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PART A: ASSESSMENT REPORT

1. TITLE

Generic name: Pregabalin

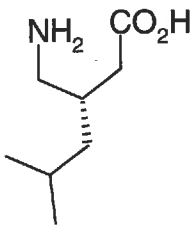
Trade name: Lyrica

Company making submission: Pfizer

Purpose of the application: Evaluation of an application to market Lyrica capsules for treatment of neuropathic pain in adults and as adjunctive therapy for patients (12 years of age or older) with partial seizures with or without secondary generalisation.

2. FORMULATIONS / INTENDED ROUTE OF ADMINISTRATION

Pregabalin is known chemically as (S)-3-(aminomethyl)-5-methylhexanoic acid and is structurally related to the naturally occurring amino acids L-leucine and ϒ-aminobutyric acid (GABA). Pregabalin and the anticonvulsant drug gabapentin are structural analogues and both are substrates of the system L neutral amino acid transporter in the CNS tissues. The molecular weight of pregabalin is 159.23, and the molecular formula is $C_8H_{17}NO_2$. The chemical structure of pregabalin is shown below:-



Although, the application states that the sponsor is seeking approval for 25, 50, 75, 100, 150, 200, 225 and 300mg capsules, the proposed PI mentions only 25, 50, 75, 150 and 300mg capsules for oral administration (the 100, 200 and 225mg capsules are not included). All strengths of pregabalin capsules, except 225mg were evaluated in clinical studies.

3. THERAPEUTIC INDICATIONS

The proposed indications of Lyrica (pregabalin) are (i) treatment of neuropathic pain in adults and (ii) as adjunctive treatment for patients (>12 years) with partial seizures, with or without secondary generalisation.

The proposed starting dose for both indications is 150mg/day in two divided doses, which may be increased, based on individual patient assessment of tolerability and efficacy, to a maximum recommended dose of 600mg/day, as two divided doses.

4. STATUS IN OTHER COUNTRIES

Marketing applications for Lyrica (pregabalin) have been submitted in USA, Europe and Canada and these applications are currently under evaluation.

No regulatory application has been withdrawn or rejected and this product has not received marketing approval in any country at the time of the present evaluation.

Pregabalin is the structural analogue of gabapentin; gabapentin has been approved in Australia and USA for treatment of refractory partial seizures (usual dose is 900 to 1800mg/day in three divided doses, max. dose 2400mg/day). It is also used for neuropathic pain (max dose 3600mg/day).

OVERVIEW OF THE CLINICAL STUDIES

All studies in this submission were well designed and executed and documentation of results was adequate; deviations from protocol were clearly presented, appropriately treated and objectively analysed. All studies received Institutional Ethics Board Approval and were carried out in accordance with guidelines for Good Clinical Practice (GCP) and the declaration of Helsinki.

Eleven placebo-controlled studies evaluated the efficacy of pregabalin in over 2500 patients with neuropathic pain due to diabetic peripheral neuropathy (n=1378) or post-herpetic neuralgia (n=1250). Five placebo-controlled studies evaluated efficacy of pregabalin in over 1000 patients with partial epilepsy, with or without secondary generalisation. Another 14 uncontrolled studies provided supportive evidence for efficacy in neuropathic pain and epilepsy. Safety data were provided from the above controlled and uncontrolled studies. An additional 19 special safety studies evaluated various safety aspects of pregabalin treatment.

6. PHARMACOLOGICAL EFFECTS AND MECHANISMS OF ACTION

Three studies, summarised in **Table 6.1 (p.45)**, examined the effect of pregabalin in combination with other agents on respiratory function, psychomotor and cognitive performance in healthy volunteers.

The interaction between ***oxycodone*** and pregabalin was studied in twelve healthy volunteers in a randomised, double-blind, placebo-controlled four-way crossover study (**Vol 24, 1000-078-0**). The four dosing periods were separated by washout periods of 7 days. Subjects received 300mg of pregabalin or a placebo every 12 hours for three doses with a single dose of either placebo or 10mg of oxycodone taken with the last dose of pregabalin. Cognitive and gross motor function was assessed using a variety of tasks including simple and choice reaction time, critical flicker fusion, visual tracking, numeric working memory, picture recognition, body sway and visual analogue scales of mood. These tasks were evaluated before the initial dose of each treatment and at 1, 2.5, 4, 6, 9, 12 and 24 hours after the last dose of each treatment. Tidal volume and respiratory rate were evaluated using a similar schedule but without the 9 and 12 hour evaluations. Blood samples were also collected for the determination of pregabalin and oxycodone kinetics. For the pharmacodynamic measurements, changes from baseline were analysed by analysis of variance. Pharmacokinetic parameters were compared by using an analysis of variance of the log transformed Cmax and AUC values and calculating the 90% confidence intervals for the ratio of treatment means. There were no statistically significant differences in the change from baseline of tidal volume or respiratory rate for the combination of pregabalin and oxycodone compared to the placebo-placebo combination or either drug taken with placebo. With respect to the cognitive and psychomotor evaluations some statistically significant decrements in performance relative to baseline were noted. The major finding was that pregabalin alone prolonged reaction times and times required for task completion by 20 to 100 msec. Oxycodone produced relatively few decrements in performance. When pregabalin was administered with oxycodone, decrements in performance were generally similar in magnitude to those produced by pregabalin alone; simple reaction time was increased by 16 to 48 msec between 1 and 24 hours post-treatment, choice reaction time was prolonged by 29 to 63 msec from 1 to 9 hours, speed and accuracy on digital vigilance and numeric working memory were decreased by up to 13% at various times post dose and body sway increased by about 15 units at 2.5 and 6 hours. Neither drug appeared to alter the pharmacokinetics of the other when taken in combination.

A similar four-way, double-blind, placebo-controlled, cross-over study was conducted in twelve healthy volunteers to evaluate the potential interaction between pregabalin and ***lorazepam*** (**Vol 21, 1008-076-0**). This study employed identical methodology to that used in the previous evaluation and included the same cognitive, psychomotor and respiratory parameters outcome measures. The dose of lorazepam employed was 1mg. As in the previous study, there was no evidence for an interaction effect based on pharmacokinetic data. Neither respiratory rate nor tidal volume measurements were affected by either drug alone or the combination of the two. No clinically important respiratory depression occurred in the study. On the other hand both pregabalin and lorazepam administered alone produced consistent decrements in performance on the following tasks: simple and choice reaction times, body sway and alertness. In general, lorazepam alone produced larger decrements than pregabalin. When co-administered, the deficits in performance were more extensive and of longer duration. For some variables the effects were synergistic, not merely additive. In particular, simple and choice reaction times as well as body sway up to 24 hours after the dose were all synergistically increased.

The final pharmacodynamic study also evaluated a potential interaction between pregabalin and ***ethanol*** **(Vol 17, 1008-079-0)**. This study also evaluated the effect in healthy volunteers using a randomised double-blind, placebo-controlled, four-way crossover study and the same dosing schedule for pregabalin as previously. The dose of ethanol was 0.7 g/kg administered 30 minutes after the doses of pregabalin or placebo. Respiratory function, psychomotor / cognitive tests and pharmacokinetics were evaluated as previously. There was no effect of either drug alone or in combination on respiratory function. Similarly there was no evidence of a pharmacokinetic interaction between the two drugs. Cognitive function was impaired by ethanol alone while pregabalin appeared to be without significant effects. Compared to ethanol alone, the combination of pregabalin and ethanol prolonged simple and choice reaction time by about 50 msec. The combination also had a greater effect than ethanol alone with regard to visual tracking and body sway between 1 and 2.5 hours post dose. Thus, pregabalin appeared to potentiate ethanol-related impairment of cognitive and gross motor function.

7. PHARMACOKINETICS

7.1 Absorption

Oral absorption of pregabalin after single or multiple doses was rapid and independent of the dose. After a single oral dose of 100mg in the fasting state, the mean Tmax was 0.62 hours (Vol 1, 1008-003). Similarly for subjects receiving a single dose of 300mg the mean Tmax was 1 hour (Vol 8, 1008-023). In the same subjects who continued to receive 300mg every 8 hours the Tmax after the last dose was 1.08 hours. The rate of absorption following administration of pregabalin as a solution and a capsule was 0.62h and 0.58h respectively (Vol 1, 1008-003). The extent of absorption in this study was identical for the two formulations. Based on urinary excretion data, the mean bioavailability of pregabalin capsules was >90%. A high fat meal was shown to reduce the rate of absorption of pregabalin but not to affect the extent of absorption (Vol 2, 1008-128). The mean Tmax was prolonged from 1.25h in the fasting state to 2.29h with the high fat meal. Similarly, mean Cmax was decreased from 3.47 to 2.6µg/ml in the fasting versus the fed state. Using a lower fat content meal, similar results were obtained (Vol 1, 1008-003). In a rising-dose study, pregabalin was administered as a single dose from 1 to 300mg to healthy volunteers (Vol 3, 1008-001). The time to maximum plasma concentration was shown to be independent of the dose (values ranged from 0.7 to 1.2 hours). Following multiple dose administration, mean Tmax (0.8 to 1.4 hours) was also independent of the dose (Vol 4, 1008-002; Vol 8, 1008-023).

7.2 Distribution

Pregabalin has an apparent volume of distribution similar to that of total body water. An apparent volume of distribution of 0.56 L/kg was determined after a single dose of 300mg of pregabalin in healthy volunteers (Vol 8, 1008-023). The same volunteers continued to receive pregabalin 300mg every 8hours for 28 days. After a further single dose on day 29 of the study the volume of distribution was ~0.6 L/kg. Population analysis of data from healthy controls and patients with epilepsy or pain disorders estimated a similar volume of distribution of 0.55 L/kg.

Pregabalin does not bind to any significant extent to rat, monkey or human plasma proteins at clinically relevant doses (RR-764-02316).

Partitioning between red blood cells and plasma was measured indirectly in a mass balance study in healthy volunteers (Vol 4, 1008-005). The mean RBC to plasma ratio was 0.76 and was independent of concentration and time after the dose.

7.3 Metabolism

The metabolic profile of pregabalin was determined in an open label, single dose study in six healthy male volunteers who each received 100mg of drug containing 107.9µCi of [^{14}C]-labelled compound (Vol 4, 1008-005). Blood samples were collected serially up to 60 hours and urine and faeces to 96 hours after the dose. Metabolic profiling of plasma and urine was performed by HPLC with radioactivity detection and

etabolites were identified by LC-MS. The mean cumulative urinary recovery of total radioactivity was 92.0% (± 8.7%) of the dose with <0.1% recovered in the faeces. The HPLC radioactivity profiling of plasma samples showed primarily unchanged pregabalin in the plasma while in the urine three radio-labelled compounds were indicated. The major component (89.9%) was identified as unchanged pregabalin. One of the two minor components (0.9%) was identified as an N-methylated derivative of pregabalin. The second minor component (0.4%) was not identified. Thus, pregabalin undergoes negligible metabolism in healthy volunteers, with urine as the primary route of elimination.

The lack of hepatic biotransformation is consistent with *in vitro* studies which showed no appreciable metabolism of [^{14}C]-labelled pregabalin by human liver cytosolic and microsomal preparations (RR-764-02235; RR-764-03070).

The ability of pregabalin to inhibit the major isoforms of CYP450 (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4) was examined using an *in vitro* study (RR-764-03016). There was no evidence for significant inhibition for any of the cytochrome P450 isoforms tested with pregabalin concentrations up to 1000µM.

7.4 Elimination

Pregabalin is almost exclusively renally excreted, with >90% of unchanged drug recovered in the urine. Following increasing single oral doses of pregabalin between 25 and 300mg in healthy volunteers, the renal clearance ranged from 67.0 to 80.9 ml/min (Vol 4, 1008-002-0). This corresponded to an elimination half-life of 5.5 to 6.6 hours. In an oral rising single dose study, the elimination half life of pregabalin ranged from 4.6 to 6.6 hours and was independent of the dose in the range 1 to 300mg (Vol 3, 1008-001). In a study examining the effect of renal dysfunction on pregabalin kinetics, clearance of the drug was correlated with creatinine clearance (Vol 9, 1008-049). In the six normal controls included in this study, renal clearance of pregabalin ranged from 53.4 to 91.5 ml/min and the plasma elimination half life from 4.5 to 12.3 hours.

7.5 Dose Proportionality of Kinetics

The proportionality of single dose kinetics was available from two studies. In a randomised, double-blind, two-way crossover, rising dose study the pharmacokinetics of pregabalin were determined after administration of solution and capsule in the range 1 to 300mg (Vol 3, 1008-001) **(Table 7.1, p.46)**. Mean values of Cmax ranged from 0.04 to 9.46µg/ml and for AUC $_{(0-\infty)}$ from 0.22 to 66.3µg.h/ml. Both were proportional to the dose of drug administered.

In a randomised, double-blind, placebo-controlled, parallel group, rising single and multiple dose study, pregabalin was administered to 57 healthy volunteers (Vol 4, 1008-002). A single dose of drug was administered on day 1 and kinetics determined up to 60 hours after the dose. Subjects then received pregabalin every 8 hours for 14 days with kinetics determined during a dosing interval. Doses were 25, 100, 250 or 300mg. After single doses, mean Cmax and $AUC_{(0-\infty)}$ values increased in proportion to the dose from 0.864 to 8.59µg/ml and from 5.63 to 71.4µg.h/ml, respectively. Similarly during multiple doses, Cmax and the $AUC_{(0-8)}$ values increased in proportion to the dose from 1.39 to 13.4µg/ml and from 6.67 to 67.4µg.h/ml respectively.

7.6 Repeated dose kinetics

The pharmacokinetics of pregabalin following repeated doses was examined in two studies conducted in healthy volunteers. In a randomised double-blind, placebo controlled, parallel group study, pregabalin was administered for 14 days (Vol 4, 1008-002). Subjects received 75, 300, 600 and 900mg/day as divided doses (every 8 or 12 h in the case of 600mg/day only). Serial plasma and urine specimens were collected up to 60h hours post-dose after a single morning dose on day 15. Pregabalin was rapidly absorbed, with a mean Cmax and AUC values being dose proportional (see section 7.5 above). Mean elimination half life ranged from 5.9 to 6.7 hours and was independent of the dose. Accumulation of plasma pregabalin concentrations after 8 and 12 hourly administration was consistent with the half life and predictable from single dose data. Observed average accumulation ratios were 1.62 to 1.76 after 8 hourly and 1.40 after 12 hourly administration. Steady

ate was achieved within 24 to 48 hours of dose initiation. The percentage of pregabalin recovered unchanged in the urine was 82.0 to 108% and was independent of dose.

Multiple dose kinetics were assessed in a double-blind, placebo-controlled study in 16 volunteers who received 900mg/day as a divided dose (300mg every 8 hours) for 28 days with a single 300mg dose on day 29 (Vol 8, 1008-023) **(Table 7.3, p.47)**. Kinetics was determined after the first (up to 8 hours) and last dose of drug (up to 48 hours). Pregabalin was rapidly absorbed, with mean Tmax values of ~1 hour. Plasma elimination half life was similar after single and multiple doses and ranged from 6.0 to 6.6 hours. The pharmacokinetic parameters determined in this study after 4 weeks administration were generally similar to those determined after two administrations in study 1008-002.

7.7 Pharmacokinetics in special populations

7.7.1 Renal impairment

The pharmacokinetics of pregabalin was evaluated in 12 subjects with severe renal impairment requiring haemodialysis (Vol 10, 1008-121-0). The study was conducted as an open-label, single dose evaluation in which each subject received 2 X 25mg capsules of pregabalin after an overnight fast. The dose of pregabalin was administered 24 hours before the beginning of the first scheduled 4-hour haemodialysis treatment. Plasma and urine specimens were collected serially up to 168h after the dose and dialysate samples were collected serially during each dialysis. Kinetic parameters were derived by non-compartmental methods and compared to those of subjects with severe renal impairment derived in another study. The mean t½ of 54.7 hours was substantially longer than that in subjects with normal renal function (ClCr >60ml/min) and those with severe renal failure (ClCr <30ml/min), where values were 9 and 28 hours respectively. During dialysis the mean t½ was 3 hours, reflecting a high pregabalin clearance by dialysis. The study is summarised in **Table 7.5 (p.49)**.

A second study to evaluate the effect of impaired renal function was conducted in 26 subjects with varying degrees of renal function as assessed by creatinine clearance (Vol 9, 1008-049). In this open-label, single dose study, subjects received 2 X 25mg capsules of pregabalin after an overnight fast. There were four groups: healthy controls (ClCr >80ml/min); mildly impaired (ClCr 51to 80 ml/min); moderately impaired (ClCr 30 to 50 ml/min); and severely impaired (ClCr <30ml/min, but not requiring dialysis). Kinetic parameters were determined by non-compartmental methods from plasma and urine specimens collected up to 168 h after the dose. Changes in pregabalin kinetic parameters tended to correlate with decreases in renal function. Tmax ranged from 0.5 to 4 hours and Cmax and AUC increased with decreasing renal function. Decreases in CL/F and CLr values correlated with decreasing values of creatinine clearance as shown by regression analysis (correlation coefficients ~ 0.89). Non-renal clearance accounted for only a minor route of elimination.

7.7.2 Impaired Hepatic Function

No studies were presented as the mass balance and *in vitro* studies showed that pregabalin is not hepatically metabolised to any significant extent.

7.7.3 Age and Gender

Pharmacokinetic parameters were assessed following single oral doses of 100mg of pregabalin in healthy, elderly Japanese subjects (1008-2J). A detailed report of this study was not available in the application only in the clinical summary. Pregabalin was administered in the fasted state to subjects with a mean age of 71 years. Compared to young non-Japanese and young Japanese subjects, there was a small mean increase in systemic exposure (~ 15-20%). This difference was likely to be related to decline in renal function with age.

7.7.4 Ethnicity

The single oral dose kinetics of pregabalin was evaluated in healthy Japanese male volunteers in a rising dose study (1008-1J). A detailed report of this study was not available in the application only in the clinical summary. Subjects received 50, 100, 200, 250 and 300mg of pregabalin under fasted conditions as well as 100mg in the fed state. It was reported that pharmacokinetic parameters in Japanese subjects were comparable to those observed in non-Japanese subjects receiving the same doses. Administration of the drug with food resulted in decreased Cmax and prolonged Tmax values without an effect on AUC.

3 Drug interaction studies

The potential for pregabalin to interact with other prescribed drugs was assessed in a series of studies summarised in **Table 7.6 (p.50)**.

The potential interaction between pregabalin and a series of **antiepileptic agents** was assessed in patients with epilepsy who were maintained on mono-therapy with various agents: ***lamotrigine***, ***carbamazepine, sodium valproate*** and ***phenytoin***. These studies were conducted as open, multiple dose evaluations in which pregabalin was administered as 2 X 100mg capsules every 8 hours for 7 days and a single dose on day 8. The number of patients studied was usually 12. Trough plasma samples for both drugs were collected on days 1, 2, 3, 4, 6, 7 and 8 of the study with additional trough samples collected on days 9 and 10 for the antiepileptic agents and serial samples for pregabalin kinetics to 48h after the last dose. Carbamazepine and carbamazepine epoxide plasma concentrations were not significantly altered by co-administration of pregabalin (Vol 12, 1008-019-0). The pharmacokinetic data for pregabalin compared to historical controls and the 90% confidence intervals for the ratio of Cmax and AUC were calculated. They were within accepted bioequivalence limits suggesting that no pharmacokinetic interaction took place. Lamotrigine was similarly evaluated with the trough concentrations of the drug affected by pregabalin co-administration (Vol 13, 1008-020). Compared to historical controls, there was some increase in systemic exposure to pregabalin, however this was not regarded as clinically significant. Phenytoin steady state plasma concentrations were not affected by 7 days co-administration with pregabalin (Vol 20, 1008-140). On the other hand, compared to retrospective control data both Cmax and Tmax were reduced by phenytoin co-administration. This effect was explained by the fact that study patients received the drug in the fed state but the historic controls were obtained in the fasted state. The magnitude of the effects observed was similar to that noted in the food effect studies. It was concluded that there was unlikely to be a clinically meaningful interaction effect. The differences in valproic acid plasma concentration prior to, during and after pregabalin administration differed by <11% suggesting that there was no substantial kinetic interaction effect (Vol 11, 1008-018; 1008-126). As previously seen, pregabalin kinetics were compared to retrospective control data and showed a modest elevation of systemic exposure to pregabalin. Given the nature of the comparison, it was concluded that there was no effect on pregabalin kinetics.

Two studies examined the interaction between pregabalin and ***gabapentin*** in healthy volunteers. An open label, randomised, three-way cross-over study was conducted in 12 healthy subjects who each received a single dose of 100mg pregabalin, 300mg gabapentin and the combination of both (Vol 16, 1008-077). Doses were administered after an overnight fast and separated by a 7-day washout period. Pharmacokinetic parameters were estimated using non-compartmental methods and results from ANOVA of log-transformed Cmax and AUC values were used to calculate 90% confidence intervals for the ratios of treatment means. For gabapentin, the mean Cmax and AUC values were ~10% lower when administered with pregabalin than when taken alone. Mean pregabalin Cmax was ~26% lower with gabapentin than when taken alone, while the AUC value was within acceptable limits for no interaction. The lack of effect of pregabalin on gabapentin kinetics in the single dose study was confirmed in a repeated dose evaluation in healthy volunteers (Vol 27, 1008-144-0). A total of 18 healthy volunteers were randomly assigned to receive pregabalin, gabapentin or the combination for three days each. Dosing periods were separated by a 7-day washout. For pregabalin the dose was 1 X 100mg every 8h on day 1, 2 X 100mg every 8 h on day 2 and a single AM dose of 2 X 100mg on day 3. Gabapentin followed a similar dosing schedule: 1 X 400mg every 8h on days 1 and 2 and a single AM dose of 1 X 400mg on day 3. In the third dosing period, subjects received the same individual drug schedules combined. Steady state kinetic parameters, ratios and 90% confidence intervals were calculated as before. For gabapentin there was no effect of pregabalin on the Cmax and AUC values, the 90% confidence intervals being in the 80-125% range. establishing a lack of interaction. While Cmax for pregabalin was lowered by 18% by gabapentin co-administration, the AUC was within accepted bioequivalence limits. It was concluded that there was no kinetic interaction between these two drugs at steady state.

The effect of pregabalin on the pharmacokinetics of the ***oral contraceptive pill*** was evaluated in healthy female volunteers over three menstrual cycles in an open-label, multiple dose study (Vol 14, 1008-075). Ortho-Novum 1/35 tablet was administered orally once daily for the first 21 days of each of the three menstrual cycles. In the third menstrual cycle, subjects also received 2 X 100mg capsules of pregabalin every 8 hours for the first 22 days. Plasma samples were collected serially for 48h after the last dose of contraceptive in the second and third menstrual cycles. Ethinyl oestradiol and norethindrone concentrations

ere measured by GC-MS and trough levels of pregabalin determined throughout the study. Progesterone concentrations were measured during the middle to late luteal phase of the cycles as a marker of the suppression of ovulation; these did not exceed 2.1 ng/ml in any of the cycles suggesting that ovulation did not occur, even in the presence of pregabalin. Cmax, Tmax and AUC for both ethinyl oestradiol and norethindrone were not significantly altered by pregabalin co-administration, suggesting the absence of an interaction.

7.9 Bioavailability and bioequivalence studies

The relative bioavailability of pregabalin capsules compared to a solution was evaluated in healthy volunteers (Vol 1, 1008-003) **(Table 7.7, p.52)**. The study was an open-label, three-way, crossover design with a 7-day washout between doses. Each subject received a single 100mg dose of pregabalin as a capsule in the fasted and fed state and as a solution in the fasted state. A total of 11 subjects completed the study. Capsules and solution were bioequivalent in the fasted state based on the 90% confidence intervals for the ratio of Cmax and AUC. Food delayed the absorption of pregabalin as assessed by Tmax (0.62 h fasted v 3.2 h fed) while Cmax was also reduced (3.8µg/ml fasted v 2.6µg/ml fed). On the other hand, systemic exposure as assessed by AUC was not affected (26.7 µg.h /ml fasted v 25.4 µg.h /ml fed).

The effect of food on the pharmacokinetics of a market image capsule was assessed in healthy volunteers using an open-label, single dose, two-way, cross-over study (Vol 2, 1008-128). Subjects received 1 X 150mg capsule following an overnight fast or on completion of a high fat breakfast. Pharmacokinetic parameters were estimated using non-compartmental methods and compared using log transformed values for Cmax and AUC by ANOVA. The results were used to calculate the 90% confidence intervals for the ratios. A total of 14 subjects completed the study. The absorption of pregabalin was slower following a high fat meal than in the fasted state (Tmax 2.29 v 1.25h) while Cmax was also reduced by the meal (2.6 v 3.47µg/ml). On the other hand, AUC was not affected significantly (27.3 µg.h /ml fasted v 25.5µg.h /ml fed) and the 90% confidence intervals were within accepted limits (0.91 to 0.95).

7.10 Population pharmacokinetic studies

Population pharmacokinetic analyses used pregabalin concentration-time data from 5 clinical pharmacology studies and 19 phase II/III studies in patients with epilepsy, pain disorders and generalised anxiety disorder. All analyses were conducted using nonlinear mixed effects modelling (NONMEM software). The effects of the following covariates on pregabalin Cl/F were investigated: patient category, gender, age, race, hormonal status and dosing regime (bd versus tds) (Vol 31, RR-754-00013). The full dataset contained information on dosing, plasma concentration-time data and covariate information and comprised 6137 data points from 2276 subjects. The initial model was a one-compartment model described in terms of total oral clearance (Cl/F) and volume of distribution (Vd/F), with first order rate constant (ka) and lag time to describe absorption. Dose was expressed on a milligram basis. Inter-subject variability on all kinetic parameters was described using an exponential error model and residual variability was modelled using a combined proportional/additive model. Covariates were incorporated into the model one at a time. The final model incorporating the covariates showed:

1. Gender: Vd/F for females was slightly lower than for males;
2. Body Weight: Vd/F is proportional to weight;
3. Meal status: absorption is greater for the fasted than fed state;
4. Creatinine clearance: Cl/F is proportional to creatinine clearance.

A population kinetic analysis was performed to examine the effects of co-administration of seven antiepileptic agents (carbamazepine, lamotrigine, phenobarbital, phenytoin, tiagabine, topiramate and valproate) on pregabalin kinetics (Vol 28, RR-03298; Vol 29, RR-764-03771). There was no apparent effect of these seven drugs on the clearance of pregabalin. Subject compliance was confirmed by plasma monitoring. Similarly, the effect of pregabalin on the kinetics of the antiepileptic agents was also investigated using population kinetics (Vol 32, RR-764-03729). From this evaluation, pregabalin appeared to have no significant effect on carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate and valproic acid kinetics. On the other hand tiagabine clearance appeared to be increased by pregabalin.

The effect of co-administration of oral hypoglycaemics, diuretics and insulin on pregabalin kinetics was assessed with population kinetic modelling (Vol 28, RR-764-03296). The dataset included adult subjects with pain syndromes, four studies in healthy controls and one study in renally impaired subjects. The same information as previously was included in the model. Concomitant administration of these agents with pregabalin changed mean pregabalin oral clearance by less than 10% when compared to patients not using these medications. It was concluded that there was no clinically relevant effect on pregabalin clearance.

7.11 Exposure-response analysis

An exposure-response analysis was conducted using the data from 5 diabetic neuropathy studies and 4 post-herpetic neuralgia studies (Vol 32, RR-754-00011). A dataset which included subject identification, daily pain scores, pregabalin dose and demographic data was created. A subject specific random effects model was used to characterise the relationship between daily pain score and pregabalin exposure in individual patients, taking into account placebo effects. Covariates for age, gender, body weight, race, ClCr, average baseline pain score, disease and dose regimen were investigated in the model. A total of 1761 patients provided 68,247 pain score observations. A nonlinear, mixed effect, logistic regression model was used to fit the responses. The model was used to predict mean daily pain scores and to describe temporal aspects of the model. The model suggested that the pregabalin effect was rapid and durable with a half-life of drug-effect onset of 16.3h. Overall treatment effect steady state was achieved within 9 to 12 weeks. The pregabalin effect increased over the dose range 75 to 600mg/day. The ED_{50} was approximately 400mg/day. Average baseline pain scores had a substantial effect on endpoint mean change from baseline pain: scores >6.43 (median of dataset) had a mean endpoint change ≥ 1point lower than for patients with scores <6.43, for 300 and 600 mg/day.

7.12 Summary of Pharmacological Studies

- ***In combination with alcohol, oxycodone or lorazepam, pregabalin potentiated effects on respiratory function.***
- ***Pregabalin alone prolonged reaction times and times required for psychomotor and cognitive task completion, by 20 to 100msec.***
- ***Combined with alcohol, lorazepam or oxycodone, pregabalin tended to prolong the effects on simple and choice reaction times of these agents taken alone.***
- ***Pregabalin was rapidly absorbed following oral doses in the fasting state.***
- ***Food tended to delay the rate, but not the extent of absorption.***
- ***Pregabalin has a total distribution similar to that of total body water, the apparent volume of distribution being about 0.55L/kg.***
- ***Pregabalin is not extensively metabolised by the liver, with >90% of drug recovered unchanged in urine.***
- ***Pregabalin does not bind to any significant extent to human plasma proteins at clinically relevant doses.***
- ***There was no evidence for significant inhibition of any cytochrome P450 isoforms by pregabalin.***
- ***Pregabalin is almost exclusively renally excreted.***
- ***Renal clearance was ~70.0ml/min, corresponding to an elimination half-life of ~6 hours.***
- ***Pregabalin pharmacokinetics is proportional to the dose of drug administered.***
- ***Accumulation of plasma pregabalin concentrations after repeated doses was consistent with the half life and predictable from single dose data.***
- ***Steady state plasma levels are achieved after 3 to 4 doses.***
- ***The dose of pregabalin should be adjusted for creatinine clearance in subjects with impaired renal function.***
- ***Pregabalin clearance was reduced with aging but there did not appear to be an effect of ethnicity.***

There did not appear to be any pharmacokinetic interactions between pregabalin and phenytoin, gabapentin, sodium valproate, carbamazepine, lamotrigine or an oral contraceptive preparation.

- ***A population kinetic analysis suggested an effect of gender and body weight on Vd.***
- ***The population kinetic analysis suggested that drug clearance was proportional to creatinine clearance.***
- ***A non-linear, mixed effect, logistic regression model suggested that the pregabalin effect was rapid and durable with a half-life of drug-effect onset of 16.3h.***
- ***Treatment effect on pain at steady state was achieved within 9 to 12 weeks.***
- ***The pregabalin analgesic effect increased over the dose range 75 to 600mg/day.***

8. EFFICACY

8.1 Preamble

Pregabalin was evaluated in over 2500 patients for the treatment of neuropathic pain and in over 1600 patients as add-on treatment for partial epilepsy in 14 placebo-controlled studies. Uncontrolled, extension, long-term studies were conducted for both neuropathic pain and epilepsy studies. The clinical studies included bd and tds dosing regimens. The earlier studies in the pain program used tds dosing regimens and later pain studies used bd dosing. The epilepsy studies used both bd and tds dosing regimens throughout the clinical program.

8.2 Efficacy in neuropathic pain

Two models of neuropathic pain were evaluated in the clinical trials, i.e diabetic peripheral neuropathy (DPN) and post-herpetic neuralgia (PHN). Eleven randomised, placebo-controlled studies (**DPN** studies **014, 029, 040, 131, 149, 173** and **PHN** studies **030, 045, 127, 132** and **196**) evaluated the efficacy of pregabalin in over 2500 patients, of whom 1831 were randomised to treatment with pregabalin and received at least one dose of pregabalin (979 in the DPN studies and 852 in the PHN studies). Studies **132** (PHN) and **173** (DPN) terminated early due to restrictions instituted by regulatory authorities in light of findings of haemangiosarcoma in mouse studies; hence, data from these studies provided only supportive evidence of efficacy (see also section 9.7.4, p.33 of the present report). Two Japanese studies in patients with PHN **(1008-3J, Vol.125)** and trigeminal neuralgia **(1008-4J, Vol.126)** were also terminated early and did not provide any definitive evidence of efficacy. **There were no direct comparisons between pregabalin and the other approved treatments for neuropathic pain such as gabapentin, tricyclic antidepressants, anticonvulsants or opiates; furthermore, the use of pregabalin in combination with other analgesics for neuropathic pain was not evaluated.**

8.2.1 Study design and patient population

All the neuropathic pain studies had a 1-week baseline phase (for screening of eligibility) followed by a 5 to 13 week double-blind treatment phase. All eligible patients were randomised to pregabalin or placebo except in study **040 (Table 8.3, p.55),** where patients were randomised to placebo, pregabalin or amitryptiline. In the majority of studies, pregabalin doses were titrated over the first 2 to 12 days and titration schedules varied with each study. Doses were not titrated in studies **030, 040** and **131**; only the 600mg/day dose was titrated in study **029**. Patients remained at a fixed dose for the remainder of the double-blind phase. Study **040** had an additional 1-week withdrawal phase. In studies **149, 127** and **196**, patients randomised to the 300/600mg/day pregabalin group received either 300 or 600mg based on their estimated creatinine clearance (CLcr<60ml/min received 300mg/day and CLcr>60ml/min received 600mg/day).

The **diabetic peripheral neuropathy (DPN)** studies included male or non-pregnant, non-lactating female patients with painful, diabetic, distal, symmetrical, sensiromotor polyneuropathy of 1 to 5 years duration, with HbA_{1c} <11%. The patient had to complete at least 4 daily pain diary entries during baseline, with a mean pain score ≥4 over the 7-day baseline period. The other main inclusion criterion was a pain rating of at least 40mm on the 0 to 100mm visual analog scale (VAS) of the Short-form McGill Pain Questionaire (SF-MPQ). Patients were excluded if they had not responded previously to gabapentin treatment; however, the

tocol for DPN study **149** was modified to remove this exclusion criterion and, in the PHN study **196**, this was not an exclusion criterion. Patients were also excluded if they had severe non-neuropathic pain or clinically significant or unstable medical or psychological conditions that may confound the interpretation of response to pregabalin. Patients were also required to discontinue all analgesic medications (including NSAIDs, narcotics and tramadol) prior to baseline and antidepressants were prohibited (except selective serotonin reuptake inhibitors). However, aspirin (upto 325mg/day) for myocardial infarction and stroke prophylaxis and paracetamol (up to six 500mg tablets/day) were allowed. In study **149 (Table 8.5, p.57),** there were many patients who reported prior (within 30 days) or concurrent use of prohibited neuropathic pain medications such as anti-depressants (10%), anti-convulsants (18%), opiates (11%) or NSAIDs (22% took NSAIDS other than paracetemol), but their intake was similar across the treatment groups. As changes in glycaemic control could affect the symptomatology of diabetic neuropathy, each patient's antidiabetic medication was stabilised prior to initiation of the study medication and was maintained for the duration of the study. **Use of other therapeutic measures such as physiotherapy, psychotherapy and acupuncture in the different treatment groups was not documented.** The majority of the 1378 patients in the DPN studies were male (58%) and Caucasian (92%) with type 2 diabetes mellitus (88%), with a mean age of 57-60 years. The mean duration of diabetes was approximately 10 years. At baseline, most patients had a mean pain score of 6-6.5, the VAS ranging from 69 to 80mm and present pain intensity (PPI) score of 2.2 to 3. Almost 95% of the patients were on some anti-diabetic medications (oral hypoglycaemics or insulin). Aspirin, cholesterol-lowering, anti-hypertensive drugs and vitamins were the other most frequently used prior and concomitant medications. The estimated mean creatinine clearance in the DPN population was 98.8ml/min (31 to 268ml/min); studies **149** and **173** enrolled patients with low creatinine clearance (>30 but ≤60ml/min).

The **post-herpetic neuralgia (PHN)** studies included male or female patients with post-herpetic neuralgia present for more than 3 months after healing of the herpes zoster rash. The patients had to complete at least 4 daily pain diary entries during baseline, with a mean pain score ≥4 pain rating and VAS pain score of at least 40mm (SF-MPQ) over the 7-day baseline period. The exclusion criteria were similar to those in the DPN studies, except for the fact that concomitant administration of non-narcotic analgesics, narcotic analgesics (eg opioids), NSAIDS and antidepressants was allowed, provided a stable regimen was in place prior to randomisation and was continued for the duration of the study. However, phenothiazines, anti-arrhythmics, macrolides, anti-histamines, medications used commonly for PHN (tramadol, benzodiazepines, skeletal muscle relaxants, steroids, capsaicin, mexiletine, dextromethorphan), and antiepileptics were prohibited and an adequate washout period was allowed for patients taking these medications prior to study entry. The majority of the 1250 patients in the PHN studies were females (52%) and Caucasian (97%), with a mean age of 71-72 years. Approximately 44.5% of PHN patients were ≥75 years of age. The mean estimated creatinine clearance was 69.7ml/min (23 to 201ml/min). All 5 controlled PHN studies enrolled patients with CLCr>30ml/min, and studies **127, 132** and **196** stratified patients with low CLCr (>30 but ≤60ml/min) for treatment with pregabalin doses <600mg/day. The duration of post-herpetic neuralgia showed wide variations in all PHN studies (range from 3 to 267 months, median of 19-30 months), except study **030 (Table 8.6, p.58),** where it ranged between 26-37 months (median=32months). **Baseline demographics, disease characteristics and concomitant medications were similar across treatment groups in all DPN and PHN studies.**

At baseline, most patients had a mean pain score of 6-6.5, visual analogue scale (VAS) ranging from 69 to 80mm and present pain intensity (PPI) score of 2.2 to 3.

8.2.2 Efficacy endpoints and statistical considerations

The primary efficacy parameter in all the neuropathic pain studies was pain as recorded by the patient in a daily diary. The diary consisted of an 11-point Likert-type scale ranging from 0 (no pain) to 10 (worst possible pain). Upon awakening, patients characterised their pain during the previous 24-hours by circling the appropriate number on the scale.

The secondary efficacy parameters in most of the studies were:-

- sleep interference determined from the daily sleep diary, which utilised an 11-point Likert scale (0=did not interfere with sleep, 10=unable to sleep due to pain).
- Short-Form McGill Pain Questionaire (SF-MPQ), comprised of 3 sections. These were (1) pain descriptors, which provided a sensory, affective and total score: patient rated intensity of each type of pain over the past week on a 4-point intensity scale (0=none, 1=mild, 2=moderate, 3=severe).

Sensory score was the sum of responses to the first 11 pain descriptors: throbbing, shooting, stabbing, sharp, cramping, gnawing, hot-burning, aching, heavy, tender, and splitting. [1] The affective score was the sum of responses to the last 4 pain descriptors: tiring-exhausting, sickening, fearful and punishing-cruel. Total score was sensory and affective scores combined[2].; (2) visual analog scale (VAS): patient rating from 0 (no pain) to 100mm (worst possible pain) and (3) Present Pain intensity (PPI) scale, an overall 6-point pain intensity rating scale: 0=no pain, 1=mild, 2=discomforting, 3=distressing, 4=horrible, 5=excruciating).

- Clinical (CGIC) and Patient Global Impression of Change (PGIC) to assess the status of change ranging from 1 (very much improved) to 7 (very much worse).
- SF-36: Quality of life questionnaire (SF-36-QOL), a self-administered 36-item questionnaire that measures 8 health concepts or domains including physical functioning, role limitations caused by physical and emotional problems, social functioning, bodily pain, mental health, vitality and general health perception. For all domains, a higher score indicated a better quality of life.

The sleep interference diary and the SF-MCQ were assessed at each study visit. All the other secondary efficacy parameters were assessed at randomisation and at termination. The impact on quality of life was also assessed using the EuroQOL EQ-5D[3] in studies 149 and 196. Effect on mood was assessed using the Profile of Mood states (POMS)[4] in two DPN (029 and 131) and two PHN studies (030 and 127). The DPN study 029 assessed mood using the Hospital anxiety and depression scale (HADS). Furthermore, studies 149, 127 and 196 also explored the effects of pregabalin on different aspects of sleep using the Medical Outcomes Study (MOS) sleep scale[5]. Studies 149 and 196 also evaluated the effects of pregabalin on the signs and symptoms of allodynia and hyperalgesia.

The sample size in all DPN and PHN studies was adequate and had 90% power to detect a difference of 1.3 in the endpoint weekly mean pain scores between high dose of pregabalin and placebo, assuming 2-sided testing at the 0.025 level. Mean pain scores, SF-MPQ scores, mean sleep interference scores, POMS scales, and SF-36 domains were analysed using an analysis of covariance (ANCOVA), with baseline as the covariate. If the primary efficacy parameter did not show a normal distribution (tested using the Shapiro-Wilks test), the ANCOVA was also performed using the rank-transformed data. PGIC, CGIC and responder rates were analysed using the Cochran-Mantel-Haenszel (CMH) test, adjusting for study centres. Primary and secondary efficacy analyses were done with the ITT population, except in study **149**, where the modified ITT (MITT) population was used for all efficacy analyses- these included all randomised patients who had received at least one dose of study medication and who had not withdrawn due to Ministry of Health/Ethics committee decisions. For most studies, per protocol analyses were not done as there were few serious protocol violations. However, the European studies **(040, 045, 149** and **196)** did perform a per protocol efficacy analysis, results of which confirmed the efficacy results in the ITT population.

8.2.3 Efficacy in diabetic peripheral neuropathy (DPN)

8.2.3.1 Primary efficacy (mean pain score at endpoint)

Pregabalin showed statistically significant relief from neuropathic pain in terms of the mean endpoint pain scores in 4 of the 5 completed DPN studies (studies **014, 029, 131** and **149**). Pregabalin 300mg/day had a

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[1] The throbbing, shooting, stabbing, sharp, hot-burning, aching, tender, and tiring-exhausting pain descriptors were chosen by at least 75% of the patients in each treatment group at randomisation, suggesting that these pain descriptors are characteristic of painful diabetic peripheral neuropathy. In the PHN studies, most of the pain descriptors were chosen by at least 50% of all patients at baseline, while the sharp, aching and tender descriptors were chosen by at least 75% of patients in each treatment group at baseline.

[2] Pregabalin studies conducted in Europe, South Africa and Australia (studies 040, 045, 149 and 196) used multiple language-specific versions of the SF-MCQ, using descriptors of pain specific to those languages [(eg. in English, the sensory score of SF-MCQ includes 11 items (for a range of 0 to 33), while in French, the sensory score includes 8 items (for a range of 0-24)]. Hence, the results of the sensory, affective and total scores of SF-MCQ were valid within a language, but were not comparable across languages in studies 040, 045, 149 and 196.

[3] EQ-5D is a patient-completed instrument designed to assess the impact of QOL in 5 domains: mobility, usual activities, pain/discomfort and anxiety/depression, combined into a single index value rated from 0 (worst imaginable health) to 100 (best imaginable health).

[4] POMS comprised of 65 mood descriptors and asked the patient to assess how each applied to him/her using a scale of 0 (not at all) to 4 (extremely). These items were added together to yield scores for 6 scales (tension-anxiety, depression-dejection, anger-hostility, vigour-activity, fatigue-inertia and confusion-bewilderment) as well an overall score of total mood disturbance. A lower score indicated an improvement for all mood states, except vigour-activity

[5] MOS sleep scale is a patient-completed questionnaire consisting of 12 items assessing the various characteristics of sleep such as sleep disturbance, snoring, awaken short of breath, quantity of sleep, optimal sleep, sleep adequacy and somnolence.

tistically significantly better mean pain score compared to placebo in two of the 3 studies which tested that dose (studies **029** and **131**). Three of the 4 studies which tested the 600mg/day dose of pregabalin showed statistically significantly greater efficacy compared to placebo (**014, 029** and **149**). The 75mg/day (study **029**) and 150mg/day doses (studies **014** and **149**) of pregabalin were not effective. In study **040**, pregabalin 600mg/day failed to show any statistically significant efficacy over placebo; however, in the same study, amitryptiline 75mg/day showed a statistically significant improvement over placebo in mean endpoint pain score **(Table 8.12, p.64).** Although the study was not designed to compare the two active treatments (pregabalin vs amitryptiline), amitryptiline did show a trend towards better efficacy compared to pregabalin.

It should be noted that diabetic patients in 4 of the 5 DPN studies were required to have normal creatinine clearance (>60ml/min). However, DPN patients with diabetes of >10 years duration may have associated mild renal dysfunction and the reduced CLcr may increase exposure to pregabalin. Hence, a lower starting dose of 150mg/day may be justified in all DPN patients. The onset of significant pain relief was during the first two weeks of pregabalin treatment and was maintained for the duration of the pivotal DPN studies, i.e., for 5 to 12 weeks.

8.2.3.2 Secondary efficacy analysis

The proportion of responders (showing >50% reduction in mean endpoint pain score) was significantly greater ($p \leq 0.0006$) with pregabalin (39-48% with 600mg/day and 33-46% with 300mg/day), compared with placebo (15-30%), **(Table 8.13, p.65).**

Across the DPN studies, the VAS **(Table 8.14, p.66)** and PPI scores **(Table 8.15, p.67)** improved significantly at pregabalin doses of 300 and 600mg/day. In study **149**, pregabalin 150 and 300mg/day significantly reduced the PPI scores, despite lack of significant effect on the primary efficacy endpoint **(Table 8.15, p.67)**. In DPN studies **014** and **029**, approximately 23-27% of the patients had no pain (according to PPI scores) at endpoint, compared to 10% in the placebo group. Similar details about numbers of patients without pain at endpoint were not provided for the other DPN studies. In DPN studies, where the pain descriptor data could be analysed, pregabalin (at doses of 300 and 600mg/day) was significantly ($p<0.006$) more effective than placebo at improving endpoint SF-MCQ sensory **(Table 8.16.1, p.68)**, affective **(Table 8.16.2, p.69)** and total scores **(Table 8.16.3, p.70).** Pregabalin (>300mg/day) had the greatest effect on 3 of the 4 affective descriptors (sickening, fearful, and punishing-cruel), reducing the percentage of patients who reported each of those at endpoint to less than half the percentage reported at randomisation.

Pregabalin 300 and 600mg/day produced statistically significantly greater reduction in sleep interference scores, compared to placebo (except the 300mg dose in study 149 which produced reductions which only approached statistical significance, $p=0.084$) **(Table 8.17, p.71);** improvement in sleep was observed during the first week of pregabalin treatment and was maintained throughout the duration of the studies. In study **149**, some aspects of sleep (sleep disturbance, quantity of sleep and overall sleep problem index) showed more favourable results for the pregabalin treatment groups (but only sleep adequacy was statistically significantly better than placebo). In all DPN studies, the patient's global impression of change (PGIC) scores for patients receiving pregabalin 300mg/day (except study 149) and 600mg/day (except study 040) were statistically significantly better than those of placebo. Approximately 65-88% of patients treated with 300 or 600mg/day pregabalin showed improvement of the PGIC, compared with approximately 40-66% of placebo patients. Similar results were observed for the CGIC scores.

The 75 and 150mg/day doses of pregabalin failed to produce significant improvements in any of the secondary efficacy endpoints (except the significant improvement in PPI scores with 150mg/day pregabalin in study **149, Table 8.15, p.67**).

In all DPN studies, the bodily pain subscale of the SF-36 improved significantly more for pregabalin-treated patients than for placebo (except study 149) at doses ranging from 150 to 600mg/day. Significant improvement over placebo were also observed in the social functioning, mental health and general health perception subscales with the higher doses of pragabalin (300 and 600mg/day) **(Table 8.18.1, p.72).** Pregabalin did not show any consistent improvements in mood; the POMS showed statistically significant improvement in the tension-anxiety and total mood disturbance subscales with 300mg/day **(029 and 131),**

at the 600mg/day dose failed to show significant improvement over placebo in any of the POMS subscales (study **029**). However, the 600mg/day dose of pregabalin showed significant improvement in the anxiety subscale of the HADS in DPN study **040**.

In study **029**, 44% of patients from the 600mg/day pregabalin group with allodynia at baseline had no allodynia at termination, compared to 35% from the 300mg/day group, 26% from the 75mg/day group and 25% from the placebo group.

As the study endpoint of pain was subjective, the high incidence of dizziness (15% with pregabalin 300/600mg vs. 2% with placebo) and somnolence (8% with pregabalin 300/600mg vs. 1% with placebo) in study 149 (**Table 8.5, p.57**), may have resulted in "unblinding" of the study, biasing the results of the efficacy analysis. Hence, an additional analysis was done in patients who reported dizziness or somnolence in study **149.** When the primary analysis of endpoint mean pain scores was repeated after using the baseline mean pain score for patients who did not complete the study or removing patients who reported dizziness or somnolence, none of the pregabalin treatment groups were statistically significantly different from placebo. In contrast, when a similar analysis was done for gabapentin, efficacy was confirmed in DPN patients after exclusion of patients with dizziness/ somnolence (M. Backonja, et al, 1998). **These results could mean that inclusion of patients who experienced dizziness and somnolence may have been responsible for the overall efficacy seen in the trial. Similar efficacy analyses were not done for the other pivotal neuropathic pain studies.**

An additional analysis was performed in study **149** to compare patients with similar plasma concentrations of pregabalin to patients who received placebo, i.e., patients with low CLcr (30-60ml/min) who received 150mg/day were pooled with patients with normal CLcr (>60ml/min) who received 300mg/day to form the 300mg/day adjusted dose group. Likewise, the 600mg/day adjusted dose group consisted of patients with low CLcr who received 300mg/day and those with CLcr>60ml/min, who received 600mg/day. **This analysis showed that only patients with plasma concentrations equivalent to a 600mg/day dose (not 300mg/day) in patients with normal renal function showed statistically significant improvement in mean pain scores compared to placebo (page 90 of Vol.40).**

8.2.4 Efficacy in post-herpetic neuralgia (PHN)

8.2.4.1 Primary efficacy analysis in PHN

In the pivotal PHN studies **(045, 127** and **196, Tables 8.7, 8.8, 8.9, pp.59-61),** pregabalin doses >300mg/day showed statistically significant greater reductions in endpoint mean pain scores compared with placebo **(Table 8.12, p.64).** Study **030 (Table 8.6, p.58)** showed that 75mg/day is a sub-therapeutic dose. The 150mg/day dose of pregabalin showed statistically significant greater pain relief in two of the three pivotal studies, which evaluated this dose **(045** and **196) (Table 8.12, p.64).** The size of the treatment effect was consistent across the 4 pivotal PHN studies.

8.2.4.2 Secondary efficacy analysis in PHN

The proportion of responders (showing >50% reduction in mean endpoint pain score) was significantly greater ($p \leq 0.0006$) with pregabalin doses of 300 to 600mg/day (27-50%), compared with placebo (10-20%). The 150mg/day dose also had more responders (22-25%) compared to placebo (10-17%), but the difference was statistically significant in only 2 studies **(045** and **196) (Table 8.13, p.65).**

In the PHN studies, statistically significant improvements in VAS scores were observed at all pregabalin doses >300mg/day and for the 150mg/day dose group in 1 of the 3 PHN studies **(045) (Table 8.14, p.66).** Pregabalin 300/600mg/day also showed statistically significant improvements in PPI scores (**127** and **196, Table 8.15, p.67).**

Pregabalin was effective in 1 of the 2 PHN studies, where pain descriptor data could be analysed. In study 127, pregabalin (300/600mg/day) showed significant improvement in the SF-MCQ sensory, affective and total scores ($p<0.0047$ vs placebo) **(Tables 8.16.1, 8.16.2, 8.16.3, pp.68-70).** Pregabalin 300/600mg/day had the greatest effect on 2 of the 4 affective descriptors (fearful and punishing-cruel), reducing the percentage who reported each of those at endpoint to less than half the percentage reported at baseline. Pregabalin

300mg/day) also showed statistically significant reduction in sleep interference scores in the PHN studies 045, 127 and 196 **(Table 8.17, p.71).** Unlike the DPN studies, the 150mg/day dose of pregabalin also produced statistically significant reduction in sleep interference scores ($p<0.0007$ vs placebo) in 2 of the 3 PHN studies and the reduction approached statistical significance in the third study (030, $p=0.082$ vs placebo). Pregabalin 300/600mg produced statistically significant improvement in all aspects of sleep (all MOS subscales), except somnolence in study 127 and produced non-significant, but favourable results in study 196. In all PHN studies, 48-84% of pregabalin (>300mg/day) patients showed improvement in PGIC compared with 26-36% of placebo patients; the 150mg/day dose of pregabalin showed significant improvement over placebo in only one study **(196).** Similar results were observed for the CGIC scores. The SF-36 bodily pain subscale improved significantly with pregabalin at doses >300mg/day **(Table 8.18.2, p.72).** Compared to placebo, pregabalin 75/150mg/day **(030)** or 300/600mg/day **(127)** failed to show any significant improvement in any of the subscales of POMS. However, in study 045 **(Table 8.7, p.59),** pregabalin 300mg/day showed significant improvement in the self-rating Zung depression scale.

8.2.5 Effect of pregabalin on hyperalgesia and allodynia in neuropathic pain studies

Hyperalgesia was assessed in 7 of the placebo-controlled neuropathic pain studies (DPN studies 029, 131 and 149 and PHN studies 030, 045, 127 and 196). The baseline incidence of hyperalgesia was slightly higher in the PHN studies (66%) compared to the DPN studies (54%). Approximately 20% of the DPN patients (compared to 15% of placebo patients) and 30% of the PHN patients (vs 19% of placebo patients) in the 300 and 600mg/day pregabalin groups had relief of hyperalgesia at study endpoint **(Tables 8.19.1, 8.19.2, p.73).** At baseline, allodynia was twice as prevalent in the PHN studies (62%) compared to the DPN studies (30%). Over 33% of DPN patients had relief of allodynia following treatment with pregabalin 600mg/day, compared to 21% of patients treated with placebo. Thirty-five percent of PHN patients treated with pregabalin 600mg/day had relief of allodynia compared to 19% of placebo patients **(Tables 8.20.1, 8.20.2, p.74).**

8.2.6 Dose-response, dose interval time course and efficacy in subgroups

When data from all 9 placebo-controlled, pivotal neuropathic pain studies was combined, the proportion of responders (showing >50% reduction in pain) increased over the effective dose range of 150 to 600mg/day (18%, 21%, 26%, 34% and 45% with placebo, pregabalin 75mg, 150mg, 300mg and 600mg/day, respectively) **(Table 8.21.1, p.75).** The proportion of patients with any reduction in pain from baseline, including complete pain relief, increased with dose across the effective dose range of pregabalin 150 to 600mg/day **(Table 8.21.2, p.75);** 24 patients (5%) treated with pregabalin 600mg/day showed total relief from pain (compared to 0.9% with placebo). Additional evidence for dose-response across the effective dose range of 150-600mg/day was seen in the combined PGIC results from the 9 pivotal placebo-controlled neuropathic pain studies **(Table 8.21.3, p.75).** The proportion of patients describing themselves as much/very much improved increased with dose of pregabalin (24%, 27%, 32%, 41% and 54% with placebo, 75mg, 150mg, 300mg and 600mg/day pregabalin, respectively).

Dosing tds was evaluated in 7 pivotal studies (014, 029, 040, 131, 030, 045 and 127). Pregabalin 150mg/day was effective in 1 of 3 studies, in which it was studied (PHN study 045) and pregabalin 300 and 600mg/day were effective in 5 of the 6 studies in which these doses were studied; an exception was the DPN study 040, in which 600mg/day was not statistically significantly better than placebo **(Table 8.3, p.55).**

Dosing bd was evaluated in 4 studies, 2 completed pivotal studies (149 and 196) and 2 uncompleted studies (132 and 173). In DPN study **149 (Table 8.5, p.57),** efficacy was demonstrated for the 300/600mg/day pregabalin dose given bd and in PHN study **196 (Table 8.9, p.61),** bd dosing with all doses of pregabalin (150, 300, and 300/600mg/day) showed significant efficacy. In DPN study 132 and PHN study 173, bd dosing with pregabalin 150, 300, 300/600mg/day produced statistically significantly greater pain relief than placebo at the 5 week endpoint **(Table 8.22, p.76).**

Additional *post hoc* analysis were done to establish onset of significant pain relief. This was done by an analysis of the daily pain scores during first 2 weeks in the 7 pivotal neuropathic pain studies (014, 029, 045, 127, 131, 149 and 196). In groups of patients receiving pregabalin 300mg/day starting on day 1, statistically significant reduction of pain was seen within the first day of treatment. In the remaining treatment groups, where initial doses ranged from 75 to 150mg/day, reduction of pain was generally seen within the first 3 days. There were no patients started at doses higher than 300mg/day on day 1. ***Overall, statistically significant reduction in pain scores was observed within 3 days of starting pregabalin treatment and***

...icacy was sustained throughout **(RR-MEMO 720-30220, Module 5, Vol. 76) (Tables 8.22a-8.22p, pp.76-86** and **Figures 8.1-8.8, pp.39-42).**

The primary efficacy of pregabalin was not affected by gender, race or menopausal status. However, there was a trend towards better efficacy with increasing age; this was most likely due to the reduced CLcr observed in older patients as there was no significant effect of age on efficacy of pregabalin after controlling for baseline CLcr.

8.2.7 Supportive evidence for efficacy of pregabalin in neuropathic pain

8.2.7.1 Data from uncompleted placebo-controlled studies

In the uncompleted studies **(132** and **173, Tables 8.10, 8.11, p.62),** 363 patients were randomised and took at least 1 dose of study medication. Although these were 12-week studies, only 9 patients (2 patients in study 132 and 7 patients in study 173) completed the study and most patients received ≤3 weeks of study medication. Although the results were consistent with results from the pivotal completed studies, the small numbers of patients and variable exposure to pregabalin in each treatment group confounds interpretation **(Table 8.22, p.76).**

8.2.7.2 Uncontrolled neuropathic pain studies

Patients in the 11 placebo-controlled neuropathic pain studies had the option of receiving pregabalin treatment in long-term, open-label, follow-on studies. The majority of these open-label studies used tds dosing **(Tables 8.24-8.26, p.90-92);** however, studies **165** and **198** used bd dosing regimens **(Table 8.27, p.93).** Overall, 1862 patients enrolled in the open-label studies and 656 patients were treated with pregabalin for at least 420 days. In these studies, patients were allowed to adjust their dose within the range of 75 to 600mg/day, the most commonly selected pregabalin doses being 300 to 450mg/day. Approximately 64% of the patients enrolled in the open-label studies withdrew, the most common reason being "other" (which includes study terminated by the sponsors), followed by adverse events (16%) and lack of efficacy (9%). Although these studies were mainly designed to evaluate long-term safety of pregabalin, efficacy was also assessed in terms of the SF-MCQ VAS pain scale. Overall, the endpoint score remained 17 to 37mm lower than baseline **(Table 8.23, p.89).** Results from study **174 (Module 5, Vol. 67)** were not included as it was terminated early (only 9 patients were treated for ≤26 days). Furthermore, study **183 (Module 5, Vol. 69),** which was designed to evaluate safety in patients with cervical radiculopathy (extension of study 060) was also terminated early (only 5 patients treated for 3 weeks). Study **197 (Table 8.26, p.92)** studied efficacy and safety of pregabalin (150-600mg/day) in 106 patients with neuropathic pain (due to DPN, PHN and fibromyalgia), which was refractory to treatment with gabapentin, tricyclic antidepressants or other third line neuropathic pain medications such as anti-convulsants, opioids, etc. Pregabalin (150-600mg/day, given tds) produced reductions in sensory, affective and total scores (SF-MCQ) and also reduced the VAS (by 25mm) and PPI scores from baseline in this subgroup of patients **(Table 8.26, p.92).**

In open label studies **061, 074 (Table 8.24, p.90), 197 (Table 8.26, p.92), 165** and **198 (Table 8.27, p.93),** all Australian patients were required to undergo a mandatory drug holiday (minimum duration of 3 days) after every 3 months of treatment - patients who relapsed (pain categorised as worsened moderately, much or very much) during the drug holiday period were allowed to restart pregabalin treatment for an additional 3 month period. This was done to make sure that the pain relief was due to efficacy of the study drugs. Patients who did not relapse (pain categorised as not worsened at all or a little worse) within 28 days of beginning the drug holiday were terminated from the study. Most of the patients who went on drug holidays showed relapse of pain (95-100%)

8.2.8 Efficacy in other neuropathic studies

Both flexible (150-600mg/day) and fixed dosing (600mg/day) with pregabalin was equally effective (study **155, Table 8.28.1, p.94).** The onset of efficacy was from the first week in the fixed-dose pregabalin group and from the second week in the flexible-dose pregabalin group. The primary efficacy results were supported by significant improvements in terms of responder analysis, SF-MCQ-VAS, PPI scores, PGIC scores, sleep interference (significantly better than placebo for first 6 weeks only), sleep disturbance and overall sleep index subscales of MOS. There were fewer withdrawals due to lack of efficacy in the pregabalin groups **(Table 8.28.2, p.94)** and SF-MCQ sensory, affective and total scores failed to show significant improvement

/er placebo (these were analysed only in English in 68 patients). Compared to placebo, both pregablin groups did not reduce the incidence of allodynia or hyperalgesia in PHN and DPN patients and did not show any significant improvement in SF-36 or EQ-5D QOL scores (except improved mental health in SF-36 with flexible dose pregabalin). However, this study showed that gradual titration (flexible dose group) would enhance pregabalin's tolerability compared to forced titration (fixed dose group), which was shown by a lower incidence of AEs (68.8% and 74.2% with flexible and fixed dose, respectively) and fewer withdrawals due to AEs (17% and 25%, respectively) **(Table 8.28.1, p.94).**

Study 160 (Module 5, Vol. 52) was designed as a 4-week, placebo-controlled study to evaluate the effect of pregabalin 300mg/day (vs that of alpazolam 0.5mg/day) on sleep quality and sleep architecture. However, early termination of this study did not permit adequate efficacy analysis (only 19 patients were randomised and only 5 completed the study). Study **060 (Module 5, Vol. 53)** was also terminated early and did not enable investigation of the effect of pregabalin on time to relapse of chronic cervical radiculopathy over the 5-week double-blind phase. The safety profile in studies 160 and 060 was similar to that of other pregabalin studies.

8.3 Efficacy in partial seizures

8.3.1 Introduction

Three pivotal, phase III, placebo-controlled studies **(009, 011** and **034, Tables 8.29-8.31, p.95-97)** evaluated the efficacy of 12 weeks adjunctive treatment with pregabalin in 1052 patients with medically uncontrolled partial seizures. Another phase II study **007 (Table 8.32, p.98),** explored the role of pregabalin as monotherapy in patients undergoing presurgical evaluation for refractory partial seizures. There were no specific controlled studies investigating monotherapy or conversion to monotherapy. Another study designed to investigate the effects of a longer titration period (study **145, Vol.60)** was terminated early (only 3 patients treated for $\leq$2 weeks).

8.3.2 Study design and patient population

Three pivotal, phase III, randomised, double-blind, placebo-controlled, parallel group studies evaluated the efficacy of pregabalin as add-on treatment in 1052 patients with medically uncontrolled partial seizures. Study **009 (Table 8.29, p.95)** compared pregabalin 600mg/day administered twice or thrice daily with placebo. Study **011 (Table 8.30, p.96)** compared two doses of pregabalin (150 and 600mg/day) administered tds, while study **034 (Table 8.31, p.97)** evaluated 4 doses of pregabalin (50, 150, 300 and 600mg/day) administered bd.

Each pivotal study had 3 main phases: (1) an eight–week baseline phase in which all patients maintained their concurrent anti-convulsant therapies and recorded their seizures in a daily diary, (2) a 12-week double-blind phase, in which patients were assigned to add-on therapy with either pregabalin or placebo. In studies 009 and 011, doses of pregabalin were titrated to their full dose over one week, while pregabalin doses were not titrated in study 034 (patients received their full study dose on day 1) and (3) patients who withdrew early or completed the double-blind phase had the option of either entering the follow-on, open-label study or discontinuing treatment over 6 days, in a blinded fashion. Patients were also evaluated for safety, 2 to 4 weeks after the final dose of study medication.

Eligible patients had a diagnosis of epilepsy with partial seizures (simple partial, complex partial, and/or secondarily generalised tonic-clonic), as defined in the International League against Epilepsy Classification of Seizures along with an EEG within the preceding 2 years consistent with the diagnosis of focal-onset epilepsy. Additionally, patients were to have a minimum of 3 seizures during the 1 month prior to screening and a minimum of 6 partial seizures during the 8-week baseline period, with no 4-week seizure-free period. At screening, patients had to be on 1 to 3 standard anti-convulsant drugs at doses within a clinically acceptable therapeutic range and within the range of tolerability for the patient. Furthermore, a history of being refractory to at least 2 marketed anti-convulsants at maximum tolerated doses was required for inclusion. Patients with a history of haematologic, cardiovascular, renal, hepatic or significant psychiatric disorders were excluded. Furthermore, patients with absence seizures, treatable causes of seizures (identified aetiologies including metabolic, neoplastic or active infectious origin), Lennox-Gastaut syndrome, progressive neurologic or systemic disorders or status epilepticus (within the previous year) were also excluded.

A total of 1056 patients were randomised in the 3 pivotal studies, but 1 patient randomised to placebo and 3 to pregabalin did not take study medication and the ITT population comprised 1052 patients (758 treated with pregabalin and 294 treated with placebo). Overall, the majority of patients in the pivotal studies were Caucasian (87%). There were comparable numbers of male (n=520) and female (n=532) patients and the mean age was 37-39 years (ranging from 12 to 75 years). Within each pivotal study, the treatment groups had similar demographics. The CLcr ranged from 39 to 297ml/min, with a mean >100ml/min. The mean duration of epilepsy was approximately 25 years and the most common seizure type for all treatment groups were complex partial seizures (50%). The 28-day baseline seizure rates showed a wide range from 6 to 350; the median 28-day baseline seizure rates were approximately 10, while the mean was 21-25, with no significant differences between the pregabalin and placebo groups. Approximately half of the patients were taking 2 anti-convulsants at baseline; 18% to 29% of pregabalin and 16% to 31% of placebo patients were taking 3 at baseline. Overall, carbamezepine (56%) and lamotrigine (28%) were the most common concurrent anti-convulsants. Others commonly used were phenytoin sodium (19%), topiramate (19%), valproate (14%), tiagabine (9%), phenytoin (8%) and phenobarbital (8%). There were no significant differences between the treatment groups in the distribution of concurrent anti-convulsants.

8.3.3 Efficacy parameters and statistical considerations

The primary criterion to establish the efficacy of pregabalin was the reduction in the frequency of all partial seizures, standardised over a 28-day period. The seizures were recorded by the patient, a family member, caregiver or legal guardian and documented in a daily seizure diary. As the amount of diary data and the duration of time in the double-blind period of the study varied from patient to patient, the 28-day seizure rate was defined as follows:

$$\text{28 day seizure rate} = \frac{\text{\# of partial seizures in period}}{[\text{\# of days in period} - \text{\# of missing diary days in period}]}$$

The primary efficacy endpoint was the response ratio (RRatio or symmetrized percent change), a comparison of baseline seizure frequency (B) with treatment seizure frequency (T). The RRatio is calculated by dividing the difference between 28 day seizure rates during treatment and baseline by the sum of baseline and treatment seizures:

$$\text{RRatio} = \frac{T-B}{T+B} \times 100$$

The RRatio is always between 100 and -100. Negative values for the RRatio indicate a reduction in seizures, with an RRatio of –33 being equivalent to a 50% reduction in seizures from baseline.

Secondary efficacy parameters were the responder rate (defined as the percent of patients who had at least a 50% reduction in 28-day seizure rate during treatment compared to baseline) and the percent change in 28-day seizure frequency during treatment compared with baseline. Additional secondary parameters assessed by descriptive statistics were the length of seizure-free intervals and number of seizure-free days per 28-day period; RRatio, responder rate and percent change for each seizure type were also evaluated. The impact of pregabalin add-on therapy on the patient's health-related quality of life (HRQOL) were also assessed using the following patient-rated instruments: QOL in epilepsy scale (QOLIE-31), Mastery scale, Headache pain scale, treatment satisfaction and compliance scale and QOL change scale.

The sample size was based on the RRatio and the responder rate of previous add-on studies with gabapentin. Sample size in the pregabalin studies was adequate to detect a 12-point difference in RRatio or a 20% difference in responder rate between pregabalin and placebo (80% power, α=0.05, 2 –sided). The primary efficacy analysis was performed on the ITT population using an analysis of variance (ANOVA) model with treatment and cluster (which is a single centre of at least 18 randomised patients or an aggregation of centres located in the same country or region) as main effects. Analysis of the responder rate was performed using the Cochran-Mantel-Haenszel (CMH) chi-square test, adjusting for cluster to test for a treatment difference. An *ad hoc* analysis of the patients who were seizure-free during their last 28, 42, 56 and 70 days of double-blind treatment was also performed. The primary and secondary efficacy analyses were also done on the evaluable population, defined as all patients who were randomised to study medication and received 28 days

of study medication who had a minimum of 28 days of evaluable seizure diary data within both the baseline and the double-blind phase.

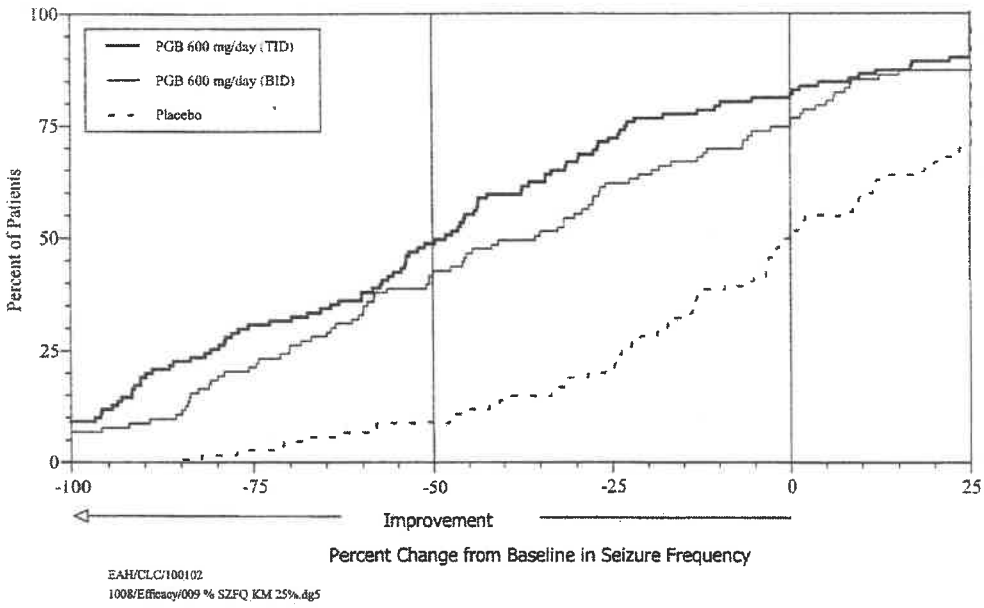
8.3.4 Efficacy results in pivotal studies

Pregabalin 150-600mg/day produced statistically significant reduction ($p \leq 0.001$) in seizure frequency (RRatio was -11 to -20 with pregabalin 150mg/day, -28 with 300mg/day, -31 to -37 with 600mg/day, and +0.6 to -3.6 with placebo). Both bd and tds dosing with pregabalin produced similar significant improvements over placebo. The 50mg/day dose of pregabalin was sub-therapeutic. Pregabalin demonstrated robust and consistent reduction in RRatio at doses of 150, 300 and 600mg/day in all 3 pivotal studies **(Table 8.33.1, p.99).** The efficacy analyses in the evaluable population were similar to the analyses in the ITT population **(Table 8.33.2, p.99).**

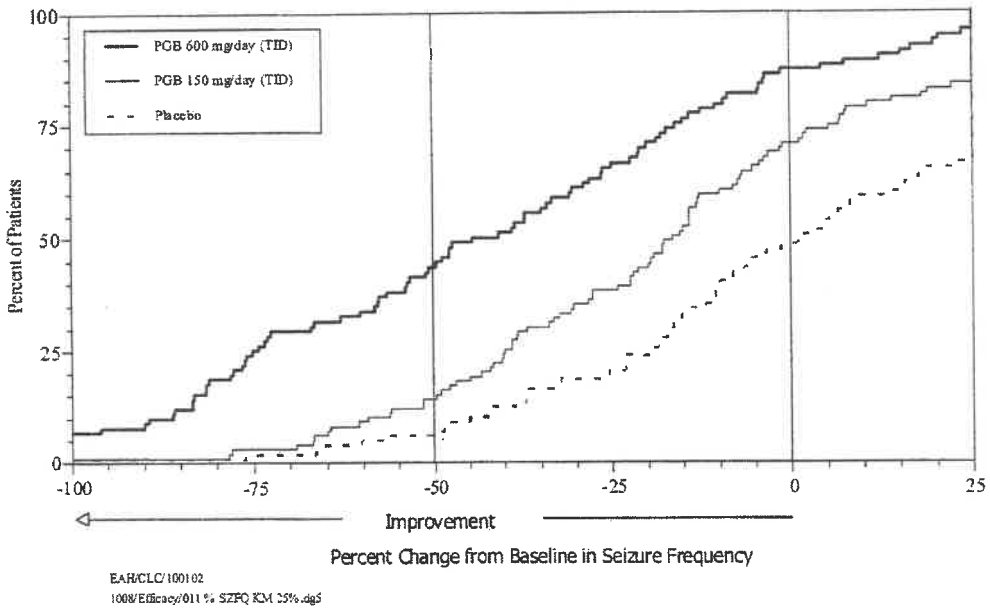
Across all 3 studies, the responder rate (>50% reduction in seizure rate from baseline) was stastistically significantly greater ($p \leq 0.001$) with pregabalin 150 to 600mg/day, with the exception of the 150mg/day dose from study **011**, which approached statistical significance ($p=0.087$). Approximately 40 to 51% of patients treated with pregabalin doses ≥300mg/day were responders, compared to 6 to 14% of the placebo patients **(Table 8.34, p.100).**

Compared with placebo, the median percent change from baseline in seizure frequency (defined as percent change in 28 day seizure frequency during treatment compared with baseline) was greater for the pregabalin (150-600mg/day) treatment groups, i.e a 17-51% reduction compared to ≤1% with placebo **(Table 8.35, p.100).** The number of patients showing at least 25%, 50 % or 75% reduction in seizure frequency were consistently greater with pregabalin (150-600mg/day) compared with placebo. Cumulative distribution plots of percent change for the 3 pivotal studies are shown in the following figures:

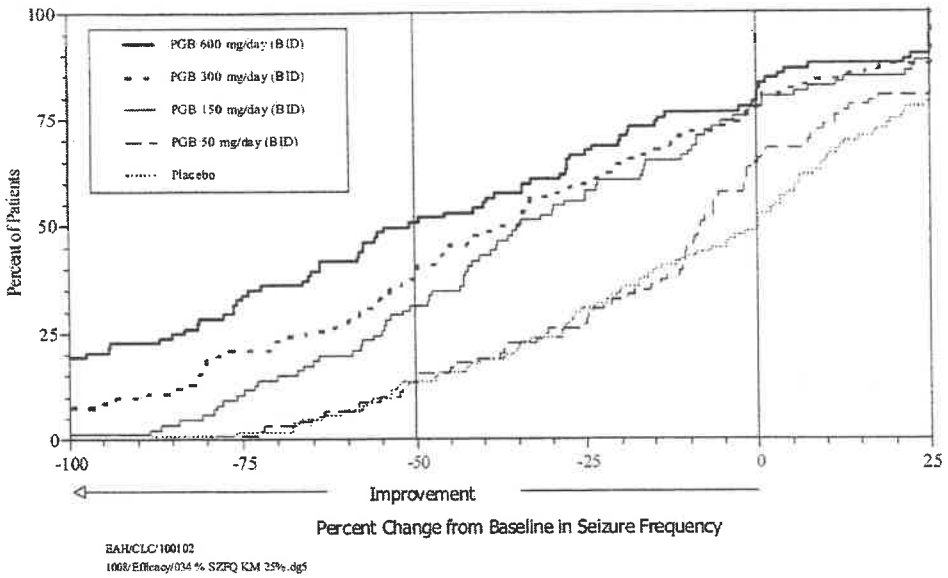
Cumulative Distribution Plot - Study 009



Cumulative Distribution Plot - Study 011



Cumulative Distribution Plot - Study 034



Results from studies **011** and **034** showed a statistically significant dose response in the RRatio and responder rate ($p<0.001$). Furthermore, the percentage of patients with clinically meaningful increase in seizure frequency (>25% increase from baseline) was greater in the placebo-treated patients (21-33%) compared to those treated with pregabalin (4-16%) **(Table 8.36, p.101)**.

The 150 and 300mg/day doses of pregabalin showed consistently better RRatio and responder rates than placebo in reducing the frequency of complex partial and combined seizures (simple and complex partial seizures), but were not effective in reducing simple partial or secondarily generalised tonic-clonic (SGTC) seizure frequency. Only pregabalin 600mg/day produced statistically significant reductions in frequency of all seizure types including SGTC **(Tables 8.37.1, 8.37.2, p.102).**

In studies 009 and 011, statistically significantly more patients ($p<0.01$) in the pregabalin 600mg/day (tds) dose groups (12-14%) were seizure-free in the last 28 days compared to placebo groups (1-3%). In study 034, more patients in the pregabalin 600mg/day (bd) group were seizure-free during the last 28 days compared to placebo (17% vs 8%, $p=0.076$) **(Table 8.38, p.103).** The effective doses of pregabalin (150, 300

...d 600mg/day) showed significant reduction in seizures (RRatio) during the first week of double-blind treatment; these effects were maintained for 12 weeks with pregabalin (600mg/day) in all 3 studies, but were not maintained consistently with the lower doses of pregabalin (150 and 300mg/day) in studies 011 and 034.

A *post hoc* analysis to determine the onset of pregabalin efficacy as add-on treatment in patients with partial seizures from all 3 pivotal studies was also done (RR-MEMO 720-30109, Module 5, Vol.76). The proportion of patients free of partial seizures on each study day for the pregabalin (150-600mg/day pooled) and placebo groups was compared. A statistically significant difference in favour of pregabalin was observed, starting with study day 2, and this was maintained for the entire 12-week duration of the study ($p<0.05$).

Two *post hoc* analyses were also conducted to assess the effect of pregabalin on SGTC seizures. Of the 1052 patients in the 3 pivotal studies, 409 (39%) had at least 1 SGTC seizure during the baseline and/or double-blind phase. These 409 patients were used for the primary RRatio analysis of SGTC (ANOVA using rank-transformed RRatio) to determine if pregabalin was effective in reducing the absolute frequency of SGTC seizures; pregabalin >300mg/day showed statistically significant reduction ($p=0.005$) in SGTC seizure frequency compared with placebo (median=-41% vs -6%, $p=0.0047$) **(Table 8.39.1, p.104)**.

As recommended by the FDA, a conditional analysis of whether pregabalin reduces the probability of suffering an SGTC seizure in the aftermath of a partial seizure was also investigated. This conditional risk of an SGTC was measured by the proportion of SGTC to all partial seizures during the double-blind treatment phase, compared to the baseline phase. The same SGTC population was used for this analysis; however, 16 of these patients became seizure-free during the double-blind period and the double-blind proportion remained undefined and hence these 16 patients were excluded entirely from the analysis. It should be noted that 14 of these 16 patients were in the pregabalin 600mg/day group. Pregabalin did not show any consistent treatment-related or statistically significant reduction in the proportion of the SGTC to all partial seizure rate **(Table 8.39.2, p.105)**. The percentage of patients with a decrease in the proportion of SGTC seizures was 49-58% in the placebo groups and it was 50-63% in the pregabalin 600mg/day groups. However, it should be noted that the conditional analysis was limited by the fact that it does not consider the actual magnitude of change of the seizure rates between the baseline and double-blind phases and is also confounded by the fact that the patients who became seizure-free and in effect responded well to pregabalin treatment, were excluded from this analysis due to mathematical considerations.

8.3.5 Efficacy results in subgroups

For subset analysis, efficacy data across studies and effective doses were pooled and stratified by age, race, gender and menopausal status. The difference from placebo in mean RRatio always favoured pregabalin and was comparable among the subgroups by age, gender, race and menopausal status **(Table 8.40, p.106).** **In study 009, pregabalin 600mg/day (given tds) showed slightly better efficacy and tolerability compared to bd dosing. However, a greater number of patients in the pregabalin bd group received 3 anti-convulsant drugs (30%) compared to the pregabalin tds (15.3%) or placebo (16.3%) groups; hence, the pregabalin bd group appeared to have more severe epilepsy requiring 3 anti-convulsants. This may have confounded the results and resulted in the trend favouring tds dosing. Although the other pivotal studies did not have head-to-head comparison of bd vs tds dosing, they showed comparable efficacy with pregabalin 150 to 600mg/day, given bd (011) or tds (034).**

8.3.6 Long-term efficacy and tolerance

Patients from study 007 and from the 3 pivotal studies **(009, 011** and **034)** were eligible to enter open-label, long-term studies **(008, 010, 012** and **035,** respectively) **(Table 8.38, p.103).** New patients were also allowed entry into the open-label studies 010, 012 and 035. The main efficacy parameter in the open-label studies was the reduction in frequency of all partial seizures [assessed as percent change and responder rate (with >50% reduction)] during open-label treatment compared with seizure frequency during the baseline period of the preceding double-blind study. The efficacy was analysed in the evaluable population (ITT patients who entered open-label from preceding double-blind study with at least 1 day of open-label and at least 1 day of baseline seizure diary data). Efficacy was also assessed using subsets of these populations who had remained in the study for 6 months, for 1 year and for 2 years (6 month, 1 year and 2 year cohorts). Due to limitations imposed by the FDA, continuing participation in the open-label studies in the USA was limited to those patients who were refractory to other anti-convulsants and who were responding to pregabalin (who continued to show at least 30% reduction in seizure frequency compared to baseline); as this created a bias in

...vour of pregabalin, seizure data collected after re-qualification was not included in the analysis of responder rate and percent change.

As of the cutoff date of February 14, 2003, 1480 patients had participated in the open-label studies. One thousand, one hundred and forty-three (1143) patients were treated for ≥24 weeks, 879 patients for ≥1year, 512 for ≥2years and 248 for ≥3 years. Of the 1480 patients, only 881 (60%) were included in the evaluable population for efficacy analysis (mainly due to inadequate or missing baseline data or re-qualification criteria in US centres). Overall, the majority of patients were Caucasian (87%), with a mean age of 38 years at study entry and there were equal numbers of male and female patients. The mean duration of epilepsy was 25 years, and approximately half of these patients were taking 2 anti-convulsants on day 1 of the open-label studies; carbamazepine (53%) and lamotrigine (31%) were the most frequent. As of the cut-off date, 23% of the ITT patients were still participating in the 4 open-label studies. Of the 1136 patients who withdrew from the studies, 34% withdrew due to lack of efficacy, 15% due to other/administrative reasons, 12% did not meet re-qualification criteria, 13% withdrew due to AEs and 3% showed lack of compliance.

In the ongoing uncontrolled studies, the responder rate was 37% during the initial 12-week period of open-label treatment and ranged from 41% to 60% at subsequent intervals, with a responder rate of 35% over the total open-label period **(Table 8.41.1,p.107).** Responder rates results for the 6-month (n=671) and 1-year (n=535) cohorts were 41% and 46%, respectively over the total open-label period and these results were consistent with those of the 2-year cohort (51%) **(Table 8.41.2, p.107)**. These results showed that patients did not appear to develop tolerance and that efficacy was sustained over the long-term.

The median percent reduction in seizure frequency for the evaluable population was 38% during the first 12 weeks of open-label treatment and 35% over the total open-label period **(Table 8.42.1, p.108).** The median percent seizure reduction from baseline for the 2-year cohort was 51% during the initial 12 week period of open-label and this was maintained at subsequent intervals (49%-58%) **(Table 8.42.2, p.108).** Over the total open-label period, 59% of the patients had a ≥25% reduction in seizures, 20% had 0 to <25% decrease and 21% had an increase in % of seizures from baseline, with 12% of the patients showing a ≥25% increase in % of seizures **(Table 8.42.3, p.109).**

Approximately 21% of the ITT patients (excluding data after initial re-qualification) were seizure-free for 28 days and 8% were seizure-free for 6 months at the last observation.

After all the double-blind research reports were issued, additional records of seizure events as well as corrections to study medication dosing records were discovered in 18 patients while processing data for the 3 associated open-label follow-on studies. The primary and secondary efficacy analysis of the 3 pivotal studies incorporating these additional data did not change the statistical analysis conclusions. Negligible reduction in RRatio and responder rates of the pregabalin 600mg (bd) groups were observed in study 009 **(RR-MEMO 720-30120, Module 5, Vol.76).**

8.3.7 Other epilepsy studies

In study **007 (Table 8.32, p.98)**, the efficacy and safety of 600mg/day pregabalin was compared with 300mg/day in hospitalised patients with complex partial seizures, with or without secondary generalisation, who had their concomitant anti-convulsants discontinued as part of an inpatient hospitalisation for clinical seizure monitoring. Results in time to exit from the study due to pre-defined seizure criteria based on seizure occurrences **(Table 8.32, p.98)** favoured pregabalin 600mg/day but did not reach statistical significance (191hrs and 88hrs with pregabalin and gabapentin, respectively, p=0.080, log rank test). However, significantly greater number of pregabalin patients completed the 8-day double-blind treatment period (57% vs 23.5% with pregabalin and gabapentin, respectively, p=0.003).

8.4 Summary of efficacy

8.4.1 Summary of efficacy in neuropathic pain

- ***The efficacy of pregabalin was demonstrated in over 2500 patients with neuropathic pain due to diabetic peripheral neuropathy (DPN) or post-herpetic neuralgia (PHN). In both DPN and PHN patients, pregabalin at doses > 300mg/day showed statistically significantly greater pain relief in***

terms of mean endpoint pain score, VAS and "Present Pain Intensity"(PPI) scores and more than 40% of patients treated with 600mg/day showed >50% reduction in pain and 5% showed total relief from pain. The pain relief was also associated with significant improvements in sleep interference, patients' and clinicians' global impression of change and the bodily pain subscale of the SF-36 QOL assessment. Pregabalin was associated with significant reduction in tension-anxiety and overall improvement of mood in DPN patients; this effect was not observed in PHN patients.

- *The 75mg/day dose of pregabalin was not efficacious. The 150mg/day dose of pregabalin produced statistically significant pain relief in 2 PHN pivotal studies. Although the 150mg/day dose showed favourable response in DPN studies, the difference from placebo was not statistically significant. However, the proposed starting dose of 150mg/day is justified considering the fact that reduced CLcr associated with diabetes may increase exposure to pregabalin. Pregabalin (150 to 600mg/day) showed a linear dose-response in terms of responder analysis (patients showing >50% reduction in pain) and also in terms of the patients' global impression of change.*
- *The onset of significant pain relief was during the first 2 weeks of pregabalin treatment (generally within the first 3 days) and was maintained for up to 12 weeks of double-blind treatment.*
- *The long-term efficacy of pregabalin was evaluated in 1222 patients for 6 months, 720 patients for one year and 272 patients for two years. Efficacy was demonstrated in terms of consistent reductions in VAS and PPI. Furthermore, an open-label, uncontrolled study (197) demonstrated the efficacy of pregabalin in patients with neuropathic pain refractory to gabapentin, tricyclic antidepressants or other third-line neuropathic pain medications such as anticonvulsants, opioids, etc.*
- *After correcting for baseline creatinine clearance, efficacy was not affected by age, sex, race or menopausal status.*
- *The main limitations of the efficacy studies in neuropathic pain were:*

- *Subjective pain efficacy results may have been biased by the increased incidence of somnolence and dizziness in pregabalin groups as shown in study 149, where pregabalin failed to show significant efficacy over placebo when patients with dizziness/somnolence were excluded from the efficacy analysis. Similar analysis was not done for the other pivotal neuropathic pain studies.*
- *In study 040, pregabalin failed to demonstrate significant efficacy over placebo, although the active comparator amitryptiline 75mg in the same study showed significant pain relief over placebo.*

8.4.2 Efficacy of pregabalin as add-on treatment for partial seizures

- *Pregabalin (150 to 600mg/day) showed a dose-dependent reduction in the frequency of partial seizures in over 1000 patients in 3 placebo-controlled, pivotal studies. Pregabalin produced statistically significant reductions in RRatio (-28 to -37 with pregabalin >300mg/day vs -3.6 with placebo), responder rate (40-51% of pregabalin patients showed >50% reduction in seizure frequency, compared to 6-14% with placebo) and median percent decrease in seizure frequency (17-51% reduction with pregabalin compared to 1% with placebo). Furthermore, pregabalin treatment was not associated with increased frequency of seizures as only 4-16% of pregabalin-treated patients showed clinically significant (>25%) increase in seizure frequency compared to 21-33% of placebo-treated patients.*
- *Pregabalin (150 to 600mg/day) showed a statistically significant dose-response in terms of response ratio and responder rate. The dosing regimen (tds vs bd) did not appear to affect the overall efficacy of pregabalin.*
- *The onset of action of pregabalin was rapid with statistically significant differences over placebo evident within 2-3 days of starting treatment, and effects were maintained for the 12 weeks of double-blind treatment. The maximum dose of pregabalin (600mg/day) was effective in reducing all types of partial seizures (simple, complex, combined and secondarily generalised tonic-clonic). Efficacy was not affected by age, sex, race or menopausal status.*

- ***Long-term efficacy was evaluated in 1143 patients for ≥ 6months, 879 patients for ≥1 year, 512 patients for ≥ 2 years and 248 patients for ≥3 years. There was a median 35% decrease in seizure frequency over the entire open-label period and it was greater in patients who continued treatment for >2 years (51%). Furthermore, approximately 59% of patients had a clinically significant, ≥25% reduction in seizure frequency during long-term treatment. Thus, patients did not appear to develop tolerance and long-term efficacy was sustained, with only 12% showing a clinically significant (≥25%) increase in seizure frequency.***
- ***The efficacy of pregabalin as adjunctive treatment of partial seizures was evaluated in only 11 patients <16 years of age and only 12 patients over 65 years. Hence, there are insufficient data to provide evidence of efficacy of pregabalin in adolescents/children and elderly patients.***

9. SAFETY

9.1 Safety database

A total of 9469 patients received pregabalin in the clinical program: 8666 patients in the integrated phase II/III safety dataset (53 studies, either controlled or long term phase II/III studies), 51 patients in two phase II/III Japanese studies, 267 patients in three acute dental pain studies, 439 patients in 29 phase I/ clinical pharmacology studies (an additional 21 patients received pregabalin as either solution or modified release formulation) and 46 subjects in two phase I Japanese studies. However, in this report, the safety of pregabalin for the proposed indications, i.e., neuropathic pain (DPN and PHN) and as add-on treatment for partial seizures will be discussed in the greatest detail.

9.2 Safety of pregabalin when used for treatment of neuropathic pain

9.2.1 Exposure to pregabalin:

Safety was evaluated in 2524 patients with DPN and PHN exposed to pregabalin in 11 controlled pivotal studies and 13 other uncontrolled studies. These included 1831 pregabalin-treated patients in the 11 controlled studies and 693 newly exposed patients in open-label studies **(Table 9.1, p.110).**

The duration of treatment was 5 to 8 weeks in the 4 controlled **DPN** studies with tds dosing (014, 029, 040, 131) and 12 weeks in the 2 bd studies (149 and 173). Except for study 131, which had 8 weeks of treatment with pregabalin 300mg/day without titration, all studies had a 1-2 week titration period followed by 4 to 11 weeks of fixed dosing. With combined exposure from the controlled and uncontrolled studies, 948 (67%) DPN patients received at least 24 weeks of pregabalin and 578 (41%) received at least 52 weeks of exposure. In total patient-years, 38% of pregabalin exposure in the uncontrolled studies occurred at doses of 300 to <450mg/day (491 patient-years) and 36% occurred at the highest dose (>600mg/day, 460 patient-years). A total of 297 DPN patients had at least 52 weeks exposure at the highest dose of pregabalin.

The duration of treatment was 5 to 8 weeks in the 3 controlled **PHN** studies with tds dosing (030, 045, 127) and 12 or 13 weeks in the bd studies (132 and 196). Except for study 030, which had 5 weeks of treatment without titration, all studies had a 1 week titration followed by 7 to 12 weeks of fixed dosing. With combined exposure from the controlled and uncontrolled studies, 448 (40.3%) PHN patients received at least 24 weeks of pregabalin and 199 (18%) received at least 52 weeks of exposure. In total patient years, approximately 60% of pregabalin exposure in the uncontrolled studies occurred at doses >150 to <450mg/day (314 patient-years). Twenty-eight patients had at least 52 weeks exposure at the highest dose (600mg/day) and another 51 patients were exposed to 300-450mg/day for 52 weeks.

The pregabalin exposure was similar when all neuropathic pain studies were summarised together **(Tables 9.2.1-9.2.3, p.111-113)**. The main difference between the DPN and PHN patient population was the greater proportion of elderly patients in the PHN studies (44.5% and 7.5% of patients were ≥75 years in the PHN and DPN studies, respectively). Furthermore, the PHN studies allowed restricted use of non-narcotic analgesics, narcotics/opioids, NSAIDs, tricyclic antidepressants and SSRIs, while these drugs were not allowed in the DPN studies.

..2.2 *Adverse events in neuropathic pain studies*

In the controlled DPN studies, 68.8% of pregabalin-treated and 54.9% of placebo-treated patients experienced AEs, with pregabalin (>300mg/day) groups showing significantly higher incidences of AEs than placebo. However, the incidence of AEs was similar in the pregabalin 150mg/day and placebo groups. Dizziness (21%), somnolence (12%) and peripheral oedema (9.4%) were the most common AEs in the pregabalin groups. The incidence of dizziness and somnolence was generally higher at pregabalin doses >300mg/day, but there was no clear dose-response or relationship to dosing regimen (tds or bd). Other common AEs with a significantly higher incidence compared to placebo were asthenia, dry mouth, weight gain, constipation, amblyopia and confusion **(Table 9.3.1, p.114).** Vertigo was specific to the DPN population and was reported mainly in the bd studies (2.7%, n=26).

In the controlled PHN studies, 73.6% of pregabalin-treated and 57% of placebo-treated patients experienced AEs. Dizziness (25.6%), somnolence (16.2%), peripheral oedema (11.5%), dry mouth, amblyopia, constipation, ataxia, weight gain, abnormal gait and confusion had significantly higher incidences in the pregabalin-treated patients compared to the placebo-treated patients **(Table 9.3.2, p.115).** Furthermore, most of these AEs were more frequent at the higher dose of pregabalin (600mg/day). Unlike the DPN studies, the overall incidence of AEs with 150mg/day pregabalin was significantly greater than placebo, which may be due to greater enrolment of elderly patients in the PHN studies.

The combined AE profile for controlled studies was similar to that of the individual DPN and PHN studies with dizziness, somnolence, peripheral oedema, dry mouth, amblyopia, constipation, weight gain, ataxia, confusion and abnormal gait significantly higher in the pregabalin groups compared with placebo. Furthermore, most of these AEs were more commonly observed at pregabalin doses of 300 and 600mg/day **(Table 9.3.3, p.116).**

Dizziness and **somnolence** were the most common treatment-related AEs in each of the 3 controlled neuropathic pain populations (i.e. DPN, PHN and combined neuropathic pain populations), followed by peripheral oedema, asthenia, dry mouth and headache in the DPN population and peripheral oedema, dry mouth, amblyopia and ataxia in the PHN population. More patients in the 300 and 600mg/day pregabalin groups had treatment-related AEs, but there was no clear pattern of dose-response **(Table 9.4, p.117).**

Most of the AEs were mild to moderate with only 10.6% of all pregabalin-treated patients having severe AEs. Dizziness (1.7%), somnolence (1.6%), headache (0.8%) and asthenia (0.7%) were the most common severe AEs and these were more likely to occur at higher doses of pregabalin. Dizziness and somnolence started within 1 to 2 days of treatment in all pregabalin groups and within 3 to 5 days in the placebo group. Many other common AEs such as headache, asthenia, ataxia, amblyopia, vertigo (only in DPN patients) and dry mouth had median times to onset within the first week of treatment in the pregabalin 300 and 600mg/day groups and generally started earlier in these groups compared to the 150mg/day pregabalin and placebo groups. Peripheral oedema, pain, accidental injury, infection, weight gain, oedema and "neuropathy" had longer median times to onset in all treatment groups. The median duration of dizziness was longer in the pregabalin groups (6.5 to 25 days) compared to the placebo group (4 days). Oedema, dry mouth, asthenia, somnolence and amblyopia had the longest median durations in all treatment groups, while ataxia and weight gain had longer median durations in the pregabalin groups compared to placebo. Of all pregabalin-treated patients who had dizziness in the controlled neuropathic pain studies but did not withdraw because of it, dizziness resolved in 57% **(Figure 9.1, p.43).** Similarly, somnolence resolved in 42% of patients with somnolence who did not withdraw because of it **(Figure 9.2, p.43).**

9.2.3 Long-term safety: AEs in uncontrolled open-label neuropathic pain studies

Of the 1164 patients in the uncontrolled DPN studies, 434 (37.3%) had not been previously exposed to pregabalin. The AE profile for the uncontrolled studies was similar to that seen in the controlled studies, with 80% of patients experiencing AEs. Infection (17.8%), dizziness (15.1%), peripheral oedema (14.1%), accidental injury (13%) and pain (12%) were common **(Table 9.5.1, p.118)**. Compared to the controlled DPN studies, the incidence of somnolence (9.4%) was less, while that of infection, peripheral oedema, weight gain, accidental injury and flu syndrome were higher.

Of the 735 patients in the uncontrolled PHN studies, 259 (35.2%) had not been previously exposed to pregabalin. Approximately 78% of patients in the uncontrolled studies experienced AEs, with dizziness

being the most common **(Table 9.5.2, p.119).** The incidence of somnolence (13.3%) was similar between the controlled and uncontrolled studies, but the incidences of peripheral oedema (15%), accidental injury (13%) and weight gain (7.5%) were higher in the uncontrolled studies.

The AE profile in the combined neuropathic pain studies (DPN and PHN studies) was similar to that observed in DPN and PHN populations **(Table 9.5.3, p.119).**

Dizziness (17%), somnolence (11%), peripheral oedema (14.5%), weight gain and asthenia were the most common treatment-related AEs associated with long-term pregabalin treatment in the DPN, PHN and combined patient populations **(Table 9.6, p.120).**

In the uncontrolled DPN and PHN studies, no individual severe AE was reported in more than 1.8% of pregabalin-treated patients. Severe CNS AEs were less common in the uncontrolled DPN population, where accidental injury, pain, infection and cardiovascular events were the most common severe AEs. However, severe AEs of dizziness, somnolence, accidental injury and peripheral oedema were more common in the PHN population.

Emergent signs and symptoms following discontinuation of pregabalin treatment were analysed prospectively in only 1 study **(DPN study 040, Table 8.3, p.55)**, in which no withdrawal signs or symptoms were observed.

9.2.4 Serious AEs, withdrawals due to AEs and deaths

In the neuropathic studies, more pregabalin-treated patients (11.4%) withdrew due to AEs compared with placebo (5%). Based on data from all controlled neuropathic pain studies, dizziness (3.5%), somnolence (2.6%) and confusion (1.2%) were the most common AEs leading to withdrawal from pregabalin treatment. All other AEs leading to discontinuations had an incidence of <1%. There was a dose response for both the overall incidence of discontinuations and for each of the common AEs leading to discontinuations **(Table 9.7, p.121).**

The incidence of withdrawals due to AEs (8.8% and 3.7% with pregabalin and placebo, respectively) were generally lower in the controlled DPN studies than that seen in the overall neuropathic pain population, but it was still dose-related. Dizziness, somnolence, confusion, headache, asthenia, dry mouth, incoordination, tremor and vertigo were the most common reasons for discontinuations in the DPN patients. Confusion and dry mouth were relatively more common reasons for discontinuation among DPN patients than in the overall discontinuation data. A few patients (2.6%) also had their dose reduced or interrupted due to AEs, mainly due to somnolence (0.5%), dizziness (0.4%) or nausea (0.4%). The incidence of withdrawals due to AEs were generally higher in the controlled PHN studies (10.2 to 30% with pregabalin and 6.5% with placebo), with somnolence, dizziness, confusion, peripheral oedema and asthenia being the most common causes of discontinuation. A dose-response for discontinuations was also evident in the PHN studies, especially for somnolence, dizziness and confusion, suggesting that these AEs were less well-tolerated in the elderly PHN patients. A few PHN patients (3.8%) also had their dose interrupted or reduced due to AEs, mainly due to vomiting (0.7%), diarrhoea (0.6%) and dizziness (0.5%). Approximately 24.5% (466/1899) of patients in the uncontrolled neuropathic pain studies discontinued due to AEs. Peripheral oedema (1.9%), dizziness (1.3%), somnolence (1.1%) and weight gain (0.9%) were the most common reasons for discontinuation in the uncontrolled studies **(Table 9.8, p.122).** Approximately 19% of patients showed SAEs in the long-term, uncontrolled neuropathic pain studies.

In the DPN and PHN controlled studies, the incidence of serious AEs (SAEs) was slightly higher in the pregablin treatment groups compared with placebo (3.6% vs 2.5%). In the overall controlled and uncontrolled, open-label, long term neuropathic pain studies, 389 pregabalin patients (15.4%) experienced SAEs, of whom 42 (1.7%) experienced treatment-related SAEs. The most common SAEs were chest pain, accidental injury, pneumonia, congestive heart failure and myocardial infarction.

A total of 36 deaths occurred during the neuropathic pain controlled or long-term uncontrolled studies, of which 35 were among pregabalin-treated patients (equivalent to 17 deaths per 1000 patient-years). Five pregabalin-treated patients (5/1831, 0.3%) died during or after withdrawal from the controlled studies (placebo=1/857, 0.1%). Review of death narratives (Mod. 5, Vol. 77) showed that cardiovascular events

AMI, cardiac arrest, heart failure), carcinoma and respiratory events in patients with predisposing risk factors were the most common causes of death. Death rates were higher in the PHN studies than the DPN studies, which was most likely due to the greater proportion of elderly patients in the PHN population.

9.2.5 Laboratory parameters and vital signs

In all the controlled neuropathic pain studies, many of the lab parameters showed a statistically significant change with pregabalin treatment compared with placebo. Although most of these changes were small and not likely to be clinically relevant, a decrease in platelets (-11.01x10^3/uL) and increase in creatine kinase (9.9084U/L) were consistent. Compared with placebo, more pregabalin-treated patients showed clinically significant decreases ($\leq$75 x 10^3/μL) in platelets (4.3% vs 1.8%). In the long-term studies, 140 patients (8.9%) had potentially clinically significant decreases in platelet values and 8 (0.5%) had potentially clinically significant increases ($\geq$700 x 10^3/μL). The number of patients showing clinically important increases ($\geq$3 x ULN) in creatine kinase (pregabalin vs placebo: 0.6% vs 1.3%), AST (0.4% vs 0.2%) and ALT (0.5% vs 0.4%) was similar in the pregabalin and placebo groups. Although the mean BUN values showed a dose-dependent significant increase with pregabalin treatment **(Table 9.9, p.123),** the number of patients with clinically important increases in BUN (>34mg/dL) were similar in the pregabalin and placebo groups (5.8% vs 4.5%). There were, moreover, no significant changes in serum creatinine.

Blood pressure and heart rate showed small, inconsistent, clinically irrelevant changes from baseline, with no significant difference between pregabalin and placebo groups. The number of patients who did not have orthostatic hypotension at baseline, but had it at study termination was similar between pregabalin-treated and placebo-treated patients (5.6% vs 5.5%). Overall, 7% of pregabalin-treated and 1.6% of placebo-treated patients in the controlled neuropathic pain studies experienced $\geq$7% increase in body weight from baseline to termination. The proportion of patients who gained $\geq$7% body weight increased with long-term exposure. In the combined controlled and uncontrolled studies, 27.7% had $\geq$7% weight gain from baseline to anytime on treatment, whereas 19% had $\geq$7% weight gain from baseline to termination.

The DPN patients did not show any clinically meaningful change in glucose control based on mean change in glycosylated haemoglobin (mean change of 0.266%).

9.2.6 Effect of age, sex, race and menopausal status on safety of pregabalin when used for treatment of neuropathic pain

Although there were few pre-menopausal and non-Caucasian patients in the neuropathic pain studies, the overall pattern of AEs did not appear to be significantly affected by menopausal status or race. The overall incidence of AEs in all controlled neuropathic pain studies was higher in females in both the pregabalin and placebo groups (**Table 9.10, p.123**). Dry mouth, constipation, peripheral oedema, weight gain, dizziness, somnolence, confusion, abnormal gait and amblyopia were significantly higher in both pregabalin-treated men and women compared with the respective gender-corrected placebo groups. Except for peripheral oedema, which had a higher incidence in pregabalin-treated women than men, the overall incidences of these AEs were similar between pregabalin-treated men and women. In all controlled neuropathic pain studies, the overall incidence of AEs was higher in the older pregabalin-treated patients (65-74 years and >75 years) than in younger pregabalin-treated patients (18-64 years) **(Table 9.10, p.123),** with dry mouth, peripheral oedema and dizziness more common in the older patients (>65 years) compared to the younger patients (18-64 years), whereas the incidence of somnolence and weight gain was similar across all age categories. Patients aged over 75 years had the highest incidence of ataxia and abnormal gait.

9.3 Safety of pregabalin used as adjunctive therapy for partial seizures

9.3.1 Exposure to pregabalin in epilepsy studies

Safety of adjunctive therapy with pregabalin was assessed in 1613 patients with partial seizures in 3 controlled, 12-week, pivotal epilepsy studies (009, 011 and 034) and their uncontrolled, open-label extensions (010, 012, 035). Of the 758 patients who received pregabalin in the 3 pivotal studies, 80.3% had at least 10 weeks of exposure and 61% had at least 12 weeks exposure **(Table 9.11.1, p.124).** Another 810 patients were exposed to pregabalin in 4 open-label, long-term, uncontrolled studies. With the combined controlled and uncontrolled studies, pregabalin exposure was 1206 patients (75%) for at least 24 weeks, 918 (57%) for at least 52 weeks and 557 (34.5%) for at least 104 weeks **(Table 9.11.2, p.124)**. In total patient-

, ears, over 65% of pregabalin exposure in the uncontrolled studies was at doses >450mg/day, with approximately 45% (1035.6 patient-years) exposed to the 600mg/day dose of pregabalin. Overall, 401 patients received >600mg/day for at least 1 year. Two controlled studies evaluated the role of monotherapy (007) and titration (145) in another 96 patients. However, these were not included in the controlled studies safety dataset as they were of different study design and were terminated early due to minimal enrollment.

9.3.2 Adverse events in controlled epilepsy studies

In the controlled epilepsy studies, 84% of pregabalin-treated patients and 70.1% of placebo-treated patients had AEs. The overall incidence of AEs was similar between pregabalin 150mg/day and placebo; however, the AEs increased with increasing dose of pregabalin (300 to 600mg/day). The most frequent AEs in the pregabalin-treated patients were dizziness (29%), somnolence (20.8%), ataxia (13.2%), asthenia (11.2%), weight gain (10.4%) and accidental injury (9.9%). Furthermore, the following AEs had significantly higher incidence with the 600mg/day dose of pregabalin than with placebo: tremor, abnormal thinking, speech disorder, incoordination, abnormal gait, twitching, myoclonus, amblyopia, diplopia, peripheral oedema, dry mouth, increased appetite, constipation and abnormal vision **(Table 9.12, p.125)**. Compared with the overall safety profile of pregabalin in all indications, relatively more ataxia, weight gain and tremor and relatively less dry mouth were reported in the controlled epilepsy studies. The dosing regimen (bd or tds) did not appear to have any consistent effect on the incidence of AEs (study **009, Table 9.13, p.127**); however, it should be noted that the tds dosing regimen was associated with fewer withdrawals due to AEs (18.9% and 26.2% in pregabalin tds and bd groups, respectively). The majority of AEs in the controlled epilepsy studies were considered related to pregabalin treatment, especially CNS events in the higher dose groups. Dizziness, somnolence, ataxia, asthenia and weight gain were the common treatment-related AEs, while accidental injury was considered related to treatment in only 1% of pregabalin patients **(Table 9.14, p.128).** Most of the AEs were mild to moderate in intensity and only 9% of the AEs were of severe intensity. Common severe AEs reported in >4 pregabalin-treated patients were dizziness (2%), somnolence (2%), ataxia (1.6%), headache (1.1%) and accidental injury (0.9%).

The most common CNS AEs had an early onset (within the first week of treatment of pregabalin) and the time to onset of both dizziness and somnolence was much shorter in the pregabalin groups (0 to 3 days) compared to the placebo groups (7-13 days). With the exception of shorter median times to onset for tremor and abnormal thinking in the pregabalin 300 and 600mg/day groups, time to onset of other CNS AEs was similar across all pregabalin groups. Weight gain and accidental injury had longer median times to onset **(Table 9.17.1, p.130).** Among patients who completed the controlled studies, abnormal thinking, increased appetite and weight gain were the AEs with the longest duration **(Table 9.17.2, p.130).** In contrast to the neuropathic pain studies, the median duration of dizziness was shorter for pregabalin groups (12-28 days) than for placebo group (43 days). The median duration of somnolence varied among completers in the pregabalin groups (26-28 days). Among all pregabalin-treated patients who had dizziness, but did not withdraw because of it, dizziness had resolved in 64% of those patients prior to the last dose of study medication **(Figure 9.3, p.44).** Similarly, somnolence resolved in 46% of patients **(Figure 9.4, p.44).**

9.3.3 Long-term safety: AEs in uncontrolled, open-label studies

Of the 1410 patients in the 4 uncontrolled epilepsy studies, 810 had not been previously exposed to pregabalin (298 from placebo group in preceding double-blind studies and 512 *de novo* patients). During the long-term uncontrolled studies, 94.5% of patients reported AEs and 79.5% reported treatment-related AEs. The AE profile following long-term treatment was similar to that observed in the short-term controlled studies, except for a higher incidence of weight gain and accidental injury in the uncontrolled studies **(Table 9.15, p.129).** Dizziness (26.3%), somnolence (21.5%), weight gain (21.3%) and asthenia (13.5%) were the most common treatment-related AEs in the uncontrolled studies **(Table 9.16, p.129).** The majority of AEs in the uncontrolled studies were mild or moderate. Accidental injury (43 patients, 2.9%) was the most common severe AE in the uncontrolled studies, followed by somnolence (1.7%), headache (1.4%), dizziness (1.1%), ataxia (1%) and asthenia (0.9%).

9.3.4 Withdrawals due to AEs, serious AEs and deaths

The number of withdrawals due to AEs were significantly greater in the pregabalin groups (116/758, 15%) compared to placebo (18/294, 6.1%). Nervous system AEs, mainly dizziness (5.3%), somnolence (3.3%), ataxia (3%), tremor (1.5%), confusion (1.3%) and abnormal thinking (1.3%) were the most common reasons for withdrawal. Other common AEs leading to withdrawal were body as a whole AEs (4.4%), such as

asthenia, headache and accidental injury. In the controlled studies, 3% of pregabalin-treated patients had their dose interrupted or reduced due to AEs (dizziness, somnolence, diplopia, stupor and twitching were the most common reasons). The incidence of serious AEs was similar in the placebo (4.4%, 13/294) and pregabalin groups (3.8%, 29/758); nervous system SAEs were more common in the placebo group (2.7% and 1.1% in placebo and all pregabalin groups, respectively), while accidental injury was more common in the pregabalin groups (0.3% and 1.2%, respectively). There were no deaths in the 12 week pivotal controlled epilepsy studies.

In the uncontrolled studies, 12.8% (189/1480) of patients discontinued pregabalin due to AEs. In the combined controlled and uncontrolled epilepsy studies, 210 patients (13%) reported SAEs; accidental injury and pneumonia were more common than nervous system AEs with only 3 SAEs of dizziness and 1 of somnolence. There were 15 deaths in the uncontrolled, long-term studies and review of the death narratives showed that the cause of death in most cases was cerebrovascular, respiratory or cancer. One patient (44 year-old male) in open-label study 035 died due to terminal generalised tonic-clonic seizure and intractable epilepsy after 1090 days of treatment with pregabalin 600mg/day.

9.3.5 Laboratory parameters and vital signs

There were many statistically significant changes in clinical laboratory parameters between pregabalin and placebo; however, not all of these were clinically meaningful. The mean decrease in platelets was -4.974×10^3/uL, with 36 pregabalin-treated patients (4.9%) showing clinically important decreases, compared to 10 placebo-treated patients (3.6%). The mean increase in creatine kinase was 62.725U/L, with only 5 patients showing clinically important increases (compared to none in placebo group) **(Table 9.18, p.131).**

In the uncontrolled, open-label extensions, there was a mean increase in platelets (3.1×10^3/uL); potentially clinically significant decreases in platelets were, however, observed in 107 patients (7.5%) and only 18 patients (1.3%) had potentially clinically significant increases. There was a mean increase in creatine kinase (39.3U/L) with 20 patients (2.8%) showing potentially clinically significant increases in creatine kinase at some time during the open-label treatment with pregabalin. Very few pregabalin-treated patients showed clinically important increases in BUN (3), AST (5) and ALT (4).

Overall, pregabalin did not produce any clinically significant changes in heart rate, blood pressure, respiratory rate or ECG.

There was a mean weight gain of 2.1kg in pregabalin-treated patients compared to no change in the placebo-treated patients. Overall, 18% of pregabalin-treated and 2.1% of placebo-treated patients experienced a 7% or greater increase in body weight during the controlled epilepsy studies. The ≥7% increase in weight associated with pregabalin was dose-related (26.5%, 13.8% and 8.3% of patients treated with pregabalin 600, 300 and 150mg/day). In the controlled/uncontrolled epilepsy population, pregabalin treatment was associated with a mean increase in weight of 4.7kg and 49.3% of patients showed a >7% increase in body weight from baseline to anytime on treatment (40.2% showed increase when measured from baseline to study termination).

9.3.6 Effect of age, sex, race and menopausal status on safety of pregabalin when used as add-on therapy for partial seizures

Twenty patients aged >65 years (n=20) and only 11 patients aged between 12 and 16 years were evaluated. Of the 10 children who received pregabalin, 6 experienced at least one AE (2 randomised to 600mg/day, 2 to 300mg/day and 1 each to 150 and 50mg/day). Five of these children had AEs related to the nervous system. However, there was only 1 report of dizziness and none of somnolence. Four children had AEs related to emotional/behavioural changes (hostility, agitation, personality disorder, emotional lability). One child who received placebo did not report any AEs.

There were too few non-Caucasian patients to enable a definite interpretation about effect of race on safety of pregabalin. More women than men had AEs in the controlled epilepsy studies **(Table 9.19, p.131).** The overall incidence of dizziness, somnolence, asthenia and amblyopia was higher in pregabalin-treated women, while incidences of abnormal gait was higher in pregabalin-treated men. However, most of the other common AEs associated with pregabalin showed similar profiles in both women and men.

Among women, the incidence of AEs was higher in post-menopausal patients compared to pre-menopausal patients. Although the incidences of few specific AEs were different between pre- and post-menopausal women, the overall AE profile of pregabalin was similar. Specifically, ataxia and accidental injury were more common in post-menopausal women, while weight gain and incoordination were more common in pre-menopausal pregabalin-treated patients.

9.3.7 Appearance of new seizures:

There were unexpected generalised seizures in 6 patients who received pregabalin while participating in the phase II/III studies. Five of these patients were enrolled in 2 clinical pharmacology studies investigating drug interactions of pregabalin in patients maintained on a stable dose of 1 concomitant anti-convulsant (valproic acid and carbamazepine); the sixth patient was involved in an acute pain study. Unexpected generalised seizures occurred within the first 2 days after initiation of pregabalin treatment; 4 of these patients had an established diagnosis of idiopathic generalised epilepsy (IGE) and/or partial seizures **(Table 9.20, p.132)**.In all of these patients, study medication was discontinued and patients were withdrawn from study. All patients recovered without sequelae within 24 hours of the acute seizure. **Based on review of these 6 cases, although no clear pattern was discernible, the role of pregabalin in induction of these new seizures cannot be excluded and the sponsor should continue to monitor such cases.**

9.3.8 Worsening of SGTC seizures:

Across the 3 pivotal controlled epilepsy studies, 35-43% of pregabalin-treated patients and 26-51% of placebo-treated patients had SGTC seizures **(Table 9.21.1, p.133).** Change in SGTC seizure rate was measured by comparing the 28 day SGTC seizure rate during the treatment period with that in the baseline phase; if the rate in the treatment phase exceeded the baseline rate, the change was defined as worse, and if it was double the baseline rate, the change was defined as ≥100% worse. There was no significant difference in the median percentage of patients showing worsening of SGTC rate during the first 2 days (placebo vs pregabalin: 15% vs 14%), the first week (31% vs 26%), first month (44% vs 28%) or all 3 months of double-blind treatment (44% vs 31%) **(Table 9.21.2, p.133).** Thus, pregabalin was not more likely than placebo to be associated with an increased incidence of worsening in the SGTC seizure rate;

Due to the 6 patients reporting new generalised seizures during the first 2 days of pregabalin treatment, mentioned above, another *post hoc* analysis was done to evaluate worsening of SGTC during the first 2 days of pregabalin treatment. Of the 58 patients with 1 or more SGTC seizures during the first 2 days of double-blind treatment, only 8 had 1 to 8 more SGTC seizures than during their most active 2-day baseline period [*]. One of these patients received placebo and of the 7 patients receiving pregabalin, 5 had only 1 more seizure than during the maximum baseline interval. Hence, only 2 pregabalin-treated patients had 2 or more additional SGTC seizures during the first 2 days of double-blind treatment.

9.3.9 Withdrawal symptoms

Withdrawal signs or symptoms following discontinuation of pregabalin treatment in epilepsy patients was not investigated.

9.4 Weight gain, peripheral oedema and accidental injury

AEs that are not predictable from the known pharmacology of pregabalin include weight gain and peripheral oedema. Although these AEs have been reported with gabapentin, the mechanisms involved remain unclear. The onset of any weight gain was within 6 months of starting pregabalin treatment in the majority of patients, but weight gain appeared to continue with continued therapy. Most of the patients with clinically significant increase in weight had no more than 10% increase from baseline; however, 79 pregabalin-treated patients had >25% increase in weight, representing approximately 1% of all pregabalin-treated patients. Baseline BMI, age, concomitant medications, changes in cardiovascular parameters, cardiorespiratory events and glucose control did not appear to influence the incidence of weight gain. Of those patients in the controlled studies with significant weight gain, only 12.7% reported concurrent oedema (28.6% in neuropathic pain studies and 8.3% in epilepsy studies). There was a slightly higher reporting of the AE of increased appetite in patients with weight gain compared to those without weight gain (5.3% vs 2.9%).

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[*] The baseline period was divided into 28 successive, 2 day intervals. The number of SGTC seizures during first 2 days of double-blind treatment was then compared with the maximum 2 day baseline interval.

In the controlled studies, the incidence of peripheral oedema was greatest in the neuropathic pain studies (10.4%) compared with the epilepsy studies (4.2%), with a similar pattern seen in the long-term uncontrolled studies. The overall incidence of peripheral oedema in the controlled studies was 6.1%, with a median time to onset of 17 days and with a median duration of 27 days. Few patients discontinued pregabalin due to peripheral oedema. There were 2 SAEs involving peripheral oedema. Review of the laboratory data did not show any associated changes in renal function (eg. proteinuria) or any changes in laboratory parameters different from those seen in the overall population. The incidence of peripheral oedema generally increased with increasing dose of pregabalin in the controlled studies, although it was similar in the 300 and 600mg/day groups. BMI and gender did not appear to influence peripheral oedema; the incidence increased, however, in elderly PHN patients (>65 years) and some elderly DPN patients (65-74 years). There was increased reporting of hypertension and dyspnoea in patients with peripheral oedema (7.7%) compared to those without (2.6%). However, peripheral oedema was not associated with an increased incidence of heart failure, arrhythmias, hypotension, or other cardiovascular disorders.There was no evidence to suggest that the oedema was indicative of a hypersensitivity reaction.

In the controlled studies, the incidence of accidental injury was similar in pregabalin and placebo-treated patients (4 % vs 3%), with only a small proportion of these considered serious (0.3% vs 0%, respectively). Of those with CNS AEs, a similar number of patients had events of accidental injury in the pregabalin and placebo groups (3.3% and 3.2%, respectively). Hence, the CNS events associated with pregabalin treatment did not appear to increase the patient's risk of incurring an accidental injury.

9.5 Ophthalmologic safety of pregabalin

A comprehensive analysis of the ophthalmologic safety of pregabalin (visual acuity, visual field defects, fundoscopy data and vision-related AEs) was performed at the request of the FDA **(RR-MEMO 720-04341, Vol.85).** There were 3600 patients with baseline and follow-up opthalmologic examinations, of which 2229 (61.7%) were treated with pregabalin for ≥ 24 weeks, 1390 (38.5%) for ≥ 52 weeks and 292 (8.1%) for ≥104 weeks.

9.5.1 Visual field defects

The incidence of treatment-emergent visual field abnormalities[6] in the controlled studies (for all indications) was similar among all pregabalin-treated patients (12.4%) and placebo-treated patients (11.7%) **(Table 9.23.1, p.135)**; similar results were observed in controlled diabetic neuropathy (13.6% and 13.1% with pregabalin and placebo, respectively), post-herpetic neuralgia (16.2% and 16%, respectively) and epilepsy (11.1% and 9.9%, respectively) patient populations. In the combined data from all controlled and uncontrolled studies for all indications, 16.8% of all pregabalin-treated patients showed treatment-emergent visual field abnormalities (5.4% were expert-validated cases); the incidence was higher for the combined controlled and uncontrolled population in the diabetic neuropathy (23.9%) and post-herpetic neuralgia (24.5%) studies, compared to the epilepsy studies (15.1%) **(Table 9.23.2, p.136).** Interpretation of the visual field results were confounded by the fact that different visual field testing procedures were performed for the same patient at different visits. Review of potential cases by experts revealed that most of the cases of visual field progression were due to artefacts related to testing procedures or to poor cooperation on the part of the patient (eg. superior visual field defects due to droopy eyelids due to patients feeling sleepy). The visual field findings did not show any consistent relationship to pregabalin dose and there was no evidence of vigabatrin-like constriction of visual field.

9.5.2 Visual acuity loss

In the controlled studies (for all indications), there was a significantly higher incidence of treatment-emergent visual acuity loss[7] in the pregabalin 600mg/day (7.4%, p=0.02) group and the all doses pregabalin group (6.5%, p=0.046) compared with placebo (4.5%). *Post hoc* analysis of clinically relevant visual acuity loss however showed no significant difference between pregabalin and placebo groups **(Table 9.23.2, p.136).** Furthermore, only 2.1% (50/2400) of pregabalin-treated patients had unexplained visual acuity loss

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[6] Patients who showed a change of 10 or more in the number of targets seen for the 120 point visual field stimulus configuration, i.e., Humphrey visual field examination at any study visit.

[7] deterioration in visual acuity of >0.15logMAR, i.e., at least 2 lines of Snellen acuity.

compared with 1.4% for placebo). In the 21 controlled and uncontrolled studies, 9.4% of patients had treatment-emergent visual acuity loss. Overall, the percentage of patients experiencing visual acuity loss was higher in the post-herpetic neuralgia (18.3%) and diabetic neuropathy (15.8%) studies compared to the epilepsy studies (7.5%). Clinically meaningful deterioration of visual acuity was seen in 7.8% (281/3602) of all pregabalin-treated patients; however, a pre-existing progressive ophthalmologic condition was present in 156 of these patients and only 125 patients (3.5%, 125/3602) had unexplained clinically significant loss of acuity of at least 2 Snellen lines.

Overall, the incidence of treatment-emergent fundoscopic abnormalities in controlled studies was low and similar amongst pregabalin (0.9%) and placebo (2.1%) groups. Of the 203 (5.9%) patients with fundoscopic abnormalities in the combined controlled/ uncontrolled population, 132 patients were from the diabetic neuropathy studies.

9.5.3 Vision-related adverse events

As might be expected, the incidence of any visual abnormalities at baseline was higher in the neuropathic pain studies (66.5% and 77.1% with diabetic and post-herpetic neuralgia, respectively) than in the epilepsy studies (47.5%). Overall, the incidence of vision-related AEs was higher for pregabalin-treated patients (15%) than for patients treated with placebo (7%), mainly due to a higher incidence of blurred vision, diplopia and abnormal vision. The incidence of blurred vision was dose-related, with the highest incidence in the 600mg/day pregabalin group **(Table 9.24, p.137).** The majority of these AEs were transient, not associated with decreased visual acuity, and occurred concurrently with other CNS AEs. It is possible that there may be a relationship between increased oedema and visual symptoms in pregabalin-treated patients; however, corneal or retinal oedema would most likely lead to decreased visual acuity and the sponsor's safety summary states that most patients with blurred vision did not report decreased visual acuity; however, the exact incidence of decreased visual acuity in patients with blurred vision was not provided.

Vision-related AEs led to discontinuation of pregabalin in 98 patients, with blurred vision being the most common reason for withdrawal (46 patients). Only 5 patients had blurred vision reported as the only AE leading to withdrawal. Most of the other patients with blurred vision had other vision-related AEs (abnormal vision[8], eye disorder[9], diplopia, visual field defect) or CNS AEs (dizziness, somnolence, ataxia, confusion, asthenia) that also contributed to withdrawal. Serious vision-related AEs were present in 23 pregabalin-treated patients, leading to discontinuation in 7 of these patients.

Overall, data from 3600 patients with baseline and post-baseline ophthalmic examinations indicates that pregabalin is not likely to cause any retinal or optic nerve toxicity.

9.5.4 Updated ophthalmologic safety summary

RR-MEMO 720-30218 (Vol.88) was an updated report on the ophthalmologic safety in patients with a more prolonged exposure to pregabalin as of the cut off date of February, 2003 **(Table 9.25, p.138).** More patients were treated for longer periods, with approximately 1662 patients (45%) in this database treated with pregabalin for ≥52 weeks and 672 (18.2%) for ≥104 weeks. Results of this updated analysis were similar to that of the earlier report **(Tables 9.26.1-9.26.3, p.139-140).**

9.5.5 Summary of ophthalmologic safety

The incidence of visual AEs related to pregabalin treatment was low. Many of the visual field and visual acuity defects were related to pre-existing ophthalmologic conditions (especially in patients with DPN and PHN), or to progressive changes related to these conditions. Over the entire program, 6 cases of validated (blinded review of all visual field cases by ophthalmologic experts), unexplained visual field defects were identified and 7 cases of medically relevant, binocular visual acuity loss (i.e., at least 3 lines of acuity in one eye and 2 lines in the other eye) were identified. Review of all follow-up information on these cases did not reveal any consistent pattern.

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[8] Abnormal vision incidence was dose-related and this term was just a variation of investigator terms for blurred vision and focus problems.

[9] eye disorder showed no dose response and investigator terms relating to eye infection and weak or tired eyes were commonly reported.

9.6 Integrated summary of ECG results

ECG data were collected from 17 double-blind, placebo-controlled and one active-controlled study at baseline and at least once during double-blind treatment (mostly at study termination); these data were read by a central ECG laboratory in St. Louis. Pregabalin did not appear to have any consistent effect on QTc (linear corrected QT intervals), QRS or ventricular rate (VR). Premature ventricular contractions (PVCs) occurred more frequently in the pregabalin-treated diabetic neuropathy studies only (not when pregabalin was used for other indications), but there was no clear dose-response relationship. Furthermore, this increase in PVC in pregabalin-treated diabetic neuropathy patients was not associated with an increased incidence of cardiovascular AEs (4.4% and 4.5% wih pregabalin and placebo, respectively), SAEs (0.9% vs 0.6%) or withdrawals due to cardiovascular AEs (0.7% and 0.3%).

Pregabalin produced statistically significant increases in the PR interval at doses >300mg/day, but this mean increase (3-6 msec) was not clinically relevant. The number of patients with an absolute post-baseline PR ≥220msec and a maximum increase of ≥40msec from baseline was very low and similar in the placebo (n=6, 0.005%) and the pregabalin groups (50mg/day=1; 600mg/day=5, 0.005%). There was no significant difference in the number of patients with AV block as an AE between the pregabalin (n=8, 0.24%) and placebo groups (n=1, 0.06%). These AV blocks in pregabalin-treated patients were not serious AEs and did not lead to withdrawal of the patient.

9.7 Other safety studies

9.7.1 Abuse potential

Study **098** (Module 5, Vol.82) was designed to evaluate the abuse potential of pregabalin versus that of diazepam and placebo. It was single-centre, crossover study in which 15 volunteers who were recreational sedative users or moderate alcohol users were given a single oral dose of pregabalin 200mg, 450mg, diazepam 15 and 30mg, and placebo with a ≥ 5days washout between treatments. A modified version of human drug self-administration procedures, the Multiple Choice Procedure (MCP) was used to assess the reinforcing effects of pregabalin. However, in this study, the MCP failed to differentiate placebo and the test drugs and thus could not assess the reinforcing effects of pregabalin.

9.7.2 Psychomotor and cognitive function

A phase I, double-blind, 3-way crossover study **(097, Table 9.22, p.134)** in 23 healthy subjects evaluated the effects of pregabalin 450mg/day (given tds) on psychomotor, cognitive function, sensory-motor coordination, sleep and brake reaction time (while driving); alprazolam was used as the positive control. Pregabalin showed mild impairment of information processing capacity and sensory-motor coordination, but, these effects were less pronounced that those of alprazolam. Furthermore, pregabalin did not cause psychomotor impairment and had no effects on memory **(Table 9.22, p.134).** Pregabalin did produce subjective effects of increased sedation and reduced coordination. Both pregabalin and alprazolam improved sleep as measured by latency to sleep onset, total sleep time, and number of awakenings. Pregabalin also increased slow wave sleep (SWS), while alprazolam decreased SWS; both pregabalin and alprazolam reduced REM sleep. Pregabalin did not cause significant impairment of brake reaction time, which is a measure of cognitive and psychomotor performance including attentional efficiency.

9.7.3 Effects of pregabalin on reproductive function in healthy males

Preclinical studies had shown reversible effects on sperm parameters and fertility in male rats at approximately 10 times the anticipated maximum human exposure (Cmax of 9.46ug/ml at the maximal suggested dose of 600mg/day). Extensive evaluation of male reproductive organs and semen parameters in the chronic monkey study and in mouse studies failed to identify any drug-related effects. The effect of pregabalin (200mg tds for 14 weeks) on human male reproductive function was evaluated in a phase II, double-blind, placebo-controlled, randomised, parallel group study in 46 healthy males **(072, Table 9.27, p.141).** Pregabalin did not demonstrate any detrimental effect on male reproductive function, as assessed by semen analysis in healthy males. However, the incidence of decreased libido was higher in the pregabalin group compared with placebo (10% vs 0%), but this may have been related to the higher incidence of somnolence, abnormal thinking and dizziness in the pregabalin-treated patients.

7.4 *Effects of pregablin on platelet function*

Pregabalin produced an increased incidence of haemangiosarcoma in male and female mice at 1000 and 5000mg/kg, exposures 5 to 31 times the mean human exposure at the maximum recommended clinical dose. Furthermore, carcinogenicity studies in mice showed a strong association between platelet and bone marrow changes and increased incidence of haemangiosarcoma. Given the role of bone marrow and platelets in endothelial homeostasis and the endothelial origin of haemangiosarcoma, the exposure of endothelial cells to elevated levels of growth factors resulting from increased megakaryopoiesis and increased activation of platelets was considered as the most plausible mode of action for development of haemangiosarcoma. However, pregabalin did not induce haemangiosarcoma in other species such as rats or monkeys. The effects of pregabalin on endothelial cell proliferation could not be assessed in humans, but other parameters such as platelet activation and aggregation were evaluated.

In a phase 1, randomised, double-blind, placebo-controlled, parallel group study **(A0081022, Vol.92)** in 42 healthy subjects, 28 days treatment with pregabalin 300mg bd did not have significant effect on platelet activation assessed by surface expression of platelet P-selectin or Annexin V binding. The level of maximum platelet aggregation was not affected and there was a small, statistically significant reduction in ADP aggregation threshold at 15 days, i.e., a lower concentration of ADP was more likely to increase aggregation. This was in contrast to the findings in mice, where a 28-46% decrease in aggregation was observed. Pregabalin did not have any clinically relevant effect on PFA closure time with ADP or epinephrine and had no effect on soluble thrombomodulin.

Furthermore, a pilot study **(203, Vol.91)** in 16 epilepsy patients showed no apparent change in platelet growth factors - basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF) and thrombopoietin following pregabalin treatment for 1 year. However, the variability was very high and results should be interpreted with caution.

Overall, there were no new malignancies or haemangiosarcomas during the phase II/III pregabalin studies. **However, due to the rare occurrence of haemangiosarcoma, the carcinogenic role of pregabalin in humans cannot be excluded and continuous monitoring of long-term effects on platelets, RBCs and growth factors is recommended.**

Clinically minor, but statistically significant, apparently drug-related increases in mean platelet volumes and decreases in platelet counts were observed in healthy volunteers receiving pregabalin (300mg/day) (RR-MEMO 724-20005, Vol.96- studies 002 and 023); pregabalin did not have any significant effect on platelet aggregation in the same studies in healthy volunteers. The effect of long-term treatment with pregabalin (doses up to 600mg/day) for 2-3 years on platelet counts and RBC counts was analysed in 921 patients (546 in epilepsy studies; 362 in pain studies, 336 being for neuropathic pain; and 13 patients in generalised anxiety disorder studies). Median changes were evaluated every 3 months. In this long-term, non-placebo-controlled dataset, platelet counts showed a slight decrease during 3 to 12 months of pregabalin treatment; this reduction was not sustained and platelet counts returned to baseline by 15 months and then showed a slight increase over baseline by 21 months through 2 to 3 years of treatment **(Tables 9.28.1-9.28.2, p.142).** The frequency of patients with platelet counts shifting to above normal range at endpoint was similar in the placebo-treated (0.5%), pregabalin-treated in double-blind studies only (0.2%) and pregabalin-treated patients in the combined double-blind, open-label dataset (0.3%). The same was true for patients shifting below the normal range (placebo-treated=2.1%, pregabalin-treated in double-blind studies only=2.9% and pregabalin-treated in open-label, long-term studies=2.8%). Data from mouse studies showed increased platelet counts; however, pregabalin treatment was not associated with any persistent elevation in platelet counts in humans.

RBC counts did not show any consistent change over 2 to 3 years of pregabalin treatment. However, interpretation of the above data is limited by lack of long-term placebo-controlled data. Slides from 1415 patients with peripheral blood smears at baseline and during study treatment were examined for platelet abnormalities (Wright-Giemsa stains evaluated using bright-field, oil immersion microscopy); these data were obtained from 6 studies (3 double-blind and 3 open-label) involving 516 epilepsy patients, 671 patients with painful diabetic neuropathy and 228 patients with generalised anxiety disorder or social phobia **(RR-MEMO 720-30207, Vol.95).** Only 4 of the 1125 pregabalin-treated patients had platelet abnormalities during treatment that were not observed at baseline. Each of these cases showed normal fully granulated

platelet aggregates, suggesting *in vitro* partial sample clotting. There were no giant platelets or degranulated platelets. Hence, the morphological changes in platelets found in the 2-year mouse bioassays were not corroborated in humans.

9.8 Summary of safety

- ***The safety of pregabalin was evaluated in over 2500 patients with neuropathic pain due to diabetic peripheral neuropathy (DPN) or post-herpetic neuralgia (PHN) and in over 1600 patients with partial seizures. Dizziness, somnolence, peripheral oedema, asthenia, dry mouth, weight gain, amblyopia and confusion were the most common AEs associated with pregabalin treatment in the DPN and PHN studies and had a significantly higher incidence compared to placebo in the pivotal controlled studies. Vertigo was associated with pregabalin treatment only in the DPN studies. Ataxia (13%), weight gain (10.4%) and tremor were more common in the epilepsy studies compared to the neuropathic pain studies, while dry mouth was less common.***
- ***Dizziness, somnolence, dry mouth, asthenia, nausea and abnormal thinking had an early onset (median time to onset was 1-3 days), while weight gain (8-14 days) and peripheral oedema (15-21 days) had a delayed onset. Dizziness usually continued for a median duration of 10 days, while most other AEs lasted for >21 days.***
- ***Compared to placebo (5-6%), more patients treated with pregabalin withdrew due to AEs (11-15%), mainly due to dizziness, somnolence, confusion and other CNS AEs such as ataxia and tremor. The higher doses of pregabalin were associated with more withdrawals. The incidence of SAEs was small (3%) and involved mainly cardiovascular and respiratory events. None of the deaths in the pregabalin studies appeared to be treatment-related.***
- ***The safety profile of the 150mg/day dose was similar to that of placebo and there was no clear evidence of a dose-response at pregabalin doses >300mg/day. The pattern or severity of AEs was not altered appreciably whether pregabalin was taken 2 or 3 times daily.***
- ***Almost 1500 patients were treated for >52 weeks (548 and 918 in neuropathic pain and epilepsy studies, respectively). The long-term safety profile did not reveal any new concerns and was similar to that observed in the short-term, placebo-controlled studies.***
- ***Although there are no safety data following withdrawal of pregabalin, any risk of withdrawal effects could be minimised by tapering the dose gradually and this has been adequately covered in the proposed PI.***
- ***Most of the vision-related AEs were transient, not associated with reduced visual acuity and occurred concurrently with other CNS AEs. Pregabalin was not associated with any constrictive visual field defects as observed with the other new anti-convulsant vigabatrin. Blurry vision was the most common cause of withdrawals due to vision-related AEs.***
- ***Pregabalin did not cause any clinically significant changes in ECG or BP. There were modest decreases in platelet numbers in the controlled studies, which were not associated with altered platelet function. There were no effects on male reproductive function.***

10. POSTMARKETING EXPERIENCE

There are no postmarketing data as pregabalin has not yet been approved in any country.

11. COMMENTS ON PROPOSED PRODUCT INFORMATION

The following changes are recommended:

i) The application letter states that the sponsor is seeking approval for 25, 50, 75, 100, 150, 200, 225 and 300mg capsules. However, the proposed PI does not mention the 100, 200 and 225mg capsules, The sponsor needs to clarify this.

ii) Clinical studies (page 4 of PI)

Comments: There is no information about the long-term efficacy of pregabalin in the treatment of neuropathic pain or partial seizures. A statement mentioning that efficacy was demonstrated in open-label, uncontrolled studies needs to be incorporated.

iii) Indications: Lyrica (pregabalin) is indicated for the treatment of neuropathic pain in adults and as adjunctive treatment for patients 12 years of age and older with partial seizures with or without secondary generalisation (page 4 of proposed PI)

Comments: The efficacy and safety of pregabalin was evaluated in only 11 epilepsy patients <16 years old. Data in these 11 adolescents suggests that pregabalin treatment was not associated with as much dizziness or somnolence as seen in the adult population, but was associated with behavioural/emotional changes. Due to inadequate data on efficacy and safety of pregabalin as adjunctive treatment of partial seizures in patients <16 years, it is recommended that the indications be changed as follows:

"Lyrica (pregabalin) is indicated for the treatment of neuropathic pain in adults. It is indicated as adjunctive treatment for patients >16 years old with partial seizures with or without secondary generalisation."

12. CONCLUSIONS AND RECOMMENDATIONS

Pregabalin, a structural analogue of gabapentin, produced statistically and clinically significant pain relief in patients with the 2 most common forms of neuropathy- painful diabetic neuropathy and post-herpetic neuralgia. Pregabalin had a rapid onset of action (within the first 2 weeks of treatment) and efficacy was maintained over long-term treatment. Furthermore, an open-label study showed that pregabalin was also effective in patients with neuropathic pain refractory to treatment with gabapentin, tricyclic antidepressants, opioids or other anti-convulsants.

The statistically significant efficacy in terms of mean endpoint pain scores (Likert scale, VAS and PPI) were supported by clinically significant pain relief (>50% reduction from baseline) in more than 40% of patients treated with maximal dose of pregabalin (refer **Table 8.21.1, p.75**). Pain relief was associated with significant improvements in sleep interference scores, bodily pain subscales of SF-36 QOL assessment and clinical and patient global assessment of change (CGIC and PGIC). Overall, a greater percentage of pregabalin-treated patients showed various degrees of pain relief (>20%, >30% to100%) compared to placebo (refer **Table 8.21.2, p.75**).

Pregabalin produced statistically significant meaningful reduction in seizure frequency in patients with partial seizures. Considering the nature of patients enrolled in the epilepsy studies (those who were not responding to treatment with 2-3 anti-convulsants), the observed reductions in seizure frequency with pregabalin treatment were clinically meaningful.

Pregabalin in the dose range 150 to 600mg/day showed a linear dose-response in both neuropathic pain and epilepsy studies.

CNS adverse events such as dizziness and somnolence were commonly associated with pregabalin treatment; other AEs not commonly associated with CNS drugs were weight gain and peripheral oedema. There does

...ot appear to be any sign of platelet abnormality or haemangiosarcoma in humans, as seen in mouse studies, but postmarketing surveillance is required.

Considering the severity of the diseases being treated and the need for new drugs, pregabalin offers a relatively safe and effective option for neuropathic pain and an adjunctive therapy for partial seizures.

- ***Recommendation***

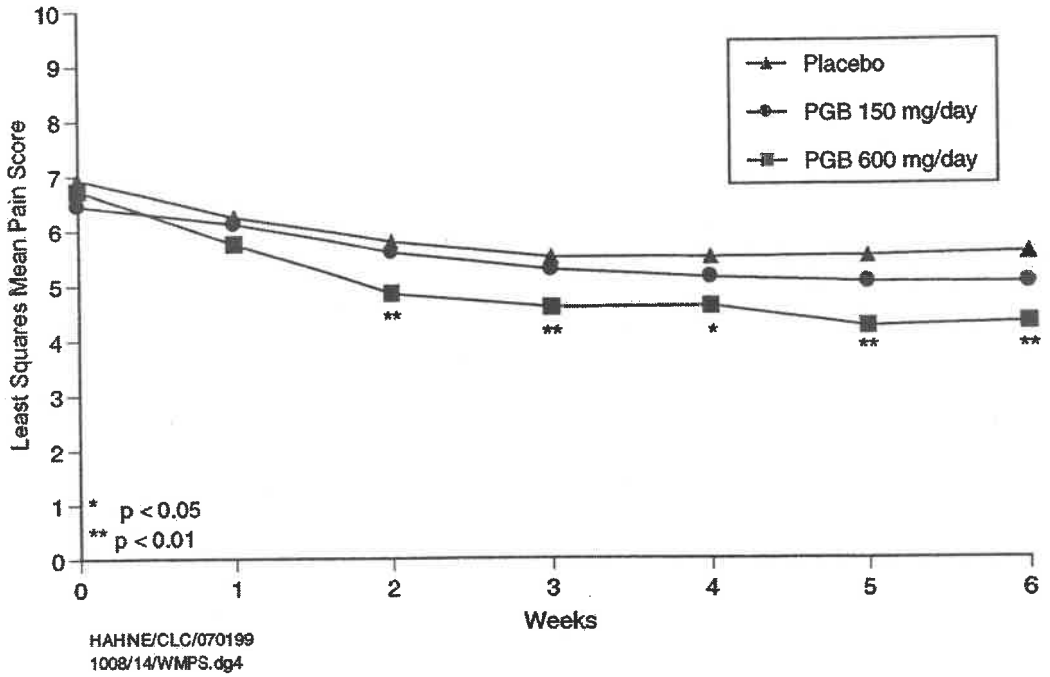
It is recommended that pregabalin (150 to 600mg/day given in 2 divided doses) be approved for treatment of neuropathic pain in adults. It is also recommended as add-on therapy in adults with partial seizures with or without secondary generalisation. The above approval is subject to incorporation of the suggested changes in the proposed PI.

13. REFERENCES:

M. Backonja, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus. JAMA, 1998; 280:1831-1836.

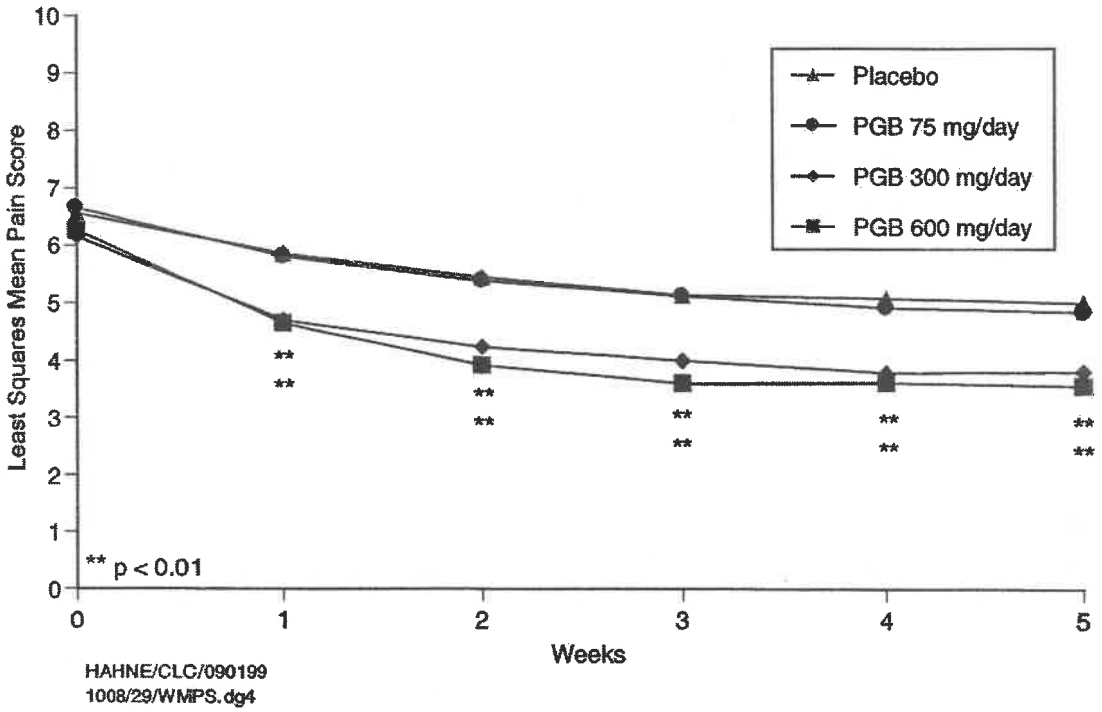
PART B: FIGURES AND TABLES

Figure 8.1: DPN 014



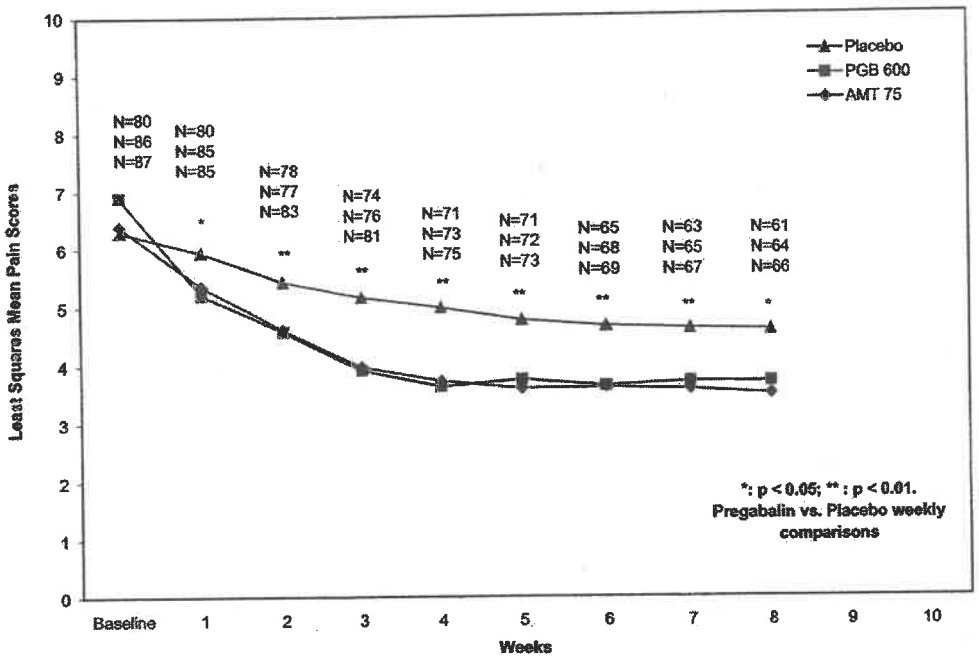
Weekly Least-Squares Mean Pain Scores

Figure 8.2: DPN 029



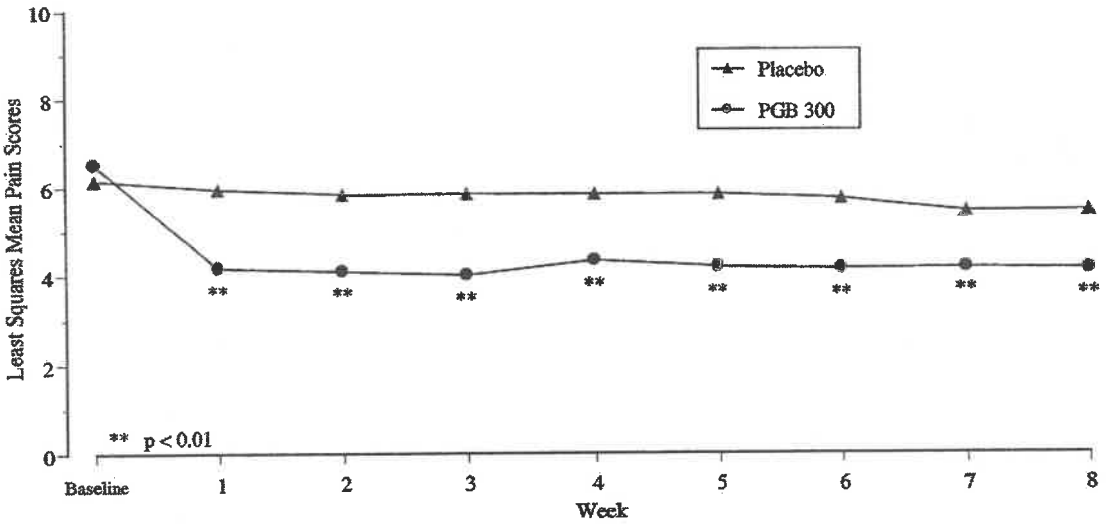
Weekly Least Squares Mean Pain Scores

Figure 8.3: DPN 040



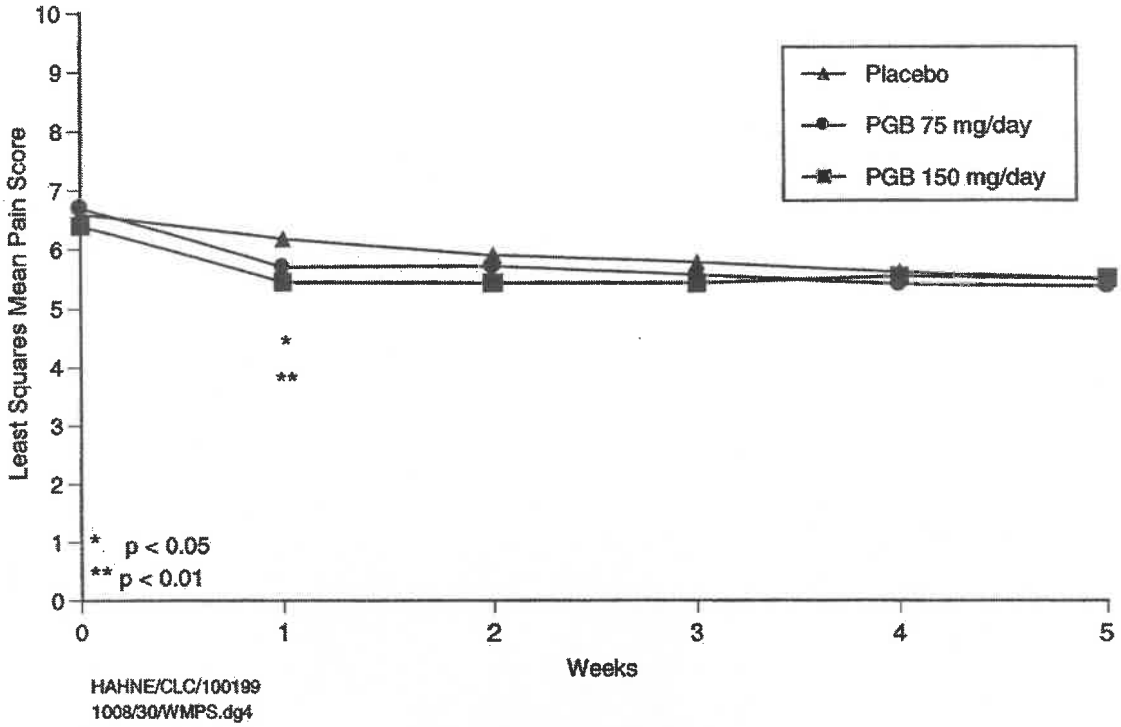
Weekly Least-Squares Mean Pain Scores, Multivariate Analysis

Figure 8.4: DPN 131



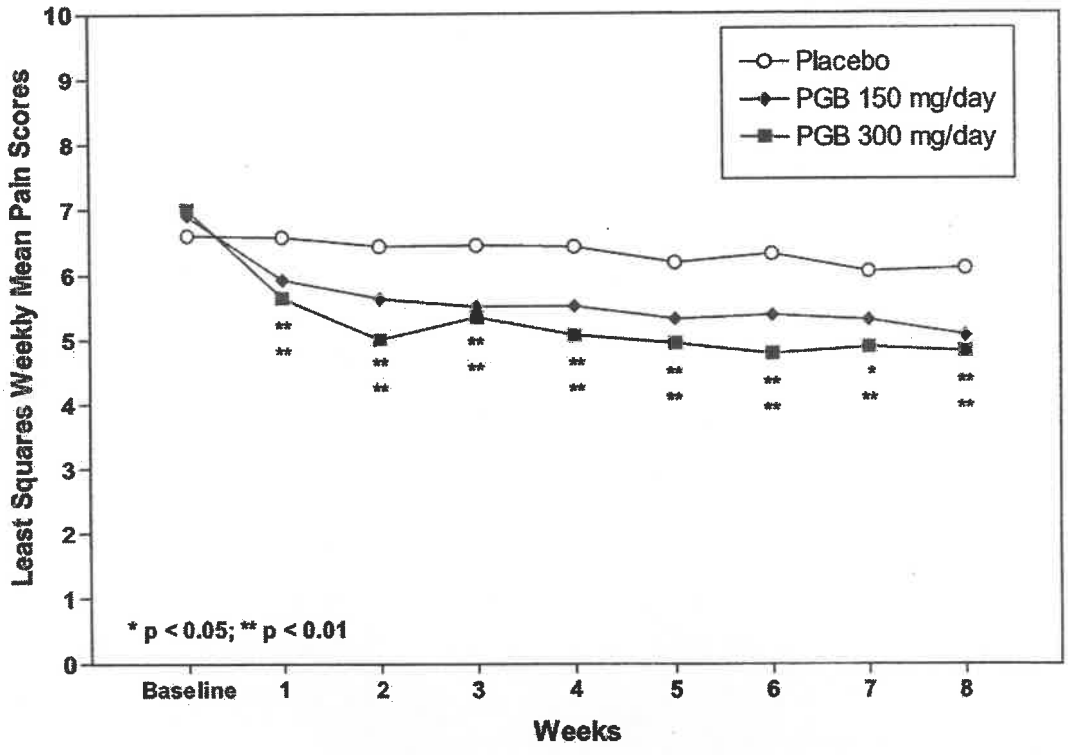
Weekly Least-Squares Mean Pain Scores

Figure 8.5: PHN 030



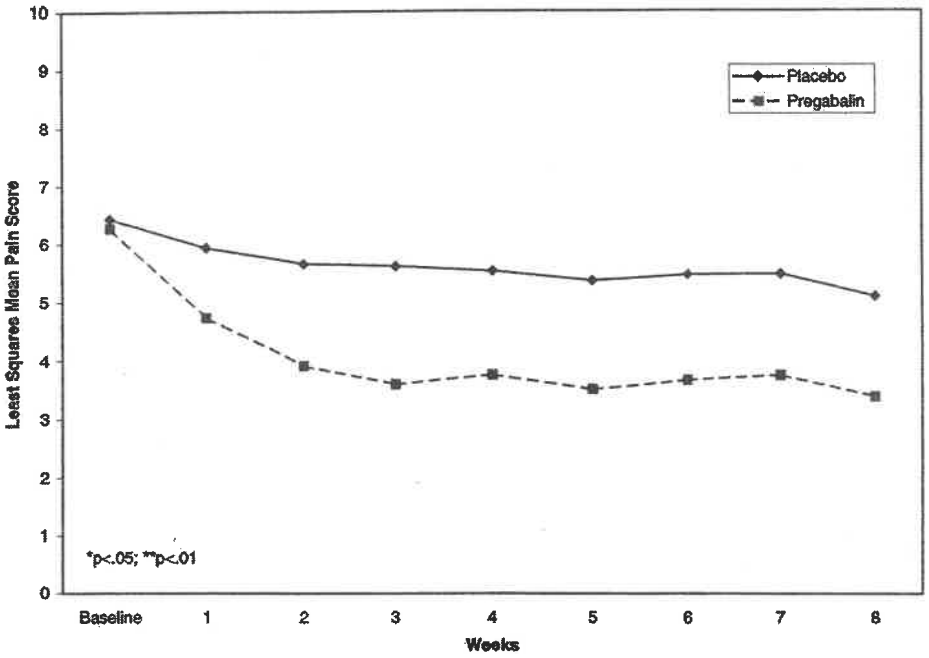
Weekly Least-Squares Mean Pain Scores

Figure 8.6: PHN 045



Weekly Least-Squares Mean Pain Scores, Observed Cases

Figure 8.7: PHN 127



Weekly Least-Squares Mean Pain Scores

Figure 8.8: PHN 196

Weekly Mean Pain Scores: Repeated Measures Analysis

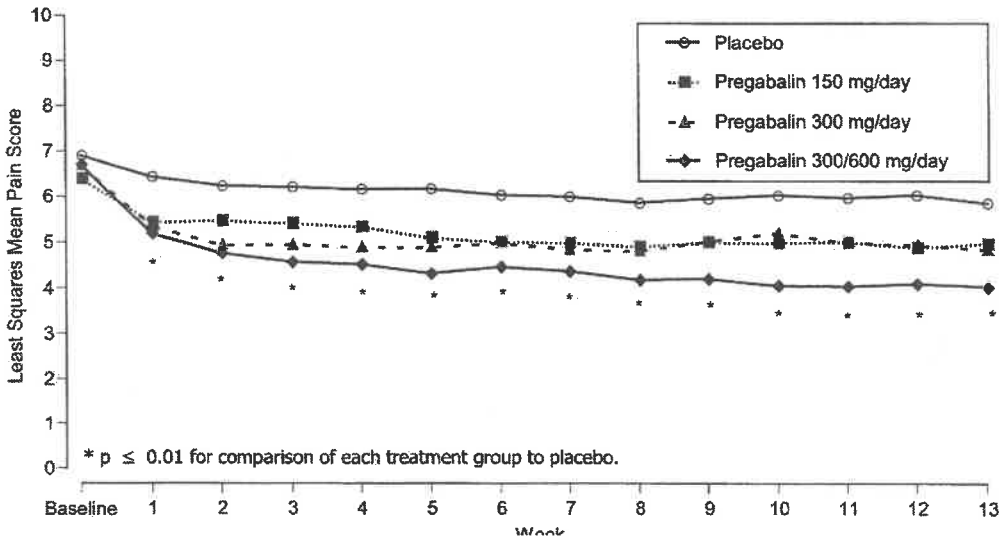


Figure 9.1:

Dizziness Flowchart – All Pregabalin-Treated Patients: Controlled NeP Studies

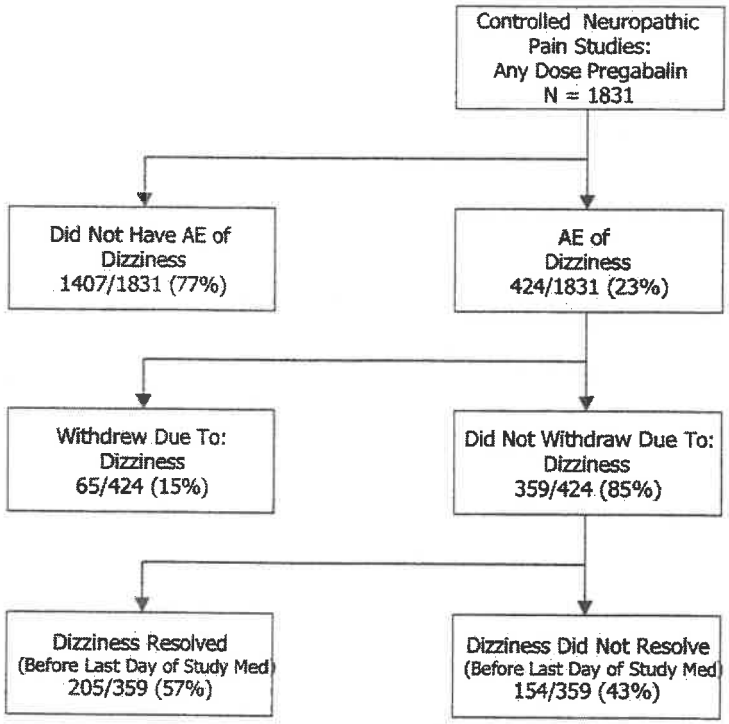


Figure 9.2:

Somnolence Flowchart – All Pregabalin-Treated Patients: Controlled NeP Studies

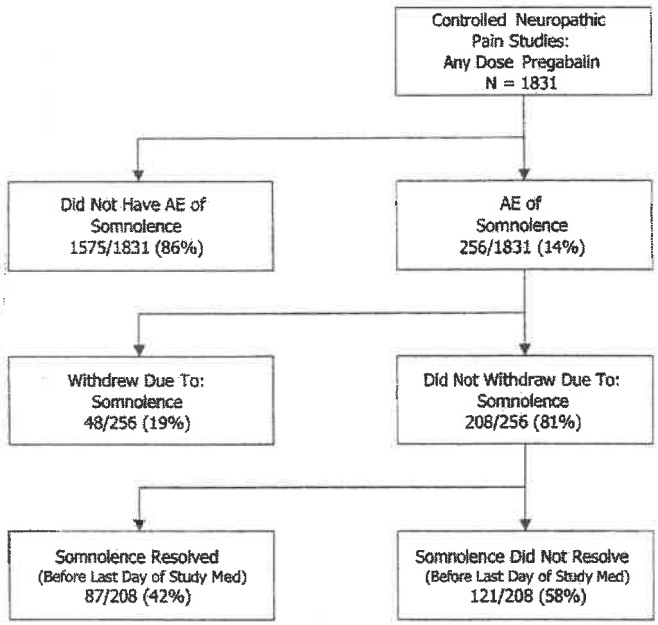


Figure 9.3:

Dizziness Flowchart – All Pregabalin-Treated Patients: Controlled Epilepsy Studies

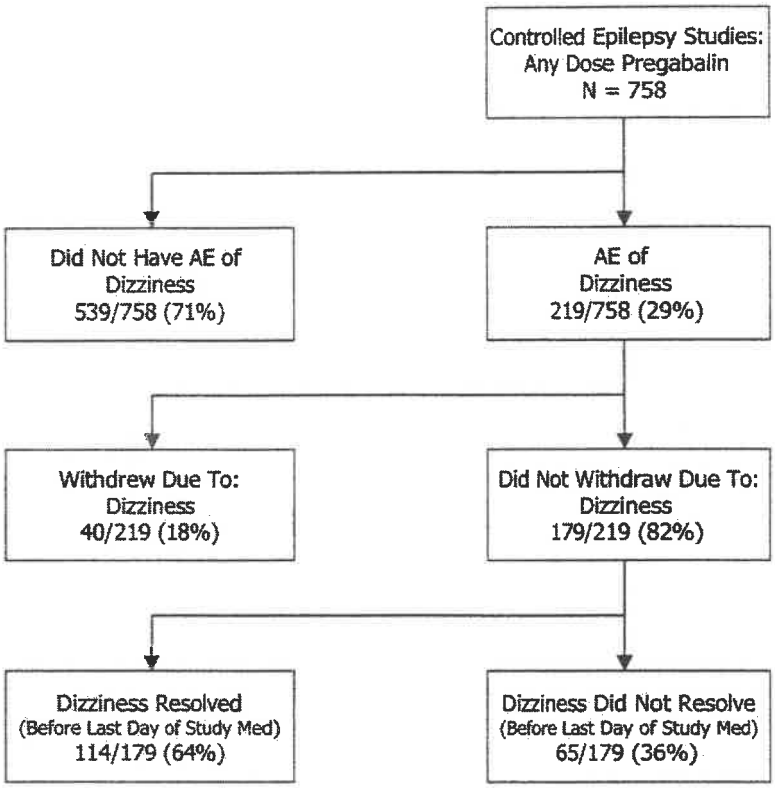


Figure 9.4:

Somnolence Flowchart – All Pregabalin-Treated Patients: Controlled Epilepsy Studies

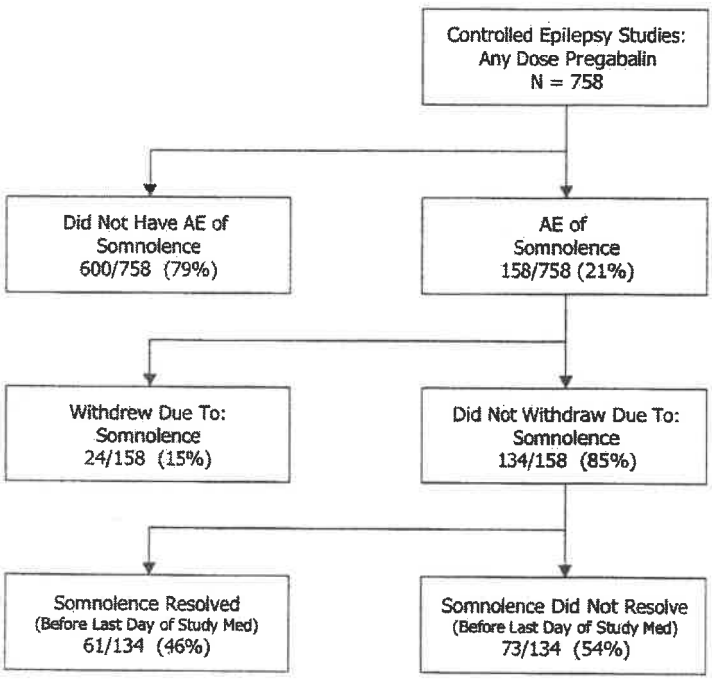


TABLE 6.1: Pharmacodynamic Studies with Pregabalin

Vol, Pages, Study, Author	Subjects, Dose	Objectives, Design of Study	Results, Safety
1008-078-0 O'Connell	9M, 3F (20-50y) 300mg capsules GAB 10mg tablets oxycodone	Objectives: evaluate interaction between pregabalin and oxycodone in healthy subjects Design: randomised, double blind, four-way crossover study; GAB 300mg every 12h for 3 doses or placebo given with 10mg OXY or placebo; treatments separated by 7 day washout; motor and cognitive function, tidal volume, respiratory rates assessed up to 24h after last dose; GAB,OXY kinetics from bloods to 24h; non-compartment methods; data analysed by ANOVA; safety data throughout study.	Results: no effect of combination on respiratory function; no kinetic interactions between GAB and OXY; GAB prolonged reaction time and other tests between 1 and 6h; combined with OXY similar effects were observed; no further effects with the combination Safety: asthenia, somnolence, dizziness, headache main side effects; no clinically significant findings for lab tests, vital signs or physical exams.
1008-076-0 Freestone	8M, 4F (26-47y) 300mg capsules GAB 1mg tablets lorazepam	Objectives: evaluate interaction between pregabalin and lorazepam in healthy volunteers Design: randomised, double blind, four-way crossover study; GAB 300mg every 12h for 3 doses or placebo given with 1mg LOR or placebo; treatments separated by 7 day washout; motor and cognitive function, tidal volume, respiratory rates assessed up to 24h after last dose; GAB, LOR kinetics from bloods to 24h; non-compartment methods; data analysed by ANOVA; safety data throughout study.	Results: no effect of combined treatment on respiratory function; no kinetic interaction between GAB and LOR; significant effects of GAB, LOR alone on reaction time, body sway, alertness; greater decrements when administered together on reaction time, speed of performing tasks, postural stability. Safety: dizziness, nervousness, somnolence main side effects; no clinically significant changes in vital signs, lab tests or physical examinations.
1008-079-0 Freestone	11M, 2F (19-46y) 300mg capsules GAB	Objectives: evaluate interaction between pregabalin and ethanol in healthy volunteers Design: randomised, double blind, placebo controlled, four-way crossover study; GAB 300mg every 12h for 3 doses or placebo given with 0.70g/kg ETOH or placebo 30min later; treatments separated by 7 day washout; motor and cognitive function, tidal volume, respiratory rates assessed up to 24h after last dose; GAB, ETOH kinetics from bloods to 24h; non-compartment methods; data analysed by ANOVA; safety data throughout study.	Results: no evidence for respiratory effects of either drug alone or in combination; ethanol alone adversely affected cognitive function; combination prolonged reaction times; body sway adversely affected by combination; all other tasks similar to ethanol alone; no kinetic interaction. Safety: dizziness, nausea, headache main side effects; no clinically significant effects on lab tests, vital signs or physical exams.

TABLE 7.1: Single Dose Pharmacokinetic Studies with Pregabalin

Vol, Pages, Study, Author	Subjects, Dose	Objectives, Design of Study	Results, Safety
1008-001-0 Hunt	14M, 15F (29-49y) 1, 2 mg solution 5, 10, 25, 50, 75, 125, 200, 300mg capsule doses	Objectives: determine kinetics and safety of rising single doses of pregabalin as a solution and capsule in healthy volunteers Design: double-blind, placebo-controlled, randomised, two-way crossover study; 6 groups of 6 subjects; single doses of drug (n=3) or placebo (n=3) week 1 then crossed over week 2; GAB dose doubles in week 2 up to 600mg maximum; solution doses to group 1 only; 7 days between doses; blood, urine to 60h; GAB levels by HPLC; non-compartment kinetic methods; safety data throughout study.	Results: rapid absorption GAB Tmax ~ 1.3h; Cmax, AUC were dose proportional to 300mg; t½ 4.6 to 6.8h; bioavailability ~ 90% based on urinary excretion data; Safety: headache, dizziness, somnolence main adverse events reported; no clinically significant effects on lab tests, ECGs, vision tests, vital signs.

TABLE 7.2: Single Dose Pharmacokinetic Parameters for Pregabalin

Parameter	*Results*
Cmax (µg/ml)	8.99 (18.5)
Tmax (h)	1.00 (21.5)
AUC(0-∞) (µg . h/ml)	64.1 (19.8)
Cl/F (ml/min)	80.4 (16.7)
Vd/F (L)	41.4 (19.4)
t½ (h)	6.01 (15.5)

Data are means (%RSD)
Data from study 1008-023

TABLE 7.3: Multiple Dose Kinetic Studies with Pregabalin

Vol, Pages, Study, Author	Subjects, Dose	Objectives, Design of Study	Results, Safety
1008-002-0 Hunt	33M, 24F (19-50y) 25, 100, 200, 300mg GAB capsules PBO	Objectives: determine the kinetics of pregabalin after multiple oral doses in healthy subjects Design: randomised, double-blind, placebo controlled; seven groups of 5-10 subjects: single dose of GAB days1, 22; repeated doses every 8hours days 2-21; 1-2 subjects per group on PBO; bloods, urine days 1, 22 to 60h; trough levels days 8,9,10, 12, 15, 18; GAB levels by HPLC; non-compartment kinetic methods; safety data throughout.	Results: GAB rapidly absorbed after single, multiple doses; Tmax 0.8-1.4 h; Cmax, AUC dose proportional; t½ 5.5- 6.7h; independent of dose; steady state achieved within 24-48h; 90-97% of dose excreted in urine; renal clearance 67-80.9ml/min independent of dose. Safety: dizziness, somnolence, headache main side effects; no clinically significant effects on safety parameters.
1008-023-0 Hunt	14M, 2F (18-48y) 300mg capsules PBO	Objectives: determine multiple dose kinetics of pregabalin in healthy volunteers Design: randomised, double-blind, placebo controlled; 12 subjects received GAB, 3 subjects placebo; doses repeated every 8h for 4 weeks; single dose day 29; bloods to 8h after first dose day 1, to 48h after day 29; GAB levels by HPLC; non-compartment kinetic methods; safety data throughout study: physical exams, vital signs, ECG, clinical lab tests.	Results: GAB rapidly absorbed after single, repeated doses; Tmax ~1h; t½ ~6h after single and multiple doses. Safety: dizziness, somnolence, constipation main side effects; no clinically important changes in vital signs, ECGs, clinical lab tests, physical exams.

TABLE 7.4: Repeated Dose Pharmacokinetic Parameters for Pregabalin

Parameters	*Results*
Cmax (µg / ml)	13.2 (16.8)
Tmax (h)	1.08 (43.3)
AUC (µg . h / ml)	67.4 (14.5)
Cl/F (ml/min)	75.6 (14.4)
Vd/F (L)	42.8 (17.4)
t½ (h)	6.55 (11.2)

Data are means (%RSD)
Data from study 1008-023

TABLE 7.5: Pharmacokinetics of Pregabalin in Special Populations

Vol, Pages, Study, Author	Subjects, Dose	Objectives, Design of Study	Results, Safety
1008-121-0 Sack	8M, 4F (30-66y) 2 X 25mg capsules	Objectives: determine kinetics of pregabalin in patients undergoing chronic haemodialysis Design: open label, single dose study; patients with end stage renal disease undergoing dialysis three times weekly; dose 24h before a scheduled dialysis; blood, urine samples to 168 and 48h respectively; GAB levels by HPLC; non-compartment kinetic methods; safety data throughout study.	Results: t½ ~ 55h; substantially prolonged from normal volunteers, severe renal failure; during dialysis t½ ~ 3h; high dialysis clearance of GAB. Safety: leg cramps, headache, nausea, diarrhoea main side effects; no important changes in clinical lab tests, physical exams, ECGs, vital signs.
1008-049 Swan	15M, 11F (38-75y) 2 X 25mg capsules	Objectives: determine the effects of varying degrees of renal failure on pregabalin kinetics Design: open label, parallel group, single dose study; four groups of 6-8 subjects: controls CrCl > 80ml.min; CrCl 51-80ml/min; CrCl 30-50ml/min; CrCl < 30ml/min; 50mg given after overnight fast; bloods, urine for up to 168h after dose; GAB levels by HPLC; non-compartment kinetic methods; relationship between kinetics and CrCl by regression; safety data throughout study.	Results: Cmax, AUC, t½ increased with decreasing renal function; Vd independent of renal function; decreases in Cl/F, Clr correlated with decreasing CrCl; non-renal clearance minor route of elimination for GAB Safety: asthenia, headache, dizziness, somnolence main side effects; no other clinically significant safety issues

TABLE 7.6: Drug Interaction Studies with Pregabalin

Vol, Pages, Study, Author	Subjects, Dose	Objectives, Design of Study	Results, Safety
1008-020 Hounslow	7M, 5F (26-61y) 2 X 100mg capsules	Objectives: to investigate the potential kinetic interaction between pregabalin and lamotrigine in patients with epilepsy. Design: open label study in patients maintained on lamotrigine; subjects received 200mg GAB every 8h for 7days with a single dose on day 8; AM doses given after 8h fast; trough bloods days 1, 2, 3, 4, 6, 7, 8 with sampling to 48h day 8; GAB levels by HPLC; lamotrigine trough levels day 1, 2, 3, 4, 6, 7, 8, 9, 10; lamotrigine levels by LC-MS; non-compartment kinetic methods; effect on plasma lamotrigine by ANOVA; safety data throughout.	Results: trough levels lamotrigine not altered by GAB; differences in mean levels<10%; steady state GAB kinetic data similar to retrospective control data. Safety: dizziness, dry mouth, asthenia, somnolence main side effects; two serious events: seizures; no clinically significant effects on physical exam, lab tests, vital signs.
1008-019-0 Brodie	8M, 6F (22-62y) 2 X 100mg capsules	Objectives: to investigate the potential kinetic interaction between pregabalin and carbamazepine in patients with epilepsy. Design: open label study in patients maintained on carbamazepine; subjects received 200mg GAB every 8h for 7days with a single dose on day 8; AM doses given after 8h fast; trough bloods days 1, 2, 3, 4, 6, 7, 8 with sampling to 48h day 8; GAB levels by HPLC; carbamazepine trough levels day 1, 2, 3, 4, 6, 7, 8, 9, 10; carbamazepine levels by HPLC; non-compartment kinetic methods; effect on plasma carbamazepine by ANOVA; safety data throughout.	Results: no change in carbamazepine, epoxide levels across the 10 days of sampling; steady state GAB kinetic data similar to retrospective controls. Safety: dizziness, nystagmus, asthenia, dry mouth main side effects; four serious events seizures; no clinically important changes in vital signs, lab tests, ECGs; some minor physical changes on examination (nystagmus, abnormal movements).

Table 7.6 (cont.):

Vol, Pages, Study, Author	Subjects, Dose	Objectives, Design of Study	Results, Safety
1008-075 Hunt	15F (32-43y) 2 X 100mg Capsules GAB Ortho-Novum 1/35 tablets	**Objectives:** to examine the interaction between pregabalin and oral contraceptives in healthy women **Design:** open label, multiple dose study over three menstrual cycles; 200mg GAB every 8h for 22days in third cycle; Ortho-Novum for three cycles; plasma samples to 48h days 49, 77 for ethinyl oestradiol, norethindrone; levels by GC-MS; trough levels of Gab days 57,73,75, 77; non-compartment kinetics; ANOVA on log transformed Cmax, AUC with CIs; safety data throughout.	**Results:** pregabalin achieved steady state during test period; no effect of GAB on kinetics of ethynyl oestradiol or norethindrone; (90% CIs within equivalence limits). **Safety:** urogenital symptoms, headache most common side effects; no clinically significant effects on lab test, ECGs.
1008-077 Posvar	10M, 2F (21-44y) 1 X 100mg capsule GAB 1 X 300mg Capsule gabapentin	**Objectives:** examine the interaction between pregabalin and gabapentin in healthy volunteers **Design:** single-dose, randomised, open label, three-way crossover study; 1 X 100mg GAB, 1 X 300mg gabapentin; both capsules together; 7 day washout between doses; all given after overnight fast; serial blood s to 48h after each regimen; drug levels by LC-MS; non-compartment kinetics; ANOVA on log transformed values; safety data throughout study.	**Results:** mean Cmax, AUC gabapentin reduced by about 10% by GAB; mean Cmax GAB reduced by ~26% by gabapentin; AUC not affected; no clinically relevant interaction. **Safety:** somnolence, dizziness main side effects reported; no clinically significant findings on lab tests, vital signs, physical examinations.
1008-144-0 Hunt	15M, 6F (21-49y) 1 X 100mg capsules 8h day 1 2 X 100mg capsules 8h day 2 2 X 100mg capsules single dose day 3 GAB 1 X 400mg capsules 8h day 1, 2 1 X 400mg capsule single dose day 3 gabapentin	**Objectives**: examine the interaction of pregabalin and gabapentin after repeated doses in healthy volunteers. **Design:** single blind, randomised three-way crossover study; 3 day treatment periods with GAB, gabapentin and combination; 5 day washout between treatment periods; serial blood samples days 3, 10 and 17 for 36h; drugs assayed by LC-MS; non-compartment kinetic methods; ANOVA on log-transformed data and 90% CIs calculated; safety data throughout study.	**Results:** gabapentin reduced Cmax of GAB by 18%; no effect on AUC; no effect of GAB on gabapentin kinetics; no significant interaction between the two drugs. Safety: somnolence, dizziness, abnormal thinking main side effects; 1 withdrawal due to abdominal pain (cholecystitis); no clinically significant effects vital signs, ECGs or lab tests.

TABLE 7.7: Bioequivalence and Bioavailability Studies with Pregabalin

Vol, Pages, Study, Author	Subjects, Dose	Objectives, Design of Study	Results, Safety
1008-003 Anderson	1M, 11F (38-65y) 1 X 100mg capsule	**Objectives**: determine the effect of food on pregabalin bioavailability in healthy volunteers **Design:** open label, randomised, three-way crossover; single dose GAB given after 8hr overnight fast, 15 minutes after breakfast, dissolved in water after 8hr overnight fast; minimum 10 days washout between doses; bloods to 60h after each dose; GAB levels by HPLC; non-compartment kinetic methods; comparisons by ANOVA on log transformed data with 90% confidence intervals on mean ratios; safety data throughout study.	**Results**: food reduced Cmax and delayed Tmax but no difference in AUC (90% CI: 0.92-0.98); no difference for Cmax, Tmax or AUC for solution or capsule (90% CI: 0.96-1.02) **Safety:** dizziness, somnolence, euphoria main side effects;1 withdrawal due to elevated amylase levels; no clinically significant effects on physical exams, vital signs, ECGs or vision tests.
1008-128 Sedman	12 M, 2 F (31-65y) 1 X 150mg capsule (market image)	**Objectives:** determine the effect of food on pregabalin bioavailability in healthy volunteers **Design:** Open label, randomised, two-way crossover study; single dose GAB given 10h after overnight fast, immediately after high fat breakfast; 7 day washout between doses; bloods to 48h after dose; GAB levels by HPLC; non-compartment kinetic methods; comparisons by ANOVA on log transformed data with 90% confidence intervals on mean ratios; safety data throughout study.	**Results:** high fat meal delayed Tmax and reduced Cmax; no effect on AUC (90% CI: 0.91-0.95) **Safety:** dizziness, somnolence, headache main side effects; no clinically significant findings on physical exams, vital signs, lab tests

Table 8.1: Pivotal placebo-controlled diabetic peripheral neuropathy (DPN) studies

Study nos, location, investigators	Study design	Subjects demographics	Dosage, duration, route and form of study medication	Endpoints	Efficacy results	Safety/AEs
1008-14, Mod.5-Vol.35 at 29 centres in USA & Canada. 27/3/1998 to 18/3/1999.	Randomised, DB, parallel-gp, placebo-controlled study. 1-week baseline phase, foll by 6wks of DB Rx (2 week titration phase, then max fixed dose for next 4 wks).	246 patients with painful, diabetic distal, symmetrical, sensiromotor polyneuropathy for 1-5 years with HbA1c≤11%.Daily pain score ≥4 and VAS pain scale≥40mm Sex: 149M: 97F Age: 26-78yrs, mean=57yrs. Race: White=206, Black=19, Hispanic=18, Others=3. Type 1 diabetes=23; type 2 diabetes=223; mean duration:8-10yrs	Pregabalin 25 and 100mg capsules & matching placebo capsules. Daily dose given orally, TID Pregabalin 600mg/day (n=82) Pregabalin 150mg/day (n=79), Placebo (n=85)	Primary: mean endpoint pain score rated by patient. Secondary: SF-MPQ scores, sleep interference, Clinical global impression of change (CGIC) and patient global impression of change (PGIC), SF-36 quality of life (QOL) questionnaire	PGB 600mg showed stat. sig greater efficacy compared with placebo for all efficacy endpoints, except POMS; 150mg PGB not sig. better than placebo. Both 600mg and 150mg showed sig. improvements in only the bodily domain of SQ-36 QOL, no sig. changes in other 7 domains. Responders (>50% decrease in mean pain score) was PGB 600=39%, 150mg=19%, placebo=15%. 1 patient each from PGB 600mg and placebo gp withdrew due to lack of efficacy.	AE incidence: PGB 600mg=85%, 150mg=56%, placebo=57%.Dizziness (38%, 10% & 2.4%, resp), somnolence (22, 5, 3.5%, resp), peripheral oedema (17, 4, 4.8%, resp), headache, asthenia (12, 3.8, 3.5%, resp), accidental injury, weight gain, amblyopia & dry mouth more frequent in PGB 600mg gp. SAEs: 600mg=5 (retinal oedema, migraine, dyspnea/gen oedema, bronchitis/CHF, accidental injury); 150mg=1 (CAD), placebo=2. No deaths; 13 withdrawals due to AEs (pregabalin 600mg=7, 150mg=2, placebo=4)-somnolence, dizziness, headache most common. No sig. changes in vital signs or lab parameters.

Table 8.2: Pivotal placebo-controlled DPN studies

Study nos, location, investigators	Study design	Subjects demographics	Dosage, duration, route and form of study medication	Endpoints	Efficacy results	Safety/AEs
1008-029, Mod.5-Vol.36 at 45 centres in USA. 21/08/1998 to 24/06/1999.	Randomised, DB, parallel-gp, placebo-controlled study. 1-week baseline phase, foll by 5wks of DB Rx (1 week titration phase, only for the 600mg PGB gp, fixed dose for next 4 wks).	337 patients with painful, diabetic distal, symmetrical, sensiromotor polyneuropathy for 1-5 years with HbA1c≤11%.Daily pain score ≥4 and VAS pain scale≥40mm Sex: 202M: 135F Age: 26-85yrs, mean=60yrs. Race: White=318, Black=12, Hispanic=6, Others=1. Type 1 diabetes=31; type 2 diabetes=306; mean duration:8-11yrs	Pregabalin 25 and 100mg capsules & matching placebo capsules. Daily dose given orally, TID Pregabalin 600mg/day (n=82) Pregabalin 300mg/day (n=81), Pregabalin 75mg/day (n=77) Placebo (n=97)	Primary: mean endpoint pain score rated by patient. Secondary: SF-MPQ scores, sleep interference, Clinical global impression of change (CGIC) and patient global impression of change (PGIC), SF-36 quality of life (QOL) questionnaire, POMS.	PGB 300mg & 600mg showed stat. sig greater efficacy compared with placebo for all efficacy endpoints, except for POMS only 300mg sig better than placebo for tension/anxiety mood scale and for SQ-36QOL, 300 & 600mg sig better than placebo for social func & bodily pain domains. Responders (>50% decrease in mean pain score) was PGB 600=48%, 300mg=46%, 75mg=22%, placebo=18%. Withdrawals due to lack of efficacy: plac=2, 75mg=4, 300mg=0, 600mg=0.	AE incidence: PGB 600mg=87%, 300mg=75%, 75mg= 62%, placebo=67%. Dizziness (39%, 27%, 8% & 5%, resp), somnolence (27, 23, 4 &4%, resp), peripheral oedema (13, 7, 4 & 2%, resp), amblyopia (8.5, 5, 2.6 & 1%, resp) accidental injury more frequent in PGB 600 &300mg gp. SAEs: 600mg=4 (accidental injury, chest pain, sinus bradycardia, ruptured spleen); 300mg=0, 75mg=1(chest pain), placebo=3. No deaths; 18 withdrawals due to AEs (pregabalin 600mg=10, 300mg=3, 75mg=2, placebo=3)- somnolence, dizziness, headache most common. Clinically imp ↓ in platelets counts in 4 pts (2, 1, 1 & 0, resp)

Table 8.3: Pivotal placebo-controlled DPN studies

Study nos, location, investigators	Study design	Subjects demographics	Dosage, duration, route and form of study medication	Endpoints	Efficacy results	Safety/AEs
1008-040, Mod.5-Vol.38 at 49 centres in Europe, Australia & South Africa. 6/9/1999 to 14/12/2000.	Randomised, DB, parallel-gp, placebo-controlled study. 1-week baseline phase, foll by 9 wks of DB Rx (2 week titration phase, then 6 ks of fixed dose DB Rx & ending with a 1-week DB withdrawal phase).	254 patients with painful, diabetic distal, symmetrical, sensiromotor polyneuropathy for ≥1 years with HbA1c≤11%.Dail y pain score ≥4 and VAS pain scale≥40mm Sex: 146M: 108F Age: 22-80yrs, mean=60yrs. Race: White=235, Black=2, Others=17. Type 1 diabetes=36; type 2 diabetes=218; mean duration:11-12yrs	Pregabalin (PGB)100mg capsules, amitryptiline 25mg tablets & matching placebo capsules/tablets. Daily dose given orally, TID Pregabalin 600mg/day (n=86) Amitryptiline 75mg/day (n=87), Placebo (n=81)	Primary: mean endpoint pain score rated by patient. Secondary: SF-MPQ scores, sleep interference, Clinical (CGIC) and patient global impression of change (PGIC), SF-36 quality of life (QOL) questionnaire . Mood assessment by HADS.	PGB600mg not ss better than placebo for primary efficacy endpoint, while amitryp was ss better than placebo. Nos of responders also ss better only with amitryp: 29.6%, 39.5% & 46% with placebo, PGB & amitryp, resp. However, PGB ss better than placebo in mean pain scores (weeks 1-8), VAS scores, PPI index, mean sleep interference scores, 5 domains of the SF-36, & the anxiety subscale of the HADS. Primary efficacy endpoint slightly in favour of amitryp compared to PGB.51% decrease in pts showing allodynia in PGB gp.	AE incidence: PGB 600mg=66%, amitryp75mg=68%, placebo=47%. Dizziness (21%) most common with PGB600mg & dry mouth (25%) most common with amitryp75mg. SAEs: PGB600mg=4 (infection, cholecystitis, pneumonia, DM); amitryp=5 (accidental injury, suicide attempt, tachycardia, endomaterial CA, GI disorder),placebo=3. 32 withdrawals due to AEs: PGB 600mg=11(13%, dizziness, somnolence most common), Amitryp=16 (18%, somnolence, vertigo), placebo=5(6%). 1 death unrelated, 73 days after discontinuing PGB Rx. Clinically sig (>7%) weight gain in more PGB pts (10%, 1% &3% with PGB, amitryp & placebo, resp). Orthostatic hypotension-4% each in PGB & amitryp vs 1% of placebo pts.

Table 8.4: Pivotal placebo-controlled DPN studies

Study nos, location, investigators	Study design	Subjects demographics	Dosage, duration, route and form of study medication	Endpoints	Efficacy results	Safety/AEs
1008-131, Mod.5-Vol.39 at 25 centres in USA. 10/12/99 to 9/5/2000.	Phase 2/3 randomised, DB, parallel-gp, placebo-controlled study. 1-week baseline phase, foll by 8 wks of DB Rx. At end of Rx- pts either continued in open-label study 1008-134 at 300mg/day or discontinued Rx.	146 patients with painful, diabetic distal, symmetrical, sensiromotor polyneuropathy for ≥1 years with HbA1c≤11%.Dai ly pain score ≥4 and VAS pain scale≥40mm Sex: 82M: 64F Age: 21-83yrs, mean=60yrs. Race: White=128, Black=9, Hispanic=8, Others=1. Type 1 diabetes=19; type 2 diabetes=127; mean duration:9yrs	Pregabalin (PGB)100mg capsules & matching placebo capsules. Daily dose given orally, TID Pregabalin 300mg/day (n=76) Placebo (n=70)	Primary: mean endpoint pain score rated by patient. Secondary: SF-MPQ scores, sleep interference, Clinical (CGIC) and patient global impression of change (PGIC), SF-36 quality of life (QOL) questionnaire Mood assessment by POMS.	PGB300mg ss better than placebo for primary efficacy endpoint. Nos.of responders also ss better 40% vs 14.5%. PGB300mg also ss better than placebo in mean pain scores (weeks 1-8), VAS scores, PPI index, mean sleep interference scores, bodily pain domain of the SF-36, & the anxiety/tension & total mood disturbance subscales of the POMS. PGIC & CGIC showed ss greater nos. of PGB with improvement (63-67%) vs placebo (39%). Pts withdrawn due to lack of efficacy: plac=3 (4.3%), PGB300mg=1 (1.3%).	AE incidence: PGB 300mg=79%, placebo=58.6%. Dizziness (36% vs 11%), somnolence (20 vs 3%) & peripheral oedema (10.5% vs 1.4%) more common with PGB300mg compared to placebo. SAEs: PGB300mg=1 (angina), placebo=1 (chest pain). 10 withdrawals due to AEs: PGB 300mg=8(10.5%, dizziness, somnolence most common), placebo=2(3%). No deaths. Clinically sig (>7%) weight gain in more PGB pts (4.3% & 1.4% with PGB & placebo, resp). Orthostatic hypotension-in 2 PGB and 3 placebo pts. No other clinically sig changes in lab parameters/vital signs.

Table 8.5: Pivotal placebo-controlled DPN studies

Study nos, location, investigators	Study design	Subjects demographics	Dosage, duration, route and form of study medication	Endpoints	Efficacy results	Safety/AEs
1008-149, Mod.5-Vol.40-42 at 58 centres in Europe, Australia & South Africa. 30/11/2000 to 23/5/2002.	Phase 3 randomised, DB, parallel-gp, placebo-controlled study. 1-week baseline phase, foll by 12 wks of DB Rx, incl. 1-week titration phase. At end of Rx-pts either continued in open-label study 1008-165 or discontinued Rx.	395 patients with painful, diabetic distal, symmetrical, sensiromotor polyneuropathy for ≥1 years with HbA1c≤11%.Daily pain score ≥4 and VAS pain scale≥40mm Sex: 219M: 176F Age: 21-85yrs, mean=59yrs. Race: White=380, Black=2, Others=13. Normal CLcr (>60ml/min)=348, Low CLcr (30-60ml/min)=47. MITT population, n=384: Type 1 diabetes=56; type 2 diabetes=328; mean duration:12-13yrs.	Pregabalin (PGB) 75, 150, 200 & 300mg capsules & matching placebo capsules. Daily dose given orally, BID 1)Pregabalin 150mg/day (n=99), 2)300mg/day (n=99), 3)300/600mg/day based on CLcr (n=101), low given 300mg & normal CLcr given 600mg/day. 4)Placebo (n=96).	Primary: mean endpoint pain score rated by patient. Secondary: SF-MPQ scores, sleep interference, Clinical (CGIC) and patient global impression of change (PGIC), medical outcomes study (MOS) sleep scale; SF-36 health survey, EuroQOL health state profile (EQ-5D) & signs/symptoms of allodynia & hyperalgesia.	Only PGB300/600mg gp was ss better than placebo for primary efficacy endpoint, from week 2 to 12. Similar results for ITT & PP analysis. Nos.of responders also ss better only with 300/600mg gp (46%, 33.3%, 34.4% & 30% with PGB 300/600, 300, 150mg & placebo, resp). PGB300/600mg ss better than placebo in VAS, PPI index, CGIC, PGIC, SF-MPQ sensory& total; & EQ-5D QOL utility scores. All PGB dose gps ss better than placebo most of the MOS-study sleep scales. Pts withdrawn due to lack of efficacy: plac=11 (11.5%), PGB150mg=8 (8.1%), 300mg=5 (5.1%) &300/600mg=3 (3%).	AE incidence: PGB 300/600mg=67%, 300mg=64%, 150mg=51%, placebo=41%. Dizziness (15, 11, 4 & 2%, resp), somnolence (8, 4, 5 & 1%, resp) & peripheral oedema (12, 11, 7 &3%, resp) more common in PGB. 2 deaths –unrelated 1 each in 150mg & 300mg gps (heart failure & MI). SAEs: PGB300/600mg=6 , 300mg=3, 150mg=4, placebo=2. 32 withdrawals due to AEs: PGB 300/600mg=13(13%),300mg=11 (11%), 150mg=5 (5%), placebo=3(3%)- dizziness, vertigo & peripheral oedema most common in PGB gps. Clinically sig (>7%) weight gain in more PGB pts (25 in any PGB gp vs 1 in placebo gp). Orthostatic hypotension-in 8%, 3%, 4% &7% of PBG 300/600, 300, 150mg & placebo pts, resp. No other clinically sig changes in lab parameters/vital signs.

Table 8.6: Pivotal placebo-controlled postherpetic neuralgia (PHN) studies

Study nos, location, investigators	Study design	Subjects demographics	Dosage, duration, route and form of study medication	Endpoints	Efficacy results	Safety/AEs
1008-030, Mod.5-Vol.44. at 29 centres in USA. 14/10/98 to 26/7/99.	Phase 2/3 randomised, DB, parallel-gp, placebo-controlled study. 1-week baseline phase, foll by 5 wks of DB Rx, incl. 1-week titration phase. At end of Rx-pts either continued in open-label study 1008-165 or discontinued Rx.	255 patients with pain present for >3mths after healing of a herpes zoster rash. Daily pain score ≥4 and VAS pain scale≥40mm Sex: 129M: 126F Age: 34-87yrs, mean=71yrs. Race: White=246, Black=3, Hispanic=4, Others=2. Duration of PHN: 26-37mths (mean=32mths).	Pregabalin (PGB) 25 & 50mg capsules & matching placebo capsules. Daily dose given orally, TID 1)Pregabalin 75mg/day (n=84), 2)150mg/day (n=84), 3)Placebo (n=88).	Primary: mean endpoint pain score rated by patient. Secondary: SF-MPQ scores, sleep interference, Clinical (CGIC) and patient global impression of change (PGIC), SF-36 QOL, POMS. Safety: visual & neurological exams, vital signs, lab parameters.	Compared to placebo, no ss improvement in mean endpoint pain score with either PGB gps, except at week 1. No diff. in responder rates: 22%, 20.5% &17.2% with PGB 150mg, 75mg/day & placebo, resp. Sig efficacy with both doses of PGB seen for 1-3 weeks for SF-MCQ scores, sleep interference scores. No ss diff. seen in the PGIC, CGIC, SF-36 QOL or POMS with either 75 or 150mg/day PGB. Withdrawals due to LOE: none in PGB gps & 2 in placebo gp.	AE incidence: PGB150mg=67.5%, 75mg=63.1%, placebo=52.3%. Dizziness (15.7%, 10.7% &3.4%, resp), amblyopia (10.8, 1.2 & 5.7%, resp), somnolence (9.6, 8.3 & 4.5%, resp) & headache (8.4, 4.8 & 2.3%, resp) more common in PGB gps. No deaths. SAEs: 150mg=1 (chest pain), 75mg=2 (chest pain/ CHF, lymphoma like reaction/pain), placebo=1. 13 withdrawals due to AEs: PGB 150mg=5(6%), 75mg=2 (2.4%), placebo=6(6.8%). No diff in nos. of pts showing weight gain: 0, 3 & 4 in 150mg, 75mg & placebo gps, resp. Orthostatic hypotension-in 3 pts each in 75mg & 150mg PGB gps & 2 placebo pts. No other clinically sig changes in lab parameters/vital signs.

Table 8.7: Pivotal placebo-controlled postherpetic neuralgia (PHN) studies

Study nos, location, investigators	Study design	Subjects demographics	Dosage, duration, route and form of study medication	Endpoints	Efficacy results	Safety/AEs
1008-045, Mod.5-Vol.45-46 at 53 centres in Europe & Australia 17/2/1999 to 19/6/2000	Phase 3 randomised, DB, parallel-gp, placebo-controlled study. 1-week baseline phase, foll by 8 wks of DB Rx, incl. 1-week titration phase. Pts may continue into open-label study 061.	238 patients with pain present for >3mths after healing of a herpes zoster rash. Daily pain score ≥4 and VAS pain scale≥40mm Sex: 107M: 131F Age: 32-96yrs, mean=72yrs. Race: White=236, Black=2. Duration of PHN: 5 to 267mths, median=30mths.	Pregabalin (PGB) 25 &100mg capsules & matching placebo capsules. Daily dose given orally, TID 1)Pregabalin 150mg/day (n=81), 2)300mg/day (n=76), 3)Placebo (n=81).	Primary: mean endpoint pain score rated by patient. Secondary: SF-MPQ scores, sleep interference, Clinical (CGIC) and patient global impression of change (PGIC), SF-36 QOL, Zung self-rating depression scale. Safety: visual & neurological exams, vital signs, lab parameters.	Both PGB300 &150mg gps were ss better than placebo for primary efficacy endpoint, from weeks 1 to 8. Similar results for PP analysis. Nos.of responders also ss better with both PGB gps (28%, 26% & 10% with PGB 300, 150mg & placebo, resp). Both PGB doses ss better than placebo in sleep interference, VAS, PPI index, CGIC, SF-MPQ sensory& total & SF-36 mental health domain. Only 300mg PGB shoed ss improvements in PGIC, depression rating scale & SF-36 bodily pain & vitality domains. Pts withdrawn due to lack of efficacy: plac=7, PGB150mg=0, 300mg=1..	AE incidence: PGB 300mg=83%, 150mg=65%, placebo=58%. Greater incidence of AEs in women compared to men (81% vs 66%). Dizziness (28%, 12% & 15%, resp), somnolence (24, 15 & 7%, resp), peripheral oedema (13.2, 2.5 & 0%, resp), headache (10.5, 11 &3.7%) & dry mouth (6.6, 11 &3.7%) more common in PGB gps. One death in placebo gp. SAEs: PGB300mg=1(urinary tract infection), 150mg=4 (dyspnoea, confusion, arrythmias), placebo=3. 29 withdrawals due to AEs: PGB 300mg=12(16%), 150mg=9 (11%), placebo=8(10%)- dizziness & somnolence most common in PGB gps. Clinically sig (>7%) weight gain in more PGB 300mg pts (14%, 3.7% &4% with 300, 150mg & placebo, resp). No other clinically sig changes in lab parameters/vital signs, incl. orthostatic hypoptension.

Table 8.8: Pivotal placebo-controlled postherpetic neuralgia (PHN) studies

Study nos, location investigators	Study design	Subjects demographics	Dosage, duration, route and form of study medication	Endpoints	Efficacy results	Safety/AEs
1008-0127, Mod.5-Vol.47 at 29 centres in USA & Canada. 17/12/1999 to 11/5/2000	Phase 2/3 randomised, DB, parallel-gp, placebo-controlled study. 1-week baseline phase, foll by 8 wks of DB Rx, incl. 1-week titration phase. Pts may continue into open-label study 134.	173 patients with pain present for >3mths after healing of a herpes zoster rash. Daily pain score ≥4 and VAS pain scale≥40mm Sex: 81M: 92F Age: 31-100yrs, mean=72yrs. Race: White=164, Hispanic=7, Others=2. Duration of PHN: 3 to 187mths, median=19mths.	Pregabalin (PGB) 50, 100 &200mg capsules & matching placebo capsules. Daily dose given orally, TID 1)Pregabalin 300 or 600mg/day depending on Clcr (n=89), 2)Placebo (n=84). CLcr>60ml/min: 600mg/day & CLcr:30-60ml/min: 300mg/day.	Primary: mean endpoint pain score rated by patient. Secondary: SF-MPQ scores, sleep interference, Clinical (CGIC) and patient global impression of change (PGIC), SF-36 QOL, POMS & MOS sleep questionnaire (exploratory). Safety: visual & neurological exams, vital signs, lab parameters.	PGB300/600mg/day ss better than placebo for primary efficacy endpoint, from weeks 1 to 8. Nos.of responders also ss better with PGB (50% & 20% with PGB & placebo, resp). PGB ss better than placebo in sleep interference, all subscales of SF-MPQ, CGIC, PGIC, & bodily & general health domains of SF-36. No sig. diff in POMS. Pts withdrawn due to lack of efficacy: plac=6 (7.1%), PGB=0.	AE incidence: PGB =87%, placebo=63%. Dizziness (28% vs 12%), somnolence (24% vs 7%), peripheral oedema (19% vs 2%), dry mouth (10 vs 2.4%) & amblyopia (9 vs 1.2%) more common in PGB gp. No deaths. SAEs: PGB=2(CVA & gastroenteritis), placebo=1. 32 withdrawals due to AEs: PGB=28(32%), placebo=4(5%)- dizziness & somnolence most common in PGB gps. Clinically sig (>7%) weight gain in more PGB pts (15% & 0% with PGB & placebo, resp). No other clinically sig changes in lab parameters/vital signs, incl. orthostatic hypoptension.

Table 8.9: Pivotal placebo-controlled postherpetic neuralgia (PHN) studies

Study nos, location investigators	Study design	Subjects demographics	Dosage, duration, route and form of study medication	Endpoints	Efficacy results	Safety/AEs
1008-196, Mod.5-Vol.49-50. at 76 centres in Europe & Australia. 9/11/2001 to 30/10/2002	Phase 3 randomised, DB, parallel-gp, placebo-controlled study. 1-week baseline phase, foll by 13 wks of DB Rx, incl. 1-week titration phase. Pts may continue into open-label study 198.	368 patients with pain present for >3mths after healing of a herpes zoster rash. Daily pain score ≥4 and VAS pain scale≥40mm Sex: 168M: 200F Age: 18-92yrs, mean=71yrs. Race: White=364, Black=2, Others=2. Duration of PHN: 2 to 263 mths, median=27mths.	Pregabalin (PGB) 75, 150, 200 &300mg capsules & matching placebo capsules. Daily dose given orally BID 1)PGB 150mg/day (n=87). 2)PGB 300mg/day (n=98). 3)PGB 300 or 600mg/day depending on Clcr (n=90). 4)Placebo (n=93). CLcr>60ml/min: 600mg/day & CLcr:30-60ml/min: 300mg/day.	Primary: mean endpoint pain score rated by patient. Secondary: SF-MPQ scores, sleep interference, Clinical (CGIC) and patient global impression of change (PGIC),SF-36 & EQ-5D QOL scales, s/s of allodynia/ hyperalgesia, MOS sleep questionnaire (exploratory). Safety: visual & neurological exams, vital signs, lab parameters.	All PGB gps ss better than placebo for primary efficacy endpoint. Similar results for PP analysis. Nos.of responders also ss better with all PGB gps (26, 26, 33 &7% with PGB 150, 300, 300/600 & placebo, resp). PGB ss better than placebo in sleep interference, all subscales of SF-MPQ. CGIC, PGIC, & bodily pain domain of SF-36 sig better only with PGB 300/600mg. Non-sig improvement in s/s of allodynia/ hyperalgesia. Pts withdrawn due to lack of efficacy: PGB150=16(18%), 300mg=13(13%), 300/600mg=6(7%), plac=22 (24%).	AE incidence: PGB 150=69%, 300mg=71%, 300/600mg=84.4%, placebo=57%. Dizziness (16, 33, 37 &10% with PGB 150, 300, 300/600 & placebo, resp), somnolence (9, 11, 26 & 4%, resp), peripheral oedema (13, 14, 13 & 11%, resp), ataxia (3, 6, 12 & 0%, resp) & dry mouth (6, 4, 12 &0%, resp) more common in PGB gps. No deaths. SAEs: PGB150=2, 300=4, 300/600mg=4, placebo=2. 46 withdrawals due to AEs: PGB150=7(8%), 300mg=15(15%), 300/600mg=19(21%), placebo=5(5%)- dizziness & somnolence most common in PGB gps. Clinically sig (>7%) weight gain in more PGB pts (9-10% PGB pts vs 0 plac pts). Orthostatic hypotension: 11%, 9%, 9% & 2% with PGB150, 300, 300/600 & placebo gps, resp. No other clinically sig changes in lab parameters/vital signs.

Table 8.10: Supportive, non-pivotal, uncompleted placebo-controlled postherpetic neuralgia (PHN) studies

Study nos, location investigators	Study design	Subjects demographics	Dosage, duration, route and form of study medication	Endpoints	Efficacy results	Safety/AEs
1008-132, Mod.5-Vol.48 at 38 centres in USA. 15/11/2000 to 12/2/2001	Phase 3 randomised, DB, parallel-gp, placebo-controlled study. 1-week baseline phase, foll by 12 wks of DB Rx, incl. 1-week titration phase. Study terminated early & only 2 pts completed study. Efficacy analysed after only 8weeks of Rx.	216 patients with pain present for >3mths after healing of a herpes zoster rash. Daily pain score ≥4 and VAS pain scale≥40mm Sex: 114M: 102F Age: 21-97yrs, mean=71yrs. Race: White=204, Black=4, Hispanic=6, Others=2. Duration of PHN: 3 to 218mths, median=19mths. 178pts withdrawn due to restrictions on PGB studies.	Pregabalin (PGB) 75, 150, 200, 300mg capsules & matching placebo capsules. Daily dose given orally, BID; few pts received study Rx for >5weeks. 1)PGB 150mg/day (n=51). 2)PGB 300mg/day (n=62). 3)PGB 300 or 600mg/day depending on Clcr (n=51). 4)Placebo (n=52). CLcr>60ml/min: 600mg/day & CLcr:30-60ml/min: 300mg/day.	Primary: mean endpoint pain score rated by patient. Secondary: SF-MPQ scores, sleep interference, Clinical (CGIC) and patient global impression of change (PGIC),SF-36 & EQ-5D QOL scales, s/s of allodynia/ hyperalgesia, MOS sleep questionnaire (exploratory). Safety: visual & neurological exams, vital signs, lab parameters.	After 8 weeks of Rx(LOCF ITT analysis), all PGB gps administered twice daily, ss better than placebo for primary efficacy endpoint. Nos.of responders also ss better with PGB (14%, 24%, 32% & 2% with PGB 150mg, 300mg & 300/600mg & placebo, resp). PGB ss better than placebo in sleep interference, CGIC, PGIC. Slight ↓ in s/s of allodynia/ hyperalgesia with PGB. No ss improvement in SF-36 or EQ-5D QOL. Pts withdrawn due to lack of efficacy: plac=4 (7.7%), PGB150=2 (4%), PGB300mg and 300/600mg=0.	AE incidence: PGB150=65%, 300mg=73%, 300/600mg=80%, placebo=54%. Dizziness (30%, 31%, 39% & 6% in PGB 150, 300 & 300/600mg & placebo gps, resp), somnolence (18, 14.5, 22 &2%, resp), peripheral oedema (10, 14, 22 &2%, resp), abnormal gait, amblyopia & dry mouth more common in PGB gps. No deaths. SAEs: PGB150mg=1, 300mg=3, 300/600mg=2, placebo=1 (only CVA exp by >1 pt). 29 withdrawals due to AEs: PGB150mg=8(16%), 300mg=6 (10%), 300/600=12 (23.5%), placebo=3(6%)- dizziness & abnormal gait most common in PGB gps. Clinically sig (>7%) weight gain seen in only 2 PGB300mg pts. Orthostatic hypotension: PGB150=4(8%), 300mg=2(3%), 300/600=3(7%) & placebo=2(4%). No other clinically sig changes in lab parameters/vital signs.

Table 8.11: Supportive non-pivotal, uncompleted placebo-controlled DPN study

Study nos, location, investigators	Study design	Subjects demographics	Dosage, duration, route and form of study medication	Endpoints	Efficacy results	Safety/AEs
1008-173, Mod.5-Vol.43 at 27 centres in USA. 26/10/2000 to 18/2/2001.	Phase 3 randomised, DB, parallel-gp, placebo-controlled study. 1-week baseline phase, foll by 12 wks of DB Rx, incl. 1-week titration phase.	147 patients with painful, diabetic distal, symmetrical, sensiromotor polyneuropathy for ≥1 year score ≥4 and VAS pain scale≥40mm Sex: 90M: 57F Age: 34-87yrs, mean=62yrs. Race: White=127, Black=8, Others=12. Normal CLcr (>60ml/min)=119, Low CLcr (30-60ml/min)=28. Type 1 diabetes=16; type 2 diabetes=101; mean duration:12yrs.	Pregabalin (PGB) 75, 150, 200 & 300mg capsules & matching placebo capsules. Daily dose given orally, BID 1)Pregabalin 150mg/day (n=34), 2)300mg/day (n=44), 3)300/600mg /day based on CLcr (n=39), 4)Placebo (n=30).	Primary: mean endpoint pain score rated by patient. Limited analysis of secondary efficacy endpoints due to early termination.	Efficacy assessed only till 3weeks due to early termination. Only PGB300/600mg gp was ss better than placebo for primary efficacy endpoint, from week 1 till week3. Nos.of responders not ss greater in any of the PGB gps (34%, 16%, 32% & 17% with 300/600mg, 300mg, 150mg & placebo, resp).No significant improvement in sleep interference scores. 5 pts withdrawn due to lack of efficacy: plac=1, PGB150mg=1 300mg=2 (5.1%) &300/600mg=1..	AE incidence: PGB 300/600mg=82%, 300mg=66%, 150mg=62%, placebo=70%. Dizziness, somnolence & peripheral oedema more common in PGB gps. One death (PGB 300/600mg/day) due to chest pain & dyspnea. 6 SAEs (1 in plac & 5 in PGB gps). 15 withdrawals due to AEs: PGB 300/600mg=9,300mg=3, 150mg=2, placebo=1-dizziness, amblyopia, somnolence & confusion most common in PGB gps. Clinically imp ↓ in platelets in 4 pts (3 on 300mg/day & 1 in 300/600mg/day gps). sig (>7%) weight gain in only 1 300mg PGB pt. Orthostatic hypotension-in 6%, 2%, 0 and 0% of PBG 300/600, 300, 150mg & placebo pts, resp. No other clinically sig changes in lab parameters/vital signs.

Table 8.12:

Endpoint[a] Mean Pain Scores: Results of Analysis of Covariance, Placebo-Controlled Neuropathic Pain Studies - ITT Population

Study/Treatment Group	Least Squares			Treatment Comparisons (Pregabalin - Placebo)			
	N	Mean	SE	Difference	95% CI	Unadjusted p Value	Adjusted[b] p Value
DPN Pain Model							
Study 014 [TID]							
Placebo	82	5.55	0.23				
PGB 150 mg/day	79	5.11	0.24	-0.44	(-1.08, 0.20)	0.1763	0.1763
PGB 600 mg/day	82	4.29	0.23	-1.26	(-1.89, -0.64)	0.0001	0.0002
Study 029 [TID]							
Placebo	97	5.06	0.21				
PGB 75 mg/day	77	4.91	0.24	-0.15	(-0.76, 0.46)	0.6267	--
PGB 300 mg/day	81	3.80	0.23	-1.26	(-1.86, -0.65)	0.0001	0.0001
PGB 600 mg/day	81	3.60	0.23	-1.45	(-2.06, -0.85)	0.0001	0.0001
Study 040 [TID]							
Placebo	80	4.60	0.26				
PGB 600 mg/day	86	3.96	0.26	-0.64	(-1.37, 0.08)	0.0822	--
AMT 75 mg/day	87	3.67	0.25	-0.93	(-1.65, -0.22)	0.0110	--
Study 131 [TID]							
Placebo	69	5.46	0.28				
PGB 300 mg/day	75	3.99	0.26	-1.47	(-2.19, -0.75)	0.0001	--
Study 149 [BID]							
Placebo	93	4.66	0.26				
PGB 150 mg/day	96	4.33	0.26	-0.33	(-0.94, 0.28)	0.2849	0.5580
PGB 300 mg/day	96	4.48	0.26	-0.18	(-0.79, 0.43)	0.5580	0.5580
PGB 300/600 mg/day[c]	98	3.69	0.25	-0.97	(-1.58, -0.36)	0.0018	0.0054
PHN Pain Model							
Study 030 [TID]							
Placebo	87	5.59	0.21				
PGB 75 mg/day	83	5.46	0.21	-0.14	(-0.71, 0.43)	0.6361	0.7999
PGB 150 mg/day	82	5.52	0.22	-0.07	(-0.64, 0.50)	0.7999	0.7999
Study 045 [TID]							
Placebo	81	6.33	0.22				
PGB 150 mg/day	81	5.14	0.22	-1.20	(-1.81, -0.58)	0.0002	0.0002
PGB 300 mg/day	76	4.76	0.23	-1.57	(-2.20, -0.95)	0.0001	0.0002
Study 127 [TID]							
Placebo	84	5.29	0.24				
PGB 300/600 mg/day[c]	88	3.60	0.24	-1.69	(-2.33, -1.05)	0.0001	--
Study 196 [BID]							
Placebo	93	6.14	0.23				
PGB 150 mg/day	87	5.26	0.24	-0.88	(-1.53, -0.23)	0.0077	0.0077
PGB 300 mg/day	98	5.07	0.23	-1.07	(-1.70, -0.45)	0.0008	0.0016
PGB 300/600 mg/day[c]	88	4.35	0.24	-1.79	(-2.43, -1.15)	0.0001	0.0003

ITT = Intent-to-treat; SE = Standard Error; CI = Confidence Interval; DPN = Diabetic peripheral; neuropathy; PGB = Pregabalin; AMT = Amitriptyline; AMT = Amitriptyline.

[a] Endpoint = Mean of last 7 available diary entries up to the last day on study medication. For Study 040, if fewer than 7 postbaseline scores (7-x) were available, the last x scores from baseline were also used in the calculation of endpoint.

[b] Adjustment is based on Hochberg's procedure and applies to all treatment comparisons except PGB 75 mg/day in Study 029 (as stated in protocol), and protocols with only 1 PGB treatment group (Studies 040, 127, and 131).

[c] In Studies 127, 149, and 196, patients randomized to the 300/600 mg/day pregabalin group received either 300 or 600 mg/day based on their CLcr.

Table 8.13:

Responder Analysis: 9 Placebo-Controlled Neuropathic Pain Studies

Treatment Group	No. Assessed	Responders, N (%)	p Value	Adjusted p Value[a]
DPN Pain Model				
Study 014 [TID]				
Placebo	82	12 (14.6)		
PGB 150 mg/day	79	15 (19.0)	0.423	0.423
PGB 600 mg/day	82	32 (39.0)	0.001	0.002
Study 029 [TID]				
Placebo	97	17 (17.5)		
PGB 75 mg/day	77	17 (22.1)	0.407	--
PGB 300 mg/day	81	37 (45.7)	0.001	0.001
PGB 600 mg/day	81	39 (48.1)	0.001	0.001
Study 040 [TID]				
Placebo	81	24 (29.6)		
PGB 600 mg/day	86	34 (39.5)	0.239	--
AMT 75 mg/day	87	40 (46.0)	0.034	--
Study 131 [TID]				
Placebo	69	10 (14.5)		
PGB 300 mg/day	75	30 (40.0)	0.001	--
Study 149 [BID]				
Placebo	93	28 (30.1)		
PGB 150 mg/day	96	33 (34.4)	0.461	0.738
PGB 300 mg/day	96	32 (33.3)	0.738	0.738
PGB 300/600 mg/day[b]	98	45 (45.9)	0.012	0.036
PHN Pain Model				
Study 030 [TID]				
Placebo	87	15 (17.2)		
PGB 75 mg/day	83	17 (20.5)	0.439	0.465
PGB 150 mg/day	82	18 (22.0)	0.465	0.465
Study 045 [TID]				
Placebo	81	8 (9.9)		
PGB 150 mg/day	81	21 (25.9)	0.006	0.006
PGB 300 mg/day	76	21 (27.6)	0.003	0.006
Study 127 [TID]				
Placebo	84	17 (20.2)		
PGB 300/600 mg/day[b]	88	44 (50.0)	0.001	--
Study 196 [BID]				
Placebo	93	7 (7.5)		
PGB 150 mg/day	87	23 (26.4)	0.001	0.001
PGB 300 mg/day	98	26 (26.5)	0.001	0.001
PGB 300/600 mg/day[b]	88	33 (37.5)	0.001	0.001

DPN = Diabetic peripheral neuropathy; PGB = Pregabalin;
AMT = Amitriptyline; PHN = Postherpetic neuralgia.

[a] Adjustment is based on Hochberg's procedure and applies to all treatment comparisons except PGB 75 mg/day in Study 029 (as stated in protocol), and protocols with only 1 PGB treatment group (Studies 040, 127, and 131).

[b] In Studies 127, 149, and 196, patients randomized to the 300/600 mg/day pregabalin group received either 300 or 600 mg/day based on their CLcr.

Table 8.14:

Endpoint[a] ANCOVA Analysis of VAS Scores for the SF-MPQ: Placebo-Controlled Neuropathic Pain Studies

Study/Treatment Group	Least-Squares			Treatment Comparisons (Pregabalin - Placebo)			
	N	Mean	SE	Difference	95% CI	Unadjusted p Value	Adjusted[b] p Value
DPN Pain Model							
Study 014 [TID]							
Placebo	82	58.05	2.68				
PGB 150 mg/day	79	53.27	2.75	-4.78	(-12.20, 2.64)	0.2058	0.2058
PGB 600 mg/day	82	43.38	2.70	-14.66	(-21.92, -7.41)	0.0001	0.0002
Study 029 [TID]							
Placebo	97	53.49	2.46				
PGB 75 mg/day	77	49.70	2.74	-3.79	(-10.90, 3.32)	0.2947	--
PGB 300 mg/day	81	37.40	2.69	-16.09	(-23.11, -9.08)	0.0001	0.0001
PGB 600 mg/day	81	34.48	2.65	-19.01	(-26.00, -12.01)	0.0001	0.0001
Study 040 [TID]							
Placebo	81	49.26	3.02				
PGB 600 mg/day	85	38.87	2.93	-10.39	(-18.68, -2.11)	0.0142	--
AMT 75 mg/day	86	37.55	2.91	-11.71	(-19.95, -3.47)	0.0055	--
Study 131 [TID]							
Placebo	69	57.02	3.21				
PGB 300 mg/day	75	40.83	3.04	-16.19	(-24.52, -7.86)	0.0002	--
Study 149 [BID]							
Placebo	93	46.91	2.79				
PGB 150 mg/day	96	40.59	2.78	-6.32	(-12.95, 0.32)	0.0619	0.1238
PGB 300 mg/day	95	45.35	2.81	-1.55	(-8.20, 5.09)	0.6458	0.6458
PGB 300/600 mg/day[c]	98	34.36	2.72	-12.55	(-19.16, -5.94)	0.0002	0.0006
PHN Pain Model							
Study 030 [TID]							
Placebo	87	57.01	2.43				
PGB 75 mg/day	83	56.05	2.47	-0.97	(-7.53, 5.60)	0.7719	0.9869
PGB 150 mg/day	83	57.07	2.48	0.05	(-6.46, 6.57)	0.9869	0.9869
Study 045 [TID]							
Placebo	80	62.05	2.56				
PGB 150 mg/day	80	52.03	2.56	-10.02	(-17.15, -2.90)	0.0060	0.0060
PGB 300 mg/day	76	48.41	2.63	-13.64	(-20.87, -6.40)	0.0003	0.0006
Study 127 [TID]							
Placebo	84	56.30	2.93				
PGB 300/600 mg/day[c]	89	38.69	2.90	-17.62	(-25.37, -9.86)	0.0001	--
Study 196 [BID]							
Placebo	93	61.16	2.49				
PGB 150 mg/day	86	55.19	2.61	-5.98	(-12.89, 0.93)	0.0898	0.0898
PGB 300 mg/day	98	52.83	2.43	-8.33	(-14.99, -1.67)	0.0144	0.0288
PGB 300/600 mg/day[c]	90	45.35	2.54	-15.81	(-22.60, -9.02)	0.0001	0.0003

ANCOVA = Analysis of Covariance; VAS = Visual Analog Score; SF-MPQ = Short-Form McGill Questionnaire; ; SE = Standard error; CI = Confidence interval; DPN = Diabetic peripheral neuropathy; PGB = Pregabalin; AMT = Amitriptyline; PHN = Postherpetic neuralgia.

[a] Endpoint = Last observation after randomization.

[b] Adjustment is based on Hochberg's procedure and applies to all treatment comparisons except PGB 75 mg/day in Study 029 (as stated in protocol), and protocols with only 1 PGB treatment group (Studies 040, 127, and 131).

[c] In Studies 127, 149, and 196, patients randomized to the 300/600 mg/day pregabalin group received either 300 or 600 mg/day based on their CLcr.

Table 8.15:

Endpoint[a] ANCOVA Analysis of PPI Scores for the SF-MPQ: Placebo-Controlled Neuropathic Pain Studies

Study/Treatment Group	Least-Squares			Treatment Comparisons (Pregabalin - Placebo)			
	N	Mean	SE	Difference	95% CI	Unadjusted p Value	Adjusted[b] p Value
DPN Pain Model							
Study 014 [TID]							
Placebo	82	1.96	0.11				
PGB 150 mg/day	79	1.78	0.12	-0.17	(-0.49, 0.14)	0.2836	0.2836
PGB 600 mg/day	82	1.30	0.12	-0.66	(-0.97, -0.35)	0.0001	0.0002
Study 029 [TID]							
Placebo	97	1.79	0.10				
PGB 75 mg/day	77	1.67	0.11	-0.12	(-0.41, 0.18)	0.4286	--
PGB 300 mg/day	81	1.20	0.11	-0.59	(-0.88, -0.30)	0.0001	0.0001
PGB 600 mg/day	81	1.18	0.11	-0.61	(-0.90, -0.32)	0.0001	0.0001
Study 040 [TID]							
Placebo	81	1.95	0.14				
PGB 600 mg/day	85	1.63	0.14	-0.32	(-0.66, 0.01)	0.0591	--
AMT 75 mg/day	86	1.42	0.14	-0.54	(-0.87, -0.20)	0.0019	--
Study 131 [TID]							
Placebo	69	1.79	0.13				
PGB 300 mg/day	75	1.42	0.13	-0.37	(-0.72, -0.02)	0.0364	--
Study 149 [BID]							
Placebo	93	1.89	0.12				
PGB 150 mg/day	96	1.61	0.12	-0.28	(-0.56, -0.01)	0.0439	0.0490
PGB 300 mg/day	95	1.61	0.12	-0.28	(-0.56, -0.00)	0.0490	0.0490
PGB 300/600 mg/day[c]	98	1.43	0.11	-0.46	(-0.74, -0.19)	0.0011	0.0033
PHN Pain Model							
Study 030 [TID]							
Placebo	87	2.15	0.11				
PGB 75 mg/day	83	2.16	0.11	0.012	(-0.29, 0.31)	0.9372	0.9372
PGB 150 mg/day	83	2.06	0.11	-0.091	(-0.39, 0.21)	0.5466	0.9372
Study 045 [TID]							
Placebo	79	2.28	0.13				
PGB 150 mg/day	80	2.06	0.13	-0.21	(-0.57, 0.14)	0.2372	0.2653
PGB 300 mg/day	76	2.07	0.13	-0.20	(-0.57, 0.16)	0.2653	0.2653
Study 127 [TID]							
Placebo	84	1.98	0.12				
PGB 300/600 mg/day[c]	89	1.58	0.12	-0.40	(-0.71, -0.09)	0.0127	--
Study 196 [BID]							
Placebo	93	2.30	0.10				
PGB 150 mg/day	87	2.02	0.11	-0.28	(-0.57, 0.01)	0.0612	0.0612
PGB 300 mg/day	98	2.02	0.10	-0.28	(-0.56, -0.00)	0.0496	0.0612
PGB 300/600 mg/day[c]	89	1.87	0.11	-0.42	(-0.71, -0.14)	0.0039	0.0117

ANCOVA = Analysis of Covariance; PPI = Present pain intensity; SF-MPQ = Short-Form McGill Questionnaire; SE = Standard error; CI = Confidence interval; DPN = Diabetic peripheral neuropathy; PGB = Pregabalin; AMT = Amitriptyline; PHN = Postherpetic neuralgia.

[a] Endpoint = Last observation after randomization.

[b] Adjustment is based on Hochberg's procedure and applies to all treatment comparisons except PGB 75 mg/day in Study 029 (as stated in protocol), and protocols with only 1 PGB treatment group (Studies 040, 127, and 131).

[c] In Studies 127, 149, and 196, patients randomized to the 300/600 mg/day pregabalin group received either 300 or 600 mg/day based on their CLcr.

Table 8.16.1:

Endpoint[a] ANCOVA Analysis of Sensory Scores for the SF-MPQ: 5 of 9 Placebo-Controlled Neuropathic Pain Studies[b]

Study/Treatment Group	Least Squares			Treatment Comparisons (Pregabalin - Placebo)			
	N	Mean	SE	Difference	95% CI	Unadjusted p Value	Adjusted[c] p Value
DPN Pain Model							
Study 014 [TID]							
Placebo	82	14.61	0.73				
PGB 150 mg/day	79	12.65	0.76	-1.96	(-3.99, 0.06)	0.0570	0.0570
PGB 600 mg/day	82	10.07	0.74	-4.54	(-6.53, -2.56)	0.0001	0.0002
Study 029 [TID]							
Placebo	97	12.06	0.66				
PGB 75 mg/day	77	12.34	0.74	0.28	(-1.64, 2.20)	0.7738	0.7738
PGB 300 mg/day	81	8.40	0.72	-3.66	(-5.55, -1.77)	0.0002	0.0002
PGB 600 mg/day	81	8.39	0.71	-3.67	(-5.56, -1.78)	0.0002	0.0002
Study 131 [TID]							
Placebo	69	12.13	0.89				
PGB 300 mg/day	75	8.90	0.83	-3.23	(-5.51, -0.94)	0.0060	--
PHN Pain Model							
Study 030 [TID]							
Placebo	87	13.05	0.67				
PGB 75 mg/day	83	12.44	0.68	-0.61	(-2.42, 1.21)	0.5100	0.5100
PGB 150 mg/day	83	11.07	0.69	-1.97	(-3.78, -0.17)	0.0322	0.0644
Study 127 [TID]							
Placebo	84	11.90	0.74				
PGB 300/600 mg/day[d]	89	8.15	0.73	-3.75	(-5.71, -1.79)	0.0002	--

ANCOVA = Analysis of Covariance; SF-MPQ = Short-Form McGill Questionnaire; SE = Standard error; CI = Confidence interval; DPN = Diabetic peripheral neuropathy; PGB = Pregabalin; PHN = Postherpetic neuralgia.

[a] Endpoint = Last observation after randomization.

[b] Studies 040, 045, 149, and 196 used multiple, language-specific versions of this instrument; therefore, Sensory Score data are not presented.

[c] Adjustment is based on Hochberg's procedure and applies to all treatment comparisons except PGB 75 mg/day in Study 029 (as specified in the protocol), and protocols with only 1 PGB treatment group (Studies 040, 127, and 131).

[d] In Study 127, patients randomized to the pregabalin group received either 300 or 600 mg/day based on their CLcr.

Table 8.16.2:

Endpoint[a] ANCOVA Analysis of Affective Scores for the SF-MPQ: 5 of 9 Placebo-Controlled Neuropathic Pain Studies[b]

Study/Treatment Group	Least Squares			Treatment Comparisons (Pregabalin — Placebo)			
	N	Mean	SE	Difference	95% CI	Unadjusted p Value	Adjusted[c] p Value
DPN Pain Model							
Study 014 [TID]							
Placebo	82	3.35	0.29				
PGB 150 mg/day	79	2.78	0.30	-0.57	(-1.38, 0.24)	0.1664	0.1664
PGB 600 mg/day	82	2.04	0.30	-1.31	(-2.10, -0.51)	0.0014	0.0028
Study 029 [TID]							
Placebo	97	2.98	0.23				
PGB 75 mg/day	77	2.77	0.26	-0.21	(-0.89, 0.47)	0.5457	--
PGB 300 mg/day	81	1.77	0.26	-1.22	(-1.88, -0.55)	0.0004	0.0004
PGB 600 mg/day	81	1.49	0.25	-1.49	(-2.16, -0.83)	0.0001	0.0002
Study 131 [TID]							
Placebo	69	2.73	0.30				
PGB 300 mg/day	75	1.62	0.28	-1.11	(-1.89, -0.33)	0.0054	--
PHN Pain Model							
Study 030 [TID]							
Placebo	87	3.10	0.26				
PGB 75 mg/day	83	2.57	0.27	-0.52	(-1.23, 0.18)	0.1446	0.2892
PGB 150 mg/day	83	2.76	0.27	-0.33	(-1.04, 0.37)	0.3498	0.3498
Study 127 [TID]							
Placebo	84	2.82	0.28				
PGB 300/600 mg/day[d]	89	1.75	0.27	-1.07	(-1.81, -0.33)	0.0047	--

ANCOVA = Analysis of Covariance; SF-MPQ = Short-Form McGill Questionnaire; SE = Standard error; CI = Confidence interval; DPN = Diabetic peripheral neuropathy; PGB = Pregabalin; PHN = Postherpetic neuralgia.

[a] Endpoint = Last observation after randomization.

[b] Studies 040, 045, 149, and 196 used multiple, language-specific versions of this instrument; therefore Affective Score data are not presented.

[c] Adjustment is based on Hochberg's procedure and applies to all treatment comparisons except PGB 75 mg/day in Study 029 (as stated in protocol), and protocols with only 1 PGB treatment group (Studies 040, 127, and 131).

[d] In Study 127, patients randomized to the pregabalin group received either 300 or 600 mg/day based on their CLcr.

Table 8.16.3:

Endpoint[a] ANCOVA Analysis of Total Scores for the SF-MPQ: 5 of 9 Placebo-Controlled Neuropathic Pain Studies[b]

Study/Treatment Group	Least-Squares			Treatment Comparisons (Pregabalin - Placebo)			
	N	Mean	SE	Difference	95% CI	Unadjusted p Value	Adjusted p Value
DPN Pain Model							
Study 014 [TID]							
Placebo	82	17.97	0.96				
PGB 150 mg/day	79	15.48	0.99	-2.49	(-5.14, 0.16)	0.0651	0.0651
PGB 600 mg/day	82	12.14	0.97	-5.83	(-8.43, -3.23)	0.0001	0.0002
Study 029 [TID]							
Placebo	97	15.06	0.84				
PGB 75 mg/day	77	15.06	0.94	0.01	(-2.43, 2.44)	0.9966	--
PGB 300 mg/day	81	10.17	0.92	-4.89	(-7.29, -2.48)	0.0001	0.0001
PGB 600 mg/day	81	9.88	0.91	-5.18	(-7.58, -2.79)	0.0001	0.0001
Study 131 [TID]							
Placebo	69	14.92	1.13				
PGB 300 mg/day	75	10.51	1.06	-4.41	(-7.32, -1.49)	0.0033	--
PHN Pain Model							
Study 030 [TID]							
Placebo	87	16.17	0.86				
PGB 75 mg/day	83	14.98	0.88	-1.19	(-3.52, 1.14)	0.3147	0.3147
PGB 150 mg/day	83	13.88	0.89	-2.29	(-4.61, 0.02)	0.0524	0.1048
Study 127 [TID]							
Placebo	84	14.72	0.96				
PGB 300/600 mg/day[d]	89	9.85	0.95	-4.87	(-7.41, -2.34)	0.0002	--

ANCOVA = Analysis of Covariance; SF-MPQ = Short-Form McGill Questionnaire; SE = Standard error; CI = Confidence interval; DPN = Diabetic peripheral neuropathy; PGB = Pregabalin; PHN = Postherpetic neuralgia.

[a] Endpoint = Last observation after randomization.

[b] Studies 040, 045, 149, and 196 used multiple, language-specific versions of this instrument; therefore total score data are not presented.

[c] Adjustment is based on Hochberg's procedure and applies to all treatment comparisons except PGB 75 mg/day in Study 029 (as stated in protocol), and protocols with only 1 PGB treatment group (Studies 040, 127, and 131).

[d] In Study 127, patients randomized to the pregabalin group received either 300 or 600 mg/day based on their CLcr.

Table 8.17:

Endpoint[a] ANCOVA Analysis of Mean Sleep Interference: 9 Placebo-Controlled Neuropathic Pain Studies

Study/Treatment Group	Least Squares			Treatment Comparisons (Pregabalin — Placebo)			
	N	Mean	SE	Difference	95% CI	Unadjusted p Value	Adjusted[b] p Value
DPN Pain Model							
Study 014 [TID]							
Placebo	82	4.051	0.224				
PGB 150 mg/day	79	3.622	0.226	-0.43	(-1.04, 0.18)	0.1670	0.1670
PGB 600 mg/day	82	2.899	0.224	-1.15	(-1.75, -0.55)	0.0002	0.0004
Study 029 [TID]							
Placebo	97	4.17	0.21				
PGB 75 mg/day	77	3.74	0.23	-0.43	(-1.02, 0.17)	0.1609	--
PGB 300 mg/day	81	2.86	0.23	-1.30	(-1.89, -0.71)	0.0001	0.0001
PGB 600 mg/day	81	2.62	0.22	-1.55	(-2.14, -0.96)	0.0001	0.0001
Study 040 [TID]							
Placebo	79	3.96	0.25				
PGB 600 mg/day	86	2.89	0.24	-1.07	(-1.75, -0.39)	0.0023	--
AMT 75 mg/day	87	2.69	0.24	-1.27	(-1.95, -0.59)	0.0003	--
Study 131 [TID]							
Placebo	69	4.32	0.29				
PGB 300 mg/day	75	2.78	0.27	-1.54	(-2.28, -0.80)	0.0001	--
Study 149 [BID]							
Placebo	93	4.11	0.25				
PGB 150 mg/day	96	3.67	0.25	-0.45	(-1.05, 0.15)	0.1444	0.1444
PGB 300 mg/day	96	3.49	0.25	-0.62	(-1.22, -0.02)	0.0422	0.0844
PGB 300/600 mg/day[c]	98	3.11	0.25	-1.01	(-1.60, -0.41)	0.0010	0.0030
PHN Pain Model							
Study 030 [TID]							
Placebo	87	3.82	0.21				
PGB 75 mg/day	83	3.79	0.21	-0.03	(-0.58, 0.53)	0.9212	0.9212
PGB 150 mg/day	82	3.23	0.21	-0.58	(-1.15, -0.02)	0.0410	0.0820
Study 045 [TID]							
Placebo	81	4.24	0.21				
PGB 150 mg/day	81	3.13	0.21	-1.11	(-1.71, -0.51)	0.0003	0.0003
PGB 300 mg/day	76	2.81	0.22	-1.43	(-2.04, -0.82)	0.0001	0.0002
Study 127 [TID]							
Placebo	84	3.51	0.23				
PGB 300/600 mg/day[c]	88	1.93	0.23	-1.58	(-2.19, -0.97)	0.0001	--
Study 196 [BID]							
Placebo	93	4.10	0.21				
PGB 150 mg/day	87	3.07	0.22	-1.03	(-1.62, -0.44)	0.0007	0.0007
PGB 300 mg/day	98	2.84	0.21	-1.26	(-1.84, -0.68)	0.0001	0.0002
PGB 300/600 mg/day[c]	88	2.17	0.22	-1.93	(-2.52, -1.34)	0.0001	0.0002

ANCOVA = Analysis of Covariance; SE = Standard error; CI = Confidence interval; DPN = Diabetic peripheral neuropathy; PGB = Pregabalin; AMT = Amitriptyline; PHN = Postherpetic neuralgia.

[a] Endpoint = Mean of last 7 available diary entries up to the last day on study medication.

[b] Adjustment is based on Hochberg's procedure and applies to all treatment comparisons except PGB 75 mg/day in Study 029 (as stated in protocol), and protocols with only 1 PGB treatment group (Studies 040, 127, and 131).

[c] In Studies 127, 149, and 196, patients randomized to the 300/600 mg/day pregabalin group received either 300 or 600 mg/day based on their CLcr.

Table 8.18.1:

Summary of Statistically Significant SF-36 Quality of Life Results: Placebo-Controlled DPN Neuropathic Pain Studies

SF–36 Subscale	DPN Studies				
	014	029	040	131	149
	Pregabalin Dose (mg/day) Achieving Significance From Placebo				
Physical Functioning	--	--	600[a]	--	--
Physical Role Limitations	--	--	--	--	--
Social Functioning	--	300, 600	600	--	--
Bodily Pain	150, 600	300, 600	600[a]	300	--
Mental Health	--	--	600[a]	--	--
Emotional Role Limitations	--	--	[b]	--	--
Vitality	--	75, 300	[b]	--	--
General Health Perception	--	--	600[a]	--	--

SF-36 = SF-36 Health Survey, DPN = Painful Diabetic Peripheral Neuropathy; -- = No Significance found.

[a] Amitriptyline 75 mg/day also significantly better than placebo.

[b] Only amitriptyline 75 mg/day statistically significantly better than placebo.

Table 8.18.2:

Summary of Statistically Significant SF-36 Quality of Life Results: Placebo-Controlled PHN Neuropathic Pain Studies

	PHN Studies			
	030	045	127	196
SF–36 Subscale	Pregabalin Dose (mg/day) Achieving Significance From Placebo			
Physical Functioning	--	--	--	--
Physical Role Limitations	--	--	--	--
Social Functioning	--	--	--	--
Bodily Pain	--	300	300/600[a]	300/600[a]
Mental Health	--	150, 300	--	--
Emotional Role Limitations	--	--	--	--
Vitality	--	300	--	--
General Health Perception	--	--	300/600[a]	--

SF-36 = SF-36 Health Survey; PHN = Postherpetic neuralgia; -- = No Significance found.

[a] In Studies 127 and 196, patients randomized to the 300/600 pregabalin group received either 300 or 600 mg/day based on their CLcr.

Table 8.19.1:

Summary of Hyperalgesia in Placebo-Controlled DPN Studies (Studies 029, 131, and 149)

Treatment Group	Baseline Hyperalgesia	Termination[a] Hyperalgesia	
		Yes N (%)	No N (%)
Placebo	Yes (N = 123)	105 (85.4)	18 (14.6)
	No (N = 131)	21 (16.0)	110 (84.0)
PGB 75 mg/day	Yes (N = 38)	30 (78.9)	8 (21.1)
	No (N = 37)	3 (8.1)	34 (91.9)
PGB 150 mg/day	Yes (N = 62)	59 (95.2)	3 (4.8)
	No (N = 30)	13 (43.3)	17 (56.7)
PGB 300 mg/day[b]	Yes (N = 130)	102 (78.5)	28 (21.5)
	No (N = 122)	15 (12.3)	107 (87.7)
PGB 600 mg/day[b]	Yes (N = 94)	75 (79.8)	19 (20.2)
	No (N = 63)	10 (15.9)	53 (84.1)

DPN = Painful Diabetic Peripheral Neuropathy; PGB = Pregabalin.

[a] Termination = Last available (nonfollow-up) record.

[b] In Study 149, patients randomized to the 300/600 mg/day pregabalin group received either 300 or 600 mg/day based on their CLcr, and are summarized here according to those doses.

Table 8.19.2:

Summary of Hyperalgesia in Placebo-Controlled PHN Studies (Studies 030, 045, 127, and 196)

Treatment Group	Baseline Hyperalgesia	Termination[a] Hyperalgesia	
		Yes N (%)	No N (%)
Placebo	Yes (N = 216)	175 (81.0)	41 (19.0)
	No (N = 120)	14 (11.7)	106 (88.3)
PGB 75 mg/day	Yes (N = 57)	46 (80.7)	11 (19.3)
	No (N = 22)	2 (9.1)	20 (90.9)
PGB 150 mg/day	Yes (N = 154)	123 (79.9)	31 (20.1)
	No (N = 88)	15 (17.0)	73 (83.0)
PGB 300 mg/day[b]	Yes (N = 147)	109 (74.1)	38 (25.9)
	No (N = 68)	10 (14.7)	58 (85.3)
PGB 600 mg/day[b]	Yes (N = 76)	50 (65.8)	26 (34.2)
	No (N = 41)	6 (14.6)	35 (85.4)

PHN = Postherpetic neuralgia; PGB = Pregabalin.

[a] Termination = Last available (non-follow-up) record.

[b] In Studies 127 and 196, patients randomized to the pregabalin group received either 300 or 600 mg/day based on their CLcr, and are summarized here according to those doses.

Table 8.20.1:

Summary of Allodynia: 5 Placebo-Controlled DPN Studies Combined (Studies 014, 029, 040, 131, and 149)

Treatment Group	Baseline Allodynia	Termination[a] Allodynia	
		Yes N (%)	No N (%)
Placebo	Yes (N = 156)	124 (79.5)	32 (20.5)
	No (N = 253)	19 (7.5)	234 (92.5)
PGB 75 mg/day	Yes (N = 31)	23 (74.2)	8 (25.8)
	No (N = 44)	2 (4.5)	42 (95.5)
PGB 150 mg/day	Yes (N = 87)	72 (82.8)	15 (17.2)
	No (N = 80)	17 (21.3)	63 (78.8)
PGB 300 mg/day[b]	Yes (N = 119)	103 (86.6)	16 (13.4)
	No (N = 133)	13 (9.8)	120 (90.2)
PGB 600 mg/day[b]	Yes (N = 148)	98 (66.2)	50 (33.8)
	No (N = 171)	10 (5.8)	161 (94.2)
Amitriptyline 75 mg/day	Yes (N = 30)	16 (53.3)	14 (46.7)
	No (N = 52)	0 (0.0)	52(100.0)

DPN = Painful Diabetic Peripheral Neuropathy; PGB = Pregabalin.

[a] Termination = Last available (nonfollow-up) record.

[b] In Study 149, patients randomized to the 300/600 mg/day pregabalin group received either 300 or 600 mg/day based on their CLcr, and are summarized here according to those doses.

Table 8.20.2:

Summary of Allodynia: 4 Placebo-Controlled PHN Studies Combined (Studies 030, 045, 127, and 196)

Treatment Group	Baseline Allodynia	Termination[a] Allodynia	
		Yes N (%)	No N (%)
Placebo	Yes (N = 206)	167 (81.1)	39 (18.9)
	No (N = 130)	12 (9.2)	118 (90.8)
PGB 75 mg/day	Yes (N = 43)	40 (93.0)	3 (7.0)
	No (N = 36)	5 (13.9)	31 (86.1)
PGB 150 mg/day	Yes (N = 154)	128 (83.1)	26 (16.9)
	No (N = 88)	13 (14.8)	75 (85.2)
PGB 300 mg/day[b]	Yes (N = 149)	117 (78.5)	32 (21.5)
	No (N = 65)	9 (13.8)	56 (86.2)
PGB 600 mg/day[b]	Yes (N = 58)	38 (65.5)	20 (34.5)
	No (N = 59)	6 (10.2)	53 (89.8)

PHN = Postherpetic neuralgia; PGB = Pregabalin.

[a] Termination = Last available (nonfollow-up) record.

[b] In Studies 127 and –196, patients randomized to the pregabalin group received either 300 or 600 mg/day based on their CLcr, and are summarized here according to those doses.

Table 8.21.1:

Proportion of Responders by Treatment Group: 9 Placebo-Controlled Neuropathic Pain Studies

Treatment Group	No. Assessed	No. of Responders, (%)
Placebo	766	138 (18.0)
Pregabalin 75 mg/day	160	34 (21.3)
Pregabalin 150 mg/day	425	110 (25.9)
Pregabalin 300 mg/day[a]	495	170 (34.3)
Pregabalin 600 mg/day[a]	453	204 (45.0)

[a] In Studies 127, 149, and 196, patients randomized to the 300/600 mg/day pregabalin group received either 300 or 600 mg/day based on their CLcr, and are summarized here according to those doses.

Table 8.21.2:

Percent Change in Endpoint Mean Pain Score by Dose: 9 Placebo-Controlled Neuropathic Pain Studies

	Placebo	Pregabalin Dose, mg/day			
		75 mg/day	150 mg/day	300 mg/day[a]	600 mg/day[a]
	(N = 766)	(N = 160)	(N = 425)	(N = 495)	(N = 453)
Any Increase	205 (26.8)	36 (22.5)	93 (21.9)	76 (15.4)	54 (11.9)
No Change (0%)	58 (7.6)	10 (6.3)	19 (4.5)	22 (4.4)	8 (1.8)
Decrease					
>0%	503 (65.7)	114 (71.3)	313 (73.6)	397 (80.2)	391 (86.3)
≥20%	293 (38.3)	75 (46.9)	209 (49.2)	300 (60.6)	324 (71.5)
≥30%	227 (29.6)	55 (34.4)	168 (39.5)	252 (50.9)	274 (60.5)
≥40%	179 (23.4)	42 (26.3)	130 (30.6)	205 (41.4)	241 (53.2)
≥50%	138 (18.0)	34 (21.3)	110 (25.9)	170 (34.3)	204 (45.0)
≥60%	96 (12.5)	24 (15.0)	70 (16.5)	118 (23.8)	153 (33.8)
≥70%	64 (8.4)	13 (8.1)	47 (11.1)	73 (14.7)	110 (24.3)
≥80%	34 (4.4)	9 (5.6)	32 (7.5)	43 (8.7)	66 (14.6)
≥90%	15 (2.0)	2 (1.3)	16 (3.8)	25 (5.1)	37 (8.2)
=100%	7 (0.9)	1 (0.6)	9 (2.1)	12 (2.4)	24 (5.3)

[a] In Studies 127, 149, and 196, patients randomized to the 300/600 mg/day pregabalin group received either 300 or 600 mg/day based on their CLcr, and are summarized here according to those doses.

Table 8.21.3:

PGIC Descriptive Statistics: All Double-Blind Neuropathic Pain Studies

Patient Status	Placebo	Pregabalin Dose, mg/day			
		75 mg	150 mg	300 mg[a]	600 mg[a]
	(N = 772)	(N = 161)	(N = 427)	(N = 496)	(N = 458)
Number Assessed	755	154	418	472	444
Very Much Improved	42 (5.6)	9 (5.8)	38 (9.1)	66 (14.0)	75 (16.9)
Much improved	138(18.3)	33 (21.4)	96 (23.0)	128 (27.1)	163 (36.7)
Minimally Improved	168(22.3)	42 (27.3)	103 (24.6)	118 (25.0)	120 (27.0)
No Change	294(38.9)	53 (34.4)	135 (32.3)	111 (23.5)	60 (13.5)
Minimally Worse	63 (8.3)	13 (8.4)	26 (6.2)	29 (6.1)	16 (3.6)
Much Worse	41 (5.4)	4 (2.6)	13 (3.1)	17 (3.6)	7 (1.6)
Very Much Worse	9 (1.2)	0 (0.0)	7 (1.7)	3 (0.6)	3 (0.7)

[a] In Studies 127, 149, and 196, patients randomized to the 300/600 mg/day pregabalin group received either 300 or 600 mg/day based on their CLcr, and are summarized here according to those doses.

Table 8.22:

Endpoint[a] Mean Pain Scores: Results of Analysis of Covariance: Studies 173 (DPN) and 132 (PHN) - ITT Population

Study/Treatment Group	Least Squares			Treatment Comparisons (Pregabalin — Placebo)			
	N	Mean	SE	Difference	95% CI	Unadjusted p Value	Adjusted[b] p Value
DPN Pain Model							
Study 173 [BID]							
Placebo	29	5.33	0.39				
PGB 150 mg/day	34	4.77	0.36	-0.55	(-1.54, 0.43)	0.2669	0.4795
PGB 300 mg/day	43	4.99	0.34	-0.34	(-1.29, 0.61)	0.4795	0.4795
PGB 300/600 mg/day[c]	38	4.09	0.35	-1.24	(-2.21, -0.27)	0.0125	0.0375
PHN Pain Model							
Study 132 [BID]							
Placebo	52	6.23	0.26				
PGB 150 mg/day	51	5.05	0.26	-1.18	(-1.90, -0.46)	0.0015	0.0015
PGB 300 mg/day	62	4.90	0.24	-1.33	(-2.01, -0.65)	0.0002	0.0004
PGB 300/600 mg/day[c]	50	4.21	0.26	-2.02	(-2.74, -1.31)	0.0001	0.0003

DPN = Diabetic peripheral neuropathy; PHN = Postherpetic neuralgia; ITT = Intent-to-treat; SE = Standard Error; CI = Confidence Interval; PGB = Pregabalin

[a] Endpoint = Mean of last 7 available diary entries up to the last day on study medication.

[b] Adjustment is based on Hochberg's procedure.

[c] Patients randomized to the 300/600 mg/day pregabalin group received either 300 or 600 mg/day based on their CLcr.

Table 8.22a: DPN014

Weekly Mean Pain Scores: Descriptive Statistics

Time Point	Placebo			Pregabalin 150 mg/day			Pregabalin 600 mg/day		
	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max
Baseline[a]	85	6.9 (1.6)	2.0, 10	79	6.5 (1.3)	4.0, 9.3	82	6.7 (1.7)	3.9,10
Week 1[b]	82	6.5 (1.7)	2.6, 10	79	5.9 (1.6)	2.5, 9.4	82	5.8 (2.1)	0.4, 10
Week 2	82	6.0 (2.0)	1.7, 10	79	5.4 (1.9)	0, 9.0	81	4.9 (2.5)	0, 10
Week 3	79	5.7 (2.1)	0.6, 9.3	76	5.1 (2.0)	0, 9.0	78	4.6 (2.7)	0, 10
Week 4	76	5.7 (2.1)	0.4, 9.9	75	5.0 (2.1)	0, 9.3	74	4.6 (2.7)	0, 10
Week 5	75	5.7 (2.2)	0.1, 10	75	4.9 (2.3)	0, 9.6	73	4.3 (2.7)	0, 10
Week 6	74	5.8 (2.3)	0.1, 10	74	4.8 (2.2)	0, 8.7	70	4.4 (2.7)	0, 10
End Point[c]	82	5.8 (2.2)	1.0, 10	79	4.9 (2.2)	0, 9.0	82	4.3 (2.4)	0, 10

SD = Standard deviation.

[a] Baseline = Last 7 available scores before taking study medication, up to and including Day 1.

[b] Week 1, 2, etc. All data for all patients who entered the week of interest were used in the analysis.

[c] End Point = Last 7 available scores while on study medication, up to and including day after last dose.

Table 8.22B: DPN 014

Weekly Mean Pain Scores: Results of Analysis of Covariance

Treatment	Least Squares N	Mean	SE	Treatment Comparisons (Pregabalin—Placebo) Difference	95% CI	Unadjusted p-Value	Adjusted p-Value
Week 1							
Placebo	82	6.23	0.14				
PGB150 mg/day	79	6.11	0.15	-0.123	(-0.515 0.268)	0.5350	0.5350
PGB 600 mg/day	82	5.74	0.14	-0.493	(-0.876 -0.111)	0.0118	0.0236[c]
Week 2							
Placebo	82	5.77	0.19				
PGB 150 mg/day	79	5.58	0.20	-0.190	(-0.724 0.344)	0.4835	0.4835
PGB 600 mg/day	81	4.83	0.20	-0.939	(-1.462 -0.416)	0.0005	0.0010
Week 3							
Placebo	79	5.48	0.22				
PGB 150 mg/day	76	5.25	0.23	-0.229	(-0.844 0.387)	0.4650	0.4650
PGB 600 mg/day	78	4.57	0.23	-0.907	(-1.512 -0.302)	0.0035	0.0070
Week 4							
Placebo	76	5.48	0.23				
PGB 150mg/day	75	5.11	0.23	-0.370	(-1.005 0.264)	0.2514	0.2514
PGB 600mg/day	74	4.59	0.23	-0.886	(-1.516 -0.256)	0.0061	0.0122
Week 5							
Placebo	75	5.49	0.24				
PGB 150 mg/day	75	5.01	0.24	-0.478	(-1.130 0.174)	0.1498	0.1498
PGB 600 mg/day	73	4.22	0.24	-1.269	(-1.918 -0.620)	0.0002	0.0004
Week 6							
Placebo	74	5.54	0.24				
PGB 150 mg/day	74	4.99	0.24	-0.554	(-1.210 0.101)	0.0970	0.0970
PGB 600 mg/day	70	4.28	0.25	-1.262	(-1.922 -0.602)	0.0002	0.0004

SE = Standard Error; CI = Confidence Interval.

[a] Week 1, 2, etc. All data for all patients who entered the week of interest were used in the analysis.

[b] Adjustment based on Hochberg's procedure.

[c] ANCOVA of rank-transformed data (performed due to nonnormality) did not confirm significant result. Adjusted p-value for 600 mg/day pregabalin vs placebo in rank ANCOVA was 0.1078.

Table 8.22C: DPN 029

Weekly Mean Pain Scores: Descriptive Statistics

Timepoint	Placebo			Pregabalin (mg/day) 75			300			600		
	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max
Baseline[a]	97	6.6 (1.5)	2.9, 9.6	77	6.7 (1.3)	3.7, 10	81	6.2 (1.4)	3.9, 10	82	6.2 (1.5)	3.7, 10
Week 1[b]	97	5.9 (1.8)	2.6, 9.9	77	5.9 (1.7)	2, 10	80	4.5 (1.8)	1.3, 8.4	81	4.5 (1.8)	0.7, 8.3
Week 2	92	5.5 (1.9)	1.9, 9	72	5.5 (2.3)	0.6, 10	77	4.1 (1.8)	0.9, 7.9	77	3.8 (2.2)	0, 8
Week 3	91	5.2 (2.1)	0, 9.6	69	5.3 (2.3)	0.7, 10	78	3.8 (1.8)	0, 7.6	74	3.5 (2.2)	0, 8.4
Week 4	87	5.2 (2.1)	0.3, 9.9	64	5.0 (2.4)	0.6, 10	75	3.6 (1.9)	0, 8.1	68	3.5 (2.3)	0, 9.6
Week 5	84	5.1, (2.3)	0, 10	62	5.0 (2.5)	0.2, 10	72	3.7 (2.1)	0, 8.2	67	3.4 (2.3)	0, 10
End Point[c]	97	5.2 (2.2)	0.1, 9.9	77	5.1 (2.5)	0.1, 10	81	3.6 (2.1)	0, 8.1	81	3.5 (2.3)	0, 10

SD = Standard deviation.

[a] Baseline = Last 7 available scores before taking study medication, up to and including Day 1.

[b] Week 1, 2, etc. All data for all patients who entered the week of interest were used in the analysis

[c] End point = Last 7 available scores while on study medication, up to and including day after last dose.

Table 8.22D: DPN 029

Weekly[a] Mean Pain Scores: Results of Analysis of Covariance

Treatment (mg/day)	N	Least Squares Mean	SE	Treatment Comparisons (Pregabalin-Placebo) Difference	95% CI	Unadjusted p-Value	Adjusted[b] p-Value
Week 1							
Placebo	97	5.84	0.15				
Pregabalin 75	77	5.80	0.17	-0.046	(-0.476, 0.384)	0.8347	0.8347
Pregabalin 300	80	4.70	0.16	-1.148	(-1.578, -0.719)	0.0001	0.0001
Pregabalin 600	81	4.64	0.16	-1.202	(-1.628, -0.777)	0.0001	0.0001
Week 2							
Placebo	92	5.43	0.19				
Pregabalin 75	72	5.37	0.22	-0.058	(-0.619, 0.503)	0.8396	0.8396
Pregabalin 300	77	4.23	0.21	-1.199	(-1.754, -0.643)	0.0001	0.0001
Pregabalin 600	77	3.91	0.21	-1.518	(-2.070, -0.967)	0.0001	0.0001
Week 3							
Placebo	91	5.12	0.20				
Pregabalin 75	69	5.10	0.23	-0.017	(-0.604, 0.569)	0.9542	0.9542
Pregabalin 300	78	3.99	0.22	-1.130	(-1.699, -0.560)	0.0001	0.0001
Pregabalin 600	74	3.59	0.22	-1.525	(-2.100, -0.950)	0.0001	0.0001
Week 4							
Placebo	87	5.06	0.22				
Pregabalin 75	64	4.90	0.25	-0.163	(-0.804, 0.478)	0.6174	0.6174
Pregabalin 300	75	3.78	0.23	-1.288	(-1.905, -0.670)	0.0001	0.0001
Pregabalin 600	68	3.60	0.24	-1.458	(-2.092, -0.824)	0.0001	0.0001
Week 5							
Placebo	84	4.97	0.23				
Pregabalin 75	62	4.82	0.27	-0.155	(-0.849, 0.539)	0.6606	0.6606
Pregabalin 300	72	3.79	0.26	-1.186	(-1.859, -0.514)	0.0006	0.0006
Pregabalin 600	67	3.54	0.26	-1.436	(-2.121, -0.751)	0.0001	0.0002

SE = Standard error; CI = Confidence interval.

[a] Week 1, 2, etc. All data for all patients who entered the week of interest were used in the analysis.

[b] Adjustment based on Hochberg's procedure applies to pregabalin 300 and 600 mg/day only, as stated in protocol.

Table 8.22E: DPN 040

Weekly Mean Pain Scores: Descriptive Statistics

Time Point	Placebo			Pregabalin 600 mg/day			Amitriptyline 75 mg/day		
	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max
Baseline[a]	80	6.3 (1.6)	3.1, 10	86	6.9 (1.6)	3.7, 10	87	6.4 (1.6)	3.7, 10
Week 1	81	5.7 (1.8)	1.6, 9.7	85	5.4 (1.9)	0, 10	85	5.3 (2.0)	0, 10
Week 2	79	5.2 (1.9)	1, 8.9	77	4.9 (2.0)	0, 9.7	83	4.5 (2.1)	0, 10
Week 3	75	4.9 (2.2)	0, 9.3	76	4.3 (2.3)	0, 9	81	3.9 (2.2)	0, 9.8
Week 4	72	4.7 (2.3)	0, 10	73	3.9 (2.4)	0, 9	75	3.6 (2.3)	0, 9.7
Week 5	72	4.5 (2.2)	0, 9.3	72	4.0 (2.5)	0, 8.6	73	3.5 (2.3)	0, 9.9
Week 6	65	4.3 (2.3)	0, 9.4	68	3.8 (2.5)	0, 8.7	69	3.4 (2.2)	0, 9.4
Week 7	63	4.2 (2.4)	0, 9.9	65	3.9 (2.5)	0, 9.9	67	3.3 (2.3)	0, 9.9
Week 8	61	4.2 (2.3)	0, 9.4	64	3.9 (2.5)	0, 9.3	66	3.2 (2.3)	0, 9.4
Endpoint[b]	81	4.5 (2.4)	0, 9.4	86	4.1 (2.4)	0, 9.3	87	3.6 (2.4)	0, 9.4

SD = Standard Deviation.

Weekly = Week 1, 2, etc. All data for all patients who entered the week of interest were used in the analysis.

[a] Baseline = Last 7 available scores before taking study medication, up to and including Day 1. If fewer than 7 scores, the mean was obtained from available entries.

[b] Endpoint = Last 7 available scores while on study medication, up to and including day after last dose from the titration/fixed-dose phase. If fewer than 7 postbaseline scores were available in the titration/fixed-dose phase, the mean was obtained from the x postbaseline entries available (x <7) and from the last 7 - x entries from the baseline phase.

Table 8.22F: DPN 040

Weekly Mean Pain Scores: Results of Multivariate Analysis

Treatment	N	Least-Squares Means	SE	Treatment Comparisons (Active Group — Placebo)		
				Difference	95% CI	p-Value
Week 1						
Placebo	80	5.94	0.23			
Pregabalin 600 mg/day	85	5.21	0.22	-0.73	(-1.35; -0.11)	0.0208
Amitriptyline 75 mg/day	85	5.35	0.22	-0.58	(-1.20; 0.03)	0.0622
Week 2						
Placebo	78	5.42	0.23			
Pregabalin 600 mg/day	77	4.57	0.22	-0.86	(-1.48; -0.23)	0.0073
Amitriptyline 75 mg/day	83	4.60	0.22	-0.82	(-1.44; -0.20)	0.0091
Week 3						
Placebo	74	5.15	0.23			
Pregabalin 600 mg/day	76	3.91	0.22	-1.24	(-1.87; -0.61)	0.0001
Amitriptyline 75 mg/day	81	3.97	0.22	-1.18	(-1.80; -0.56)	0.0002
Week 4						
Placebo	71	4.97	0.23			
Pregabalin 600 mg/day	73	3.63	0.23	-1.34	(-1.98; -0.70)	0.0001
Amitriptyline 75 mg/day	75	3.72	0.22	-1.25	(-1.88; -0.62)	0.0001
Week 5						
Placebo	71	4.74	0.23			
Pregabalin 600 mg/day	72	3.73	0.23	-1.01	(-1.65; -0.37)	0.0021
Amitriptyline 75 mg/day	73	3.58	0.23	-1.16	(-1.80; -0.53)	0.0003
Week 6						
Placebo	65	4.64	0.24			
Pregabalin 600 mg/day	68	3.62	0.23	-1.01	(-1.67; -0.36)	0.0024
Amitriptyline 75 mg/day	69	3.60	0.23	-1.04	(-1.68; -0.39)	0.0017
Week 7						
Placebo	63	4.59	0.24			
Pregabalin 600 mg/day	65	3.70	0.24	-0.90	(-1.56; -0.23)	0.0080
Amitriptyline 75 mg/day	67	3.56	0.23	-1.03	(-1.68; -0.37)	0.0021
Week 8						
Placebo	61	4.56	0.24			
Pregabalin 600 mg/day	64	3.69	0.24	-0.87	(-1.55; -0.20)	0.0109
Amitriptyline 75 mg/day	66	3.48	0.24	-1.09	(-1.75; -0.42)	0.0014

SE = Standard Error; CI = Confidence Interval.
Weekly = Week 1, 2, etc. All data for all patients who entered the week of interest were used in the analysis.

Table 8.22G: DPN 131

Weekly Mean Pain Scores: Descriptive Statistics

Time point	Placebo				Pregabalin 300 mg/day			
	N	Mean (SD)	Min	Max	N	Mean (SD)	Min	Max
Baseline[a]	70	6.1(1.5)	4	10	76	6.5(1.7)	3.6	9.9
Week 1[b]	68	5.9(1.7)	2.1	10	75	4.3(2.3)	0	9.1
Week 2	69	5.8(1.8)	1.9	10	73	4.2(2.5)	0	9.9
Week 3	68	5.7(2.0)	1.8	10	72	4.1(2.4)	0	9.7
Week 4	68	5.6(2.0)	1.9	10	71	4.4(2.4)	0	9.9
Week 5	67	5.7(2.1)	1.1	10	69	4.2(2.3)	0	9.7
Week 6	62	5.6(2.3)	1.4	10	68	4.1(2.3)	0	8.7
Week 7	60	5.4(2.3)	1.6	10	64	4.2(2.4)	0	9.9
Week 8	59	5.3(2.5)	0.6	10	62	4.1(2.4)	0	10
Endpoint[c]	69	5.3(2.4)	1.1	10	75	4.0(2.5)	0	10

SD = Standard deviation.
[a] Baseline = Last 7 available scores before taking study medication, up to and including Day 1.
[b] Week 1, 2, etc. All data for all patients who entered the week of interest were used in the analysis.
[c] Endpoint = Last 7 available scores while on study medication, up to and including day after last dose.

Table 8.22H: DPN 131

. Weekly[a] Mean Pain Scores: Results of Analysis of Covariance

Treatment	N	Least Squares Mean	SE	Treatment Comparisons (Pregabalin—Placebo)		
				Difference	95% CI	p-value
Week 1						
Placebo	68	5.94	0.22			
PGB 300 mg/day	75	4.15	0.20	-1.79	(-2.35, -1.23)	0.0001
Week 2						
Placebo	69	5.82	0.24			
PGB 300 mg/day	73	4.08	0.23	-1.74	(-2.37, -1.11)	0.0001
Week 3						
Placebo	68	5.83	0.26			
PGB 300 mg/day	72	3.99	0.24	-1.85	(-2.51, -1.18)	0.0001
Week 4						
Placebo	68	5.81	0.27			
PGB 300 mg/day	71	4.31	0.25	-1.50	(-2.19, -0.81)	0.0001
Week 5						
Placebo	67	5.81	0.26			
PGB 300 mg/day	69	4.17	0.25	-1.64	(-2.33, -0.96)	0.0001
Week 6						
Placebo	62	5.71	0.28			
PGB 300 mg/day	68	4.13	0.26	-1.58	(-2.31, -0.86)	0.0001
Week 7						
Placebo	60	5.43	0.31			
PGB 300 mg/day	64	4.15	0.29	-1.28	(-2.03, -0.52)	0.0012
Week 8						
Placebo	59	5.44	0.30			
PGB 300 mg/day	62	4.12	0.29	-1.32	(-2.11, -0.53)	0.0013

SE = Standard error; CI = Confidence interval; PGB = Pregabalin.

[a] Week 1, 2, etc. All data for all patients who entered the week of interest were used in the analysis.

Table 8.22I: DPN 149

Mean Pain Scores by Week[a,c]: Results of Analysis of Covariance by Week
Modified Intent-to-Treat Population

(Page 1 of 2)

Period/Treatment Group	N	Least-Squares Means	SE	Treatment Comparisons (Pregabalin — Placebo)			
				Difference	95% CI	Unadjusted p-Value	Adjusted p-Value[b]
Week 1							
Placebo	93	5.95	0.17				
PGB 150 mg	96	5.48	0.17	-0.47	(-0.86, -0.07)	0.0207	0.0207
PGB 300 mg	96	5.34	0.17	-0.61	(-1.00, -0.22)	0.0025	0.0050
PGB 300/600 mg	98	5.33	0.16	-0.62	(-1.01, -0.22)	0.0022	0.0050
Week 2							
Placebo	92	5.53	0.21				
PGB 150 mg	96	5.20	0.21	-0.33	(-0.83, 0.17)	0.1994	0.1994
PGB 300 mg	92	5.04	0.22	-0.49	(-1.00, 0.02)	0.0578	0.1156
PGB 300/600 mg	97	4.42	0.21	-1.11	(-1.61, -0.61)	0.0001	0.0003
Week 3							
Placebo	91	5.30	0.23				
PGB 150 mg	95	4.96	0.23	-0.34	(-0.89, 0.21)	0.2251	0.2251
PGB 300 mg	91	4.71	0.24	-0.58	(-1.14, -0.03)	0.0386	0.0772
PGB 300/600 mg	91	4.04	0.24	-1.25	(-1.81, -0.70)	0.0001	0.0003
Week 4							
Placebo	91	5.04	0.25				
PGB 150 mg	95	4.78	0.25	-0.26	(-0.84, 0.33)	0.3882	0.3882
PGB 300 mg	89	4.57	0.26	-0.47	(-1.06, 0.13)	0.1222	0.2444
PGB 300/600 mg	90	3.93	0.25	-1.10	(-1.70, -0.51)	0.0003	0.0009
Week 5							
Placebo	86	4.93	0.25				
PGB 150 mg	94	4.71	0.24	-0.22	(-0.79, 0.35)	0.4494	0.4494
PGB 300 mg	86	4.62	0.26	-0.31	(-0.90, 0.27)	0.2893	0.4494
PGB 300/600 mg	89	3.79	0.25	-1.14	(-1.72, -0.56)	0.0001	0.0003
Week 6							
Placebo	85	4.91	0.25				
PGB 150 mg	91	4.58	0.25	-0.33	(-0.92, 0.26)	0.2760	0.4406
PGB 300 mg	84	4.67	0.27	-0.24	(-0.84, 0.37)	0.4406	0.4406
PGB 300/600 mg	86	3.70	0.26	-1.20	(-1.80, -0.60)	0.0001	0.0003

SE = Standard error; CI = Confidence interval.

[a] Week 1, 2, etc. All data for all patients who entered the week of interest were used in the analysis.

[b] Adjustment based on Hochberg's procedure.

[c] Based on LS Means using ANCOVA model (including effects for treatment, cluster, Creatinine clearance stratum and the baseline score value as covariate).

Mean Pain Scores by Week[a,c]: Results of Analysis of Covariance by Week
Modified Intent-to-Treat Population

(Page 2 of 2)

Treatment Groups	N	Least-Squares Means	SE	Treatment Comparisons (Pregabalin — Placebo)			
				Difference	95% CI	Unadjusted p-Value	Adjusted p-Value[b]
Week 7							
Placebo	84	4.73	0.27				
PGB 150 mg	89	4.31	0.26	-0.42	(-1.03, 0.20)	0.1861	0.3656
PGB 300 mg	84	4.44	0.28	-0.29	(-0.91, 0.34)	0.3656	0.3656
PGB 300/600 mg	85	3.76	0.27	-0.97	(-1.60, -0.34)	0.0026	0.0078
Week 8							
Placebo	83	4.51	0.27				
PGB 150 mg	86	4.08	0.27	-0.43	(-1.05, 0.18)	0.1669	0.3338
PGB 300 mg	84	4.48	0.28	-0.03	(-0.66, 0.59)	0.9140	0.9140
PGB 300/600 mg	83	3.58	0.27	-0.93	(-1.55, -0.30)	0.0038	0.0114
Week 9							
Placebo	82	4.58	0.27				
PGB 150 mg	85	3.95	0.27	-0.62	(-1.24, -0.01)	0.0471	0.0942
PGB 300 mg	82	4.31	0.28	-0.26	(-0.89, 0.36)	0.4035	0.4035
PGB 300/600 mg	81	3.53	0.28	-1.05	(-1.68, -0.42)	0.0011	0.0033
Week 10							
Placebo	80	4.36	0.28				
PGB 150 mg	82	4.04	0.28	-0.32	(-0.96, 0.31)	0.3136	0.4945
PGB 300 mg	80	4.14	0.29	-0.22	(-0.86, 0.42)	0.4945	0.4945
PGB 300/600 mg	81	3.34	0.28	-1.02	(-1.65, -0.38)	0.0019	0.0057
Week 11							
Placebo	75	4.18	0.29				
PGB 150 mg	81	3.85	0.29	-0.32	(-0.98, 0.34)	0.3344	0.5940
PGB 300 mg	80	4.00	0.29	-0.18	(-0.84, 0.48)	0.5940	0.5940
PGB 300/600 mg	79	3.24	0.29	-0.94	(-1.60, -0.27)	0.0059	0.0177
Week 12							
Placebo	72	4.09	0.30				
PGB 150 mg	77	3.93	0.29	-0.16	(-0.84, 0.52)	0.6476	0.8133
PGB 300 mg	76	4.00	0.30	-0.08	(-0.77, 0.60)	0.8133	0.8133
PGB 300/600 mg	74	3.32	0.30	-0.77	(-1.46, -0.07)	0.0300	0.0900

SE = Standard error; CI = Confidence interval.

[a] Week 1, 2, etc. All data for all patients who entered the week of interest were used in the analysis.

[b] Adjustment based on Hochberg's procedure.

[c] Based on LS Means using ANCOVA model (including effects for treatment, cluster, Creatinine clearance stratum and the baseline score value as covariate).

Table 8.22J: PHN 030

Weekly Mean Pain Scores: Descriptive Statistics

Timepoint	Placebo			Pregabalin 75 mg/day			Pregabalin 150 mg/day		
	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max
Baseline[a]	88	6.6 (1.5)	3.7, 10	84	6.7 (1.6)	4.0, 9.9	83	6.4 (1.6)	3.4, 10
Week 1[b]	87	6.2 (1.8)	1.0, 10	83	5.7 (2.2)	0.9, 10	82	5.3 (2.0)	0.1, 10
Week 2	86	5.8 (2.1)	1.0, 10	82	5.7 (2.2)	0.0, 10	79	5.2 (2.1)	0.3, 10
Week 3	84	5.6 (2.2)	0.7, 10	82	5.6 (2.3)	0.0, 10	79	5.2 (2.3)	0.3, 9.7
Week 4	80	5.5 (2.4)	0.6, 10	80	5.4 (2.3)	0.0, 10	75	5.3 (2.3)	0.6, 9.9
Week 5	76	5.2 (2.4)	0.6,10	78	5.4 (2.5)	0.0, 10	74	5.3 (2.6)	0.0, 10
Endpoint[c]	87	5.5 (2.5)	0.6, 10	83	5.5 (2.5)	0.0, 10	82	5.3 (2.6)	0.0, 10

SD = Standard deviation.

[a] Baseline = Last 7 available scores before taking study medication, up to and including Day 1.

[b] Week 1, 2, etc. All data for all patients who entered the week of interest were used in the analysis.

[c] Endpoint = Last 7 available scores while on study medication, up to and including day after last dose.

Table 8.22K: PHN 030

Weekly[a] Mean Pain Scores: Results of Analysis of Covariance

Treatment	N	Least Squares Mean	SE	Treatment Comparisons (Pregabalin—Placebo)			
				Difference	95% CI	Unadjusted p-Value	Adjusted[b] p-Value
Week 1							
Placebo	87	6.17	0.16				
PGB 75 mg/day	83	5.68	0.16	-0.487	(-0.910, -0.064)	0.0244	0.0244
PGB 150 mg/day	82	5.44	0.16	-0.733	(-1.158, -0.309)	0.0008	0.0016
Week 2							
Placebo	86	5.88	0.17				
PGB 75 mg/day	82	5.69	0.17	-0.188	(-0.638, 0.262)	0.4105	0.4105
PGB 150 mg/day	79	5.41	0.17	-0.463	(-0.918, -0.009)	0.0459	0.0918
Week 3							
Placebo	84	5.75	0.18				
PGB 75 mg/day	82	5.54	0.19	-0.213	(-0.708, 0.283)	0.3980	0.3980
PGB 150 mg/day	79	5.40	0.19	-0.347	(-0.847, 0.153)	0.1728	0.3456
Week 4							
Placebo	80	5.58	0.19				
PGB 75 mg/day	80	5.38	0.19	-0.196	(-0.712, 0.320)	0.4550	0.7968
PGB 150 mg/day	75	5.51	0.20	-0.069	(-0.596, 0.458)	0.7968	0.7968
Week 5							
Placebo	76	5.46	0.22				
PGB 75 mg/day	78	5.34	0.22	-0.118	(-0.714, 0.477)	0.6956	0.9733
PGB 150 mg/day	74	5.47	0.23	0.010	(-0.594, 0.615)	0.9733	0.9733

SE = Standard error; CI = Confidence interval; PGB = Pregabalin.

[a] Week 1, 2, etc. All data for all patients who entered the week of interest were used in the analysis.

[b] Adjustment based on Hochberg's procedure

Table 8.22L: PHN 045

Weekly[a] Mean Pain Scores: Descriptive Statistics

Timepoint	Placebo			Pregabalin					
				150 mg/day			300 mg/day		
	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max
Baseline[b]	81	6.6 (1.6)	4, 10	81	6.9 (1.7)	4, 10	76	7.0 (1.6)	4, 10
Week 1	81	6.4 (1.8)	2.9, 10	81	6.0 (2.1)	0.4, 10	76	5.8 (2.0)	1.7, 9.9
Week 2	75	6.3 (1.9)	2, 10	77	5.7 (2.2)	0.9, 10	75	5.1 (2.2)	0.4, 9.3
Week 3	75	6.3 (2.0)	2, 10	76	5.6 (2.2)	0.3, 10	72	5.5 (2.3)	0, 9.8
Week 4	68	6.2 (2.0)	2, 10	74	5.5 (2.3)	0.3, 10	65	5.3 (2.3)	0, 10
Week 5	67	6.0 (2.2)	1.8, 10	74	5.4 (2.5)	0, 10	64	5.2 (2.3)	0, 10
Week 6	64	6.2 (2.2)	1.7, 10	73	5.4 (2.3)	0.6, 10	61	4.9 (2.4)	0, 10
Week 7	62	5.9 (2.3)	1.4, 10	71	5.3 (2.4)	0.1, 10	61	5.0 (2.4)	0, 10
Week 8	61	6.0 (2.4)	1.2, 10	70	5.1 (2.5)	0.1, 10	60	4.9 (2.6)	0, 10
Endpoint[c]	81	6.2 (2.3)	1.3, 10	81	5.2 (2.5)	0.1, 10	76	4.9 (2.5)	0, 10

SD = Standard deviation.

[a] Week 1, 2, etc. All data for all patients who entered the week of interest were used in the analysis.

[b] Baseline = Last 7 available scores before taking study medication, up to and including Day 1.

[c] Endpoint = Last 7 available scores while on study medication, up to and including day after last dose.

Table 8.22M: PHN 045

Weekly[a] Mean Pain Scores: Results of Analysis of Covariance
Observed Cases Analysis

Treatment	N	Least-Squares Means	SE	Treatment Comparisons (Pregabalin—Placebo)			
				Difference	95% CI	Unadjusted p-Value	Adjusted[b] p-Value
Week 1							
Placebo	81	6.57	0.14				
Pregabalin 150	81	5.92	0.14	-0.65	(-1.05, -0.26)	0.0013	0.0013
Pregabalin 300	76	5.64	0.15	-0.93	(-1.34, -0.53)	0.0001	0.0002
Week 2							
Placebo	75	6.43	0.18				
Pregabalin 150	77	5.63	0.18	-0.80	(-1.30, -0.30)	0.0018	0.0018
Pregabalin 300	75	5.00	0.18	-1.43	(-1.93, -0.92)	0.0001	0.0002
Week 3							
Placebo	75	6.44	0.18				
Pregabalin 150	76	5.50	0.18	-0.94	(-1.45, -0.43)	0.0003	0.0003
Pregabalin 300	72	5.34	0.19	-1.10	(-1.62, -0.58)	0.0001	0.0002
Week 4							
Placebo	68	6.42	0.19				
Pregabalin 150	74	5.50	0.18	-0.92	(-1.44, -0.39)	0.0007	0.0007
Pregabalin 300	65	5.06	0.20	-1.36	(-1.91, -0.81)	0.0001	0.0002
Week 5							
Placebo	67	6.17	0.22				
Pregabalin 150	74	5.30	0.21	-0.87	(-1.47, -0.27)	0.0049	0.0049
Pregabalin 300	64	4.93	0.23	-1.24	(-1.87, -0.61)	0.0001	0.0002
Week 6							
Placebo	64	6.30	0.24				
Pregabalin 150	73	5.36	0.22	-0.94	(-1.57, -0.31)	0.0038	0.0038
Pregabalin 300	61	4.77	0.24	-1.52	(-2.19, -0.86)	0.0001	0.0002
Week 7							
Placebo	62	6.03	0.25				
Pregabalin 150	71	5.28	0.23	-0.75	(-1.42, -0.07)	0.0304	0.0304
Pregabalin 300	61	4.87	0.25	-1.15	(-1.86, -0.45)	0.0015	0.0030
Week 8							
Placebo	61	6.08	0.27				
Pregabalin 150	70	5.05	0.25	-1.03	(-1.75, -0.31)	0.0052	0.0052
Pregabalin 300	60	4.81	0.27	-1.26	(-2.01, -0.51)	0.0011	0.0022

SE = Standard error; CI = Confidence interval.

[a] Week 1, 2, etc. All data for all patients who entered the week of interest were used in the analysis.

[b] Adjustment based on Hochberg's procedure.

Table 8.22N: PHN 127

Weekly Mean Pain Scores: Descriptive Statistics

Time point	Placebo			Pregabalin		
	N	Mean (SD)	Range	N	Mean (SD)	Range
Baseline[a]	84	6.4 (1.5)	4, 10	89	6.3 (1.4)	3.7, 9.1
Week 1[b]	84	6.0 (1.9)	0.6, 10	87	4.7 (1.8)	0.9, 9.1
Week 2	83	5.7 (1.9)	0.1, 10	84	3.9 (2.0)	0, 9
Week 3	81	5.6 (2.3)	0.4, 10	77	3.6 (2.2)	0, 9
Week 4	76	5.5 (2.2)	0, 10	73	3.7 (2.2)	0, 9.4
Week 5	76	5.4 (2.5)	0, 10	67	3.6 (2.2)	0, 10
Week 6	74	5.4 (2.5)	0, 10	62	3.7 (2.1)	0, 9.1
Week 7	74	5.4 (2.7)	0, 10	61	3.8 (2.3)	0, 9.4
Week 8	71	5.1 (2.7)	0, 10	54	3.5 (2.4)	0, 9.5
Endpoint[c]	84	5.3 (2.6)	0, 10	88	3.6 (2.3)	0, 9.6

SD = Standard deviation.

[a] Baseline = Last 7 available scores before taking study medication, up to and including Day 1.

[b] Week 1, 2, etc. All data for all patients who entered the week of interest were used in the analysis.

[c] Endpoint = Last 7 available scores while on study medication, up to and including day after last dose.

Table 8.22O: PHN 127

Weekly[a] Mean Pain Scores: Results of Analysis of Covariance

Treatment	N	Least-Squares Mean	SE	Treatment Comparisons (Pregabalin—Placebo)		
				Difference	95% CI	p-value
Week 1						
Placebo	84	5.94	0.16			
Pregabalin	87	4.74	0.15	-1.20	(-1.61, -0.79)	0.0001
Week 2						
Placebo	83	5.66	0.18			
Pregabalin	84	3.92	0.19	-1.75	(-2.24, -1.26)	0.0001
Week 3						
Placebo	81	5.62	0.21			
Pregabalin	77	3.60	0.22	-2.02	(-2.60, -1.44)	0.0001
Week 4						
Placebo	76	5.54	0.22			
Pregabalin	73	3.76	0.22	-1.78	(-2.36, -1.20)	0.0001
Week 5						
Placebo	76	5.37	0.25			
Pregabalin	67	3.51	0.26	-1.86	(-2.53, -1.19)	0.0001
Week 6						
Placebo	74	5.47	0.24			
Pregabalin	62	3.67	0.26	-1.81	(-2.48, -1.14)	0.0001
Week 7						
Placebo	74	5.49	0.27			
Pregabalin	61	3.75	0.30	-1.73	(-2.51, -0.96)	0.0001
Week 8						
Placebo	71	5.10	0.28			
Pregabalin	54	3.38	0.32	-1.72	(-2.52, -0.92)	0.0001

SE = Standard error; CI = Confidence interval.

[a] Week 1, 2, etc. All data for all patients who entered the week of interest were used in the analysis.

Table 8.22P: PHN 196

Weekly[a,c] Mean Pain Scores: Results of Repeated Measures Analysis of Covariance: Intent-to-Treat Population

(Page 1 of 3)

Period/ Treatment Group (mg/day)	N	Least-Squares Means	SE	Treatment Comparisons (Pregabalin — Placebo)			
				Difference	95% CI	Unadjusted p-Value	Adjusted p-Value[b]
Week 1							
Placebo	92	6.43	0.20				
PGB 150 mg	87	5.45	0.20	-0.98	(-1.53, -0.43)	0.0005	0.0005
PGB 300 mg	98	5.36	0.19	-1.07	(-1.60, -0.54)	0.0001	0.0002
PGB 300/600 mg	88	5.19	0.20	-1.24	(-1.78, -0.69)	0.0001	0.0002
Week 2							
Placebo	89	6.23	0.20				
PGB 150 mg	86	5.48	0.21	-0.75	(-1.30, -0.20)	0.0077	0.0077
PGB 300 mg	94	4.96	0.19	-1.27	(-1.81, -0.74)	0.0001	0.0002
PGB 300/600 mg	79	4.76	0.21	-1.47	(-2.02, -0.92)	0.0001	0.0002
Week 3							
Placebo	87	6.20	0.20				
PGB 150 mg	84	5.42	0.21	-0.78	(-1.33, -0.22)	0.0059	0.0059
PGB 300 mg	87	4.96	0.20	-1.24	(-1.78, -0.70)	0.0001	0.0002
PGB 300/600 mg	78	4.57	0.21	-1.63	(-2.19, -1.08)	0.0001	0.0002
Week 4							
Placebo	83	6.15	0.20				
PGB 150 mg	83	5.35	0.21	-0.80	(-1.36, -0.25)	0.0047	0.0047
PGB 300 mg	87	4.91	0.20	-1.24	(-1.78, -0.70)	0.0001	0.0002
PGB 300/600 mg	75	4.51	0.21	-1.64	(-2.20, -1.08)	0.0001	0.0002
Week 5							
Placebo	72	6.15	0.21				
PGB 150 mg	72	5.11	0.21	-1.05	(-1.62, -0.48)	0.0003	0.0003
PGB 300 mg	74	4.90	0.20	-1.26	(-1.81, -0.70)	0.0001	0.0002
PGB 300/600 mg	69	4.31	0.21	-1.84	(-2.41, -1.27)	0.0001	0.0002
Week 6							
Placebo	67	6.01	0.21				
PGB 150 mg	68	5.01	0.21	-1.00	(-1.58, -0.43)	0.0006	0.0006
PGB 300 mg	72	4.99	0.20	-1.03	(-1.59, -0.47)	0.0003	0.0006
PGB 300/600 mg	67	4.45	0.21	-1.56	(-2.14, -0.99)	0.0001	0.0003

SE = Standard error; CI = Confidence interval.

[a] Week 1, 2, etc. All data for all patients who entered the week of interest were used in the analysis.

[b] Adjustment based on Hochberg's procedure.

[c] Based on LS Means using ANCOVA model (including effects for treatment, cluster, creatinine clearance stratum and the baseline score value as covariate).

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Weekly[a,c] Mean Pain Scores: Results of Repeated Measures Analysis of Covariance: Intent-to-Treat Population

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Treatment Groups (mg/day)	N	Least-Squares Means	SE	Treatment Comparisons (Pregabalin — Placebo)			
				Difference	95% CI	Unadjusted p-Value	Adjusted p-Value[b]
Week 7							
Placebo	66	5.98	0.21				
PGB 150 mg	66	4.99	0.21	-0.99	(-1.56, -0.41)	0.0008	0.0008
PGB 300 mg	70	4.86	0.20	-1.12	(-1.69, -0.56)	0.0001	0.0002
PGB 300/600 mg	65	4.36	0.22	-1.62	(-2.20, -1.04)	0.0001	0.0002
Week 8							
Placebo	65	5.84	0.21				
PGB 150 mg	66	4.91	0.21	-0.94	(-1.52, -0.36)	0.0015	0.0015
PGB 300 mg	68	4.81	0.21	-1.03	(-1.59, -0.46)	0.0004	0.0008
PGB 300/600 mg	64	4.17	0.22	-1.67	(-2.25, -1.09)	0.0001	0.0003
Week 9							
Placebo	64	5.94	0.21				
PGB 150 mg	63	5.00	0.22	-0.93	(-1.52, -0.35)	0.0017	0.0017
PGB 300 mg	66	5.02	0.21	-0.91	(-1.48, -0.34)	0.0016	0.0017
PGB 300/600 mg	63	4.19	0.22	-1.74	(-2.32, -1.16)	0.0001	0.0003
Week 10							
Placebo	61	6.01	0.21				
PGB 150 mg	63	4.99	0.22	-1.02	(-1.60, -0.44)	0.0006	0.0012
PGB 300 mg	64	5.20	0.21	-0.81	(-1.38, -0.23)	0.0058	0.0058
PGB 300/600 mg	62	4.05	0.22	-1.96	(-2.55, -1.38)	0.0001	0.0003
Week 11							
Placebo	60	5.95	0.21				
PGB 150 mg	61	5.01	0.22	-0.94	(-1.53, -0.36)	0.0016	0.0016
PGB 300 mg	63	5.00	0.21	-0.95	(-1.52, -0.38)	0.0012	0.0016
PGB 300/600 mg	62	4.03	0.22	-1.92	(-2.51, -1.34)	0.0001	0.0003
Week 12							
Placebo	60	6.01	0.21				
PGB 150 mg	61	4.89	0.22	-1.12	(-1.70, -0.53)	0.0002	0.0003
PGB 300 mg	62	4.94	0.21	-1.07	(-1.64, -0.49)	0.0003	0.0003
PGB 300/600 mg	61	4.08	0.22	-1.93	(-2.51, -1.34)	0.0001	0.0003

SE = Standard error; CI = Confidence interval.

[a] Week 1, 2, etc. All data for all patients who entered the week of interest were used in the analysis.

[b] Adjustment based on Hochberg's procedure.

[c] Based on LS Means using ANCOVA model (including effects for treatment, cluster, creatinine clearance stratum and the baseline score value as covariate).

Weekly[a,c] Mean Pain Scores: Results of Repeated Measures Analysis of Covariance: Intent-to-Treat Population

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Treatment Groups (mg/day)	N	Least-Squares Means	SE	Treatment Comparisons (Pregabalin — Placebo)			
				Difference	95% CI	Unadjusted p-Value	Adjusted p-Value[b]
Week 13							
Placebo	54	5.83	0.22				
PGB 150 mg	58	4.97	0.22	-0.86	(-1.46, -0.27)	0.0045	0.0045
PGB 300 mg	57	4.85	0.21	-0.98	(-1.57, -0.40)	0.0010	0.0020
PGB 300/600 mg	56	4.02	0.22	-1.81	(-2.41, -1.22)	0.0001	0.0003

SE = Standard error; CI = Confidence interval.

[a] Week 1, 2, etc. All data for all patients who entered the week of interest were used in the analysis.

[b] Adjustment based on Hochberg's procedure.

[c] Based on LS Means using ANCOVA model (including effects for treatment, cluster, creatinine clearance stratum and the baseline score value as covariate).

Table 8.23:

VAS Scale Results From the SF-McGill: Open-Label Studies

Time Points[a]	Open-Label Study No.													
	015		033[b]		061		074		134		165		198	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Baseline	220	66.6 (19.4)	504	64.3 (19.2)	154	69.4 (18.7)	189	64.2 (23.0)	250	62.1 (22.1)	329	64.0 (20.4)	214	67.4 (18.5)
Week 1							185	34.5 (25.4)						
Week 4			2	72.0 (4.2)	144	48.3 (24.7)			232	33.5 (25.1)	317	33.3 (22.2)	184	46.9 (24.2)
Week 5							169	26.9 (24.9)						
Week 8			4	41.5 (29.6)	121	41.9 (26.2)			202	33.3 (24.7)	296	29.0 (22.8)	137	45.3 (24.0)
Week 9							162	24.5 (22.7)						
Week 12	186	36.0 (24.8)	17	38.1 (29.6)	114	42.8 (26.1)			201	32.6 (25.0)	299	28.3 (22.4)	99	41.8 (24.2)
Week 17							153	24.5 (23.4)						
Week 24	176	31.5 (24.9)	56	33.8 (21.4)	91	40.5 (25.1)	150	22.9 (23.6)	180	33.2 (25.0)	185	29.8 (23.9)	28	41.5 (22.1)
Week 36			98	34.4 (23.1)	77	37.1 (24.0)	135	22.0 (22.9)	164	33.8 (26.0)	91	27.1 (22.2)	2	27.0 (31.1)
Week 48	132	31.5 (23.3)												
Week 52			278	35.4 (24.6)	63	38.3 (24.6)	130	22.4 (23.5)	57	47.9 (28.2)	63	24.5 (23.2)		
Week 65			270	35.8 (24.8)	51	36.0 (25.1)	99	22.9 (22.6)			56	24.8 (24.9)		
Week 72	106	31.2 (23.6)												
Week 78			251	36.2 (24.7)	41	36.5 (27.0)	86	23.3 (22.6)			17	26.4 (24.3)		
Week 91			224	37.9 (24.8)	41	33.7 (24.2)	72	20.7 (20.9)						
Week 100	108	35.2 (26.0)												
Week 104			139	37.9 (26.9)	32	36.8 (23.2)	55	22.9 (24.3)						
Week 117			68	45.6 (28.6)	28	40.1 (25.1)	34	17.8 (21.1)						
Week 130			5	36.0 (30.6)	20	39.2 (26.4)	16	20.5 (28.0)						
Week 143					15	32.5 (22.5)	6	42.7 (31.0)						
Week 156					8	34.6 (28.3)	1	76.0						
Week 169					3	48.0 (36.5)								
Week 182					1	85.0								
Endpoint	205	41.5 (28.1)	332	45.6 (26.7)	147	49.6 (28.1)	188	27.5 (27.1)	244	45.1 (28.5)	322	30.3 (25.0)	186	44.9 (24.7)
Change[c,d]	205	-25.0 (30.0)	332	-18.7 (28.3)	147	-19.7 (27.6)	188	-36.5 (34.3)	244	-16.9 (28.4)	322	-33.7 (29.4)	186	-22.3 (23.8)

Blank cells indicate no data were collected at that time point.

VAS = Visual analog scale; SE = Standard error.

[a] Time windows for each study are defined in individual clinical study reports (see Section 9 of CSR).

[b] Includes only data from patients who entered from Studies 029 and 030.

[c] Difference in VAS score from Baseline (the last evaluation on or before Day 1 of double-blind for patients who took pregabalin in double-blind and last visit ≤Day 1 of open-label for patients who took placebo in double-blind) to Endpoint (the last observation per patient, following V1).

[d] Negative changes indicate improvement.

Table 8.24: Uncontrolled, open-label, long-term neuropathic pain studies (TID dosing)

Study number, design	Subjects demographics	Dosage, duration, route and form of study medication	Endpoints	Efficacy results	Safety/AEs
1008-015 Mod. 5, Vol.61, 1998 to Feb, 2001. Phase 2/3 open-label study. Pts continued from DPN study 014.	220 patients who completed study 014. Sex: 134M: 86F Age: 26-78yrs, mean=57yrs. Race: White=186, Black=17, Hispanic=14, Others=2. CLcr range: 49-230ml/min, median=100ml/min. 95% on antidiabetic medications.	Pregabalin (PGB) 25 &100mg capsules. Daily dose given orally, TID. Pts started with 300mg/day, dose adjusted to ↑ pain control, ↓ AEs	Safety: assessed at weeks 2, 4, 6, 12, 24, 36, 48, 60, 72, 84, 100. Efficacy: SF-MCQ assessed at weeks 12, 24, 48, 72 &100.	136 pts received drug for ≥52 weeks, 175 for ≥24 weeks, 32 pts for ≥104wks Sensory, affective and total scores ↓. **VAS (mm) PPI** Baseline: 66.6±19.4 2.2±1.1 Endpoint: 41.5±28 1.4±1.2 18 (8.2%) withdrawn due to lack of efficacy.	91% showed AEs- 59% were treatment-related. Most mild/moderate. Infection (27%), peripheral oedema(19%), dizziness (17%) & somnolence (10%) most common. 39(18%) withdrawals due to AEs, 44 pts(20%) had non-fatal SAEs, 4 deaths- all unrelated. Clinically imp ↓ in platelets in 23pts (11%)- not ass. with thrombocytopenia SAEs or withdrawals.12.5% had clinically imp ↑ in BUN & 10% showed ↑ creatinine. 42% of pts had weight gain >7%.
1008-033 Mod. 5, Vol. 62-63. Phase 2/3 open-label study. 09/1998 to 04/2001. Pts from DPN study 029, PHN 030, OA study 031, low back pain studies 032 & 104 & fibromyalgia study 105.	1517 patients. Sex: 610M: 907F Age: 19-88yrs, mean=56yrs. Race: White=1410, Black=61, Hispanic=34, Others=12. CLcr range: 27-230ml/min, median=86ml/min. 95% on antidiabetic medications.	Pregabalin (PGB) 25 &100mg capsules. Daily dose given orally, TID. Pts started with 300mg/day, dose adjusted to ↑ pain control, ↓ AEs	Safety: assessed at weeks 2, 4, 6, 12, 24, 36, 48, 60, 72, 84, 100. Efficacy: SF-MCQ assessed at weeks 12, 24, 48, 72 &100.	644 pts received drug for ≥52 weeks, 1060 for ≥24 weeks, 131 pts for ≥104wks Sensory, affective and total scores ↓. **VAS (mm) PPI** Baseline: 66.±20.2 2.3±1.1 Endpoint:47.2±27.4 1.7±1.2 236 (16%) withdrawn due to lack of efficacy.	88% showed AEs- 59% were treatment-related. Most mild/moderate. Dizziness (20%), infection (18%), peripheral oedema & somnolence (15%), accidental injury (13%) most common. Abn thinking, confusion (3-5%). 271(18%) withdrawals due to AEs; 168 pts (11.1%) had SAEs, 14 deaths- all unrelated. Sig. weight gain in 8% of pts. Clinically imp ↓ in platelets in 92pts (6.5%)- ass. with 1 case of worsening thrombocytopenia leading to withdrawal. 7.4% had clinically imp ↑ in BUN & 7.6% showed ↑ creatinine; 5% of pts showed orthostatic hypotension

Table 8.25: Uncontrolled, open-label, long-term neuropathic pain studies (TID dosing)

Study number, design	Subjects demographics	Dosage, duration, route and form of study medication	Endpoints	Efficacy results	Safety/AEs
1008-061 Mod. 5, Vol.64, 1999 to Feb, 2003. Phase 3 open-label study at 36 centres in Europe & 2 in Australia. Pts continued from PHN study 045.	154 patients who completed study 045. Sex: 73M: 81F Age: 32-96yrs, mean=72yrs. Race: White=153, Black=1. CLcr range: 31-116ml/min, median=58ml/min. 97% on concurrent medications (paracetamol-30%, aspirin=20%, amitryptiline=22%)	Pregabalin (PGB) 25 &100mg capsules. Daily dose given orally, TID. Pts started with 150mg/day, dose adjusted to ↑ pain control, ↓ AEs (75 to 600mg/day)	Efficacy (SF-MCQ) and Safety assessed at weeks 4, 6, 12, 24, 36, 52, 65, 78, 91, 104, termination	61(40%) pts received drug for ≥52 weeks, 95 (62%) for ≥24 weeks, 34(22%) pts for ≥104wks Sensory, affective and total scores ↓ (across all languages). **VAS (mm) PPI** Baseline: 69.4±18.7 2.6±1.1 Endpoint: 49.6±28 2.0±1.3 27 of 129pts with allodynia & 28 of 89 pts with hyperalgesia at baseline were free from it by endpoint; but 13 & 17 pts dev. new s/s of allodynia & hyperalgesia, resp.32 (21%) pts withdrawn due to lack of efficacy.6 of the 7 pts who went on drug holidays relapsed.	92% showed AEs-75% were treatment-related. Most mild/moderate. Dizziness (21%), accidental injury (18%), weight gain (14%), somnolence (14%), peripheral oedema(12%) & flu syndrome (10%) most common. 49(32%) withdrawals due to AEs,35 pts(23%) had non-fatal SAEs, no deaths. Clinically imp ↓ in platelets in 12pts (8.2%)- only 1 case of thrombocytopenia SAE. 9.6% had clinically imp ↑ in BUN & 10.3% showed ↑ creatinine. 60 pts (41%) had weight gain≥7%. 10% of pts dev orthostatic hypotension
1008-074. Mod. 5, Vol. 65. Phase 3 open-label study. 09/1999 to 02/2003. Pts from DPN study 040.	189 patients who completed DPN study 040. Sex: 109M: 80F Age: 22-80yrs, mean=60yrs. Race: White=173, Black=2, Others=14. CLcr range: 47-280ml/min, median=87ml/min. 96% on antidiabetic medications. Other neuropathic pain medications allowed only after 17wks open label Rx.	Pregabalin (PGB) 25 &100mg capsules. Daily dose given orally, TID. Foll. 1 week titration phase (300mg/day) pts received target dose of 600mg/day. Min dose was 150mg/day.	Safety & efficacy (SF-MCQ, CGIC, PGIC & SF-36 health survey) assessed at weeks 1, 5, 9, 17, 24, 36, 52, 65, 78, 91, 104.	123(65%) pts received drug for ≥52 weeks, 158(84%) for ≥24 weeks, 67(35%) pts for ≥104wks. Sensory, affective and total scores ↓ in all languages. **VAS (mm) PPI** Baseline: 64.2±23 2.7±1.3 Endpoint:27.5±27 1.1±1.1 CGIC & PGIC, almost all domains of SF-36 health survey also showed improvements from baseline, 15 of 64 pts with allodynia at baseline, free from it at endpoint. 18 (9.5%) withdrawn due to lack of efficacy. 10 of the 14 pts who went on drug holidays relapsed.	83% showed AEs- 49% were treatment-related. Most mild/moderate. Weight gain (14%), dizziness (13%), infection (13%), peripheral oedema (8%), somnolence (7%) & accidental injury (7%) most common. Abn thinking, confusion (0.5-1%). 32(17%) withdrawals due to AEs; 35pts (19%) had SAEs; 4 deaths- all unrelated. 8% of pts. Clinically imp ↓ in platelets in 10% of pts- not ass. with thrombocytopenia, SAEs or withdrawal. 19% had clinically imp ↑ in BUN & 8% showed ↑ creatinine; 85pts (46%) had weight gain ≥7%.

Table 8.26: Uncontrolled, open-label, long-term neuropathic pain studies (TID dosing)

Study number, design	Subjects demographics	Dosage, duration, route and form of study medication	Endpoints	Efficacy results	Safety/AEs
1008-134. Mod. 5, Vol.66. 02/2000 to 05.2001. Phase 2/3 open-label study at 46 centres in USA. Pts continued from PHN study 127 or DPN study 131.	250 patients who completed pivotal studies 127 or 131. Sex: 134M: 116F Age:21-90yrs,mean=65yrs. Race: White=232, Black=8, Hispanic=8, Others=2. CLcr range: 24-313ml/min, median=90ml/min. 99% on concurrent medications (paracetamol, antidiabetics most common)	Pregabalin (PGB) 25 &100mg capsules. Daily dose given orally, TID. Pts started with 150mg/day, dose adjusted to ↑ pain control, ↓ AEs (75 to 600mg/day)	Efficacy (SF-MCQ) and Safety assessed at weeks 4, 8, 12, 24, 36, 52, 65, 78, 91, 104, termination	173(69%) pts received drug for ≥36 weeks, only 1 pt received pregabalin for 52weeks due to early termination of study by Pfizer. Sensory, affective and total scores ↓. **VAS (mm) PPI** Baseline: 62.1±22 2.1±1.2 Endpoint: 45.1±28 1.7±1.2 40 of 76 pts with allodynia at baseline were free from it by endpoint; but 14 pts dev. new s/s of allodynia. 5% of pts withdrawn due to lack of efficacy.	88% showed AEs-61% were treatment-related. Most mild/moderate. Dizziness (33%), accidental injury (12%), somnolence (14%), peripheral oedema (17%) & infection (11%) most common. 32 (13%) withdrawals due to AEs; 24 pts(10%) had non-fatal SAEs; 3 deaths-unrelated. No clinically imp ↓ in platelets 14% had ↑ above normal in BUN & 42% showed ↑ creatinine- but clinical relevance of these changes not mentioned in study report. 73 pts (31%) had weight gain≥7%. 12 pts (5.4%) dev orthostatic hypotension
1008-197, Mod 5, Vol.68. 11/2001 to 02/2003. Phase 3, open-label, study at 28 centres in USA. Pts who did not respond to gabapentin, TCA or other 3rd line pain medications in various studies.	106 pts with Rx-refractory pain of DPN (n=45), PHN (n=36) or fibromyalgia (n=25). Sex: 56M:50F Age: 39-89yrs, mean=65yrs Race: White=102, Black=1, Hispanic=3. Clcr: range: 33 to 199ml/min, median=74ml/min. 95% took concomitant pain medications- gabepentin (49%), paracetemol (22%), ibuprofen(19%).	Pregabalin 50 & 100mg capsules. Daily dose given orally TID. Started with 150mg/day, up tot max of 600mg/day.Most common dose was 300 to 450mg/day.	Efficacy (SF-MCQ) and Safety assessed at weeks 1, 12, 24, 36, 48 & every 3 mths after the first year till termination	72% received drug for ≥24 weeks, 44% for ≥36 weeks & 1% for ≥52 weeks. Sensory, affective and total scores ↓. **VAS (mm) PPI** Baseline: 73.5±13.5 2.7±1.0 Endpoint: 48±28 1.6±1.0 Of the 89 patients who had relapse visit assessments, 85 (96%) relapsed during drug holidays. 5 pts (4.7%) withdrawn due to lack of efficacy. 13 of 36 pts (36%) with allodynia & 19 of 42 pts (45%) at baseline were free from it by endpoint.	89% reported AEs, 60% were treatment-related. Most mild/moderate. Dizziness (20%), somnolence (18%), peripheral oedema (12%), accidental injury (11%) & asthenia (11%) most common. 11 (10.4%) withdrawals due to AEs(dizziness, peripheral oedema most common); 15 pts (14.2%) had non-fatal SAEs; no deaths. Clincially imp ↓ in platelets (in 5% of pts), ↑ BUN in 14% pts & 7% showed ↑ creatinine. 28 pts (28%) had weight gain≥7%. No reports of orthostatic hypotension or other clin. Relevant changes in vitals signs or lab parameters.

Table 8.27: Uncontrolled, open-label, long-term neuropathic pain studies (BID dosing)

Study number, design	Subjects demographics	Dosage, duration, route and form of study medication	Endpoints	Efficacy results	Safety/AEs
1008-165. Mod. 5, Vol. 67. Phase 3 open-label study. 01/2001 to 02/2003. Pts from DPN study 149.	329 patients who completed DPN study 149. Sex: 187M: 142F Age: 22-80yrs, mean=60yrs. Race: White=315, Black=2, Others=12. CLcr range: 33-194ml/min, median=95ml/min. 96% on (low=29, normal=300) 99% took antidiabetic medications. Other concurrent drugs were paracetemol & anti-hypertensives.	Pregabalin (PGB) 25 &100mg capsules. Daily fixed dose of 150mg/day given orally, BID. Dose could be titrated from 150 to 600mg/day depending on efficacy & safety.	Safety & efficacy (SF-MCQ) assessed at weeks 4, 8, 12, 24, 36, termination	63(19%) pts received drug for ≥52 weeks, 171(52%) for ≥24 weeks, 292(89%) pts for ≥12wks. Sensory, affective and total scores ↓ in all languages. VAS (mm) PPI Baseline: 64±20.4 2.3±1.2 Endpoint:30.3±25 1.2±1.1 Of 49 pts that entered first drug holiday, 45 pts met relapse criteria. 48 of 80 pts with allodynia & 38 of 95 pts with hyperalgesia at baseline were free from it at endpoint. 10 pts (3%) withdrawn due to lack of efficacy.	55% showed AEs- 25% were treatment-related. Most mild/moderate. Infection, pain peripheral oedema-6% each; dizziness, accidental injury, back pain, somnolence- 5% each. Cognition AEs (0.5-1%). 16(5%) withdrawals due to AEs; 29pts (9%) had SAEs; 1 death-unrelated. 8% of pts. 15pts (5%) showed clinically imp ↓ in platelets, 10% had clinically imp ↑ in BUN & 6% showed ↑ creatinine;73pts (23%) had weight gain ≥7%. 21 pts (7%) dev. orthostatic hypotension.
1008-198. Mod 5, Vol.69. Phase 3, open label study. 02/ 2002 to 02/2003. At 58 centres in Europe & Australia. Pts from pivotal DB, PHN study 196.	214 pts who had received at least 3 weeks DB Rx in PHN study 196. Sex:101M:113F Age: 38-89yrs, mean=71yrs. Race: White=210, Black=2, Others=2. Clcr <60ml/min (low) in 30% of pts, Normal (>60ml/min in 70% of pts; median of 71ml/min. Paracetemol most common concurrent pain medication (11%).	Pregabalin (PGB) 75 &150mg capsules. Given orally, BID. Dose could be titrated from 150 to 600mg/day depending on efficacy & safety. 150-450mg/day most commonly used	Safety & efficacy (SF-MCQ) assessed at weeks 1, 2, 4, 8, 12, 24, 36, termination	74% pts received drug for ≥8 weeks, 54% for ≥12 weeks, 18% for ≥24 weeks, 1.4% for ≥36wks & none for ≥52 weeks. Sensory, affective and total scores ↓ in all languages. VAS (mm) PPI Baseline: 67.4±18.5 2.6±1.0 Endpoint: 45±24.7 1.6±0.9 Only 2 pts had undergone drug holiday at time of cut-off; both of them relapsed. 26 of 78 pts (33%) with allodynia & 23 of 70 pts (33%) with hyperalgesia at baseline were free from it at endpoint. 22 pts (10%) withdrawn due to lack of efficacy.	47% showed AEs- 36% were treatment-related. Most mild/moderate. Dizziness (10%), peripheral oedema(10%), accidental injury (5%) most common. Only study in which 22%of pts had a ↓ in incidence of peripheral oedema (15% showed ↑). Cognition AEs (0.5-1%). 16(7.5%) withdrawals due to AEs; 9pts (4.2%) had SAEs; 1 death- unrelated. 8% of pts. 11pts (6%) showed clinically imp ↓ in platelets, 6% had clinically imp ↑ in BUN & 1% showed ↑ creatinine; 37pts (20%) had weight gain ≥7%. 15 pts (9%) dev. orthostatic hypotension.

Table 8.28.1: Efficacy of flexible dose vs fixed dose in DPN and PHN patients

Study number, design	Subjects demographics	Dosage, duration, route and form of study medication	Endpoints	Safety/AEs
1008-155. Mod. 5, Vol. 50. Phase 3 randomised, DB, PC, 12-week study. At 60 centres in Europe 07/2001 to 12/2002.	338 patients with neuropathic pain due to PHN (pain for > 3mths after healing of rash) or DPN (s/s for atleast 6mths). PHN pts=89 (26.3%); DPN pts=249 (73.7%).Baseline mean pain score≥4, VAS≥40mm. Sex: 183M: 155F Age: 26-87yrs, mean=62yrs. Race: White=330, Black=1, Hispanic=5, Others=2. CLcr range: 46-178ml/min, median=84ml/min. No sig. diff b/w Rx gps in baseline demographics or disease characteristics	Pregabalin (PGB) 75, 150 & 300mg capsules. All 3 groups had BID oral dosing. 1)Flexible dose (n=140) of PGB 150, 300, 450 & 600mg/day BID titrated at weekly intervals. 2)Fixed dose (n=132)of PGB 600mg/day for 11 weeks after first week on 300mg/day. 3) Placebo BID (n=64).	Efficacy: Primary- mean pain scores. Secondary: responder analysis, SF-MCQ, sleep interference, MOS, SF-36 health survey, Euro-QOL, s/s of allodynia/ hyperalgesia. Safety: AEs, lab parameters, vital signs, neurological exam, Assessments done at weeks 1, 2, 3, 4, 8, 12 and termination.	AEs incidence: PGB flexible=69%, PGB fixed=74%, placebo=45%. Rx-related: 55%, 69% & 28%, resp. Dizziness (21%, 29% &5%, resp), peripheral oedema (16, 10 &6%, resp), weight gain (13, 14 &3%), somnolence (11, 13 & 0%) most common. Serious AEs: 7.1%, 3.9% &3.1%, resp. 2 deaths- both in PGB fixed gp. Vision abn in 10%, 11.4% & 4.6%, resp. Withdrawals due to AEs: PGB flexible=17%, PGB fixed=25%, plac=7.7%. Clinically imp ↓ in platelets in 4.5%, 2.4% &1.6% of pts in flex, fixed & plac, resp. 13%, 14% & 3%, resp had weight gain ≥7%. 5.8%, 3.3% & 1.7%, resp dev orthostatic hypotension.

Table 8.28.2: Efficacy results of study 1008-155

Efficacy parameter	Placebo	Flexible dose PGB	Fixed dose PGB
Mean endpoint pain scores	4.98±0.32	3.81±0.23	3.60±0.24
Responders (>50% ↓ from baseline)	24.2%	48.2%	52.3%
SF-MCQ VAS score (0-100mm)	51.3±3.5	36.3+2.5	35.9±2.6
SF-MCQ PPI score (0-6)	2.16±0.15	1.74±0.10	1.69±0.11
PGIC improvement (% patients)	47.5%	74.4%	71.2%
Withdrawals due to lack of efficacy	29% (19/65)	8.5% (12/141)	8.3% (11/132)

Table 8.29: Pivotal study of pregabalin as adjunctive treatment in patients with partial seizures

Study nos, location investigators	Study design	Subjects demographics	Dosage, duration, route and form of study medication	Endpoints	Efficacy results	Safety/AEs
1008-009, Mod.5-Vol.54-55. at 37 centres in USA and 6 centres in Canada. 2/6/1998 to 27/9/1999.	Phase 3 randomised, DB, parallel-gp, placebo-controlled study, add-on. 8-week baseline phase, foll by 12 wks of DB Rx(1 week titration). Pts may continue into open-label extension study 010.	312 patients with uncontrolled partial seizures, despite Rx with 1-3 AEDs. Sex: 156M: 156F Age: 17-82yrs, mean=39yrs. Race: White=266, Black=13, Hispanic=23, Others=10. Baseline median seizure freq. per 28 days=10. Nos. of pts on 3 AEDs more in 600mg BID gp (30%) compared to TID (15.3%) or placebo (16.3%) gps.	Pregabalin (PGB) 25 &100mg capsules & matching placebo capsules. All dosing orally, TID. BID regimen blinded by using placebo as middle dose. 1)PGB 600mg/day BID(n=103). 2)PGB 600mg/day TID (n=111). 3)Placebo (n=98).	Primary:RRatio(sym metrized percent change)at endpoint. Secondary: Responder analysis (>50% ↓ in 28-day seizure frequency), % change from baseline, length of seizure-free intervals, nos. of seizure-free days per a 28-day period, RRatio, responder analysis & percent change for each seizure type. Safety: visual & neurological exams, vital signs, lab parameters. Pharmacokinetics: plasma PGB concentrations.	Stat sig ↓ in seizure frequency with both PGB gps (RRatio). Similar sig efficacy shown for responder analysis(49%, 43% & 9% with PGB TID, BID & plac, resp), % change, length of seizure-free intervals, nos: of seizure-free days per 28-day period. Pts withdrawn due to lack of efficacy: PGBTID=2(1.8%), PGB BID=1 (1%), Placebo=5 (5.1%). BID & TID PGB regimens achieved similar peak & trough PGB plasma conc. & similar overall daily PGB exposure.	AE incidence: PGB TID=95%, PGB BID=99%, Plac=72.4%. Dizziness most common (39%, 44% & 14% with TID, BID & plac, resp). Other common (≥10%) AEs in PGB gps were somnolence, ataxia, abn. thinking, tremor, headache, asthenia, accidental injury, weight gain, amblyopia & diplopia. Most of AEs were moderate or mild. Withdrawals due to AEs: PGB TID=19%, PGB BID=26%, plac=7%. Non-fatal SAEs= 3.6%, 5.8% & 4.1%, resp. No deaths in study. Weight gain >7% from baseline in 28%, 26% & 0.9% of pts in PGB TID, BID & placebo gps, resp. No other clinically sig changes in lab parameters/vital signs.

Table 8.30: Pivotal study of pregabalin as adjunctive treatment in patients with partial seizures

Study nos, location investigators	Study design	Subjects demographics	Dosage, duration, route and form of study medication	Endpoints	Efficacy results	Safety/AEs
1008-011, Mod.5-Vol.56-57. at 45 international centres 23/4/1998 to 19/11/1999.	Phase 3 randomised, DB, parallel-gp, placebo-controlled study, add-on. 8-week baseline phase, foll by 12 wks of DB Rx(1 week titration). Pts may continue into open-label extension study 012.	287 patients with uncontrolled partial seizures, despite Rx with 1-3 AEDs. Sex: 145M: 142F Age: 17-73yrs, mean=37yrs. Race: White=266, Black=5, Hispanic=5, Others=4. Baseline median seizure freq. per 28 days=10.	Pregabalin (PGB) 25 &100mg capsules & matching placebo capsules. All dosing orally, TID. 1)PGB 150mg/day TID(n=99). 2)PGB 600mg/day TID (n=92). 3)Placebo (n=96).	Primary:RRatio(sym metrized percent change)at endpoint. Secondary: Responder analysis (>50% ↓ in 28-day seizure frequency), % change from baseline, length of seizure-free intervals, nos. of seizure-free days per a 28-day period, RRatio, responder analysis & percent change for each seizure type. Safety: visual & neurological exams, vital signs, lab parameters. Pharmacokinetics: plasma PGB concentrations.	Dose-dependant, stat sig ↓ in seizure frequency with 150 & 600mg/day PGB (RRatio). Responder analysis stat. sig. > than placebo only with 600mg PGB (43.5%, 14.1% & 6.2% with PGB 600, 150mg/day & plac, resp), % change, length of seizure-free intervals, nos: of seizure-free days per 28-day period. For partial seizures with generalisation, only 600mg PGB effective. Pts withdrawn due to lack of efficacy: PGB 600mg/day=1(1.1%), 150mg/day=0, Placebo=5 (5.2%).	AE incidence: PGB 600mg/day=87%, PGB 150mg/day=76%, Plac=64%. Dizziness most common (26%, 19% & 8% with PGB 600, 150mg/day & plac, resp). Other common AEs in PGB gps were somnolence (29%, 6.% &7%, resp), ataxia, headache, asthenia, accidental injury, weight gain, amblyopia & diplopia. Most of AEs were moderate or mild. Withdrawals due to AEs: PGB 600mg=18.5%, 150mg=10.1%, plac=6.2%(dizziness, asthenia, ataxia 7 somnolence most common). Non-fatal SAEs= 3.3%, 4% & 5.2%, resp. No deaths in study. Weight gain >7% from baseline in 23%, 9% & 2% of pts in PGB 600, 150mg/day & placebo gps, resp. No other clinically sig changes in lab parameters/vital signs.

Table 8.31: Pivotal study of pregabalin as adjunctive treatment in patients with partial seizures

Study nos, location investigators	Study design	Subjects demographics	Dosage, duration, route and form of study medication	Endpoints	Efficacy results	Safety/AEs
1008-034, Mod.5-Vol.58-59. at 71 US centres & 5 centres in Canada. 11/11/1998 to 17/9/1999.	Phase 3 randomised, DB, parallel-gp, placebo-controlled, add-on study. 8-week baseline phase, foll by 12 wks of DB Rx(no titration). Pts may continue into open-label extension study 035.	455 patients with uncontrolled partial seizures, despite Rx with 1-3 AEDs. Sex: 218M: 235F Age: 12-75yrs,mean=38yrs. Race: White=385, Black=31, Hispanic=26, Others=8. Baseline median seizure freq. per 28 days=9.	Pregabalin (PGB) 25 &100mg capsules & matching placebo capsules. All dosing orally, BID. 1)PGB 50mg/day (n=88). 2)PGB 150mg/day (n=88). 3)PGB 300mg/day (n=90). 4)PGB 600mg/day (n=89). 5)Placebo (n=100).	Primary:RRatio at endpoint. Secondary: Responder analysis (>50% ↓ in 28-day seizure frequency), % change from baseline, length of seizure-free intervals, nos. of seizure-free days per a 28-day period, RRatio, responder analysis & percent change for each seizure type. Safety: visual & neurological exams, vital signs, lab parameters. Pharmacokinetics: plasma PGB concentrations.	Dose-response shown in primary & sec. efficacy parameters. Stat sig ↓ in seizure frequency with 150, 300 & 600mg/day PGB (RRatio). 50mg/day not effective in any of parameters. Responder analysis stat. sig. > than placebo only with 600mg PGB (15%, 31%, 41%, 51% & 14% with PGB 50, 150, 300, 600mg/day & plac, resp), % change. Only non-sig trends in favour of 300 & 600mg PGB for length of seizure-free intervals, nos: of seizure-free days per 28-day period. No dose-response for partial seizures with generalisation, PGB less effective. Pts withdrawn due to lack of efficacy: PGB 50mg/day=1.1%, 150mg=1.1%, 300mg=2.2%, 600mg=4.5%, plac=5%.	AE incidence: PGB 50mg/day=67%, 150mg=71%, 300mg=84.4%, 600mg=89% Plac=74%. Dizziness most common (9%, 16%, 31%, 43% & 9%, resp). Other common AEs in PGB gps were somnolence (10%, 17%, 18%, 28% & 11%, resp), ataxia, headache, asthenia, accidental injury, weight gain, amblyopia,diplopia, tremor & abn thinking. Most of AEs were moderate or mild. Withdrawals due to AEs: 7%, 1.2%, 14.4%, 23.6% & 5% with PGB 50, 150, 300, 600mg/day & plac, resp (dizziness, somnolence, ataxia, abn thinking most common). Non-fatal SAEs= 3.4%, 2.3%, 3.3%, 4.5% & 4%, resp. No deaths in study. Weight gain >7% from baseline in 0%, 7%, 14%, 29% & 1% of pts in PGB 50, 150, 300, 600mg/day & placebo gps, resp. No other clinically sig changes in lab parameters/vital signs.

Table 8.32: Phase 2 study of pregabalin as monotherapy in patients with refractory partial epilepsy

Study nos, location investigators	Study design	Subjects demographics	Dosage, duration, route, form of study drugs	Endpoints	Efficacy results	Safety/AEs
1008-007, Mod.5-Vol.60. at 21 US centres & 1 centre in Germany. 01/11/1997 to 24/8/1998.	Phase 2 randomised, DB, parallel-gp, active-controlled, study. Variable prestudy period, in which pts tapered off standard AEDs. This was followed by 8-days of DB Rx. Pts could then enter open-label study 008.	93 patients with complex partial seizures, with or without sec. general-isations. Prehosp: min. of 3 seizures/ month on standard AEDs for the last 3 mths. During inpatient taper phase, 3-12 seizures during a 3-day period or 3-15 seizures during 5-day period. Sex: 51M: 42F Age: 19-65yrs, mean=36yrs. Race: White=81, Black=3, Hisp=8, Others=1.	Pregabalin (PGB) 25 &100mg capsules & gabapentin 100mg capsules. All dosing orally, TID. 1)PGB 600mg/day (n=51). 2)Gabapentin 300mg/day (n=42).	Efficacy: 1)time to exit: rules determining time of exit were: SGTC seizure with negative history, 4 CP &/or SGTC seizures, status epilepticus, prolongation or intensification of seizures, lack of efficacy, completed study) 2)proportion of pts completing the study. Safety: visual & neurological exams, vital signs, lab parameters. Pharmacokinetics: plasma PGB & gabapentin concentrations.	Median time to exit was PGB=191hrs, gabapentin=88hrs (p=0.080, log rank test). Completion rate: PGB=57% vs gabapentin=24%, p=0.003 (CMH). Trend towards better efficacy with PGB 600mg/day. Pts with <2 prestudy seizures/day remained in study longer.	AE incidence: PGB=69%, Gabapentin=59%. Dizziness (26% vs 14%), somnolence (19% vs 14%), asthenia (10% vs 8%), ataxia (7% vs 2%), constipation (7% vs 0%), nausea (7% vs 2%) more common in PGB gp. Most of AEs were moderate or mild. Only 1 PGB pt had 2 SAEs-aspiration pneumonia, gastro h"rage. No deaths or withdrawals due to AEs. No clinically sig changes in lab parameters/vital signs.

Table 8.33.1:

Summary of RRatio (All Partial Seizures) Results of Analysis of Variance - ITT Population

Study/Treatment (Total Daily Dose and Regimen)	N	Mean	SD	Median	Treatment Difference Between Pregabalin and Placebo		
					Mean (SE)	p Value	95% CI
Study 009							
Placebo	98	0.6	28.8	-0.4			
PGB 600 mg/day BID	103	-28.4	36.7	-21.7	-29.0 (5.0)	≤0.0001*	-38.9, -19.0
PGB 600 mg/day TID	111	-36.1	40	-31.7	-36.7 (5.0)	≤0.0001*	-46.4, -27.0
Study 011							
Placebo	96	0.9	26	0.7			
PGB 150 mg/day TID	99	-11.5	22.9	-9	-12.4 (4.1)	0.0007*	-20.5, -4.3
PGB 600 mg/day TID	92	-31.4	36.3	-27.1	-32.3 (4.2)	≤0.0001*	-40.6, -24.0
Study 034							
Placebo	100	-3.8	25.6	0			
PGB 50mg/day BID	88	-6.2	23.7	-4.5	-2.3 (4.8)	0.4232	-11.7, 7.1
PGB 150mg/day BID	86	-20.5	29.6	-21	-16.6 (4.8)	≤0.0001*	-26.1, -7.2
PGB 300mg/day BID	90	-27.8	36.5	-22.5	-24.0 (4.8)	≤0.0001*	-33.3, -14.6
PGB 600mg/day BID	89	-37.4	44.4	-34.1	-33.5 (4.8)	≤0.0001*	-42.9, -24.1

ITT = Intent-to-treat; SD = Standard deviation; SE = standard error; CI = confidence interval; PGB = Pregabalin.

* Statistically significant based on Hochberg's (Study 009) or the Ruberg (Studies 011 and 034) procedure ($\alpha = 0.049$ for Studies 009 and 034, $\alpha = 0.05$ for Study 011).

Table 8.33.2:

Summary of RRatio (All Partial Seizures) Results of Analysis of Variance – Evaluable Population

Study/Treatment (Total Daily Dose and Regimen)	Treatment Difference			
	N	Mean	SD	p Value
Study 009				
Placebo	91	-1.8	26.6	
PGB 600 mg/day BID	83	-27.7	31.5	≤0.0001*
PGB 600 mg/day TID	91	-33.1	35.6	≤0.0001*
Study 011				
Placebo	88	-1.0	25.2	
PGB 150 mg/day TID	91	-11.5	21.1	0.0013*
PGB 600 mg/day TID	77	-30.0	33.1	≤0.0001*
Study 034				
Placebo	97	-4.1	25.9	
PGB 50 mg/day BID	81	-7.2	21.4	0.4824
PGB 150 mg/day BID	82	-20.1	28.2	≤0.0001*
PGB 300 mg/day BID	77	-24.0	31.4	≤0.0001*
PGB 600 mg/day BID	69	-29.9	37.2	≤0.0001*

SD=Standard Deviation; PGB = Pregabalin.

* Statistically significant from placebo based on Hochberg's (Study 009) or the Ruberg (Studies 011 and 034) procedure ($\alpha = 0.049$ for Studies 009 and 034, $\alpha = 0.05$ for Study 011).

Table 8.34:

Summary of Responder Rate (All Partial Seizures) - ITT Population

Study/Treatment (Total Daily Dose and Regimen)	N	Responder (%)	Treatment Difference Between Pregabalin and Placebo %	SE	p Value	95% CI
Study 009						
Placebo	98	9 (9.2)				
PGB 600 mg/day BID	103	44 (42.7)	33.5	5.7	≤0.001*	22.4, 44.7
PGB 600 mg/day TID	111	54 (48.7)	39.5	5.6	≤0.001*	28.5, 50.4
Study 011						
Placebo	96	6 (6.2)				
PGB 150 mg/day TID	99	14 (14.1)	7.9	4.3	0.087	-0.5, 16.3
PGB 600 mg/day TID	92	40 (43.5)	37.2	5.7	≤0.001*	26.0, 48.5
Study 034						
Placebo	100	14 (14.0)				
PGB 50 mg/day BID	88	13 (14.8)	0.8	5.1	0.840	-9.3, 10.8
PGB 150mg/day BID	86	27 (31.4)	17.4	6.1	0.006*	5.5, 29.3
PGB 300mg/day BID	90	36 (40.0)	26.0	6.2	≤0.001*	13.8, 38.2
PGB 600mg/day BID	89	45 (50.6)	36.6	6.3	≤0.001*	24.1, 49.0

ITT = Intent-to-treat; SE = Standard error; CI = confidence interval; PGB = Pregabalin.

* Statistically significant based on Hochberg's (Study 009) or the Ruberg (Studies 011 and 034) procedure ($\alpha = 0.049$ for Studies 009 and 034, $\alpha = 0.05$ for Study 011).

Table 8.35:

Summary of Median Percent Change From Baseline in Seizure Frequency (All Partial Seizures) - ITT Population

Study Treatment (Total Daily Dose and Regimen)	N	Median Percent Change	Treatment Difference[a] Median	95%CI
Study 009				
Placebo	98	-0.8		
PGB 600 mg/day BID	103	-35.6	-41.6	-55.8, -27.6
PGB 600 mg/day TID	111	-48.1	-51.8	-64.4, -38.6
Study 011				
Placebo	96	1.3		
PGB 150 mg/day TID	99	-16.5	-21.6	-33.2, -9.5
PGB 600 mg/day TID	92	-42.6	-48.9	-62.1, -35.8
Study 034				
Placebo	100	0		
PGB 50 mg/day BID	88	-8.6	-5.2	-15.8, 6.7
PGB 150 mg/day BID	86	-34.8	-25.9	-38.3, -13.9
PGB 300 mg/day BID	90	-36.7	-33.0	-46.0, -20.4
PGB 600 mg/day BID	89	-50.9	-43.9	-57.8, -31.1

ITT = Intent-to-treat; CI = Confidence interval; PGB = Pregabalin.

[a] Between pregabalin and placebo.

Table 8.36:

Proportion of Patients With ≥25% Increase in Seizure Frequency (All Partial Seizures): ITT Population

Study	Treatment Group	n/N	%
009	Placebo	29/98	30
	PGB 600 mg/day BID	13/103	13
	PGB 600 mg/day TID	11/110	11
011	Placebo	32/96	33
	PGB 150 mg/day BID	16/99	16
	PGB 600 mg/day TID	4/92	4
034	Placebo	21/100	21
	PGB 50 mg/day BID	17/88	19
	PGB 150 mg/day BID	10/86	12
	PGB 300 mg/day BID	11/90	12
	PGB 600 mg/day BID	9/89	10

ITT = Intent-to-treat; PGB = Pregabalin.

Table 8.37.1:

Summary of RRatio by Seizure Type – Meta Analysis: ITT Population

Seizure Type	Placebo	Pregabalin Dose (mg/day) and Regimen					
		50 BID	150 BID	150 TID	300 BID	600 BID	600 TID
Simple Partial, N	144	44	42	32	46	94	89
Mean (SE)	2.3 (5.0)	0.3 (9.0)	-10.7 (9.2)	-11.4 (10.6)	-23.5 (8.8)	-27.7 (6.2)	-33.8 (6.3)
p Value		0.3727	0.7904	0.2165	0.1601	≤0.0001*	≤0.0001*
Complex Partial, N	260	82	75	88	79	174	180
Mean (SE)	-2.8 (2.6)	-5.8 (4.6)	-18.0 (4.8)	-14.3 (4.4)	-25.5 (4.7)	-33.7 (3.2)	-36.4 (3.1)
p Value		0.5189	0.0008*	0.0142*	≤0.0001*	≤0.0001*	≤0.0001*
Simple and Complex Partial, N	289	87	84	96	87	187	197
Mean (SE)	1.2 (2.2)	-5.1 (4.0)	-21.4 (4.1)	-10.6 (3.8)	-28.3 (4.0)	-29.1 (2.7)	-32.5 (2.7)
p Value		0.7754	≤0.0001*	0.007*	≤0.0001*	≤0.0001*	≤0.0001*
SGTC, N	120	33	34	40	29	74	79
Mean (SE)	-3.7 (6.0)	18.5 (11.5)	1.5(11.3)	6.8 (10.4)	-24.7 (12.3)	-30.6 (7.7)	-35.3 (7.4)
p Value		0.1819	0.7101	0.5965	0.1805	0.0139*	0.0005*
All Partial, N	294	88	86	99	90	192	203
Mean (SE)	-0.8 (1.9)	-6.2 (3.5)	-20.5 (3.5)	-11.6 (3.3)	-27.8 (3.4)	-32.5 (2.4)	-34.0 (2.3)
p Value		0.6346	≤0.0001*	0.0004*	≤0.0001*	≤0.0001*	≤0.0001*

SGTC = Secondarily generalized tonic clonic.
* Statistically significant.

Table 8.37.2:

Summary of Responder Rate by Seizure-Type - Meta Analysis: ITT Population

Seizure Type	Placebo	Pregabalin Dose (mg/day) and Regimen					
		50 BID	150 BID	150 TID	300 BID	600 BID	600 TID
Simple Partial							
N	144	44	42	32	46	94	89
n (%)	34 (24)	9 (20)	15 (36)	8 (25)	15 (33)	50 (53)	45 (51)
% Difference		-3.2	12.1	1.4	9	29.6	27
95% CI		-16.9, 10.6	-4, 28.2	-15.1, 17.9	-6.2, 24.2	17.3, 14.8	14.5, 39.4
p Value		0.663	0.117	0.868	0.225	≤0.001*	≤0.001*
Complex Partial							
N	260	82	75	88	79	174	180
n (%)	44 (17)	13 (16)	30 (40)	19 (22)	32 (41)	83 (48)	94 (52)
% Difference		-1.1	23.1	4.7	23.6	30.8	35.3
95% CI		-10.2, 8.1	11.1, 35.1	-5.1, 14.4	11.8, 35.3	22.1, 39.5	26.7, 43.9
p Value		0.821	≤0.001*	0.326	≤0.001*	≤0.001*	≤0.001*
Simple and Complex Partial							
N	289	87	84	96	87	187	197
n (%)	35 (12)	12 (14)	32 (38)	15 (16)	34 (39)	82 (44)	91 (46)
% Difference		1.7	26.0	3.5	27.0	31.7	34.1
95% CI		-6.5, 9.8	14.9, 37.0	-4.7, 11.7	16.0, 37.9	23.7, 39.8	26.2, 42.0
p Value		0.677	≤0.001*	0.375	≤0.001*	≤0.001*	≤0.001*
SGTC							
N	120	33	34	40	29	74	79
n (%)	35 (29)	8 (24)	10 (29)	7 (18)	17 (59)	37 (50)	41 (52)
% Difference		-4.9	0.2	-11.7	29.5	20.8	22.7
95% CI		-21.7, 11.8	-17.1, 17.6	-26, -2.6	9.8, 49.1	6.8, 34.8	9.0, 36.4
p Value		0.557	0.978	0.146	0.003*	0.004*	≤0.001*
All Partial							
N	294	88	86	99	90	192	203
n (%)	29 (10)	13 (15)	27 (31)	14 (14)	36 (40)	89 (46)	94 (46)
% Difference		4.9	21.5	4.3	30.1	36.5	36.4
95% CI		-3.3, 13.1	11.1, 31.9	-3.4, 11.9	19.5, 40.8	28.7, 44.3	28.8, 44.1
p Value		0.197	≤0.001*	0.238	≤0.001*	≤0.001*	≤0.001*

ITT = Intent-to-treat; CI = Confidence interval; SGTC = Secondarily generalized tonic-clonic.
* Statistically significant

Table 8.38: Phase 2 study of pregabalin as monotherapy in patients with refractory partial epilepsy

Study nos, location investigators	Study design	Subjects demographics	Dosage, duration, route, form of study drugs	Endpoints	Safety/AEs
Studies 1008-008, 010, 012, and 035. Mod.5-Vol.70. Data cutoff date for all studies was 14/2/2003.	Phase 3, uncontrolled, open-label efficacy & tolerance study. In studies 010 & 012, doses of pts from DB study were titrated up or down during a blinded transition period. IN studies 008 and 035, all pts introduced directly to the target dose.	1480 patients with partial seizures, with or without sec. generalisations, who received study medication in DB studies 007, 009, 011 & 034. Also included new pts with ≥4 partial seizures in past 2 mths who wished to receive pregabalin Rx. Sex: 747M: 733F Age: 12-82yrs, mean=38yrs. Race: White=1277, Black=71, Hisp=89, Others=43.	Pregabalin (PGB) 25 &100mg capsules. All dosing orally. Study Nos. target dose range dosing (mg/day) 008 450 TID 150 to 600TID 010 450 TID 225 to 600TID or BID 012 450 TID 75 to 600 TID or BID 035 400 BID 100 to 600 BID	% change in 28-day seizure rates; responder rate (≥50% reduction from baseline) at 2, 4, 8, 12, 16 weeks & then every 3 mths till end of study. Safety also assessed similarly.	AE incidence: 95% with 80% being Rx-related. Dizziness (33%), somnolence (27%), accidental injury (26%), weight gain (22%), infection(19%), asthenia (18.5%), headache (18%), ataxia (13.5%), amblyopia(13%), diplopia(11%), abn thinking (11%), nausea & tremor (10% each) & peripheral oedema (8%) most common. Most of the AEs were moderate or mild. 186 pts (13%) had SAEs(accidental injury, pneumonia, depression, psychosis most common). 185 pts (13%) withdrew due to AEs(weight gain, somnolence, dizziness, asthenia common). 15 deaths during or after open-label studies- none related to PGB. 52% of pts had >7% ↑ in weight from baseline. ; 4 deaths related to epilepsy- seizures, aspiration, injury, etc. Clinically imp ↓ in platelets in 8% of pts, in sodium in 13% of pts; Imp ↑ in alkaline phosphatase in 13% of pts & in creatine kinase in 3% of pts. No other clinically sig changes in vital signs, ECG or other lab parameters..

Table 8.39.1:

Summary of RRatio (Partial Secondarily Generalized Seizures): ITT Population (Studies 1008-009, -011, -034 Combined)

		Pregabalin Dose (mg/day)							
	Placebo	50 BID	150 BID, TID	150 - 600 BID + TID	300 BID	300 + 600 BID + TID	600 BID	600 TID	600 BID + TID
1008-009									
N	45						45	36	
Mean	-8						-33.2	-32.1	
SD	70.6						74.3	66.0	
Median	-11.9						-64.0	-38.6	
p-value[a]							0.0611	0.1025	
1008-011									
N	49		40					43	
Mean	3.5		6.8					-37.9	
SD	61.0		57.0					56.9	
Median	8.3		3.3					-48.1	
p-value[a]			0.9689					0.0028[b]	
1008-034									
N	26	33	34		29		29		
Mean	-10.0	18.5	1.5		-24.7		-26.4		
SD	67.8	72.7	65		71.2		67		
Median	-15.9	9.7	-6.9		-40.8		-21.1		
p-value[a]		0.1862	0.5781		0.2493		0.3607		
All Studies Combined									
N	120	33	74	256	29	182			153
Mean	-3.7	18.5	4.4	-21.2	-24.7	-31.7			-33.0
SD	66.0	72.7	60.5	66.8	71.2	66.6			65.9
Median	-5.8	9.7	2.2	-21.7	-40.8	-40.5			-38.0
p-value[a]				0.0546		0.0047[b]			0.0005[b]

[a] Difference between pregabalin group and placebo

[b] Statistically significant ($p \leq 0.05$)

Table 8.39.2:

Summary of Percent of Patients With a Decrease in SGTC Seizures Proportion:ITT Population
(Studies 1008-009, -011, -034 Combined)

		Pregabalin Dose (mg/day)							
	Placebo	50 BID	150 BID, TID	150 - 600 BID + TID	300 BID	300 + 600 BID + TID	600 BID	600 TID	600 BID + TID
1008-009									
N	45						39	32	
n	24						22	20	
%	53%						56%	63%	
p-value[a]							0.778	0.423	
1008-011									
N	49		39					42	
n	24		15					25	
%	49%		38%					60%	
p-value[a]			0.324					0.314	
1008-034									
N	26	33	34		28		26		
n	15	12	15		17		13		
%	58%	36%	44%		61%		50%		
p-value[a]		0.103	0.297		0.821		0.578		
All Studies Combined									
N	120	33	73	240	28	167			139
n	63	12	30	127	17	97			80
%	53%	36%	41%	53%	61%	58%			58%
p-value[a]				0.940		0.348			0.415

[a] Difference between pregabalin group and placebo

Table 8.40:

Summary of RRatio by Subpopulations of Age, Race, Gender, and Menopausal Status: ITT Population

Subpopulation	N	Mean	SD	Median	Minimum	Maximum
AGE[a]						
12 Through 16 Years[b]						
Placebo	1	43.8	--	43.8	44	44
All Effective Pregabalin Doses	9	-16	44.4	-10.3	-100	53
17 Through 64 Years						
Placebo	285	-1.1	27	-0.2	-100	88
All Effective Pregabalin Doses	649	-27.6	36.5	-22.8	-100	99
65 Through 74 Years[a]						
Placebo	7	6.2	14.4	4.1	-10	36
All Effective Pregabalin Doses	10	-51.5	37.4	-51.8	-100	-1
RACE						
White						
Placebo	260	-1.1	26.5	-0.8	-100	75
All Pregabalin	581	-26.7	37	-21.1	-100	99
Black						
Placebo	12	3.4	32.8	7.3	-56	46
All Pregabalin	32	-26.9	31.3	-22.7	-100	50
Hispanic						
Placebo	12	1.5	33.4	1.3	-37	88
All Pregabalin	39	-38.5	35.5	-36.7	-100	39
Other						
Placebo	10	-1.1	24.4	6.4	-47	30
All Pregabalin	18	-36.8	32.9	-33.6	-100	14
GENDER						
Male						
Placebo	156	-1.6	24.1	-0.3	-70	73
All Pregabalin	324	-25.5	33.6	-21.1	-100	96
Female						
Placebo	138	0	29.7	0	-100	88
All Pregabalin	346	-29.7	39.2	-24.8	-100	99
MENOPAUSAL STATUS						
Premenopausal						
Placebo	99	0.2	32.5	0	-100	88
All Pregabalin	261	-27.5	37.9	-21.7	-100	99
Postmenopausal						
Placebo	39	-0.3	21.4	0	-50	60
All Pregabalin	83	-38.2	41.5	-34.3	-100	92

ITT = Intent-to-treat; SD = Standard Deviation.

[a] Age Category ≥75 years is not presented due to the small sample size (N = 2; 1 patient given 150 mg/day and the other given 600 mg/day).

[b] Patient ages were: 12, 12, 13, 13, 15, 15, 15, 15, and 16 years for pregabalin and 16 years for placebo.

Summary of RRatio, Dose Administered, and Estimated Creatinine Clearance by Age Category

Age Subpopulation	RRatio	Dose Administered (mg/day)	CLcr (mL/min)
12 Through 16 Years (N = 9)			
Mean (SD)	-16 (44.4)	283 (190.4)	118 (32.7)
Median	-10.3	150	101
Minimum, Maximum	-100, 53	150, 600	82, 164
17 Through 64 Years (N = 649)			
Mean (SD)	-27.6 (36.5)	437 (201.8)	110 (32.1)
Median	-22.8	600	105
Minimum, Maximum	-100, 99	150, 600	46, 297
65 Through 74 Years (N = 10)			
Mean (SD)	-51.5 (37.4)	465 (217.4)	71 (9.6)
Median	-51.8	600	71
Minimum, Maximum	-100, -1	150, 600	53, 82

CLcr = Creatinine clearance; SD = Standard deviation.

Table 8.41.1:

Summary of Responder Rate[a]: Evaluable Population: Open-Label Studies 1008-010, -012, and -035

Period (Study Days)	Pregabalin N = 881	
	N	Responders (%)
OL 1 (1-84)	881	329 (37.3%)
OL 2 (85-168)	785	322 (41.0%)
OL 3 (169-252)	687	302 (44.0%)
OL 4 (253-336)	610	291 (47.7%)
OL 5 (337-420)	550	272 (49.5%)
OL 6 (421-504)	507	268 (52.9%)
OL 7 (505-588)	481	258 (53.6%)
OL 8 (589-672)	429	240 (55.9%)
OL 9 (673-756)	310	183 (59.0%)
OL 10 (757-840)	186	106 (57.0%)
OL 11 (841-924)	134	81 (60.4%)
OL 12 (925-1008)	106	62 (58.5%)
All OL	881	308 (35.0%)

[a] Data collected after Initial Requalification not included for Studies 1008-010 and -035

Table 8.41.2:

Summary of Responder Rate[a]: Evaluable Population, 2-Year Cohort[b]: Open-Label Studies 1008-010, -012, and -035

Period (Study Days)	Pregabalin N = 220	
	N	Responders (%)
OL 1 (1-84)	220	114 (51.8%)
OL 2 (85-168)	220	109 (49.5%)
OL 3 (169-252)	220	109 (49.5%)
OL 4 (253-336)	220	120 (54.5%)
OL 5 (337-420)	220	115 (52.3%)
OL 6 (421-504)	220	128 (58.2%)
OL 7 (505-588)	220	128 (58.2%)
OL 8 (589-672)	220	121 (55.0%)
OL 9 (673-756)	220	127 (57.7%)
All OL	220	115 (52.3%)

[a] Data collected after Initial Requalification not included for Studies 1008-010 and -035

[b] 2-Year Cohort defined by open-label exposure at Initial Requalification for Studies 1008-010 and -035, and by total open-label exposure for Study 1008-012

Table 8.42.1:

Summary of Percent Change From Baseline in Seizure Frequency[a]: Evaluable Population: Open-Label Studies 1008-010, -012, and -035

	Pregabalin N = 881					
Period (Study Days)	N	Mean	SD	Median	Minimum	Maximum
OL 1 (1-84)	881	-26.4	65.8	-37.8	-100	653.8
OL 2 (85-168)	785	-11.3	339	-39.4	-100	8860.8
OL 3 (169-252)	687	-25.8	199.7	-42.9	-100	4971.8
OL 4 (253-336)	610	-33.9	67.1	-46.8	-100	676.6
OL 5 (337-420)	550	-35.1	75.1	-48.9	-100	966.7
OL 6 (421-504)	507	-30	148	-52.4	-100	2700
OL 7 (505-588)	481	-36.5	147	-53.8	-100	2922
OL 8 (589-672)	429	-38.9	139.5	-58.1	-100	2615.2
OL 9 (673-756)	310	-50.3	49	-59	-100	191.7
OL 10 (757-840)	186	-35.6	113.7	-60	-100	1125
OL 11 (841-924)	134	-52.1	46.9	-57.9	-100	260
OL 12 (925-1008)	106	-51.5	52.1	-59.6	-100	304.4
All OL	881	-20.2	128.4	-35.2	-100	3228.5

[a] Data collected after Initial Requalification not included for Studies 1008-010 and -035

Table 8.42.2:

Summary of Percent Change From Baseline in Seizure Frequency[a]: Evaluable Population, 2-Year Cohort[b]: Open-Label Studies 1008-010, -012, and -035

	Pregabalin N = 220					
Period (Study Days)	N	Mean	SD	Median	Minimum	Maximum
OL 1 (1-84)	220	-45.3	39.5	-51	-100	119.3
OL 2 (85-168)	220	-42.1	45	-49.4	-100	206.7
OL 3 (169-252)	220	-44.6	39.6	-49.2	-100	108.3
OL 4 (253-336)	220	-48	37.5	-52.1	-100	77.4
OL 5 (337-420)	220	-44.5	48.4	-50.7	-100	208.3
OL 6 (421-504)	220	-48.7	44	-57.3	-100	144.4
OL 7 (505-588)	220	-47.4	48.7	-57.8	-100	214.3
OL 8 (589-672)	220	-44.2	51.2	-57.1	-100	214.3
OL 9 (673-756)	220	-48.4	47.7	-56.7	-100	191.7
All OL	220	-46.9	34.3	-51.5	-100	85.9

[a] Data collected after Initial Requalification not included for Studies 1008-010 and -035

[b] 2-Year Cohort defined by open-label exposure at Initial Requalification for Studies 1008-010 and -035, and by total open-label exposure for Study 1008-012

Table 8.42.3:

Pregabalin Open-Label, Add-On, Multicenter Studies
in Patients With Partial Seizures (Protocol 1008-010, -012, -035)

Distribution of Percent Change from Baseline in Seizure Frequency
All Partial Seizures *
Evaluable Population

Change in Seizures	Pregabalin N=881	
Decrease		
-100 to -75	119	(13.5%)
> -75 to -50	189	(21.5%)
>-50 to -25	215	(24.4%)
> -25 to 0	176	(20%)
Increase		
>0 to <26	78	(8.9%)
26 to <51	38	(4.3%)
51 to <76	20	(2.3%)
>= 76	46	(5.2%)

* Data collected after Initial Requalification not included for Studies 8, 10, and 35.

Table 9.1:

Source and Number of Patients in NeP Studies (DPN and PHN)

Controlled NeP Studies				
6 DPN Studies	Placebo	Pregabalin	Amitriptyline	Total
014[23]	85	161	--	246
029[24]	97	240	--	337
040[30]	81	86	87	254
131[25]	70	76	--	146
149[26]	96	299	--	395
173[22]	30	117	--	147
TOTAL DPN	**459**	**979**	**87**	**1525**
5 PHN Studies				
030[31]	88	167	--	255
045[27]	81	157	--	238
127[28]	84	89	--	173
132[21]	52	164	--	216
196[29]	93	275	--	368
TOTAL PHN	**398**	**852**	**--**	**1250**
TOTAL: Controlled NeP Studies	**857**	**1831**	**87**	**2775**

Uncontrolled NeP Extension Studies	Pregabalin		
Patients With DPN	Re-Exposure	New Exposure	Total
015[47]	148	72	220
033[48, a]	203	88	291
074[50]	64	125	189
134[51]	60	62	122
174[134]	3	1	4
165[52]	244	85	329
197[54]	8[c]	1	9
TOTAL DPN	**730**	**434**	**1164**
Patients With PHN			
033[48, a]	137	78	215
061[49]	102	52	154
134[51]	63	65	128
174[134]	1	0	1
197[54,c]	16	7	23
198[53]	157	57	214
TOTAL PHN	**476**	**259**	**735**
TOTAL: Uncontrolled Studies: Patients With NeP	**1206**	**693**	**1899**

TOTAL: Combined Controlled and Uncontrolled NeP Data	**Pregabalin**
	2524[b]

[a] Study 033 also enrolled patients from controlled nonneuropathic pain studies; these patients are summarized with all indications combined in Section 2.7.4.

[b] Includes 1831 pregabalin-treated patients from the 11 controlled studies and 693 new open-label exposures.

[c] 35 additional DPN patients and 13 additional PHN patients were re-exposed to pregabalin in Study 197; however, these patients were previously counted in the re-exposure column for the respective preceding open-label study.

Table 9.2.1:

Summary of Exposure to Study Medication by Treatment Group: Controlled DPN, PHN, and NeP Studies

(Page 1 of 2)

[Number (%) of Patients]

Total Exposure Time[a]	Total Daily Dose of Pregabalin in mg/day (Regimen)								
	Placebo	75 (TID)	150 (BID)	150 (TID)	300 (BID)	300 (TID)	600 (BID)	600 (TID)	Any Dose
Controlled DPN (Studies 014, 029, 040, 131, 149, 173)									
	N= 459	**N= 77**	**N= 133**	**N= 79**	**N= 164**	**N= 157**	**N= 119**	**N= 250**	**N=979**
≥1 day	459(100.0)	77(100.0)	133(100.0)	79(100.0)	164(100.0)	157(100.0)	119(100.0)	250(100.0)	979 (100.0)
≥1 week	450(98.0)	77(100.0)	127(95.5)	79(100.0)	151(92.1)	152(96.8)	118(99.2)	242(96.8)	946 (96.6)
≥2 weeks	439(95.6)	71(92.2)	120(90.2)	79(100.0)	135(82.3)	150(95.5)	104(87.4)	233(93.2)	892 (91.1)
≥4 weeks	403(87.8)	63(81.8)	109(82.0)	75(94.9)	117(71.3)	143(91.1)	91(76.5)	215(86.0)	813 (83.0)
≥6 weeks	287(62.5)	0(0)	99(74.4)	61(77.2)	107(65.2)	69(43.9)	83(69.7)	129(51.6)	548 (56.0)
≥8 weeks	183(39.9)	0(0)	93(69.9)	1(1.3)	101(61.6)	42(26.8)	77(64.7)	63(25.2)	377 (38.5)
≥10 weeks	85(18.5)	0(0)	85(63.9)	0(0)	88(53.7)	0(0)	74(62.2)	2(0.8)	249 (25.4)
≥12 weeks	68(14.8)	0(0)	68(51.1)	0(0)	77(47.0)	0(0)	56(47.1)	0(0)	201 (20.5)
Controlled PHN (Studies 030, 045, 127, 132, 196)									
	N=398	**N=84**	**N=138**	**N=164**	**N=206**	**N=106**	**N=95**	**N=59**	**N=852**
≥1 day	398(100.0)	84(100.0)	138(100.0)	164(100.0)	206(100.0)	106(100.0)	95(100.0)	59(100.0)	852(100.0)
≥1 week	389(97.7)	82(97.6)	135(97.8)	159(97.0)	194(94.2)	103(97.2)	90(94.7)	58(98.3)	821(96.4)
≥2 weeks	365(91.7)	81(96.4)	122(88.4)	156(95.1)	170(82.5)	97(91.5)	74(77.9)	53(89.8)	753(88.4)
≥4 weeks	330(82.9)	81(96.4)	100(72.5)	149(90.9)	138(67.0)	87(82.1)	67(70.5)	46(78.0)	668(78.4)
≥6 weeks	228(57.3)	5(6.0)	80(58.0)	74(45.1)	115(55.8)	80(75.5)	55(57.9)	41(69.5)	450(52.8)
≥8 weeks	172(43.2)	1(1.2)	76(55.1)	50(30.5)	101(49.0)	66(62.3)	54(56.8)	32(54.2)	380(44.6)
≥10 weeks	66(16.6)	0(0)	67(48.6)	0(0)	85(41.3)	1(0.9)	50(52.6)	1(1.7)	204(23.9)
≥12 weeks	60(15.1)	0(0)	60(43.5)	0(0)	77(37.4)	0(0)	44(46.3)	0(0)	181(21.2)

[a] Study days on which patient received zero dose during the study are included. Total exposure time includes titration and fixed-dose phases.

Table 9.2.2:

Summary of Exposure to Study Medication by Treatment Group: Controlled DPN, PHN, and NeP Studies

(Page 2 of 2)

[Number (%) of Patients]

Total Exposure Time[a]	Total Daily Dose of Pregabalin in mg/day (Regimen)								
	Placebo	75 (TID)	150 (BID)	150 (TID)	300 (BID)	300 (TID)	600 (BID)	600 (TID)	Any Dose
Combined Controlled NeP (Studies 014, 029, 030, 040, 045, 131, 127, 132, 149, 173, 196)									
	N=857	N=161	N=271	N=243	N=370	N=263	N=214	N=309	N=1831
≥1 day	857 (100.0)	161 (100.0)	271 (100.0)	243 (100.0)	370 (100.0)	263 (100.0)	214 (100.0)	309 (100.0)	1831 (100.0)
≥1 week	839 (97.9)	159 (98.8)	262 (96.7)	238 (97.9)	345 (93.2)	255 (97.0)	208 (97.2)	300 (97.1)	1767 (96.5)
≥2 weeks	804 (93.8)	152 (94.4)	242 (89.3)	235 (96.7)	305 (82.4)	247 (93.9)	178 (83.2)	286 (92.6)	1645 (89.8)
≥4 weeks	733 (85.5)	144 (89.4)	209 (77.1)	224 (92.2)	255 (68.9)	230 (87.5)	158 (73.8)	261 (84.5)	1481 (80.9)
≥6 weeks	515 (60.1)	5 (3.1)	179 (66.1)	135 (55.6)	222 (60.0)	149 (56.7)	138 (64.5)	170 (55.0)	998 (54.5)
≥8 weeks	355 (41.4)	1 (0.6)	169 (62.4)	51 (21.0)	201 (54.3)	108 (41.1)	131 (61.2)	95 (30.7)	756 (41.3)
≥10 weeks	151 (17.6)	0 (0)	152 (56.1)	0 (0)	173 (46.8)	1 (0.4)	124 (57.9)	3 (1.0)	453 (24.7)
≥12 weeks	125 (14.6)	0 (0)	128 (47.2)	0 (0)	154 (41.6)	0 (0)	100 (46.7)	0 (0)	382 (20.9)

[a] Study days on which patient received zero dose during the study are included. Total exposure time includes titration and fixed-dose phases.

Table 9.2.3:

Summary of Exposure to Pregabalin: Combined Controlled and Uncontrolled DPN, PHN and NeP Studies

	[Number (%) of Patients]
Total Exposure Time[a]	Any Dose Pregabalin
DPN (Studies 014, 015, 029, 033, 040, 074, 131, 134, 149, 165, 173, 174, 197)	
	N = 1413
≥24 weeks	948 (67.1)
≥36 weeks	779 (55.1)
≥52 weeks	578 (40.9)
≥104 weeks	272 (19.2)
PHN (Studies 030, 033, 045, 061, 127, 132, 134, 174, 196, 197, 198)	
	N = 1111
≥24 weeks	448 (40.3)
≥36 weeks	324 (29.2)
≥52 weeks	199 (17.9)
≥104 weeks	72 (6.5)
NeP (Studies 014, 015, 029, 030, 033, 040, 045, 061, 074, 127, 131, 132, 134, 149, 165, 173, 174, 196, 197, 198)	
	N = 2524
≥24 weeks	1,396 (55.3)
≥36 weeks	1,103 (43.7)
≥52 weeks	777 (30.8)
≥104 weeks	344 (13.6)

[a] Study days on which patient received zero dose during the study are included.

Table 9.3.1:

Summary of Adverse Events Occurring in ≥2% of All Pregabalin-Treated Patients by Decreasing Frequency: Controlled DPN Studies (014, 029, 040, 131, 149, 173)

Preferred Term	[Number of Patients (%)]															
	Placebo N = 459		150 mg/day PGB BID N = 133		150 mg/day PGB TID N = 79		300 mg/day PGB BID N = 164		300 mg/day PGB TID N = 157		600 mg/day PGB BID N = 119		600 mg/day PGB TID N = 250		All PGB[a] N = 979	
Dizziness	21	(4.6)	11	(8.3)	8	(10.1)	25*	(15.2)	49*	(31.2)	26*	(21.8)	81*	(32.4)	206*	(21.0)
Somnolence	12	(2.6)	9*	(6.8)	4	(5.1)	8	(4.9)	34*	(21.7)	16*	(13.4)	44*	(17.6)	118*	(12.1)
Peripheral edema	11	(2.4)	10*	(7.5)	3	(3.8)	16*	(9.8)	14*	(8.9)	16*	(13.4)	30*	(12.0)	92*	(9.4)
Headache	40	(8.7)	6	(4.5)	6	(7.6)	8	(4.9)	12	(7.6)	2*	(1.7)	25	(10.0)	64	(6.5)
Infection	28	(6.1)	6	(4.5)	10	(12.7)	8	(4.9)	19*	(12.1)	8	(6.7)	9	(3.6)	63	(6.4)
Asthenia	11	(2.4)	1	(0.8)	3	(3.8)	7	(4.3)	7	(4.5)	5	(4.2)	22*	(8.8)	48*	(4.9)
Dry mouth	5	(1.1)	4	(3.0)	0	(0.0)	8*	(4.9)	7*	(4.5)	9*	(7.6)	15*	(6.0)	45*	(4.6)
Weight gain	2	(0.4)	8*	(6.0)	1	(1.3)	10*	(6.1)	2	(1.3)	11*	(9.2)	12*	(4.8)	44*	(4.5)
Constipation	7	(1.5)	2	(1.5)	3	(3.8)	5	(3.0)	7	(4.5)	6*	(5.0)	16*	(6.4)	39*	(4.0)
Pain	18	(3.9)	6	(4.5)	3	(3.8)	2	(1.2)	6	(3.8)	5	(4.2)	13	(5.2)	39	(4.0)
Neuropathy	16	(3.5)	2	(1.5)	2	(2.5)	0*	(0.0)	7	(4.5)	0	(0.0)	20*	(8.0)	38	(3.9)
Accidental injury	13	(2.8)	3	(2.3)	2	(2.5)	2	(1.2)	5	(3.2)	4	(3.4)	17*	(6.8)	37	(3.8)
Amblyopia[b]	7	(1.5)	1	(0.8)	2	(2.5)	1	(0.6)	8*	(5.1)	5	(4.2)	16*	(6.4)	35*	(3.6)
Ataxia	6	(1.3)	1	(0.8)	1	(1.3)	3	(1.8)	4	(2.5)	2	(1.7)	14*	(5.6)	30	(3.1)
Diarrhea	22	(4.8)	2	(1.5)	4	(5.1)	2	(1.2)	4	(2.5)	3	(2.5)	8	(3.2)	27	(2.8)
Nausea	26	(5.7)	2	(1.5)	3	(3.8)	4	(2.4)	8	(5.1)	3	(2.5)	6	(2.4)	27	(2.8)
Vertigo	5	(1.1)	4	(3.0)	0	(0.0)	8*	(4.9)	0	(0.0)	7*	(5.9)	6	(2.4)	26	(2.7)
Edema	0	(0.0)	4*	(3.0)	0	(0.0)	13*	(7.9)	0	(0.0)	5*	(4.2)	2	(0.8)	24*	(2.5)
Confusion	3	(0.7)	3	(2.3)	0	(0.0)	3	(1.8)	4	(2.5)	3	(2.5)	9*	(3.6)	22*	(2.2)
Total With AEs	**252**	**(54.9)**	**71**	**(53.4)**	**44**	**(55.7)**	**104**	**(63.4)**	**121**	**(77.1)**	**88**	**(73.9)**	**198**	**(79.2)**	**674**	**(68.8)**

* Statistically significantly different from placebo based on odds ratio or Fisher's Exact test ($p \leq 0.05$)

[a] Includes all other doses of pregabalin (ie, 75 mg/day).

[b] Amblyopia was reported by the investigators mainly as blurred/blurry vision.

Table 9.3.2:

Summary of Adverse Events Occurring in ≥2% of All Pregabalin-Treated Patients by Decreasing Frequency: Controlled PHN Studies (030, 045, 127, 132, 196)

Preferred Term	[Number of Patients (%)]							
	Placebo N = 398	150 mg/day PGB BID N = 138	150 mg/day PGB TID N = 164	300 mg/day PGB BID N = 206	300 mg/day PGB TID N = 106	600 mg/day PGB BID N = 95	600 mg/day PGB TID N = 59	All PGB[a] N = 852
Dizziness	37(9.3)	31*(22.5)	23(14.0)	67*(32.5)	31*(29.2)	42*(44.2)	15*(25.4)	218*(25.6)
Somnolence	21(5.3)	17*(12.3)	20*(12.2)	31*(15.0)	25*(23.6)	23*(24.2)	15*(25.4)	138*(16.2)
Peripheral edema	14(3.5)	20*(14.5)	4(2.4)	32*(15.5)	17*(16.0)	15*(15.8)	10*(16.9)	98*(11.5)
Dry mouth	11(2.8)	7(5.1)	14*(8.5)	12(5.8)	7(6.6)	15*(15.8)	8*(13.6)	69*(8.1)
Infection	14(3.5)	16*(11.6)	9(5.5)	13(6.3)	7(6.6)	4(4.2)	0(0.0)	61*(7.2)
Headache	21(5.3)	11(8.0)	16(9.8)	4(1.9)	10(9.4)	8(8.4)	5(8.5)	58(6.8)
Amblyopia[b]	10(2.5)	4(2.9)	11*(6.7)	9(4.4)	7(6.6)	9*(9.5)	5*(8.5)	46*(5.4)
Constipation	9(2.3)	5(3.6)	9(5.5)	12*(5.8)	5(4.7)	8*(8.4)	0(0.0)	42*(4.9)
Pain	15(3.8)	8(5.8)	5(3.0)	14(6.8)	3(2.8)	6(6.3)	1(1.7)	41(4.8)
Ataxia	2(0.5)	3(2.2)	3(1.8)	14*(6.8)	3(2.8)	8*(8.4)	6*(10.2)	38*(4.5)
Asthenia	16(4.0)	7(5.1)	8(4.9)	5(2.4)	3(2.8)	6(6.3)	2(3.4)	34(4.0)
Diarrhea	16(4.0)	7(5.1)	6(3.7)	6(2.9)	5(4.7)	2(2.1)	5(8.5)	33(3.9)
Weight gain	1(0.3)	3(2.2)	2(1.2)	14*(6.8)	3*(2.8)	7*(7.4)	3*(5.1)	33*(3.9)
Abnormal gait	2(0.5)	4*(2.9)	2(1.2)	8*(3.9)	4*(3.8)	7*(7.4)	5*(8.5)	30*(3.5)
Accidental injury	6(1.5)	5(3.6)	3(1.8)	6(2.9)	4(3.8)	6*(6.3)	2(3.4)	29(3.4)
Confusion	1(0.3)	4*(2.9)	3(1.8)	6*(2.9)	3*(2.8)	4*(4.2)	6*(10.2)	27*(3.2)
Rash	12(3.0)	1(0.7)	5(3.0)	6(2.9)	3(2.8)	5(5.3)	3(5.1)	25(2.9)
Edema	5(1.3)	3(2.2)	0(0.0)	7(3.4)	0(0.0)	6*(6.3)	3(5.1)	19(2.2)
Nausea	16(4.0)	4(2.9)	3(1.8)	4(1.9)	3(2.8)	3(3.2)	1(1.7)	19(2.2)
Thinking abnormal	6(1.5)	3(2.2)	2(1.2)	3(1.5)	1(0.9)	5(5.3)	4*(6.8)	18(2.1)
Diplopia	0(0.0)	2(1.4)	3(1.8)	3(1.5)	3*(2.8)	4*(4.2)	2*(3.4)	17(2.0)
Urinary tract infection	6(1.5)	4(2.9)	3(1.8)	2(1.0)	3(2.8)	4(4.2)	1(1.7)	17(2.0)
Total With AEs	**227(57.0)**	**93(67.4)**	**109(66.5)**	**152(73.8)**	**88(83.0)**	**80(84.2)**	**52(88.1)**	**627(73.6)**

* Statistically significantly different from placebo based on odds ratio or Fisher's Exact test (p≤0.05)

[a] Includes all other doses of pregabalin (ie, 75 mg/day).

[b] Amblyopia was reported by the investigators mainly as blurred/blurry vision.

Table 9.3.3:

Summary of Adverse Events Occurring in ≥2% of All Pregabalin-Treated Patients by Decreasing Frequency: Controlled NeP Studies (014, 029, 030, 040, 045, 127, 131, 132, 149, 173, 196)

Preferred Term	[Number of Patients (%)]							
	Placebo N = 857	150 mg/day PGB BID N = 271	150 mg/day PGB TID N = 243	300 mg/day PGB BID N = 370	300 mg/day PGB TID N = 263	600 mg/day PGB BID N = 214	600 mg/day PGB TID N = 309	All PGB[a] N = 1831
Dizziness	58(6.8)	42*(15.5)	31*(12.8)	92*(24.9)	80*(30.4)	68*(31.8)	96*(31.1)	424*(23.2)
Somnolence	33(3.9)	26*(9.6)	24*(9.9)	39*(10.5)	59*(22.4)	39*(18.2)	59*(19.1)	256*(14.0)
Peripheral edema	25(2.9)	30*(11.1)	7(2.9)	48*(13.0)	31*(11.8)	31*(14.5)	40*(12.9)	190*(10.4)
Infection	42(4.9)	22(8.1)	19(7.8)	21(5.7)	26*(9.9)	12(5.6)	9(2.9)	124(6.8)
Headache	61(7.1)	17(6.3)	22(9.1)	12(3.2)	22(8.4)	10(4.7)	30(9.7)	122(6.7)
Dry mouth	16(1.9)	11(4.1)	14*(5.8)	20*(5.4)	14*(5.3)	24*(11.2)	23*(7.4)	114*(6.2)
Asthenia	27(3.2)	8(3.0)	11(4.5)	12(3.2)	10(3.8)	11(5.1)	24*(7.8)	82(4.5)
Amblyopia[b]	17(2.0)	5(1.8)	13*(5.3)	10(2.7)	15*(5.7)	14*(6.5)	21*(6.8)	81*(4.4)
Constipation	16(1.9)	7(2.6)	12*(4.9)	17*(4.6)	12*(4.6)	14*(6.5)	16*(5.2)	81*(4.4)
Pain	33(3.9)	14(5.2)	8(3.3)	16(4.3)	9(3.4)	11(5.1)	14(4.5)	80(4.4)
Weight gain	3(0.4)	11*(4.1)	3(1.2)	24*(6.5)	5(1.9)	18*(8.4)	15*(4.9)	77*(4.2)
Ataxia	8(0.9)	4(1.5)	4(1.6)	17*(4.6)	7(2.7)	10*(4.7)	20*(6.5)	68*(3.7)
Accidental injury	19(2.2)	8(3.0)	5(2.1)	8(2.2)	9(3.4)	10(4.7)	19*(6.1)	66(3.6)
Diarrhea	38(4.4)	9(3.3)	10(4.1)	8(2.2)	9(3.4)	5(2.3)	13(4.2)	60(3.3)
Confusion	4(0.5)	7*(2.6)	3(1.2)	9*(2.4)	7*(2.7)	7*(3.3)	15*(4.9)	49*(2.7)
Nausea	42(4.9)	6(2.2)	6(2.5)	8(2.2)	11(4.2)	6(2.8)	7(2.3)	46(2.5)
Abnormal gait	2(0.2)	4(1.5)	2(0.8)	9*(2.4)	5(1.9)	12*(5.6)	10*(3.2)	43*(2.3)
Edema	5(0.6)	7*(2.6)	0(0.0)	20*(5.4)	0(0.0)	11*(5.1)	5(1.6)	43*(2.3)
Neuropathy	16(1.9)	2(0.7)	2(0.8)	0(0.0)	7(2.7)	0(0.0)	20*(6.5)	39(2.1)
Total With AEs	**479(55.9)**	**164(60.5)**	**153(63.0)**	**256(69.2)**	**209(79.5)**	**168(78.5)**	**250(80.9)**	**1301(71.1)**

* Statistically significantly different from placebo based on odds ratio or Fisher's Exact test (p≤0.05)

[a] Includes all other doses of pregabalin (ie, 75 mg/day).

[b] Amblyopia was reported by the investigators mainly as blurred/blurry vision.

Table 9.4:

Summary of Treatment-Related Adverse Events Occurring in ≥4% of All Pregabalin-Treated Patients by Decreasing Frequency: Controlled DPN, PHN, and NeP Studies

Preferred Term	[Number of Patients (%)]							
	Placebo	150 mg/day PGB BID	150 mg/day PGB TID	300 mg/day PGB BID	300 mg/day PGB TID	600 mg/day PGB BID	600 mg/day PGB TID	All PGB[a]
Controlled DPN Studies (014, 029, 040, 131, 149, 173)								
	N = 459	**N = 133**	**N = 79**	**N = 164**	**N = 157**	**N = 119**	**N = 250**	**N = 979**
Dizziness	17(3.7)	9(6.8)	5(6.3)	22(13.4)	46(29.3)	25(21.0)	71(28.4)	184(18.8)
Somnolence	11(2.4)	8(6.0)	4(5.1)	7(4.3)	34(21.7)	15(12.6)	41(16.4)	112(11.4)
Peripheral edema	5(1.1)	8(6.0)	1(1.3)	11(6.7)	9(5.7)	14(11.8)	17(6.8)	61(6.2)
Asthenia	9(2.0)	1(0.8)	3(3.8)	6(3.7)	6(3.8)	5(4.2)	19(7.6)	42(4.3)
Dry mouth	5(1.1)	4(3.0)	0(0.0)	8(4.9)	6(3.8)	8(6.7)	13(5.2)	41(4.2)
Headache	27(5.9)	5(3.8)	2(2.5)	4(2.4)	6(3.8)	1(0.8)	19(7.6)	41(4.2)
Total With TR AEs	**118(25.7)**	**45(33.8)**	**15(19.0)**	**72(43.9)**	**92(58.6)**	**65(54.6)**	**144(57.6)**	**462(47.2)**
Controlled PHN Studies (030, 045, 127, 132, 196)								
	N = 398	**N = 138**	**N = 164**	**N = 206**	**N = 106**	**N = 95**	**N = 59**	**N = 852**
Dizziness	36(9.0)	29(21.0)	22(13.4)	61(29.6)	30(28.3)	42(44.2)	14(23.7)	205(24.1)
Somnolence	20(5.0)	17(12.3)	20(12.2)	31(15.0)	24(22.6)	23(24.2)	15(25.4)	136(16.0)
Peripheral edema	13(3.3)	16(11.6)	1(0.6)	30(14.6)	7(6.6)	12(12.6)	8(13.6)	74(8.7)
Dry mouth	7(1.8)	7(5.1)	12(7.3)	10(4.9)	7(6.6)	14(14.7)	7(11.9)	63(7.4)
Amblyopia	9(2.3)	3(2.2)	8(4.9)	8(3.9)	6(5.7)	8(8.4)	4(6.8)	38(4.5)
Ataxia	1(0.3)	3(2.2)	3(1.8)	13(6.3)	2(1.9)	8(8.4)	6(10.2)	35(4.1)
Total With TR AEs	**140(35.2)**	**80(58.0)**	**75(45.7)**	**129(62.6)**	**71(67.0)**	**71(74.7)**	**45(76.3)**	**498(58.5)**
Controlled NeP Studies (014, 029, 030, 040, 045, 127, 131, 132, 149, 173, 196)								
	N = 857	**N = 271**	**N = 243**	**N = 370**	**N = 263**	**N = 214**	**N = 309**	**N = 1831**
Dizziness	53(6.2)	38(14.0)	27(11.1)	83(22.4)	76(28.9)	67(31.3)	85(27.5)	389(21.2)
Somnolence	31(3.6)	25(9.2)	24(9.9)	38(10.3)	58(22.1)	38(17.8)	56(18.1)	248(13.5)
Peripheral edema	18(2.1)	24(8.9)	2(0.8)	41(11.1)	16(6.1)	26(12.1)	25(8.1)	135(7.4)
Dry mouth	12(1.4)	11(4.1)	12(4.9)	18(4.9)	13(4.9)	22(10.3)	20(6.5)	104(5.7)
Headache	42(4.9)	10(3.7)	13(5.3)	5(1.4)	12(4.6)	6(2.8)	21(6.8)	74(4.0)
Total With TR AEs	**258(30.1)**	**125(46.1)**	**90(37.0)**	**201(54.3)**	**163(62.0)**	**136(63.6)**	**189(61.2)**	**960(52.4)**

[a] Includes all other doses of pregabalin (ie, 75 mg/day).

[b] Amblyopia was reported by the investigators mainly as blurred/blurry vision.

Table 9.5.1:

Summary of Adverse Events Occurring in ≥2% of All Pregabalin-Treated Patients by Decreasing Frequency: Uncontrolled DPN Studies (015, 033, 074, 134, 165, 174, 197)

	[Number (%) of Patients]		
Preferred Term	All Pregabalin N = 1164	**Preferred Term**	All Pregabalin N = 1164
Infection	207 (17.8)	Arthralgia	38 (3.3)
Dizziness	176 (15.1)	Visual field defect	38 (3.3)
Peripheral edema	164 (14.1)	Amblyopia[a]	37 (3.2)
Accidental injury	150 (12.9)	Chest pain	37 (3.2)
Pain	139 (11.9)	Arthritis	36 (3.1)
Somnolence	109 (9.4)	Hyperglycemia	36 (3.1)
Weight gain	96 (8.2)	Edema	35 (3.0)
Flu syndrome	94 (8.1)	Pneumonia	35 (3.0)
Asthenia	82 (7.0)	Reflexes decreased	31 (2.7)
Back pain	75 (6.4)	Myasthenia	30 (2.6)
Headache	74 (6.4)	Cataract specified	29 (2.5)
Neuropathy	73 (6.3)	Dyspepsia	29 (2.5)
Diarrhea	70 (6.0)	Eye disorder	28 (2.4)
Nausea	65 (5.6)	Confusion	27 (2.3)
Dyspnea	60 (5.2)	Incoordination	27 (2.3)
Rash	56 (4.8)	Leg cramps	26 (2.2)
Ataxia	54 (4.6)	Peripheral vascular disorder	26 (2.2)
Urinary tract infection	52 (4.5)	Rhinitis	26 (2.2)
Sinusitis	47 (4.0)	Thinking abnormal	26 (2.2)
Abdominal pain	46 (4.0)	Anemia	25 (2.1)
Pharyngitis	45 (3.9)	Cellulitis	25 (2.1)
Depression	44 (3.8)	Dry mouth	25 (2.1)
Constipation	41 (3.5)	Flatulence	25 (2.1)
Retinal disorder	41 (3.5)	Hypoglycemia	25 (2.1)
Skin ulcer	41 (3.5)	Vomiting	25 (2.1)
Bronchitis	40 (3.4)	Gastrointestinal disorder	24 (2.1)
Hypertension	39 (3.4)	Skin disorder	23 (2.0)
Total Patients With Any Adverse Event			**927 (79.6)**

[a] Amblyopia was reported by the investigators mainly as blurred/blurry vision.

Table 9.5.2:

Summary of Adverse Events Occurring in ≥2% of All Pregabalin-Treated Patients by Decreasing Frequency: Uncontrolled PHN Studies (033, 061, 134, 174, 197, 198)

	[Number (%) of Patients]		
Preferred Term	All Pregabalin N = 735	**Preferred Term**	All Pregabalin N = 735
Dizziness	153 (20.8)	Back pain	27 (3.7)
Peripheral edema	111 (15.1)	Abdominal pain	25 (3.4)
Somnolence	98 (13.3)	Abnormal gait	21 (2.9)
Accidental injury	94 (12.8)	Reflexes decreased	21 (2.9)
Infection	56 (7.6)	Vomiting	21 (2.9)
Weight gain	55 (7.5)	Amnesia	19 (2.6)
Asthenia	52 (7.1)	Arthritis	19 (2.6)
Nausea	46 (6.3)	Hypertension	19 (2.6)
Pain	45 (6.1)	Pharyngitis	18 (2.4)
Constipation	44 (6.0)	Arthralgia	17 (2.3)
Ataxia	42 (5.7)	Chest pain	17 (2.3)
Rash	39 (5.3)	Dyspepsia	17 (2.3)
Dry mouth	37 (5.0)	Vertigo	17 (2.3)
Diarrhea	35 (4.8)	Sinusitis	16 (2.2)
Amblyopia[a]	34 (4.6)	Abnormal vision	15 (2.0)
Headache	34 (4.6)	Depression	15 (2.0)
Urinary tract infection	34 (4.6)	Insomnia	15 (2.0)
Flu syndrome	28 (3.8)	Lung disorder	15 (2.0)
		Tremor	15 (2.0)
Total Patients With Any Adverse Event			**572 (77.8)**

[a] Amblyopia was reported by the investigators mainly as blurred/blurry vision.

Table 9.5.3:

Summary of Adverse Events Occurring in ≥2% of All Pregabalin-Treated Patients by Decreasing Frequency: Uncontrolled NeP Studies (Studies 015, 033, 061, 074, 165, 134, 174, 197, 198)

	[Number (%) of Patients]		
Preferred Term	All Pregabalin N = 1899	**Preferred Term**	All Pregabalin N = 1899
Dizziness	329 (17.3)	Pharyngitis	63 (3.3)
Peripheral edema	275 (14.5)	Sinusitis	63 (3.3)
Infection	263 (13.8)	Dry mouth	62 (3.3)
Accidental injury	244 (12.8)	Depression	59 (3.1)
Somnolence	207 (10.9)	Hypertension	58 (3.1)
Pain	184 (9.7)	Arthralgia	55 (2.9)
Weight gain	151 (8.0)	Arthritis	55 (2.9)
Asthenia	134 (7.1)	Chest pain	54 (2.8)
Flu syndrome	122 (6.4)	Reflexes decreased	52 (2.7)
Nausea	111 (5.8)	Bronchitis	49 (2.6)
Headache	108 (5.7)	Pneumonia	49 (2.6)
Diarrhea	105 (5.5)	Retinal disorder	49 (2.6)
Back pain	102 (5.4)	Visual field defect	49 (2.6)
Ataxia	96 (5.1)	Dyspepsia	46 (2.4)
Rash	95 (5.0)	Vomiting	46 (2.4)
Urinary tract infection	86 (4.5)	Hyperglycemia	43 (2.3)
Constipation	85 (4.5)	Skin ulcer	43 (2.3)
Neuropathy	75 (3.9)	Confusion	41 (2.2)
Dyspnea	74 (3.9)	Abnormal gait	40 (2.1)
Abdominal pain	71 (3.7)	Thinking abnormal	40 (2.1)
Amblyopia[a]	71 (3.7)	Myasthenia	39 (2.1)
		Edema	38 (2.0)
Total Patients With Any Adverse Event			**1499 (78.9)**

[a] Amblyopia was reported by the investigators mainly as blurred/blurry vision.

Table 9.6:

Summary of Treatment-Related Adverse Events Occurring in ≥4% of All Pregabalin-Treated Patients by Decreasing Frequency: Uncontrolled NeP Studies

	[Number (%) of Patients]
Preferred Term	All Pregabalin
Uncontrolled DPN Studies (015, 033, 074, 134, 165, 174, 197)	
	N=1164
Dizziness	144(12.4)
Somnolence	98(8.4)
Peripheral edema	95(8.2)
Weight gain	80(6.9)
Asthenia	57(4.9)
Total Treatment Related	**563(48.4)**
Uncontrolled PHN Studies (033, 061, 134, 174, 197, 198)	
	N=735
Dizziness	141(19.2)
Somnolence	92(12.5)
Peripheral edema	76(10.3)
Weight gain	52(7.1)
Asthenia	40(5.4)
Ataxia	33(4.5)
Dry mouth	32(4.4)
Nausea	31(4.2)
Total Treatment Related	**440(59.9)**
Uncontrolled NeP Studies (015, 033, 061, 074, 134, 165, 174, 197, 198)	
	N=1899
Dizziness	285(15.0)
Somnolence	190(10.0)
Peripheral edema	171(9.0)
Weight gain	132(7.0)
Asthenia	97(5.1)
Total Treatment Related	**1003(52.8)**

Table 9.7:

Summary of Withdrawals due to Adverse Events by Decreasing Frequency
Controlled Neuropathic Pain Studies (Studies 1008-014,-029,-030,-040,-045,-127,-131,-132,-149,-173,-196) - Combined Regimens

Pregabalin Summary of Clinical Safety: Neuropathic Pain, Adjunctive Therapy for Partial Seizures, and Generalized Anxiety Disorder

	Number of Patients (%)					
Preferred Term	**Placebo** N=857	**75 mg/day PGB** N=161	**150 mg/day PGB** N=514	**300 mg/day PGB** N=633	**600 mg/day PGB** N=523	**All PGB** N=1831
Dizziness	5 (0.6)	0 (0.0)	14 (2.7)	18 (2.8)	33 (6.3)	65 (3.5)
Somnolence	1 (0.1)	0 (0.0)	6 (1.2)	17 (2.7)	25 (4.8)	48 (2.6)
Confusion	2 (0.2)	0 (0.0)	2 (0.4)	7 (1.1)	13 (2.5)	22 (1.2)
Asthenia	3 (0.4)	2 (1.2)	5 (1.0)	4 (0.6)	6 (1.1)	17 (0.9)
Peripheral edema	2 (0.2)	0 (0.0)	2 (0.4)	9 (1.4)	6 (1.1)	17 (0.9)
Ataxia	0 (0.0)	0 (0.0)	1 (0.2)	7 (1.1)	6 (1.1)	14 (0.8)
Headache	7 (0.8)	1 (0.6)	2 (0.4)	0 (0.0)	8 (1.5)	11 (0.6)
Abnormal gait	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.6)	6 (1.1)	10 (0.5)
Vertigo	1 (0.1)	0 (0.0)	1 (0.2)	5 (0.8)	2 (0.4)	8 (0.4)
Dry mouth	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.3)	7 (0.4)
Face edema	2 (0.2)	0 (0.0)	1 (0.2)	3 (0.5)	3 (0.6)	7 (0.4)
Nausea	6 (0.7)	0 (0.0)	3 (0.6)	3 (0.5)	1 (0.2)	7 (0.4)
Amblyopia	2 (0.2)	0 (0.0)	1 (0.2)	2 (0.3)	3 (0.6)	6 (0.3)
Speech disorder	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	4 (0.8)	6 (0.3)
Hallucinations	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	4 (0.8)	5 (0.3)
Incoordination	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)	4 (0.8)	5 (0.3)
Pain	2 (0.2)	2 (1.2)	3 (0.6)	0 (0.0)	0 (0.0)	5 (0.3)
Thinking abnormal	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.3)	3 (0.6)	5 (0.3)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.6)	4 (0.2)

Dose (eg, 150 mg) is the total daily dose in mg/day, given with a BID or TID regimen.

Table 9.8:

Summary of Withdrawals due to Adverse Events by Decreasing Frequency
Uncontrolled Extensions of Neuropathic Pain Studies (Studies 1008-015, -033, -061, -074, -134, -165, -174, -197, -198)

Pregabalin Summary of Clinical Safety: Neuropathic Pain, Adjunctive Therapy for Partial Seizures, and Generalized Anxiety Disorder

	Number of Patients (%)
	Any Dose Pregabalin
Preferred Term	N=1899
Peripheral edema	36 (1.9)
Dizziness	25 (1.3)
Somnolence	21 (1.1)
Weight gain	18 (0.9)
Nausea	10 (0.5)
Abdominal pain	9 (0.5)
Amblyopia	9 (0.5)
Diarrhea	9 (0.5)
Accidental injury	8 (0.4)
Asthenia	8 (0.4)
Confusion	8 (0.4)
Myocardial infarct	8 (0.4)
Ataxia	6 (0.3)
Constipation	6 (0.3)
Headache	6 (0.3)
Visual field defect	6 (0.3)
Abnormal gait	5 (0.3)
Amnesia	5 (0.3)
Congestive heart failure	5 (0.3)
Pain	5 (0.3)
Rash	5 (0.3)

Table 9.9:

Mean Change From Baseline for Clinical Laboratory Parameters With a Statistically Significant Difference Between Pregabalin and Placebo: Controlled NeP Studies—Combined Regimens

Test Name	Units	Placebo	PGB 150 mg/day	PGB 300 mg/day	PGB 600 mg/day	All PGB[a]
Hemoglobin	g/dL	-0.094	**-0.212**	**-0.224**	**-0.254**	**-0.223**
Hematocrit	%	-0.337	-0.524	**-0.473**	**-0.652**	**-0.531**
RBC	$\times 10^6/\mu L$	-0.046	-0.06	-0.062	**-0.082**	**-0.065**
WBC	$\times 10^3/\mu L$	0.0342	**-0.126**	**-0.257**	**-0.111**	**-0.178**
Differential-Neutrophils	%	-0.254	-0.944	**-1.139**	-0.713	**-0.933**
Absolute Neutrophils	$\times 10^3/\mu L$	0.0239	**-0.115**	**-0.228**	**-0.114**	**-0.165**
Differential-Lymphocytes	%	0.193	0.901	**1.055**	0.476	**0.803**
Differential Eosinophils	%	-0.004	**0.0984**	**0.0929**	**0.1648**	**0.1169**
Absolute-Basophils	$\times 10^3/\mu L$	-0.001	-0.006	**-0.005**	0.001	-0.003
Platelets	$\times 10^3/\mu L$	0.218	**-6.628**	**-12.95**	**-14.64**	**-11.01**
Glycosylated Hemoglobin	%	-0.043	0.0914	**0.0919**	0.0189	0.0484
Glucose-Non fasting	mg/dL	15.612	**0.9337**	**-3.358**	13.382	**1.4023**
CK-Creatine Kinase	U/L	-0.641	**7.6216**	**9.7996**	**13.281**	**9.9084**
Creatinine	mg/dL	0.0087	0.0045	0.0137	**0.0282**	0.014
Uric Acid	mg/dL	0.0438	**0.0898**	**0.2132**	**0.2098**	**0.1624**
BUN	mg/dL	0.2009	**0.5766**	**0.8526**	**1.3436**	**0.8315**
Bilirubin-Total	mg/dL	-0.012	**-0.026**	**-0.032**	**-0.031**	**-0.028**
Albumin	g/dL	-0.034	**-0.07**	**-0.085**	**-0.108**	**-0.087**
Total Protein	g/dL	-0.037	**-0.097**	**-0.078**	**-0.099**	**-0.091**
Alkaline Phosphatase	U/L	-0.429	4.0906	**5.5605**	**5.0136**	**4.372**
AST	U/L	-0.44	**0.7303**	**1.1487**	**0.2393**	**0.6392**
HDL Cholesterol	mg/dL	0.3883	**-0.832**	**-1.131**	**-1.854**	**-1.218**
Sodium	mEq/L	-0.121	-0.173	**0.3219**	**0.179**	0.077
Calcium	mg/dL	-0.019	**-0.087**	**-0.092**	**-0.089**	**-0.09**
Amylase	U/L	-0.934	-0.715	**-0.359**	**-1.14**	**-0.629**
Chloride	mEq/L	0.2639	0.3583	**1.0147**	0.5467	**0.6113**
Urine Protein	mg/dL	-4.698	-4.147	0.9461	**-2.809**	**-1.895**
Urine WBC	/HPF	1.1	0.3448	**-0.427**	0.375	**0.0386**

Values in **bold** = Statistically significantly different ($p < 0.05$) from placebo by Wilcoxon Rank-Sum test.

[a] Includes all other doses of pregabalin (ie, 75 mg/day).

Table 9.10:

Summary of Adverse Events by Intrinsic Factors: Controlled NeP Studies (014, 029, 030, 040, 045, 127, 131, 132, 149, 173, 196)

Placebo		All PGB	
Male	**Female**	**Male**	**Female**
N=458	N=399	N=974	N=857
234(51.1)	245(61.4)	657(67.5)	644(75.1)
Premenopausal	**Postmenopausal**	**Premenopausal**	**Postmenopausal**
N=41	N=358	N=75	N=782
25(61.0)	220(61.5)	52(69.3)	592(75.7)
≥18 to <65	**≥65 to <75**	**≥75**	**≥18 to <65**	**≥65 to <75**	**≥75**
N=376	N=275	N=206	N=851	N=528	N=452
207(55.1)	149(54.2)	123(59.7)	565(66.4)	386(73.1)	350(77.4)
White	**Black**	**Hispanic**	**Other**	**White**	**Black**	**Hispanic**	**Other**
N=810	N=18	N=17	N=12	N=1718	N=44	N=42	N=27
455(56.2)	9(50.0)	11(64.7)	4(33.3)	1234(71.8)	25(56.8)	28(66.7)	14(51.9)

Table 9.11.1:

Summary of Exposure to Study Medication by Treatment Group: Controlled Epilepsy Studies (009, 011, 034)

Total Exposure Time[a]	[Number of Patients]													
	Total Daily Dose of Pregabalin in mg/day (Regimen)													
	Placebo N = 294		50 BID N = 88		150 BID N = 86		150 TID N = 99		300 BID N = 90		600 BID N = 192		600 TID N = 203		Any Dose N = 758	
≥1 Day	294	(100.0)	88	(100.0)	86	(100.0)	99	(100.0)	90	(100.0)	192	(100.0)	203	(100.0)	758	(100.0)
≥1 Week	289	(98.3)	88	(100.0)	86	(100.0)	97	(98.0)	82	(91.1)	170	(88.5)	197	(97.0)	720	(95.0)
≥2 Weeks	286	(97.3)	84	(95.5)	85	(98.8)	93	(93.9)	81	(90.0)	164	(85.4)	185	(91.1)	692	(91.3)
≥4 Weeks	278	(94.6)	81	(92.0)	82	(95.3)	93	(93.9)	79	(87.8)	154	(80.2)	171	(84.2)	660	(87.1)
≥6 Weeks	275	(93.5)	79	(89.8)	82	(95.3)	90	(90.9)	74	(82.2)	146	(76.0)	162	(79.8)	633	(83.5)
≥8 Weeks	266	(90.5)	79	(89.8)	81	(94.2)	89	(89.9)	74	(82.2)	143	(74.5)	160	(78.8)	626	(82.6)
≥10 Weeks	258	(87.8)	78	(88.6)	80	(93.0)	88	(88.9)	72	(80.0)	136	(70.8)	155	(76.4)	609	(80.3)
≥12 Weeks	169	(57.5)	49	(55.7)	43	(50.0)	67	(67.7)	42	(46.7)	104	(54.2)	121	(59.6)	426	(56.2)

[a] The total exposure time includes titration and fixed-dose phases. Study days on which patients received zero dose during the study are included.

Table 9.11.2:

Summary of Cumulative Exposure to Pregabalin by Dosage Range: Combined Controlled and Uncontrolled Epilepsy Studies (007, 008, 009, 010, 011, 012, 034, 035, 145)

	Total Daily Dose of Pregabalin (mg/day)								
	0[a]	>0 to <75	75 to <150	150 to <300	300 to <450	450 to <600	≥600	Any dose >0[b]	Any Dose[c]
≥24 Weeks	1	5	17	87	303	313	576	1204	1206
≥36 Weeks	0	3	13	54	223	219	496	1059	1059
≥52 Weeks	0	1	9	40	167	154	401	918	918
≥104 Weeks	0	1	3	16	67	73	220	557	557
≥156 Weeks	0	0	0	3	26	33	82	268	269
Total Patient-Years	4.05	30.09	47.85	195.08	521.43	551.59	1110.36	2456.39	2460.51

[a] Indicates days off pregabalin, ie, day when pregabalin was not taken. Does not refer to days on placebo or days when dose was unknown.
[b] Indicates days on all specified pregabalin doses. Does not include days off drug or days when pregabalin dose was unknown.
[c] Indicates treatment duration, including days off drug and days when dose was unknown.

Table 9.12:

Summary of Adverse Events Occurring in ≥2% of All Pregabalin-Treated Patients by Decreasing Frequency: Controlled Epilepsy Studies (009, 011, 034)

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Preferred Term	[Number of Patients (%)]						
	Placebo N = 294	150 mg/day PGB BID N = 86	150 mg/day PGB TID N = 99	300 mg/day PGB BID N = 90	600 mg/day PGB BID N = 192	600 mg/day PGB TID N = 203	All PGB[a] N = 758
Dizziness	31 (10.5)	14 (16.3)	19* (19.2)	28* (31.1)	83* (43.2)	67* (33.0)	219* (28.9)
Somnolence	32 (10.9)	15 (17.4)	6 (6.1)	16 (17.8)	57* (29.7)	55* (27.1)	158* (20.8)
Ataxia	12 (4.1)	9* (10.5)	2 (2.0)	9 (10.0)	30* (15.6)	47* (23.2)	100* (13.2)
Asthenia	24 (8.2)	7 (8.1)	13 (13.1)	11 (12.2)	23 (12.0)	26 (12.8)	85 (11.2)
Weight Gain	4 (1.4)	2 (2.3)	7* (7.1)	6* (6.7)	32* (16.7)	31* (15.3)	79* (10.4)
Accidental Injury	16 (5.4)	5 (5.8)	8 (8.1)	10 (11.1)	23* (12.0)	16 (7.9)	75* (9.9)
Headache	34 (11.6)	8 (9.3)	6 (6.1)	5 (5.6)	20 (10.4)	24 (11.8)	69 (9.1)
Amblyopia[b]	13 (4.4)	3 (3.5)	7 (7.1)	7 (7.8)	20* (10.4)	28* (13.8)	68* (9.0)
Diplopia	11 (3.7)	4 (4.7)	6 (6.1)	6 (6.7)	19* (9.9)	28* (13.8)	64* (8.4)
Tremor	11 (3.7)	3 (3.5)	3 (3.0)	6 (6.7)	21* (10.9)	21* (10.3)	57* (7.5)
Thinking Abnormal	6 (2.0)	6* (7.0)	1 (1.0)	7* (7.8)	14* (7.3)	22* (10.8)	53* (7.0)
Infection	15 (5.1)	8 (9.3)	6 (6.1)	5 (5.6)	10 (5.2)	9 (4.4)	46 (6.1)
Amnesia	7 (2.4)	3 (3.5)	3 (3.0)	2 (2.2)	11 (5.7)	12 (5.9)	33 (4.4)
Nausea	20 (6.8)	2 (2.3)	8 (8.1)	2 (2.2)	7 (3.6)	11 (5.4)	32 (4.2)
Peripheral Edema	6 (2.0)	3 (3.5)	3 (3.0)	3 (3.3)	10 (5.2)	12* (5.9)	32 (4.2)
Speech Disorder	2 (0.7)	2 (2.3)	0 (0.0)	2 (2.2)	16* (8.3)	12* (5.9)	32* (4.2)
Dry Mouth	4 (1.4)	1 (1.2)	1 (1.0)	2 (2.2)	15* (7.8)	10* (4.9)	31* (4.1)
Incoordination	3 (1.0)	2 (2.3)	0 (0.0)	3 (3.3)	12* (6.3)	12* (5.9)	31* (4.1)
Increased Appetite	3 (1.0)	2 (2.3)	1 (1.0)	3 (3.3)	17* (8.9)	7 (3.4)	31* (4.1)
Constipation	6 (2.0)	0 (0.0)	1 (1.0)	1 (1.1)	14* (7.3)	12* (5.9)	30 (4.0)
Abnormal Vision	2 (0.7)	3 (3.5)	2 (2.0)	1 (1.1)	9* (4.7)	10* (4.9)	27* (3.6)

* Statistically significantly different from placebo based on odds ratio or Fisher's Exact test ($p \leq 0.05$).

[a] Includes all other doses of pregabalin (ie, 50 mg/day).

[b] Amblyopia was reported by the investigators mainly as blurred/blurry vision.

Table 9.12 (cont.):

Summary of Adverse Events Occurring in ≥2% of All Pregabalin-Treated Patients by Decreasing Frequency: Controlled Epilepsy Studies (009, 011, 034)

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Preferred Term	[Number of Patients (%)]													
	Placebo N = 294		150 mg/day PGB BID N = 86		150 mg/day PGB TID N = 99		300 mg/day PGB BID N = 90		600 mg/day PGB BID N = 192		600 mg/day PGB TID N = 203		All PGB[a] N = 758	
Pain	10	(3.4)	3	(3.5)	2	(2.0)	2	(2.2)	7	(3.6)	11	(5.4)	27	(3.6)
Abnormal Gait	1	(0.3)	1	(1.2)	0	(0.0)	3*	(3.3)	12*	(6.3)	9*	(4.4)	26*	(3.4)
Twitching	2	(0.7)	0	(0.0)	0	(0.0)	4*	(4.4)	11*	(5.7)	10*	(4.9)	25*	(3.3)
Confusion	5	(1.7)	2	(2.3)	0	(0.0)	2	(2.2)	10	(5.2)	10	(4.9)	24	(3.2)
Abdominal Pain	10	(3.4)	2	(2.3)	6	(6.1)	2	(2.2)	3	(1.6)	6	(3.0)	22	(2.9)
Visual Field Defect	5	(1.7)	6*	(7.0)	0	(0.0)	6*	(6.7)	5	(2.6)	2	(1.0)	20	(2.6)
Nervousness	2	(0.7)	2	(2.3)	3	(3.0)	1	(1.1)	9*	(4.7)	4	(2.0)	19	(2.5)
Nystagmus	5	(1.7)	0	(0.0)	1	(1.0)	4	(4.4)	6	(3.1)	6	(3.0)	19	(2.5)
Flu Syndrome	9	(3.1)	0	(0.0)	5	(5.1)	1	(1.1)	5	(2.6)	4	(2.0)	18	(2.4)
Vomiting	6	(2.0)	1	(1.2)	4	(4.0)	1	(1.1)	8	(4.2)	4	(2.0)	18	(2.4)
Paresthesia	3	(1.0)	1	(1.2)	2	(2.0)	0	(0.0)	6	(3.1)	5	(2.5)	16	(2.1)
Chest Pain	5	(1.7)	1	(1.2)	0	(0.0)	1	(1.1)	5	(2.6)	6	(3.0)	15	(2.0)
Diarrhea	11	(3.7)	1	(1.2)	1	(1.0)	0	(0.0)	5	(2.6)	4	(2.0)	15	(2.0)
Myoclonus	1	(0.3)	1	(1.2)	0	(0.0)	0	(0.0)	7*	(3.6)	7*	(3.4)	15	(2.0)
Total With AEs	**206**	**(70.1)**	**61**	**(70.9)**	**75**	**(75.8)**	**76**	**(84.4)**	**181**	**(94.3)**	**185**	**(91.1)**	**637**	**(84.0)**

* Statistically significantly different from placebo based on odds ratio or Fisher's Exact test ($p < 0.05$).

[a] Includes all other doses of pregabalin (ie, 50 mg/day).

Table 9.13:

Summary of Common Adverse Events in Study 009

Preferred Term	[Number of Patients (%)] Placebo N = 98		PGB 600 mg/day (BID) N = 103		PGB 600 mg/day (TID) N = 111	
Any Adverse Event	**71**	**(72.4)**	**102**	**(99.0)**	**105**	**(94.6)**
Dizziness	14	(14.3)	45	(43.7)	43	(38.7)
Somnolence	14	(14.3)	32	(31.1)	28	(25.2)
Ataxia	6	(6.1)	17	(16.5)	31	(27.9)
Weight Gain	2	(2.0)	21	(20.4)	18	(16.2)
Amblyopia[a]	5	(5.1)	11	(10.7)	19	(17.1)
Headache	6	(6.1)	15	(14.6)	13	(11.7)
Asthenia	5	(5.1)	14	(13.6)	13	(11.7)
Diplopia	4	(4.1)	12	(11.7)	15	(13.5)
Thinking Abnormal	1	(1.0)	10	(9.7)	16	(14.4)
Tremor	5	(5.1)	11	(10.7)	11	(9.9)
Accidental Injury	7	(7.1)	12	(11.7)	9	(8.1)
Speech Disorder	2	(2.0)	9	(8.7)	10	(9.0)
Amnesia	2	(2.0)	8	(7.8)	10	(9.0)
Confusion	4	(4.1)	8	(7.8)	8	(7.2)
Constipation	3	(3.1)	8	(7.8)	8	(7.2)
Increased Appetite	3	(3.1)	10	(9.7)	5	(4.5)
Peripheral Edema	3	(3.1)	8	(7.8)	6	(5.4)
Dry Mouth	3	(3.1)	6	(5.8)	7	(6.3)
Infection	3	(3.1)	7	(6.8)	6	(5.4)
Twitching	2	(2.0)	5	(4.9)	8	(7.2)
Incoordination	2	(2.0)	3	(2.9)	9	(8.1)
Pain	5	(5.1)	4	(3.9)	8	(7.2)
Nausea	6	(6.1)	5	(4.9)	6	(5.4)
Events That Led to Withdrawal	**7**	**(7.1)**	**27**	**(26.2)**	**21**	**(18.9)**
Dizziness	0	(0.0)	7	(6.8)	7	(6.3)
Ataxia	0	(0.0)	3	(2.9)	7	(6.3)
Somnolence	0	(0.0)	6	(5.8)	4	(3.6)
Confusion	0	(0.0)	5	(4.9)	3	(2.7)
Tremor	0	(0.0)	4	(3.9)	2	(1.8)
Thinking Abnormal	0	(0.0)	2	(1.9)	3	(2.7)
Accidental Injury	0	(0.0)	2	(1.9)	2	(1.8)
Diplopia	1	(1.0)	3	(2.9)	1	(0.9)

[a] Amblyopia was reported by the investigators mainly as blurred/blurry vision.

Table 9.14:

Summary of Treatment-Related Events Occurring in ≥4% of All Pregabalin-Treated Patients by Decreasing Frequency: Controlled Epilepsy Studies (009, 011, 034)

Preferred Term	[Number of Patients (%)]													
	Placebo N = 294		150 mg/day PGB BID N = 86		150 mg/day PGB TID N = 99		300 mg/day PGB BID N = 90		600 mg/day PGB BID N = 192		600 mg/day PGB TID N = 203		All PGB[a] N = 758	
Dizziness	28	(9.5)	12	(14.0)	18	(18.2)	27	(30.0)	80	(41.7)	63	(31.0)	208	(27.4)
Somnolence	26	(8.8)	14	(16.3)	6	(6.1)	16	(17.8)	56	(29.2)	49	(24.1)	150	(19.8)
Ataxia	11	(3.7)	8	(9.3)	2	(2.0)	8	(8.9)	29	(15.1)	46	(22.7)	96	(12.7)
Asthenia	21	(7.1)	6	(7.0)	12	(12.1)	11	(12.2)	23	(12.0)	26	(12.8)	83	(10.9)
Weight Gain	4	(1.4)	2	(2.3)	7	(7.1)	6	(6.7)	32	(16.7)	29	(14.3)	77	(10.2)
Amblyopia[b]	11	(3.7)	3	(3.5)	7	(7.1)	7	(7.8)	19	(9.9)	28	(13.8)	67	(8.8)
Diplopia	10	(3.4)	4	(4.7)	5	(5.1)	6	(6.7)	17	(8.9)	28	(13.8)	61	(8.0)
Tremor	9	(3.1)	3	(3.5)	2	(2.0)	6	(6.7)	20	(10.4)	21	(10.3)	55	(7.3)
Headache	20	(6.8)	4	(4.7)	3	(3.0)	4	(4.4)	13	(6.8)	19	(9.4)	46	(6.1)
Thinking Abnormal	6	(2.0)	6	(7.0)	1	(1.0)	7	(7.8)	13	(6.8)	17	(8.4)	45	(5.9)
Incoordination	2	(0.7)	2	(2.3)	0	(0.0)	3	(3.3)	12	(6.3)	12	(5.9)	31	(4.1)
Increased Appetite	3	(1.0)	2	(2.3)	1	(1.0)	3	(3.3)	17	(8.9)	7	(3.4)	31	(4.1)
Speech Disorder	2	(0.7)	2	(2.3)	0	(0.0)	2	(2.2)	16	(8.3)	11	(5.4)	31	(4.1)
Dry Mouth	4	(1.4)	0	(0.0)	1	(1.0)	2	(2.2)	15	(7.8)	10	(4.9)	30	(4.0)
Total Treatment-Related	**135**	**(45.9)**	**46**	**(53.5)**	**48**	**(48.5)**	**62**	**(68.9)**	**164**	**(85.4)**	**161**	**(79.3)**	**521**	**(68.7)**

[a] Includes all other doses of pregabalin (ie, 50 mg/day).

[b] Amblyopia was reported by the investigators mainly as blurred/blurry vision.

Table 9.15:

Summary of Adverse Events Occurring in ≥2% of All Pregabalin-Treated Patients by Decreasing Frequency: Uncontrolled Epilepsy Studies (008, 010, 012, 035)

	[Number (%) of Patients]		
Preferred Term	All Pregabalin N = 1480	**Preferred Term**	All Pregabalin N = 1480
Dizziness	485 (32.8)	Urinary tract infection	74 (5.0)
Somnolence	392 (26.5)	Hypesthesia	68 (4.6)
Accidental injury	380 (25.7)	Nystagmus	68 (4.6)
Weight gain	329 (22.2)	Visual field defect	66 (4.5)
Infection	284 (19.2)	Chest pain	65 (4.4)
Asthenia	274 (18.5)	Emotional lability	65 (4.4)
Headache	264 (17.8)	Paresthesia	65 (4.4)
Pain	223 (15.1)	Incoordination	63 (4.3)
Ataxia	200 (13.5)	Speech disorder	61 (4.1)
Amblyopia[a]	198 (13.4)	Arthralgia	59 (4.0)
Diplopia	167 (11.3)	Sinusitis	59 (4.0)
Thinking abnormal	162 (10.9)	Twitching	59 (4.0)
Nausea	145 (9.8)	Abnormal vision	57 (3.9)
Tremor	141 (9.5)	Fever	52 (3.5)
Peripheral edema	124 (8.4)	Abnormal gait	50 (3.4)
Rash	121 (8.2)	Rhinitis	48 (3.2)
Amnesia	119 (8.0)	Myoclonus	45 (3.0)
Flu syndrome	116 (7.8)	Bronchitis	43 (2.9)
Insomnia	106 (7.2)	Otitis media	42 (2.8)
Depression	100 (6.8)	Conjunctivitis	40 (2.7)
Nervousness	100 (6.8)	Dry mouth	38 (2.6)
Constipation	91 (6.1)	Allergic reaction	37 (2.5)
Anxiety	90 (6.1)	Hypertension	36 (2.4)
Confusion	90 (6.1)	Hostility	34 (2.3)
Back pain	89 (6.0)	Anorexia	33 (2.2)
Vomiting	89 (6.0)	Pneumonia	33 (2.2)
Pharyngitis	85 (5.7)	Vertigo	33 (2.2)
Abdominal pain	83 (5.6)	Eye disorder	31 (2.1)
Dyspepsia	83 (5.6)	Increased appetite	31 (2.1)
Ecchymosis	83 (5.6)	Pruritus	30 (2.0)
Diarrhea	82 (5.5)	Acne	29 (2.0)
Total Patients With Any Adverse Event			**1399 (94.5)**

[a] Amblyopia was reported by the investigators mainly as blurred/blurry vision.

Table 9.16:

Summary of Treatment-Related Adverse Events Occurring in ≥4 Pregabalin-Treated Patients by Decreasing Frequency: Uncontrolled Epilepsy Studies (008, 010, 012, 035)

	[Number (%) of Patients]
Preferred Term	All Pregabalin N = 1480
Dizziness	389(26.3)
Somnolence	318(21.5)
Weight Gain	315(21.3)
Asthenia	200(13.5)
Ataxia	158(10.7)
Amblyopia[a]	150(10.1)
Diplopia	126(8.5)
Headache	112(7.6)
Thinking Abnormal	111(7.5)
Tremor	95(6.4)
Amnesia	79(5.3)
Nausea	68(4.6)
Total Treatment Related	**1177(79.5)**

[a] Amblyopia was reported by the investigators mainly as blurred/blurry vision.

Table 9.17.1:

Median Time to Onset[a] of Common Adverse Events– Controlled Epilepsy Studies (009, 011, 034)—Combined Regimens

Adverse Event Preferred Term	Placebo N = 294			Pregabalin 150 mg/day N = 185			Pregabalin 300 mg/day N = 90			Pregabalin 600 mg/day N = 395		
	n	(%)	Days	n	(%)	Days	n	(%)	Days	n	(%)	Days
Somnolence	32	(10.9)	13	21	(11.4)	1	16	(17.8)	2	112	(28.4)	2
Dizziness	31	(10.5)	7	33	(17.8)	3	28	(31.1)	0	150	(38.0)	3
Asthenia	24	(8.2)	7	20	(10.8)	5	11	(12.2)	0	49	(12.4)	3
Thinking Abnormal	6	(2.0)	14	7	(3.8)	20	7	(7.8)	1	36	(9.1)	4
Ataxia	12	(4.1)	22	11	(5.9)	6	9	(10.0)	1	77	(19.5)	5
Diplopia	11	(3.7)	31	10	(5.4)	7	6	(6.7)	1	47	(11.9)	5
Amblyopia[b]	13	(4.4)	43	10	(5.4)	3	7	(7.8)	2	48	(12.2)	6
Tremor	11	(3.7)	23	6	(3.2)	42	6	(6.7)	11	42	(10.6)	6
Weight Gain	4	(1.4)	19	9	(4.9)	0	6	(6.7)	14	63	(15.9)	13
Headache	34	(11.6)	13	14	(7.6)	8	5	(5.6)	7	44	(11.1)	13
Accidental Injury	16	(5.4)	26	13	(7.0)	20	10	(11.1)	26	39	(9.9)	35
Infection	15	(5.1)	20	14	(7.6)	22	5	(5.6)	33	19	(4.8)	40

[a] In days from beginning of double-blind study medication, sorted by increasing median time to onset in the 600 mg/day group; median among patients who had the adverse event.

[b] Amblyopia was reported by the investigators mainly as blurred/blurry vision.

Table 9.17.2:

Median Duration[a] of Common Adverse Events: Completers[b]—Controlled Epilepsy Studies (009, 011, 034)—Combined Regimens

Adverse Event Preferred Term	Placebo N = 252			Pregabalin 150 mg/day N = 169			Pregabalin 300 mg/day N = 71			Pregabalin 600 mg/day N = 286		
	n	(%)	Days	n	(%)	Days	n	(%)	Days	n	(%)	Days
Thinking Abnormal	6	(2.4)	41	7	(4.1)	70	4	(5.6)	38	25	(8.7)	78
Increased Appetite	2	(0.8)	80	3	(1.8)	81	3	(4.2)	51	23	(8.0)	76
Weight Gain	4	(1.6)	59	9	(5.3)	74	5	(7.0)	29	59	(20.6)	71
Somnolence	26	(10.3)	50	19	(11.2)	61	9	(12.7)	26	77	(26.9)	68
Asthenia	22	(8.7)	51	15	(8.9)	31	8	(11.3)	21	34	(11.9)	63
Ataxia	10	(4.0)	41	10	(5.9)	28	6	(8.5)	22	50	(17.5)	49
Tremor	9	(3.6)	43	4	(2.4)	14	4	(5.6)	43	32	(11.2)	43
Peripheral Edema	6	(2.4)	61	6	(3.6)	40	2	(2.8)	22	21	(7.3)	38
Amblyopia[c]	11	(4.4)	11	9	(5.3)	48	4	(5.6)	3	34	(11.9)	31
Diplopia	9	(3.6)	35	7	(4.1)	3	4	(5.6)	8	31	(10.8)	29
Dizziness	25	(9.9)	43	27	(16.0)	14	23	(32.4)	12	97	(33.9)	28
Accidental Injury	12	(4.8)	19	12	(7.1)	25	9	(12.7)	12	30	(10.5)	17
Headache	27	(10.7)	17	12	(7.1)	5	2	(2.8)	3	33	(11.5)	17
Infection	13	(5.2)	8	14	(8.3)	13	5	(7.0)	6	18	(6.3)	15

[a] In days, sorted by decreasing median duration in the 600 mg/day group; median among patients who had the adverse event.

[b] Patients who completed the study according to the Patient Status CRF

[c] Amblyopia was reported by the investigators mainly as blurred/blurry vision.

Table 9.18:

Mean Change From Baseline for Clinical Laboratory Parameters With a Statistically Significant Difference Between Pregabalin and Placebo: Controlled Epilepsy Studies (009, 011, 034)—Combined Regimens

Test	Units	Placebo	150 mg/day PGB	300 mg/day PGB	600 mg/day PGB	All PGB[a]
Hemoglobin	g/dL	-0.082	-0.071	**-0.226**	-0.08	-0.103
Differential-Neutrophils	%	0.0267	**-1.491**	-0.092	-0.743	**-0.964**
Differential-Basophils	%	-0.084	-0.202	**-0.429**	-0.186	-0.196
Absolute -Basophils	$\times 10^3/\mu L$	-0.006	**-0.03**	-0.025	-0.016	-0.017
Platelets	$\times 10^3/\mu L$	6.0103	**-4.659**	**-6.114**	**-8.454**	**-4.974**
CK-Creatine Kinase	U/L	-1.234	**214.73**	-0.674	**26.189**	**62.725**
Uric Acid	mg/dL	0.016	**0.162**	-0.027	**0.118**	0.103
BUN	mg/dL	-0.014	-0.049	0.1486	**0.6784**	0.2895
Bilirubin-Total	mg/dL	-0.015	**0.017**	-0.036	0.0024	-1.30E-05
Albumin	g/dL	-0.005	0.0126	-0.038	**-0.071**	**-0.043**
Total Protein	g/dL	-0.032	0.0159	**-0.113**	-0.066	-0.051
Alkaline Phosphatase	U/L	-0.918	2.0275	-7.92	**5.3963**	2.125
AST	U/L	1.127	1.473	-2.011	**2.126**	1.385
Sodium	mEq/L	-0.366	-0.06	-0.534	**0.1654**	**-0.029**
Potassium	mEq/L	-0.002	0.0527	-0.043	**0.0756**	**0.0495**
Calcium	mg/dL	-0.093	-0.031	**-0.156**	-0.111	-0.095
Chloride	mEq/L	-0.086	0.2418	**0.8295**	**0.7585**	**0.6671**

Values in **bold** = Statistically significantly difference ($p < 0.05$) from placebo by Wilcoxon Rank-Sum test.

[a] Includes all other doses of pregabalin (ie, 50 mg/day).

Table 9.19:

Summary of Adverse Events by Intrinsic Factors: Controlled Epilepsy Studies (009, 011, 035)

Placebo				All PGB			
Male	**Female**			**Male**	**Female**		
N = 156	N = 138			N = 363	N = 395		
108 (69.2)	98 (71.0)			288(79.3)	349 (88.4)		
Premenopausal	**Postmenopausal**			**Premenopausal**	**Postmenopausal**		
N = 99	N = 39			N = 297	N = 96		
69 (69.7)	29 (74.4)			256(86.2)	92 (95.8)		
≤16	**≥17 to <65**	**≥65 to <75**	**≥75**	**≤16**	**≥17 to <65**	**≥65 to <75**	**≥75**
N = 1	N = 285	N = 7	N = 1	N = 10	N = 736	N = 10	N = 2
0 (0.0)	202 (70.9)	4 (57.1)	0 (0.0)	6(60.0)	619 (84.1)	10 (100)	2 (100)
White	**Black**	**Hispanic**	**Other**	**White**	**Black**	**Hispanic**	**Other**
N = 260	N = 12	N = 12	N = 10	N = 657	N = 37	N = 42	N = 22
186 (71.5)	10 (83.3)	6 (50.0)	4 (40.0)	551(83.9)	31 (83.8)	36 (85.7)	19 (86.4)

Table 9.20:

Patient Characteristics and Epilepsy History of 6 Patients With Unexpected Generalized Seizures

Report Date (Country) WAERS number	Patient No.	Age (yr)/ Sex	Epilepsy History	Epilepsy Duration (yr)	Time Since Last Gen Sz	Approx Seizure Freq	Acute Seizure Type	Study Day	Preseizure Dose of PGB
Dental pain study (1008-027)									
3 Sep 98 (USA) 001-1008-980012	1064	23/F	IGE[a]	N/A	13 yr	--	Tonic	2	300 mg on Day 1 500 mg on Day 2[b]
Valproic acid interaction study (1008-018)									
18 May 99 (France) 033-1008-990002	5	28/F	IGE, P	18	4 yr	q3-4 mo (P)	GTC	1	Single dose of 200 mg
18 May 99 (France) 033-1008-990003	8	24/M	IGE	5	4 mo	q3 mo (G)	GTC	1	2 Doses of 200 mg (8 hr apart)
18 May 99 (France) 033-1008-990004	108	27/F	IGE	12	4 mo	q3-4 mo (G)	GTC	2	3 Doses of 200 mg (8 hr apart)
Carbamazepine interaction study (1008-019)									
16 Jun 99 (UK) 044-1008-990003	6	25/F	P	11	2 yr	q1 wk (CP)	GTC	2	3 Doses of 200 mg (8 hr apart)
21 Jun 99 (UK) 044-1008-990004	8	23/F	P	6	5 yr	q1 yr (CP)	SGTC	1	Single dose of 200 mg

IGE = Idiopathic generalized epilepsy; P = Partial epilepsy; Gen. or G = Generalized; Approx = Approximate; Freq. = Frequency; N/A = Not applicable; PGB = Pregabalin; Sz = Seizure; GTC = Generalized tonic-clonic seizure; SGTC = Secondarily generalized tonic-clonic seizure; CP = Complex partial; q = Every.

[a] Diagnosed as idiopathic epilepsy following the study. Historic seizure was loss of consciousness induced by strobe light.

[b] Study medication consisted of a single dose of pregabalin 300 mg on Day 1. On Day 2 patient received a single dose of pregabalin 300 mg, and approximately 5 hours later she received a single dose of 200 mg.

Table 9.21.1:

Analysis Population: Number (%) of SGTC Patients

	Study 1008-009		Study 1008-011		Study 1008-034	
	Placebo N = 98	All Pregabalin N = 214	Placebo N = 96	All Pregabalin N = 191	Placebo N = 100	All Pregabalin N = 353
SGTC Patients N (%)	45 (46)	81 (35)	49 (51)	83 (43)	26 (26)	125 (35)

Table 9.21.2:

Percent SGTC Patients[a] on Placebo or Pregabalin That Were Any Worse in SGTC Rate During the First 2 Days, the First Week, the First Month, or all 3 Months of Double-Blind

Interval	Placebo Median[b] (range)%	Pregabalin Median[b] (range)%
2 Days	15 (0-17)	14 (6-28)
1 Week	31 (18-40)	26 (8-35)
1 Month	44 (33-47)	28 (21-47)
3 Month	44 (35-53)	31 (22-55)

[a] An SGTC patient is defined as any patient that received at least one dose of study medication and had any SGTCs during baseline and/or double-blind.

[b] Median and ranges are from data in Appendix B.

Table 9.22: Other safety studies: Pregabalin vs alprazolam and placebo in healthy volunteers

Study nos, location investigators	Study design	Subjects demographics	Dosage, duration, route, form of study drugs	Endpoints	Efficacy results	Safety/AEs
1008-097 Mod. 5, Vol.84 Hindmarch, et al. At 1 centre in UK. 26/6/2000 to 21/8/2000.	Phase 1 randomised, DB, 3-way crossover, study. Each Rx period of 3 days; washout of ≥7days b/w 3 Rx periods.	23 healthy volunteers with normal EEG, regular sleep wake cycle, BMI 18-30kg/m2 Sex: 11M: 12F Age: 18-50yrs, mean=29yrs. Race: White=22, Others=1. Mean BMI of 26kg/m^2.	Pregabalin (PGB) 75 mg capsules, alprazolam 0.5mg capsules& matching placebo capsules. All dosing orally, TID for 3 days:PGB 150mg TID(450mg/day); alprazolam 1mg tid (3mg/day) or placebo.	Cognitive and psychomotor func: Critical flicker fusion (CFF- mean threshold-Hz), Hick's choice reaction time (H-CRT), Compensatory tracking task (CTT- mean deviation in pixels; mean response time in ms), Line analogue rating scales (LARS- anxiety, depression, sedation & uncoordination), rapid visual information processing (RVIP), Sternberg memory scanning task (STM). Sleep: Leeds sleep evaluation qs (LSEQ), getting to sleep (GTS), quality of sleep (QOS), awakening from sleep (AFS); sleep EEG. Road driving skills: Brake reaction time (ms).	CFF: PGB prod. ss reduction ($p<0.0001$) vs placebo; alpraz also ss ↓. Plac<PGB<alpraz. H-CRT: PGB similar to placebo, but alpraz showed ss worsening of reaction time. CTT: Both PGB & alpraz showed ss greater deviation distance compared to placebo (6.14, 18.4 & 0.22pixels with PGB, alpraz & plac, resp), with alpraz. sig > PGB. Similar results for mean response time. LARS: No ss change with PGB or alpraz in anxiety & depression subscales; both PGB & alpraz showed ss diff from placebo in sedation (LSM was -0.5, 5.76 & 12.96 for plac, PGB & alprqaz, resp) & uncoordination (-0.96, 8.69 & 9.40, resp). RVIP: No change with PGB; alpraz showed sig impairment; STM: Response time similar for PGB & placebo, but sig higher for alpraz. LSEQ: Improvement in GTS & QOS with both PGB & alpraz. Sleep EEG: PGB sig ↑ SWS, minimal suppression of REM sleep. Both PGB & alpraz increased sleep efficiency relative to placebo, but not diff from each other. PGB did not alter brake reaction time, while alpraz sig slower vs both placebo & PGB (623.3, 690.5 & 654.4ms with PGB, alpraz & plac, resp).	AE incidence: PGB=91%, alprazolam=100%, placebo=57%. Most of AEs were moderate with PGB and alpraz. Severe AEs in 9%, 22% & 0% with PGB, alpraz & placebo, resp. Dizziness (PGB, alpraz: 61%, 44%), somnolence (44%, 78%), headache (48%, 17%). Other common AEs with alpraz were asthenia (30%) & abn gait (44%). No SAEs/ deaths or withdrawals due to AEs. No clinically sig changes in lab parameters/vital signs.

Table 9.23.1:

Overview of Results for Controlled Studies By Parameter—MITT Population

Pooled Subset Parameter	Placebo	Pregabalin <300	Pregabalin 300	Pregabalin 450	Pregabalin 600	All Pregabalin	Lorazepam 6 mg/day
Any Visual Field Abnormality							
All Indications	11.7%	11.0%	16.4%*	9.1%	12.0%	12.4%	7.3%
Neuropathic Pain	14.3%	13.9%	13.6%	--	16.2%	14.5%	--
Diabetic Neuropathy	13.1%	12.8%	11.8%	--	16.2%	13.6%	--
Postherpectic Neuralgia	16.0%	15.0%	24.0%	--	16.1%	16.2%	--
Other Chronic Pain	10.7%	8.5%	18.4%*	9.1%	14.4%	13.3%	--
Epilepsy	9.9%	13.1%	15.2%	--	8.4%	11.1%	--
Anxiety Disorders	8.9%	7.1%	--	--	7.2%	7.2%	7.3%
Validated Visual Field Abnormality							
All Indications	4.8%	4.4%	7.3%*	3.0%	5.3%	5.3%	3.7%
Neuropathic Pain	7.0%	5.4%	6.5%	--	6.9%	6.1%	--
Diabetic Neuropathy	5.9%	5.0%	5.6%	--	6.8%	5.8%	--
Postherpectic Neuralgia	8.6%	5.9%	12.0%	--	7.1%	6.8%	--
Other Chronic Pain	4.1%	4.3%	8.0%*	3.0%	5.9%	5.6%	--
Epilepsy	2.1%	6.6%	6.1%	--	3.7%	5.0%	--
Anxiety Disorders	3.2%	1.2%	--	--	4.6%	2.8%	3.7%
Any Visual Acuity Abnormality							
All Indications	4.8%	6.0%	6.4%	5.5%	7.4%*	6.5%*	2.5%
Neuropathic Pain	6.9%	8.8%	9.9%	--	12.1%*	10.1%	--
Diabetic Neuropathy	5.8%	8.1%	6.2%	--	12.7%*	9.1%	--
Postherpectic Neuralgia	8.4%	9.5%	30.8%*	--	10.7%	12.1%	--
Other Chronic Pain	2.9%	3.6%	5.4%	5.5%	6.1%	5.2%	--
Epilepsy	3.8%	8.6%	2.7%	--	7.8%	7.2%	--
Anxiety Disorders	4.9%	1.7%	--	--	2.5%	2.1%	2.5%
Post-Hoc Review of Visual Acuity Abnormality							
All Indications	3.3%	3.2%	5.3%	4.0%	4.2%	4.1%	0%*
Neuropathic Pain	4.9%	4.2%	8.7%	--	6.5%	6.1%	--
Diabetic Neuropathy	3.3%	3.4%	4.8%	--	5.1%	4.4%	--
Postherpectic Neuralgia	7.2%	5.1%	30.8%*	--	10.7%	9.2%	--
Other Chronic Pain	2.1%	2.1%	4.3%	4.0%	3.6%	3.6%	--
Epilepsy	1.9%	4.3%	1.3%	--	4.1%	3.7%	--
Anxiety Disorders	3.1%	1.7%	--	--	1.9%	1.8%	0%
Any Funduscopic Abnormality							
All Indications	2.1%	1.6%	1.2%	2.1%	2.1%	1.7%	0.9%
Neuropathic Pain	2.5%	2.4%	1.8%	--	4.0%	2.7%	--
Diabetic Neuropathy	3.4%	2.8%	2.1%	--	4.8%	3.2%	--
Postherpectic Neuralgia	1.2%	2.0%	0%	--	1.8%	1.7%	--
Other Chronic Pain	2.2%	0.5%	1.1%	2.1%	1.4%	1.3%	--
Epilepsy	2.7%	1.6%	0%	--	2.6%	1.8%	--
Anxiety Disorders	0%	1.2%	--	--	0%	0.6%	0.9%

* = Statistically different from placebo by Fisher's exact test.

-- = Not applicable; dose not studied.

Table 9.23.2:

Overview of Results for Combined Controlled/Uncontrolled Pregabalin Exposure By Parameter—MITT Population

Pooled Subset Parameter	Total Pregabalin Exposure[a]	All Pregabalin - Controlled Studies	Placebo - Controlled Studies
Any Visual Field Abnormality			
All Indications	16.8%	12.4%	11.7%
Neuropathic Pain	24.1%	14.5%	14.3%
Diabetic Neuropathy	23.9%	13.6%	13.1%
Postherpectic Neuralgia	24.5%	16.2%	16.0%
Other Chronic Pain	15.6%	13.3%	10.7%
Epilepsy	15.1%	11.1%	9.9%
Anxiety Disorders	NA	7.2%	8.9%
Validated Visual Field Abnormality			
All Indications	5.4%	5.3%	4.8%
Neuropathic Pain	8.8%	6.1%	7.0%
Diabetic Neuropathy	8.9%	5.8%	5.9%
Postherpectic Neuralgia	8.8%	6.8%	8.6%
Other Chronic Pain	5.0%	5.6%	4.1%
Epilepsy	3.7%	5.0%	2.1%
Anxiety Disorders	NA	2.8%	3.2%
Any Visual Acuity Abnormality			
All Indications	9.4%	6.5%	4.8%
Neuropathic Pain	16.7%	10.1%	6.9%
Diabetic Neuropathy	15.8%	9.1%	5.8%
Postherpectic Neuralgia	18.3%	12.1%	8.4%
Other Chronic Pain	7.5%	5.2%	2.9%
Epilepsy	7.5%	7.2%	3.8%
Anxiety Disorders	NA	2.1%	4.9%
Post-Hoc Review of Visual Acuity Abnormality			
All Indications	7.8%	4.1%	3.3%
Neuropathic Pain	14.0%	6.1%	4.9%
Diabetic Neuropathy	13.3%	4.4%	3.3%
Postherpectic Neuralgia	15.4%	9.2%	7.2%
Other Chronic Pain	6.0%	3.6%	2.1%
Epilepsy	6.2%	3.7%	1.9%
Anxiety Disorders	NA	1.8%	3.1%
Any Funduscopic Abnormality			
All Indications	5.9%	1.7%	2.1%
Neuropathic Pain	14.0%	2.7%	2.5%
Diabetic Neuropathy	17.9%	3.2%	3.4%
Postherpectic Neuralgia	6.7%	1.7%	1.2%
Other Chronic Pain	2.9%	1.3%	2.2%
Epilepsy	3.6%	1.8%	2.7%
Anxiety Disorders	NA	0.6%	0%

NA = Not applicable; anxiety disorder studies did not have open-label extensions.

a Combined controlled/uncontrolled pregabalin exposure

Table 9.24:

. Summary of Vision-Related TESS Adverse Events by Decreasing Frequency — ITT Population
Controlled Studies — All Indications (Studies 7, 9, 11, 14, 17, 21, 22, 25, 26, 29, 30, 31, 32, 34, 40, 45, 104, 105, 127, 131)
[Number (%) of Patients]

Adverse Event Preferred Term	Placebo N = 1567	Pregabalin <300 mg/day N = 1137	Pregabalin 300 mg/day N = 685	Pregabalin 450 mg/day N = 236	Pregabalin 600 mg/day N = 1300	All Pregabalin N = 3358	All Comparators[b] N = 336
Amblyopia[a]	37 (2.4%)	50 (4.4%)	49 (7.2%)	12 (5.1%)	126 (9.7%)	237 (7.1%)	10 (3.0%)
Diplopia	11 (0.7%)	16 (1.4%)	20 (2.9%)	4 (1.7%)	54 (4.2%)	94 (2.8%)	1 (0.3%)
Abnormal Vision	10 (0.6%)	17 (1.5%)	13 (1.9%)	2 (0.8%)	42 (3.2%)	74 (2.2%)	4 (1.2%)
Nystagmus	5 (0.3%)	5 (0.4%)	4 (0.6%)	1 (0.4%)	20 (1.5%)	30 (0.9%)	3 (0.9%)
Visual Field Defect	17 (1.1%)	14 (1.2%)	11 (1.6%)	3 (1.3%)	17 (1.3%)	45 (1.3%)	2 (0.6%)
Eye Disorder	5 (0.3%)	6 (0.5%)	6 (0.9%)	2 (0.8%)	10 (0.8%)	24 (0.7%)	1 (0.3%)
Retinal Disorder	7 (0.4%)	4 (0.4%)	2 (0.3%)	1 (0.4%)	6 (0.5%)	13 (0.4%)	1 (0.3%)
Cataract Specified	3 (0.2%)	2 (0.2%)	2 (0.3%)	0 (0.0%)	4 (0.3%)	8 (0.2%)	0 (0.0%)
Eye Pain	6 (0.4%)	9 (0.8%)	6 (0.9%)	1 (0.4%)	4 (0.3%)	20 (0.6%)	0 (0.0%)
Abnormality of Accommodation	0 (0.0%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	3 (0.2%)	5 (0.1%)	1 (0.3%)
Dry Eyes	6 (0.4%)	4 (0.4%)	7 (1.0%)	4 (1.7%)	3 (0.2%)	18 (0.5%)	0 (0.0%)
Photosensitivity Reaction	2 (0.1%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	3 (0.2%)	4 (0.1%)	0 (0.0%)
Eye Hemorrhage	2 (0.1%)	4 (0.4%)	2 (0.3%)	0 (0.0%)	2 (0.2%)	8 (0.2%)	0 (0.0%)
Glaucoma	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	3 (0.1%)	0 (0.0%)
Color Blindness	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)
Photophobia	2 (0.1%)	4 (0.4%)	3 (0.4%)	1 (0.4%)	1 (0.1%)	9 (0.3%)	0 (0.0%)
Ptosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.3%)
Retinal Detachment	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)
Retinal Edema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)	0 (0.0%)
Vitreous Disorder	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	2 (0.1%)	2 (0.6%)
Retinal Degeneration	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Retinal Hemorrhage	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
Retinal Pigmentation	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Retinal Vascular Disorder	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	**106 (6.8%)**	**116 (10.2%)**	**109 (15.9%)**	**28 (11.9%)**	**255 (19.6%)**	**508 (15.1%)**	**25 (7.4%)**

[a] Reported as "blurred" or "blurry" vision by investigators
[b] Lorazepam, amitriptyline, and gabapentin

Table 9.25:

Exposure[a] to Pregabalin — MITT[b] Population Combined Controlled/Uncontrolled Studies: All Indications
[Number (%) of Patients]

Exposure Time	Previous Database[c] N = 3615		Current Database[c] N = 3686	
≥1 Day	3615	(100.0)	3686	(100.0)
≥1 Week	3515	(97.2)	3587	(97.3)
≥2 Weeks	3441	(95.2)	3515	(95.4)
≥4 Weeks	3317	(91.8)	3390	(92.0)
≥6 Weeks	2923	(80.9)	2996	(81.3)
≥8 Weeks	2825	(78.1)	2895	(78.5)
≥10 Weeks	2710	(75.0)	2786	(75.6)
≥12 Weeks	2599	(71.9)	2676	(72.6)
≥16 Weeks	2459	(68.0)	2538	(68.9)
≥20 Weeks	2336	(64.6)	2418	(65.6)
≥24 Weeks	2229	(61.7)	2328	(63.2)
≥36 Weeks	1908	(52.8)	2080	(56.4)
≥52 Weeks	1390	(38.5)	1662	(45.1)
≥65 Weeks	1026	(28.4)	1200	(32.6)
≥78 Weeks	822	(22.7)	1026	(27.8)
≥91 Weeks	572	(15.8)	900	(24.4)
≥104 Weeks	292	(8.1)	672	(18.2)
≥117 Weeks	105	(2.9)	429	(11.6)
≥130 Weeks	26	(0.7)	306	(8.3)
≥143 Weeks	17	(0.5)	257	(7.0)
≥156 Weeks	4	(0.1)	209	(5.7)
≥169 Weeks	1	(0.0)d	169	(4.6)
≥182 Weeks	0	(0.0)	123	(3.3)
≥195 Weeks	0	(0.0)	61	(1.7)
≥208 Weeks	0	(0.0)	36	(1.0)
≥221 Weeks	0	(0.0)	16	(0.4)
≥234 Weeks	0	(0.0)	7	(0.2)
≥247 Weeks	0	(0.0)	3	(0.1)
≥260 Weeks	0	(0.0)	0	(0.0)

[a] Study days on which patient received zero dose are included in exposure summary.

[b] Intent-to-treat patients with baseline and postbaseline ophthalmology exams *or* assessments

[c] Any pregabalin dose

Table 9.26.1:

Summary of Visual Field Abnormalities — MITT Population Combined Controlled/Uncontrolled Pregabalin Studies — All Indications
[Number (%) of Patients]

	Previous Database	Current Database
Category[a]	N = 3458	N = 3534
Clinical Database		
All Clinically Significant Changes[b]	316	355
All Visual Field Outliers[c]	351	352
Patients With Any Visual Field Abnormality (Category 1-DB/OL)[d]	582 (16.8)	618 (17.5)
Expert-Validated Cases		
Patients With Any **Validated** Visual Field Abnormality (Category 2-DB/OL)[e]	186 (5.4)	176[f] (5.0)
Unexpected or Unexplained (Category 3-DB/OL)[g]	6 (0.2)	10[h] (0.3)

[a] Patients may be included in more than one category.
[b] As reported on the ophthalmologic worksheet
[c] Patients with a ≥10-point deterioration from baseline to their last 120-point Humphrey examination (listing is in Appendix B.5); 170 additional patients had changes from baseline to any visit (Appendix B.5.1)
[d] All patients with change in visual field status
[e] Subset of patients with valid deterioration in visual field status; cases in which the change was exclusively due to artifact (eg, lid, lens, poor cooperation) were excluded from the validated category.
[f] Experts reviewed all newly identified cases and all previously identified cases with new information: Some previously identified cases were not confirmed with follow-up information.
[g] Cases due to known medical cause (eg, diabetic retinopathy, macular degeneration, glaucoma) were excluded from this category.
[h] Includes the 6 patients from the previous database

Table 9.26.2:

Summary of Visual Acuity Abnormalities MITT Population Combined Controlled/Uncontrolled Pregabalin Studies — All Indications
[Number (%) of Patients]

	Previous Database N = 3602	Current Database N = 3677
Category[a]		
All Clinically Significant Deteriorations[b]	89	99
All Visual Acuity Outliers[c]	308	323
Patients With Any Visual Acuity Abnormality	337 (9.4)	358 (9.7)
Patients With Any **Validated** Visual Acuity Abnormality	281 (7.8)	294 (8.0)
logMAR Change (Termination — Baseline)[d]	N = 3376	N = 3443
≤-0.3	21 (0.6)	24 (0.7)
-0.2 to -0.2999	6 (0.2)	6 (0.2)
-0.1 to -0.1999	78 (2.3)	80 (2.3)
-0.0999 to 0.0999	2828 (83.8)	2870 (83.4)
0.1 to 0.1999	248 (7.3)	260 (7.6)
0.2 to 0.2999	79 (2.3)	75 (2.2)
≥0.3	116 (3.4)	128 (3.7)

[a] Patients may be included in more than one category.
[b] As reported on the ophthalmologic worksheet
[c] Patients with a deterioration in visual acuity defined as a logMAR change of ≥0.15 from double-blind baseline to the last examination
[d] In worst eye: Positive values indicate a deterioration of visual acuity.

Table 9.26.3:

Summary of Vision-Related TESS Adverse Events[a] by Decreasing Frequency—ITT Population (Any Pregabalin Dose) Combined Controlled/Uncontrolled Pregabalin Studies—All Indications
[Number (%) of Patients]

Preferred Term	Previous Database N = 5026	Current Database N = 8666
Amblyopia[b]	510 (10.1)	773 (8.9)
Diplopia	249 (5.0)	305 (3.5)
Abnormal Vision	166 (3.3)	246 (2.8)
Visual Field Defect	148 (2.9)	193 (2.2)
Eye Disorder[c]	90 (1.8)	136 (1.6)
Nystagmus	85 (1.7)	102 (1.2)
Retinal Disorder[d]	65 (1.3)	85 (1.0)
Eye Pain	55 (1.1)	75 (0.9)
Cataract Specified	56 (1.1)	72 (0.8)
Dry Eyes	38 (0.8)	68 (0.8)
Eye Hemorrhage	23 (0.5)	29 (0.3)
Photophobia	19 (0.4)	29 (0.3)
Photosensitivity Reaction[e]	18 (0.4)	27 (0.3)
Glaucoma	12 (0.2)	22 (0.3)
Vitreous Disorder	11 (0.2)	19 (0.2)
Retinal Edema	10 (0.2)	11 (0.1)
Abnormality of Accommodation	7 (0.1)	9 (0.1)
Retinal Vascular Disorder	6 (0.1)	9 (0.1)
Ptosis	4 (0.08)	7 (0.1)
Retinal Hemorrhage	4 (0.08)	5 (0.1)
Color Blindness	2 (0.04)	4 (0.05)
Retinal Depigmentation	2 (0.04)	4 (0.05)
Retinal Detachment	3 (0.06)	4 (0.05)
Night Blindness	1 (0.02)	3 (0.03)
Optic Atrophy	1 (0.02)	3 (0.03)
Retinal Degeneration	2 (0.04)	3 (0.03)
Cataract NOS	2 (0.04)	2 (0.02)
Papilledema	1 (0.02)	1 (0.01)

[a] Listed by decreasing frequency in the "Current Database" column.
[b] Reported as "blurred" or "blurry" vision by investigators
[c] Includes investigator terms: Heavy eyes, eye strain, itchy eyes, blisters in eyes, crossed eyes, difficulty opening eyes, droopy eyes, eye drainage, eye fatigue, eye infection, eye strain, eyelashes falling out, eyes burning, glossy eyes, glassy eyes, jumpy eyes, stye, nervous eye movement, and tired eyes (see Appendix B.6)
[d] Includes investigator terms: Age-related macular degeneration, background diabetic retinopathy, background macular degeneration, retinal scar, retinal tear, and sickle cell retinopathy (see Appendix B.6)
[e] Includes investigator terms: Face sunburn, fair damaged complexion, increased photosensitivity, increased sun sensitivity (skin), peeling skin (after sunburn), and sunburn (see Appendix B.6)

Table 9.27: Other safety studies: Effect of pregabalin on male reproductive function

Study nos, location investigators	Study design	Subjects demographics	Dosage, duration, route, form of study drugs	Endpoints	Efficacy results	Safety/AEs
1008-072 Mod. 5, Vol.91 Swerdloff R, et al. At 2 centre in USA. 21/12/1999 to 9/4/2001.	Phase 2 randomised, DB, PC, parallel group study. Duration of Rx: 14 weeks including 2 weeks titration phase. 8 week washout phase (no tapering of drug)- just FU questionnaire.	46 healthy male volunteers with normal sperm conc., motility, morphology. Age: 19-53yrs, mean=32yrs. Race: White=35,Black=3, Hispanic=5, Others=3. Baseline sperm motility was 62.6% (48-85%). No sig diff b/w Rx gps at baseline.	Pregabalin (PGB) 25, 100 & 150 mg capsules, matching placebo capsules. All dosing orally, TID for 14 weeks. PGB 200mg TID (600mg/day), n=30; placebo (n=16).	Primary: percent of sperm with normal motility (WHO class "a+b+c") at end of DB Rx. Secondary: Computer-aided sperm analysis (CASA): normal conc.of sperms, semen volume, testicular & breast exam, & percent of sperms with normal motility at end of washout phase. Safety: AEs, vital signs, ECG, haematology, blood chemistry, urinalysis, male endocrine parameters.	Sperm motility (WHO class a+b+c %) at end of RX: pregabalin=64.4%, placebo=60.5%, p=0.21 (upper limit 97.5% CI=10%). 3 PGB pts & 2 placebo pts had ↓ in sperm motility of >15% from baseline. Analysis of motility at end of washout phase also showed no diff. b/w PGB (63.7%) and placebo (62.5%). There was no sig. deterioration in sperm motility (WHO "a"%). Morphology, conc., volume, CASA parameters.	AE incidence: PGB=86.7%, placebo=93.8%. Most AEs were mild/moderate. Severe AEs: 13.3% & 12.5% with PGB & Placebo, resp. Infection (36.7% vs 12.5%), somnolence (30% vs 0%), abn thinking (16.7% vs 0%), dizziness (13.3% vs 0%), anxiety (10% vs 0%), dry mouth (10% vs 0%), insomnia (10% vs 0%) & ↓libido (10% vs 0%) more common in PGB gp. No SAEs/ deaths or withdrawals due to AEs. No clinically sig changes in lab parameters/vital signs, FSH, ECG or visual examinations. Weight gain > 7% from baseline seen only in PGB gp (n=4, 13%)..

Table 9.28.1:

Median Change and Median Percent Change in Platelet Count From Baseline to 3-Month Time Intervals—Patients Treated With Pregabalin ≥2 Years

Time Interval	N	Change From Baseline (Platelets × $10^3/\mu L$)	% Change From Baseline
3 Months	917	-9	-4
6 Months	867	-7	-3
9 Months	848	-4	-2
12 Months	817	-3	-1
15 Months	833	0	0
18 Months	825	0	0
21 Months	797	2	1
24 Months	797	5	2
>24 Months[a]	696	3	1

[a] A decrease in patient number is seen at this time point, as the cut-off for inclusion in this analysis was ≥2 years. Ninety-five percent of patients in the 2-year cohort had an observation at either 24 months or >24 months.

Table 9.28.2:

Median Change and Median Percent Change in Platelet Count From Baseline to 3 Month Time Intervals—Patients Treated With Pregabalin ≥3 Years

Time Interval	N	Change From Baseline (Platelets × $10^3/\mu L$)	% Change From Baseline
3 Months	275	-6	-3
6 Months	266	-4	-2
9 Months	257	-3	-1
12 Months	258	0	0
15 Months	248	1	0.5
18 Months	248	3	1
21 Months	245	3	2
24 Months	250	5	2.5
27 Months	241	0	0
30 Months	237	6	3
33 Months	232	6.5	3
36 Months	257	12	5
>36 Months[a]	194	7	4

[a] A decrease in patient number is seen at this time point, as the cut-off for inclusion in this analysis was ≥3 years. Ninety-six percent of patients in the 3-year cohort had an observation at 36 months or >36 months.