor's Appendix C.2, Vol. 1.95, P. 183

Titration and Dosing Results

All patients were titrated to the full dose of the randomized treatment arm assignment. One patient randomized to 1800 mg/day completed the study on 600 mg/day. One patient randomized to 2400 mg/d had dosage reductions to 1200 mg/d and finally 800 mg/d.

Table 6.25 Drug Exposure

	Placebo	Gabapentin 1800 mg	Gabapentin 2400 mg
Duration of treatment, days			
N	110[a]	114[a]	108
Mean (SD)	46.0 (10.8)	43.3 (14.8)	43.7 (14.5)
Median	49	50	50
Min, Max	1,61	2,57	1,63

a. dose stop date not recorded for one patient on placebo and one on 1800mg gabapentin
Source: Sponsor's Table 6, Vol. 1.95, P. 23

Efficacy Results

Primary Efficacy

The primary efficacy outcome measure was to be the mean weekly pain score at the end of treatment from the daily pain diary. The sponsor's ANCOVA results exhibited a non-normal distribution with a negative skew. As a result, the sponsor performed an analysis based on percent change, however, this did not fully resolve the non-normality, but reduced it to a level considered acceptable by the sponsor.

The results of the raw data are presented in Table 6.26. At the end of treatment, comparisons of gabapentin 1800 mg vs. placebo, and gabapentin 2400 mg vs. placebo

were statistically significant at $p<0.01$ (based on Dunnet's test) for weeks 1 through 7, and also when choosing End of Study. There were no statistically significant differences in baseline scores comparing either gabapentin group with placebo. There was no effect detected due to the cluster nor was there any interaction of cluster and treatment effect. There was also no baseline by treatment interaction.

Looking at the absolute change in pain score on the 11-point scale with 0 ="no pain" and 10 = "worst possible pain", from baseline to the end of the study, the gabapentin 2400 mg group had a change in mean pain score of 2.3, the gabapentin 1800 mg group a change of 2.2, and the placebo group a change of 1.1.

Table 6.26 Daily Pain Diary (raw data)

	Placebo	Gabapentin 1800 mg	Gabapentin 2400 mg
Baseline, N	111	115	108
Mean (SD)	6.4 (1.6)	6.5 (1.7)	6.5 (1.6)
Week 1, N	109	113	106
Mean (SD)	5.9 (2.0)[a]	5.1 (2.2)[a]	5.0 (1.8)[a]
Week 2, N	107	103	98
Mean (SD)	5.8 (2.0)[a]	4.7 (2.3)[a]	4.7 (2.1)[a]
Week 3, N	103	99	95
Mean (SD)	5.5 (2.2)[a]	4.4 (2.4)[a]	4.4 (2.1)[a]
Week 4, N	99	95	92
Mean (SD)	5.6 (2.1)[a]	4.4 (2.3)[a]	4.5 (2.2)[a]
Week 5, N	96	94	88
Mean (SD)	5.3 (2.3)[a]	4.4 (2.4)[a]	4.5 (2.0)[a]
Week 6, N	95	94	88
Mean (SD)	5.3 (2.3)[a]	4.3 (2.5)[a]	4.3 (2.0)[a]
Week 7, N	91	92	85
Mean (SD)	5.3 (2.4)[a]	4.1 (2.5)[a]	4.2 (2.0)[a]
End of study (LOCF), N	111	115	108
Mean (SD)	5.3 (2.3)[a]	4.3 (2.5)[a]	4.2 (2.1)[a]

a gabapentin vs. placebo, $p<0.01$
Source: Sponsor's Table 8, Vol. 1.95, P. 29

The percentage change from baseline of daily pain diary scores is presented in Table 6.27. The analyses of gabapentin 1800 mg vs. placebo and gabapentin 2400 mg vs. placebo at the end of treatment were statistically significant at $p\leq0.01$ (based on Dunnet's test, 2-sided). There was no effect due to the cluster, nor interaction of treatment and cluster. There was a statistically significant interaction of treatment and baseline ($p=0.04$). The sponsor's analysis suggests that this was a result of a number of patients in the gabapentin 1800 mg treatment group with baseline pain scores between 8 and 10 who responded poorly. The sponsor chose not to include this interaction in the primary statistical analysis.

The sponsor also compared the number of patients with a greater than 50% reduction in pain between the gabapentin treatment groups and placebo, as seen at the bottom of Table 6.27.

Table 6.27 Daily Pain Diary (percentage changes)

	Placebo	Gabapentin 1800 mg	Gabapentin 2400 mg
Week 1, N	109	113	106
Mean % change (SD)	-8 (18.3)[a]	-22 (23.9)[a]	-23 (20.9)[a]
Week 2, N	107	103	98
Mean % change (SD)	-9 (20.0)[a]	-27 (27.7)[a]	-29 (26.3)[a]
Week 3, N	103	99	95
Mean % change (SD)	-14 (23.9)[a]	-31 (29.9)[a]	-33 (28.6)[a]
Week 4, N	99	95	92
Mean % change (SD)	-14 (23.6)[a]	-32 (28.8)[a]	-31 (30.3)[a]
Week 5, N	96	94	88
Mean % change (SD)	-17 (25.7)[a]	-33 (29.7)[a]	-31 (26.6)[a]
Week 6, N	95	94	88
Mean % change (SD)	-17 (28.4)[a]	-34 (31.0)[a]	-34 (29.0)[a]
Week 7, N	91	92	85
Mean % change (SD)	-16 (30.5)[a]	-36 (31.5)[a]	-36 (28.0)[a]
End of study (LOCF), N	111	115	108
Mean % change (SD)	-16 (30.0)[a]	-35 (31.0)[a]	-35 (29.6)[a]
≥50% reduction			
N (%)	16 (14)[b]	37 (32)[b]	37 (34)[b]

a gabapentin vs. placebo, $p<0.01$
b gabapentin vs. placebo, $p = 0.001$
Source: Sponsor's Table 7, Vol. 1.95, P. 27

Secondary Efficacy Analyses

Although the sponsor refers to the first four of the following analyses as "supplemental" analyses, they are considered as secondary analyses in this review.

Analysis of Mean Pain Score for Each Week

As detailed in Table 6.27, comparisons of gabapentin 1800 mg vs. placebo, and gabapentin 2400 mg vs. placebo were statistically significant at $p<0.01$ (based on Dunnet's test) for all weeks except for Week 1 which was not statistically significantly different from placebo. There was no effect detected due to the cluster nor was there any interaction of cluster and treatment effect. There was also no baseline by treatment interaction.

Change of Weekly Mean Pain Score at Each Week.

All of the gabapentin 1800 mg vs. placebo and gabapentin 2400 mg vs. placebo comparisons were statistically significant at $p\leq0.01$ (based on Dunnet's test, 2-sided). There was no effect due to the cluster, nor interaction of treatment and cluster. There was a statistically significant interaction of treatment and baseline ($p=0.04$) as described above.

Effects of Age, Duration of Pain and Use of Tricyclic Antidepressants

The sponsor performed exploratory analyses on the effects of age, duration of PHN, duration by treatment, concurrent amitriptyline use, and amitriptyline by treatment. None of these analyses yielded statistically significant results.

Responder Analysis

A response to treatment was defined as achieving 50% reduction in mean pain score between baseline and the end of treatment. Patients withdrawing from the study due to lack of efficacy were classified as non-responders regardless of pain scores. The number of subjects with an at least 50% reduction in pain was similar in both gabapentin treatment groups, 37 (32%) for the 1800 mg group and 37 (34%) for the 2400 mg group. There were only 16 patients (14%) in the placebo group with a 50% or greater reduction in pain. The comparisons of each gabapentin group with placebo resulted in statistically significant differences (p=0.001, both comparisons).

Mean Weekly Sleep Interference Score

The analysis of the daily sleep interference diary data was considered appropriate for the originally proposed parametric analysis. The sleep interference scale was an 11 point Likert scale with 0 = "pain does not interfere with sleep" and 10 = " pain completely interferes with sleep." Baseline scores were similar between treatment groups, from 4.0 to 4.4. At the end of the study, there was a 0.8 point difference between the gabapentin treatment groups and placebo, which met the statistically significant criteria of a p-value of <0.01, but is of questionable clinical significance. The p-values were not adjusted for the multiple comparisons performed.

Table 6.28 Weekly Mean Sleep Interference Scores from Patient Daily Diary

	Placebo	Gabapentin 1800 mg	p-value vs. placebo [a]	Gabapentin 2400 mg	p-value vs. placebo [a]
Baseline, N	110	115		108	
Mean (SD)	4.0 (2.6)	4.0 (2.8)	Not sig.	4.4 (2.7)	Not sig.
Week 1, N	109	113		106	
Mean (SD)	3.6 (2.5)	2.8 (2.5)	p<0.01	2.9 (2.5)	p<0.05
Week 2, N	107	103		98	
Mean (SD)	3.3 (2.6)	2.6 (2.5)	p<0.05	2.4 (2.4)	p<0.01
Week 3, N	103	99		95	
Mean (SD)	3.1 (2.5)	2.4 (2.6)	p<0.05	2.1 (2.4)	p<0.01
Week 4, N	99	95		92	
Mean (SD)	3.1 (2.5)	2.2 (2.4)	p<0.05	2.1 (2.5)	p<0.01
Week 5, N	96	94		88	
Mean (SD)	3.1 (2.5)	2.2 (2.4)	p<0.05	2.2 (2.5)	p<0.01
Week 6, N	95	94		88	
Mean (SD)	3.1 (2.5)	2.2 (2.5)	p<0.05	2.1 (2.4)	p<0.01
Week 7, N	91	92		85	
Mean (SD)	3.2 (2.6)	2.0 (2.5)	p<0.01	2.1 (2.5)	p<0.01
End of study (LOCF), N		115		108	
Mean (SD)	3.1 (2.6)	2.3 (2.6)	p<0.01	2.3 (2.6)	p<0.01

a based on Dunnet's test

Source: Sponsor's Table 9, Vol. 1.95, P. 31

The Short Form-McGill Pain Questionnaire

The SF-MPQ was to be analyzed at Week 7 with randomization scores as a covariate. This instrument consists of pain descriptors analyzed as Total, Sensory and Affective scores, Present Pain Intensity (PPI) (0-5 scale), and Overall Pain Intensity by a 100 mm

VAS. These results are presented in Table 6.29. The results are patchy. Comparisons of the change from baseline to end of study between the gabapentin 1800 mg group and placebo demonstrated statistically significant differences for the Affective score, Total score, and VAS score (p=0.09, 0.04, and 0.06, respectively). For comparisons between the gabapentin 2400 mg group and placebo, there were statistically significant differences for the Sensory score, Total score, and VAS score (p=0.02, 0.02, and 0.01, respectively). No adjustments were made for the multiple comparisons.

The results for the pain descriptor scores fail to follow a consistent pattern calling into question whether comparisons with statistically significant differences contribute reliable information. The change in Sensory score reached statistical significance for the comparison of gabapentin 1800 mg and placebo, but not for the gabapentin 2400 mg and placebo comparison, while the change in Affective score reached statistical significance for the comparison of gabapentin 2400 mg and placebo but not for gabapentin 1800 mg and placebo. The change from baseline to the end of study for the Sensory score was -5.4 for the gabapentin 2400 mg group and -2.7 for the placebo group, on a scale of 0 to 33. The difference between treatment groups of 2.7 has little clinical relevance. Similarly, the change from baseline to end of study for the Affective score was -1.4 for the gabapentin 1800 mg group and -0.8 for the placebo group, on a scale of 0 to 12. The difference of 0.6 between treatment groups has little clinical relevance.

Even the difference in the change from baseline in the VAS between treatment groups was very small for both comparisons, a difference of 5 for the gabapentin 1800 mg to placebo comparison and 10 for the gabapentin 2400 mg to placebo comparison.

Table 6.29 The Short Form-McGill Pain Questionnaire

Score	Statistic	Placebo		Gabapentin 1800 mg		Gabapentin 2400 mg	
		Baseline	End of study	Baseline	End of study	Baseline	End of study
Sensory	N	111	106	115	105	108	95
	Mean (SD)	13.2 (5.8)	10.6 (6.9)	13.9 (6.1)	9.4 (6.5)	15.0 (6.7)	9.7 (6.3)
	Range						
	Change [a]	-2.7 (5.9)		-4.3 (6.0)		-5.4 (7.1)	
	p-value [b]			0.048		0.02	
Affective	N	111	106	115	105	108	95
	Mean (SD)	3.9 (2.8)	3.0 (3.3)	3.9 (3.1)	2.4 (2.9)	4.6 (3.0)	2.7 (2.7)
	Range						
	Change	-0.8 (3.1)		-1.4 (2.9)		-1.8 (3.2)	
	p-value			0.09		0.13	
Total	N	111	106	115	105	108	95
	Mean (SD)	17.1 (7.7)	13.7 (9.5)	17.8 (8.5)	11.9 (8.8)	19.6 (8.9)	12.5 (8.3)
	Range						
	Change	-3.5 (8.2)		-5.7 (7.8)		-7.2 (9.4)	
	p-value			0.04		0.02	
VAS	N	111	105	115	106	108	97
	Mean (SD)	68 (15)	54 (26)	67 (18)	47 (28)	70 (18)	46 (25)
	Range						
	Change	-14 (27)		-19 (25)		-24 (28)	
	p-value			0.06		0.01	
PPI	N	111	106	115	106	108	97
	Mean (SD)	2.4 (1.1)	2.0 (1.3)	2.5 (1.2)	1.9 (1.1)	2.7 (1.2)	1.9 (1.2)
	Range						
	Change	-0.4 (1.5)		-0.5 (1.2)		-0.9 (1.6)	
	p-value			0.51		0.22	

a. Negative change scores indicate improvement
b. Comparisons with placebo
Note: Ranges 0-33 for sensory score; 0-12 for affective score; 0-45 for total score; 0-100mm for VAS; 0-5 for PPI. Higher scores indicate more severe pain.
Source: Sponsor's Tables 10 and 11, Vol. 1.95, P. 33 and 34

Patient and Clinician Global Impression of Change

CGIC and PGIC were to be obtained at the final visit. The results are detailed below. The sponsor compared the number of patients with much improved and very much improved scores. For the patient rating, 41% of the gabapentin 1800 mg patients and 43% of the gabapentin 2400 mg patients compared to 23% of placebo patients rated themselves much improved or very much improved. The comparisons with placebo were statistically significantly different for both the gabapentin 1800 mg (p=0.003) and gabapentin 2400 mg (p=0.005) groups. The results were similar for the clinician ratings, with the comparisons of placebo to gabapentin 1800 mg (p=0.002) and gabapentin 2400 mg (p=0.001) groups.