This table is not easily interpreted because it includes only those subjects who completed and therefore likely excludes events of greater severity, events of particular interest. Pfizer interpreted the results as showing that for completers, weight gain and increased appetite had the longest duration. They also noted that the median duration of dizziness for completers was shorter for pregabalin subjects (12-28 days) then for placebo (43 days) and that the median duration for somnolence among pregabalin completers was variable (26-68 days).

Pfizer provided a summary of the disposition of the epilepsy controlled trial pregabalin subjects who experienced somnolence and dizziness, two of the most common treatment emergent AEs in the epilepsy trials. Eighteen percent (40/219) of the pregabalin subjects who experienced dizziness discontinued for this AE. For those subjects with dizziness who did not withdraw because of it, 64% (114/179) had their dizziness resolve prior to the end of the study. Fifteen percent (24/158) of the pregabalin subjects who experienced somnolence discontinued for this AE. For those subjects with somnolence who did not withdraw because of it, 46% (61/134) had their somnolence resolve prior to the end of the study (Summary of Safety, p.187-9). This analysis supports that these adverse events could persist in a notable percentage of subjects.

Adverse Events by Gender

In Appendix Epilepsy.098, Pfizer presented the adverse event risks occurring in epilepsy controlled trials stratified by gender. To look for variations in risk by gender, I calculated relative risks for male pregabalin subjects compared to male placebo subjects and for female pregabalin subjects compared to female placebo subjects for selected common AEs. For a majority of the more common AEs, the relative risks among females were higher than the relative risks for males. The following table summarizes the results of this analysis.

FDA Table 22. Gender Stratified AE Risks and Relative Risks, Epilepsy Controlled Trials

Adverse Event	Males		RR_M	Females		RR_F
	Pregabalin	Placebo		Pregabalin	Placebo	
	N=363	N=156		N=395	N=138	
Asthenia	8% (29)	9.6% (15)	0.8	14.2% (56)	6.5% (9)	2.2
Accidental Injury	11% (40)	8.3% (13)	1.3	8.9% (35)	2.2% (3)	4.0
Dry Mouth	2.8% (10)	1.3% (2)	2.2	5.3% (21)	1.4% (2)	3.8
Peripheral edema	2.2% (8)	0.6% (1)	3.7	6.1% (24)	3.6% (5)	1.7
Dizziness	22.9% (83)	13.5% (21)	1.7	34.4% (136)	7.2% (10)	4.8
Somnolence	17.1% (62)	9% (14)	1.9	24.3% (96)	13% (18)	1.9
Ataxia	11.6% (42)	3.8% (6)	3.1	14.7% (58)	4.3% (6)	3.4
Tremor	8% (29)	4.5% (7)	1.8	7.1% (28)	2.9% (4)	2.4
Thinking abnormal	6.3% (23)	3.2% (5)	2.0	7.6% (30)	0.7% (1)	10.9
Amnesia	3.3% (12)	3.2% (5)	1.0	5.3% (21)	1.4% (2)	3.8
Incoordination	3.6% (13)	1.3% (2)	2.8	4.6% (18)	0.7% (1)	6.6

Confusion	3.6% (13)	2.6% (4)	1.4	2.8% (11)	0.7% (1)	4.0
Amblyopia	6.6% (24)	5.1% (8)	1.3	11.1% (44)	3.6% (5)	3.1
Diplopia	8.8% (32)	3.2% (5)	2.8	8.1% (32)	4.3% (6)	1.9
Weight gain	10.2% (37)	0	-	10.6% (42)	2.9% (4)	3.7

Adverse Events by Age

The epilepsy controlled trials included twelve pregabalin and eight placebo subjects at least 65 years old and ten pregabalin and one placebo subjects less than 17 year old, too few subjects to allow meaningful comparisons of AE relative risks across Pfizer's age strata.

Combined Controlled and Uncontrolled Epilepsy Trials

Pfizer provided a table that summarized the treatment emergent AEs from the combined controlled and uncontrolled epilepsy trials through the Safety Update (Safety Update Appendix Epilepsy.9). The events included on this table were similar to the events that commonly occurred in the controlled trials. Below I list the treatment emergent AEs that occurred in at least 5% of pregabalin subjects in controlled and open label studies.

FDA Table 23. Treatment Emergent AE Risks Reported for at least 5% of Pregabalin Subjects in the Combined Controlled and Uncontrolled Epilepsy Trials through the Safety Update

Treatment Emergent AE	Risk (n=1613)	Treatment Emergent AE (continued)	Risk (n=1613)
Overall	**95.8% (n=1545)**		
Dizziness	40.6% (n=655)	Depression	7.2% (116)
Somnolence	32.3% (n=521)	Confusion	7.1% (115)
Accidental injury	26.7% (n=431)	Insomnia	7.1% (115)
Weight gain	25.8% (n=416)	Back pain	6.8% (109)
Asthenia	21.8% (351)	Abdominal pain	6.6% (107)
Headache	20.2% (n=326)	Vomiting	6.6% (107)
Infection	20.1% (n=325)	Anxiety	6.1% (99)
Ataxia	17.6% (n=284)	Diarrhea	6.1% (99)
Amblyopia	16.1% (260)	Pharyngitis	6.1% (98)
Pain	15.7% (254)	Ecchymosis	6% (96)
Diplopia	13.8% (222)	Incoordination	5.8% (94)
Thinking abnormal	13.3% (214)	Urinary Tract Infection	5.6% (90)
Tremor	12% (n=193)	Dyspepsia	5.5% (89)
Nausea	11.2% (n=180)	Nystagmus	5.3% (86)
Peripheral edema	9.6% (155)	Abnormal vision	5.2% (84)
Amnesia	9.4% (n=151)	Hypesthesia	5.2% (84)
Flu syndrome	8.7% (140)	Speech disorder	5.2% (84)
Rash	8.7% (n=140)	Paresthesia	5.1% (82)
Nervousness	7.6% (123)	Twitching	5.1% (82)
Constipation	7.4% (120)		

Adverse Events in the GAD Trials

Controlled GAD Trials

Pfizer reported that 82.2% (945/1149) of pregabalin-treated patients and 70.5% (341/484) of placebo-treated patients experienced adverse events in the controlled GAD trials. Both risks are slightly larger than were observed in the controlled trials in the integrated database as a whole, in which 79.3% (4369/5508) of pregabalin-treated patients and 64.7% (1542/2384) of placebo-treated patients experienced adverse events. The relative risk for experiencing adverse events that was associated with pregabalin treatment compared to placebo was 1.2 for both the GAD controlled trials and all controlled trials in the integrated safety database. Pfizer summarizes adverse events experienced by at least 2% of pregabalin-treated patients by dose group in Table 112 (Summary of Safety pp. 203-204). All adverse events experienced by patients in GAD controlled trials are summarized by body system in Appendix GAD.021 (Summary of Safety pp. 13675-13704). The following table summarizes the adverse events experienced by at least 2% of pregabalin-treated patients that occurred statistically significantly more frequently in the overall group of patients being treated with pregabalin for GAD than in the placebo group:

FDA Table 24. Adverse Events Occurring in =2% of Pregabalin-Treated Patients by Decreasing Frequency; GAD Controlled Trials

Preferred Term	Placebo (n=484); % ,(no.)	Pregabalin 150 mg/d tid (n=210); %,(no.)	Pregabalin 200 mg/d bid (n=78); %,(no.)	Pregabalin 300 mg/d tid (n=91); %,(no.)	Pregabalin 400 mg/d bid (n=186); %,(no.)	Pregabalin 450 mg/d tid (n=178); %,(no.)	Pregabalin 600 mg/d bid (n=110); %,(no.)	Pregabalin 600 mg/d tid (n=296) %,(no.)	Pregabalin; all doses and regimens (n=1149); % ,(no.)
Dizziness	8.9% (43)	13.8% (29)	34.6%% (27)	37.4% (34)	35.5% (66)	38.2% (68)	26.4% (29)	35.1% (104)	31.1% (357)
Somnolence	11.5% (56)	23.8% (50)	30.8% (24)	35.2% (32)	24.7% (46)	29.8% (53)	13.6% (15)	39.2% (116)	29.2% (336)
Dry Mouth	6.4% (31)	10.5% (22)	24.4% (19)	17.6% (16)	15.6% (29)	16.3% (29)	4.5% (5)	17.9% (53)	15.1% (173)
Amblyopia	2.1% (10)	4.3% (9)	6.4% (5)	7.7% (7)	5.9% (11)	11.8% (21)	3.6% (4)	9.8% (29)	7.5% (86)
Incoord-ination	1.0% (5)	0.5% (1)	3.8% (3)	4.4% (4)	8.6% (16)	12.4% (22)	3.6% (4)	10.8% (32)	7.1% (82)
Constipation	3.1% (15)	3.8% (8)	3.8% (3)	2.2% (2)	8.6% (16)	10.7% (19)	6.4% (7)	5.4% (16)	6.2% (71)
Thinking abnormal	2.3% (11)	1.9% (4)	7.7% (6)	2.2% (2)	8.6% (16)	6.2% (11)	4.5% (5)	8.8% (26)	6.1% (70)
Euphoria	1.2% (6)	0.5% (1)	10.3% (8)	3.3% (3)	4.8% (9)	11.8% (21)	0% (0)	3.4% (10)	4.5% (52)
Flatulence	1.0% (5)	2.9% (6)	10.3% (8)	3.3% (3)	1.1% (2)	8.4% (15)	0% (0)	4.1% (12)	4.0% (46)
Weight gain	1.2% (6)	1.4% (3)	1.3% (1)	1.1% (1)	3.8% (7)	7.3% (13)	2.7% (3)	5.1% (15)	3.7% (43)
Amnesia	1.4% (7)	1.9% (4)	0% (0)	3.3% (3)	0.5% (1)	3.4% (6)	2.7% (3)	7.4% (22)	3.4% (39)
Increased appetite	1.2% (6)	2.9% (6)	3.8% (3)	5.5% (5)	2.2% (4)	4.5% (8)	0.9% (1)	3.0% (9)	3.1% (36)
Ataxia	0.2% (1)	0% (0)	5.1% (4)	3.3% (3)	1.6% (3)	4.5% (8)	1.8% (2)	4.4% (13)	2.9% (33)
Deperson-alization	0.6% (3)	1.0% (2)	0% (0)	2.2% (2)	1.1% (2)	2.8% (5)	3.6% (4)	5.4% (16)	2.7% (31)
Confusion	0.2% (1)	2.9% (6)	2.6% (2)	0% (0)	2.7% (5)	4.5% (8)	0% (0)	2.4% (7)	2.4% (28)

From Pfizer Table 112 (Summary of Safety, pp. 203-204).

Dizziness and somnolence were the most common adverse events that occurred among pregabalin-treated patients with GAD, as they also were among pregabalin-treated patients in all controlled trials in the integrated safety database. As was the case with many of the events in the above table, both dizziness and somnolence were slightly more common among pregabalin-treated patients with GAD than among pregabalin-treated patients in the controlled trials as a whole. The frequency of somnolence in placebo-treated patients with GAD was also higher, however, as was the case with many of the most common adverse events listed above. The frequency of dizziness among placebo-treated patients with GAD, in contrast, was very similar to the frequency among placebo-treated patients in the controlled trials as a whole.

Notably, peripheral edema and weight gain were less common in the GAD population treated with pregabalin than in the overall pregabalin-treated controlled trial population. Weight gain was experienced by 3.7% (43/1149) of pregabalin-treated patients with GAD (vs. 1.2% [6/484] of placebo-treated patients with GAD; relative risk for weight gain associated with pregabalin=3.1 in GAD controlled trials) compared to 5.6% (311/5508) of pregabalin-treated patients in the overall controlled trial population (vs. 0.8% [19/2384] of placebo-treated patients overall; relative risk for weight gain associated with pregabalin=7.0 in controlled trials for all indications). Peripheral edema was experienced by 1.9% (22/1149) of pregabalin-treated patients with GAD (vs. 0.4% [2/484] of placebo-treated patients with GAD; relative risk for peripheral edema associated with pregabalin=4.7 in GAD controlled trials) compared to 6.1% (336/5508) of pregabalin-treated patients in the overall controlled trial population (vs. 1.8% [42/2384] of placebo-treated patients overall; relative risk for peripheral edema associated with pregabalin=3.4 in controlled trials for all indications). Although the frequency of peripheral edema in patients treated with pregabalin in the GAD population was lower than in the overall controlled trial population, the risk relative to placebo was slightly higher.

Other events that were less frequent among pregabalin-treated patients with GAD compared with the overall controlled trial population of pregabalin-treated patients were diplopia (which occurred in 0.7% [8/1149] of pregabalin-treated patients with GAD and no placebo-treated patients with GAD), tremor, confusion, ataxia, accidental injury, and asthenia. Unlike in the controlled trials as a whole, accidental injury, ataxia, and tremor did not occur statistically significantly more frequently in pregabalin-treated patients than in placebo-treated patients in the GAD population.

A greater array of adverse events occurred in at least 2% of pregabalin-treated patients with GAD than occurred in at least 2% of pregabalin-treated patients in the controlled trials in the integrated safety database as a whole. Only one of these additional events, depersonalization, occurred statistically significantly more frequently in pregabalin-treated patients with GAD than placebo-treated patients with GAD.

Most of the adverse events in the table above occurred significantly more frequently than in the placebo group at doses =200 mg/day but not in the 150 mg/day dose group. In this dose group, the frequencies of most adverse events were similar to those observed in the placebo group. Somnolence and confusion were exceptions to this pattern. Somnolence

occurred more frequently in pregabalin-treated patients than in placebo-treated patients at all doses =150 mg/day with the exception of the 600 mg/day bid dose group. Confusion occurred more frequently in pregabalin-treated patients than in placebo-treated patients in the 150 mg/day, 400 mg/day, 450 mg/day, and 600 mg/day tid dose groups.

Most adverse events demonstrated no clear dose-response relationship at doses higher than 200 mg/day. Constipation and weight gain, in contrast, were more frequent in pregabalin-treated patients than in placebo-treated patients at doses = 400 mg/day. Depersonalization among pregabalin-treated patients was significantly more frequent than among placebo-treated patients beginning at 450 mg/day. Amnesia occurred significantly more frequently than in placebo-treated patients only in the pregabalin 600 mg/day tid dose group. Tremor, although not occurring more frequently in the overall group of pregabalin-treated patients with GAD than in placebo-treated patients, was also significantly more frequent in the pregabalin 600 mg tid dose group than in the placebo group.[19]

Patients in the 600 mg tid group appeared to be at a substantially higher risk than patients in the 600 mg bid group for many of the common adverse events delineated in the table above. Constipation was the only event that occurred statistically significantly more frequently in pregabalin-treated patients overall than in placebo-treated patients for which this was not the case. Constipation occurred slightly more frequently in the 600 mg bid group than in the 600 mg tid group.

I reviewed the preferred terms for all adverse events experienced by pregabalin-treated patients in GAD controlled trials. Notably, peripheral edema, edema, generalized edema, and renal adverse events were substantially less frequent in the GAD controlled trial population of pregabalin-treated patients than in the overall controlled trial population of pregabalin-treated patients. In contrast to the overall database, there were no reports of acute kidney failure, creatinine increased, or kidney function abnormal in the GAD controlled trials. There were no adverse events in the GAD controlled trials coded as liver failure, myopathy, aplastic anemia, Stevens Johnson Syndrome, or toxic epidermal necrolysis.

Adverse Events by Intensity

In the controlled GAD studies, 9.5% (46/484) of placebo-treated and 11.8% (136/1149) of pregabalin-treated patients had at least one adverse event that was considered severe. Pfizer provides a tabulation by dose of adverse events in controlled studies judged by investigators to be severe in Table 118 (Summary of Safety, p. 210) and Appendix GAD.035 (Summary of Safety, pp. 14025-14039). The pregabalin dose group with the highest incidence of severe adverse events was the 600 mg tid dose group, in which 16.9% (50/396) of patients experienced an adverse event considered to be severe. The adverse events most frequently judged as being severe were dizziness and somnolence.

[19] Tremor occurred in 1.2% (6) of placebo-treated patients and 2.2% (25) of pregabalin-treated patients overall. In the 600 mg/day tid dose group, 4.4% (13) of patients experienced tremor. Frequency of tremor in other pregabalin dose groups ranged from 1.0% (2) to 2.2% (4).

Severe somnolence was experienced by 2.6% (30/1149) of pregabalin-treated patients and 0.4% (2/484) of placebo-treated patients. Severe dizziness was experienced by 2.3% (27/1149) of pregabalin-treated patients and 0.2% (1/484) of placebo-treated patients. Headache was the only other adverse event judged to be severe in at least 1% of pregabalin-treated patients, although the frequency of severe headache in the pregabalin group, 1.7% (19/1149), was similar to the frequency of severe headache observed in the placebo group (1.9%; 9/484).

Time to Onset and Duration of Adverse Events

Pfizer presents the time to onset of selected common adverse events in controlled GAD studies in Table 120 (Summary of Safety, p. 212). Median time to onset of all adverse events in controlled GAD studies is presented in Appendices GAD.040 (Summary of Safety, pp. 14137-14154; severe adverse events are presented by decreasing frequency with the 600 mg dose group data combined) and GAD.042 (Summary of Safety, pp. 14173-14196; in this table data from the 600 mg dose groups are presented separately). Median time to onset of dizziness and somnolence was one to two days in all dose groups =200 mg/day compared with three days in the placebo group. In the 150 mg/day dose group, the median time to onset of these adverse events was five days for dizziness and three days for somnolence.

Pfizer presents the median duration of adverse events for completers of the double-blind portions of the GAD controlled studies in Appendices GAD.041 (Summary of Safety, pp. 14155-14172) and GAD.043 (Summary of Safety, pp. 14197-14220). The median duration of dizziness among double-blind completers ranged from 4.5 to 15 days across dose groups for pregabalin-treated patients compared with eight days for placebo-treated patients. Pfizer noted that the 400 mg/day dose group was the only group in which the median duration of dizziness was longer than it was among placebo-treated patients. Median duration of somnolence in double-blind completers ranged from ten to 24 days for pregabalin-treated patients compared with ten days for placebo-treated patients. Pfizer noted that duration of dizziness in pregabalin-treated patients was longer than in placebo-treated patients in every dose group =400 mg/day. As previously discussed, it is difficult to meaningfully interpret these data regarding adverse event duration since data regarding patients who have discontinued due to adverse events are not included.

Pfizer discusses the resolution, or lack thereof, of dizziness and somnolence in the GAD controlled trials, just as they did for controlled trials in all indications pooled. They present flowcharts delineating the disposition and course of patients in GAD controlled trials who experienced the adverse events of dizziness and somnolence in Figures 17 and 18 (Summary of Safety, pp. 214-215) and Appendices GAD.044-GAD.047 (Summary of Clinical Safety, pp. 14221-14242). Of the 31% (357/1149) of pregabalin-treated patients in GAD controlled trials who experienced dizziness, 8% (29/357) of patients withdrew due to this adverse event while 92% (328/357) did not withdraw. Among the patients who did not withdraw due to dizziness, 74% (244/328) had resolution of this adverse event prior to their last dose of pregabalin. Among the 9% (43/484) of placebo-treated patients who experienced dizziness, 93% (40/43) did not withdraw due to this adverse

event. 63% (25/40) of the placebo-treated patients who did not withdraw had resolution of their dizziness prior to the last dose of study medication. The pregabalin 600 mg/day dose group had the lowest percentage of patients with resolution prior to the last dose (68% [78/115]), although this percentage was only slightly lower than was observed in the 150 mg/day (72% [21/29]), 400 mg/day (73% [46/63]), and 450 mg/day (75% [46/61]) dose groups.

Of the 29% (336/1149) of patients in GAD controlled trials who experienced somnolence, 13% (45/336) withdrew due to this adverse event, a higher proportion of patients than withdrew due to dizziness. 87% (291/336) of patients experienced somnolence but did not withdraw due to this adverse event. 56% (162/291) of these patients who did not withdraw had resolution of their somnolence prior to their last dose of pregabalin. Among the 12% (56/484) of placebo-treated patients who experienced somnolence, 91% (51/56) did not withdraw due to this adverse event. 59% (30/51) of these placebo-treated patients who did not withdraw had resolution of their somnolence prior to the last dose of placebo. The pregabalin 400 mg/day dose group had the lowest percentage of patients with resolution prior to the last dose (45% [18/40]). The percentage of patients with somnolence resolution in other dose groups ranged from 52% (52/100) in the 600 mg/day dose group to 69% (22/32) in the 300 mg/day dose group. Overall and in each pregabalin dose group, fewer patients with somnolence than with dizziness had resolution of the relevant adverse event prior to their last dose of pregabalin.

Adverse Events by Gender

The GAD controlled trial database was comprised of 680 men and 953 women. The placebo group had 206 men and 278 women while the pregabalin group had 474 men and 675 women. In the GAD controlled trials, 78.3% (371/474) of pregabalin-treated men had adverse events compared with 65.5% (135/206) of placebo-treated men; 85.0% (574/675) of pregabalin-treated women had adverse events compared with 74.1% (206/278) placebo-treated women. There did not appear to be an effect modification by gender on the overall adverse event risk. I calculated a relative risk for experiencing adverse events associated with pregabalin treatment (compared to placebo) of 1.2 for the entire database, 1.2 for men, and 1.1 for women.

Pfizer reported adverse events by gender for all GAD controlled studies in Appendix GAD.098 (Summary of Safety, pp. 14503-14516). I performed analyses of effect modification by gender for every adverse event occurring in at least 3% of pregabalin-treated patients overall and found no evidence of a marked effect of gender on the risk for any of these common adverse events. The most substantial difference in relative risk by gender was found for amblyopia. Relative risk of amblyopia associated with pregabalin treatment was 14 for men (7.0% [33/474] of pregabalin-treated men compared with 0.5% [1/206] of placebo-treated men experienced amblyopia) and 2.5 for women (7.9% [53/675] of pregabalin-treated women compared with 3.2% [9/278] of placebo-treated women experienced amblyopia). This disparity in relative risks resulted from a difference in rates in the placebo groups for men and women.

Adverse Events by Age

The GAD controlled trial database was comprised of 1588 patients ages 18-64 (465 of whom were treated with placebo and 1123 of whom were treated with pregabalin), 42 patients ages 65-74 (18 of whom were treated with placebo and 24 of whom were treated with pregabalin), and 3 patients older than 74 years (one of whom was treated with placebo and two of whom were treated with pregabalin). Pfizer stated that there are too few patients in the GAD controlled trials database older than 64 to make any definitive assessments regarding the effect of age on the frequency of individual adverse events. I analyzed the effect of age on the risk of adverse events overall and on the two most common adverse events in the overall population, dizziness and somnolence.

There was no evident effect of age on the overall risk of adverse events in the GAD population. 82.2% (923/1123) of pregabalin-treated patients <65 experienced adverse events compared to 70.5% (328/465) of placebo-treated patients <65; relative risk associated with pregabalin treatment in patients <65 was 1.2. In patients =65, 84.6% (22/26) of pregabalin-treated patients and 68.4% (13/19) of placebo-treated patients experienced adverse events;[20] relative risk associated with pregabalin treatment in patients =65 was 1.2.

Age did appear to increase the risk for dizziness that was associated with pregabalin, although this finding must be interpreted with caution given the relatively small proportion of patients older than 64. The relative risk for dizziness associated with pregabalin treatment in patients younger than 65 was 3.4 (30.6% [344/1123] of pregabalin-treated patients <65 experienced dizziness compared to 9% [42/465] of placebo-treated patients <65), whereas it was 9.4 for patients older than 64 (50.0% [13/26] of pregabalin-treated patients and 5.3% [1/19] of placebo-treated patients =65 experienced dizziness). Age did not appear to substantially modify the risk for somnolence that was associated with pregabalin. The relative risk for somnolence associated with pregabalin treatment in patients younger than 65 was 2.5 (29.1% [327/1123] of pregabalin patients <65 experienced somnolence compared to 11.6% [54/465] of placebo-treated patients <65), whereas it was 3.3 for patients older than 64 (34.6% [9/26] of pregabalin-treated patients and 10.5% [2/19] of placebo-treated patients =65 experienced dizziness).

Adverse Events by Menopausal Status

Pfizer presented adverse events by menopausal status in Appendix GAD.101 (Summary of Safety, pp. 14547-14559). They do not discuss any potential interaction between pregabalin and menopausal status on the risk of any adverse events. Given the potential for confounding by age, these data are very difficult to interpret.

Adverse Events by Race

[20] Due to the small number of patients older than 64, I combined the two older age groups (65-74 and =75) presented by Pfizer.

Pfizer summarized adverse events by race in Appendix GAD.105 (Summary of Safety, pp. 14600-14627). In the GAD controlled trials database, 84% (1372/1633) of the patients were white; 408 of the white patients were in the placebo group and 964 of the white patients were in the pregabalin group. 6.5% (106/1633) of the patients were black; 34 of these patients were in the placebo group and 72 in the pregabalin group. 6.5% (107/1633) of the patients were Hispanic; 28 of these patients were in the placebo group and 79 in the pregabalin group. 2.9% (48/1633) of patients were classified as "other;" 14 of these patients were treated with placebo and 30 were treated with pregabalin. There appeared to be no modification by race of the overall risk associated with pregabalin of experiencing any adverse event. The relatively small proportion of patients in each of the three non-white categories makes determination of effect modification by race on individual adverse events extremely difficult. I did analyze relative risks associated with pregabalin treatment by race for the two most common adverse events, dizziness and somnolence. There did not appear to be evidence of substantial risk modification by race for either of these adverse events.

Controlled GAD Trials; Safety Update

The Safety update included no new data from GAD controlled trials. All controlled trials in the GAD population had been completed by the original NDA cutoff date of February 14, 2003.

Uncontrolled GAD Trials

Pfizer reported adverse event data for the uncontrolled trials alone in addition to the controlled and uncontrolled trials combined. They did not compare the frequency of adverse events between patients who had been previously exposed to pregabalin and those who had not. 26.2% (185/706) of patients in the uncontrolled studies 84 and 100 had not been previously exposed to pregabalin. The following table summarizes the adverse events that were experienced by at least 2% of pregabalin-treated patients in uncontrolled studies 84 and 100:

FDA Table 25. Adverse Events Occurring in =2% of Pregabalin-treated Patients by Decreasing Frequency; Uncontrolled GAD Studies 84 and 100

Adverse event Preferred Term	% (number) of patients (n=706)	Adverse event Preferred Term	% (number) of patients (n=706)
Dizziness	13.3% (94)	Thinking abnormal	3.4% (24)
Somnolence	12.3% (87)	Amnesia	3.3% (23)
Infection	11.6% (82)	Dry mouth	3.1% (22)
Headache	9.5% (67)	Chest pain	2.8% (20)
Nausea	6.9% (49)	Constipation	2.8% (20)
Weight gain	5.9% (42)	Diarrhea	2.8% (20)
Depression	5.5% (39)	Urinary tract infection	2.7% (19)
Insomnia	5.4% (38)	Dyspepsia	2.5% (18)
Flu syndrome	5.2% (37)	Increased appetite	2.5% (18)

Accidental injury	5.0% (35)	Bronchitis	2.4% (17)
Pain	4.8% (34)	Libido decreased	2.1% (15)
Pharyngitis	4.4% (31)	Flatulence	2.0% (14)
Sinusitis	4.4% (31)	Incoordination	2.0% (14)
Asthenia	3.7% (26)	Otitis media	2.0% (14)
Back pain	3.7% (26)	Rash	2.0% (14)
Nervousness	3.5% (25)		

From Pfizer Table 116 (Summary of Safety, p. 208).

Somnolence and dizziness were substantially less frequent among pregabalin-treated patients in the uncontrolled studies compared to the controlled studies. Headache, nausea, asthenia, thinking abnormal, and dry mouth also occurred less frequently in the uncontrolled studies. Weight gain, accidental injury, depression, and flu syndrome occurred more frequently in the uncontrolled studies than in pregabalin-treated patients in the controlled studies.

Adverse Events by Intensity

In the uncontrolled GAD studies, only one adverse event was judged to be severe in =1% of patients; severe headache occurred in 1.0% (7/706) of pregabalin-treated patients. The other adverse events that were judged to be severe in at least two pregabalin-treated patients were dizziness (experienced by 0.8% [6/706] of patients), libido decreased, somnolence (each experienced by 0.6% [4/706] of patients), back pain (experienced by 0.4% [3/706] of patients), accidental injury, cholecystitis, constipation, depression, ecchymosis, insomnia, and sinusitis (all experienced by 0.3% [2/706] of patients each).

Adverse Events GAD Study 88

Pfizer separately reported adverse event data for study 88, a randomized withdrawal design study in which responders were randomized to pregabalin or placebo for up to six months after an eight week open-label lead-in period.[21] They reported adverse events beginning in the open-label portion that occurred in at least 5% of pregabalin-treated patients as well as adverse events beginning in the double-blind portion that occurred in at least 3% of pregabalin-treated patients. The following table summarizes adverse events that began in the open-label phase of the study and occurred in at least 5% of pregabalin-treated patients:

FDA Table 26. Adverse Events Beginning in Open-label Phase of Study 88 and Occurring in =5% of Pregabalin-Treated Patients by Decreasing Frequency

Adverse event Preferred Term	% (number) of patients; safety population (n=624)
Somnolence	31.9% (199)

[21] Data from this study are integrated into the reported data from controlled and uncontrolled studies combined although not into the reported data from the controlled studies pooled.

Dizziness	29.3% (183)
Dry mouth	16.8% (105)
Euphoria	16.7% (104)
Weight gain	13.9% (87)
Headache	13.5% (84)
Incoordination	12.3% (77)
Infection	12.3% (77)
Thinking abnormal	10.3% (64)
Amblyopia	9.5% (59)
Increased appetite	7.1% (44)
Nausea	6.6% (41)
Amnesia	6.3% (39)
Flatulence	6.1% 38)
Libido decreased	5.8% (36)
Constipation	5.6% (35)
Asthenia	5.4% (34)
Anorgasmia	5.3% (33)
Flu syndrome	5.0% (31)

From Pfizer Table 114, (Summary of Safety, p. 206).

Somnolence and dizziness were the most common adverse events, as they were in the overall integrated safety database and the GAD study groupings discussed above. Pfizer noted that euphoria, weight gain, libido decreased, and anorgasmia occurred more frequently beginning in the open-label portion of study 88 than in the controlled studies alone. In the controlled studies, 4.5% (52/1149) of pregabalin-treated patients experienced euphoria compared to 1.2% (6/484) of placebo-treated patients; 3.7% (43/1149) of pregabalin-treated patients experienced weight gain compared to 1.2% (6/484) of placebo-treated patients; 2.1% (24/1149) of pregabalin-treated patients experienced libido decreased compared to 0.8% (4/484) of placebo-treated patients; and 1.5% (17/1149) of pregabalin-treated patients experienced anorgasmia compared to 0.2% (1/484) of placebo-treated patients.

Pfizer also presented data summarizing adverse events that began in the double-blind phase of study 88 and occurred in at least 3% of pregabalin-treated patients. The following table summarizes these data for those events that occurred more frequently in pregabalin-treated patients compared to placebo-treated patients. Pfizer does not provide information regarding statistical significance of the differences.

FDA Table 27. Adverse Events Beginning in Double-blind Phase of Study 88 and Occurring in =3% of Pregabalin-Treated Patients by Decreasing Frequency

Adverse event Preferred Term	Placebo % (no.) n=170	Pregabalin 450 mg[22] % (no.) n=168

[22] Patients in the double-blind portion of study 88 received placebo or pregabalin 450 mg/day except during titration and taper periods when they received 300 mg/day for three days.

Infection	11.2% (19)	14.9% (25)
Diarrhea	5.9% (10)	7.7% (13)
Sinusitis	1.2% (2)	6.5% (11)
Somnolence	0% (0)	6.0% (10)
Pharyngitis	2.9% (5)	5.4% (9)
Accidental injury	2.4% (4)	4.8% (8)
Back pain	1.8% (3)	4.8% (8)
Depression	1.8% (3)	4.8% (8)
Weight gain	0% (0)	4.8% (8)
Dizziness	2.9% (5)	4.2% (7)
Rhinitis	3.5% (6)	3.6% (6)
Dyspepsia	2.9% (5)	3.6% (6)
Dry mouth	1.2% (2)	3.6% (6)
Myalgia	1.8% (3)	3.0% (5)
Amblyopia	0% (0)	3.6% (6)
Paresthesia	0% (0)	3.0% (5)

From Pfizer Table 115 (Summary of Safety, p.207).

Somnolence and dizziness beginning in the double-blind phase of study 88 were substantially less frequent adverse events than they were in the open-label phase of study 88 and all GAD study groupings.[23] Pfizer noted that the incidence of most adverse events was lower in the double-blind portion of study 88 than in the open-label phase. They also noted that the incidences of weight gain and depression in the long-term double-blind phase were similar to the incidences of these events in the long-term uncontrolled studies. Of note, myalgia and amblyopia occurred more frequently in the double-blind portion of study 88 than in the uncontrolled studies pooled, in which 1.1% (8/706) of patients experienced myalgia and 1.8% (13/706) of patients experienced amblyopia.

Combined Controlled and Uncontrolled GAD Trials

In the combined controlled and uncontrolled GAD studies in the integrated safety database, 87.7% (1720/1962) of pregabalin-treated patients had adverse events. Pfizer lists all adverse events experienced by pregabalin-treated patients in GAD controlled and uncontrolled trials by body system in Appendix GAD.030 (Summary of Safety, pp. 13871-13888) and in order of decreasing frequency in Appendix GAD.031 (Summary of Safety pp. 13889-13905). Dizziness and somnolence were the most frequent adverse events, occurring respectively in 31.4% (617/1962) and 30.3% (595/1962) of pregabalin-treated patients with GAD.

[23] Somnolence and dizziness were also the most frequent adverse events leading to withdrawal from the open-label portion of study 88. 31.2% (89/285) of the patients who withdrew prior to completing the open-label phase of study 88 did so because of adverse events. 24 patients (3.8% of the 624 patients who entered the open-label phase of study 88) withdrew due to somnolence and 17 patients (2.5% of the 624 patients who entered the open-label phase of study 88) withdrew due to dizziness. Thinking abnormal (which led to withdrawal in 1.8% [11/624] of patients) and weight gain (which led to withdrawal in 1.3% [8/624] of patients) were the other adverse events most frequently leading to withdrawal prior to completion of the open-label phase (see pages 71 and 120, Protocol 1008-088 report).

The following table summarizes the adverse events that occurred in at least 3% of patients:

FDA Table 28. Adverse Events Occurring in =3% of Pregabalin-Treated Patients by Decreasing Frequency; Controlled and Uncontrolled GAD Trials

Adverse event Preferred Term	% (number) of patients n=1962	Adverse event Preferred Term	% (number) of patients n=1962
Dizziness	31.4% (617)	Diarrhea	6.1% (119)
Somnolence	30.3% (595)	Nervousness	5.2% (102)
Headache	18.0% (354)	Amnesia	5.1% (100)
Infection	15.6% (307)	Accidental injury	5.0% (98)
Dry mouth	15.1% (296)	Flatulence	4.9% (96)
Nausea	11.2% (220)	Increased appetite	4.7% (93)
Weight gain	9.1% (178)	Pain	4.2% (83)
Incoordination	8.8% (173)	Depression	4.1% (80)
Euphoria	8.5% (166)	Dyspepsia	4.1% (80)
Amblyopia	8.2% (161)	Pharyngitis	4.1% (80)
Thinking abnormal	8.0% (157)	Libido decreased	3.7% (72)
Asthenia	7.1% (139)	Back pain	3.6% (70)
Insomnia	6.8% (134)	Rhinitis	3.5% (69)
Constipation	6.3% (123)	Sinusitis	3.4% (67)
Flu syndrome	6.2% (121)	Abdominal pain	3.1% (61)

From Pfizer Appendix GAD.031 (Summary of Safety pp. 13889-13905).

Many of the adverse events listed in the table above occurred at a frequency similar to or slightly greater than that observed among pregabalin-treated patients in the GAD controlled trials alone. A notable exception is weight gain, which occurred substantially more frequently among pregabalin-treated patients in the combined controlled and uncontrolled trials than among pregabalin-treated patients in either the controlled trials alone or the uncontrolled trials alone. Euphoria, flu syndrome, infection, and accidental injury were also more frequent among pregabalin-treated patients in the combined controlled and uncontrolled GAD trial population than in the controlled trial population; these events all occurred at least 2% more frequently among pregabalin-treated patients in the combined controlled and uncontrolled trials than they did in the controlled trials alone.

I reviewed the preferred terms for all other adverse events occurring in pregabalin-treated patients in the GAD controlled and uncontrolled studies. There were no adverse events coded as pancreatitis, acute liver failure, acute renal failure, myopathy, aplastic anemia, Stevens Johnson Syndrome, or toxic epidermal necrolysis.

Combined Controlled and Uncontrolled GAD Trials; Safety Update

No new patients were enrolled in any GAD studies between the original NDA cutoff date and the Safety Update data cutoff date of October 10, 2003. The safety update for the

GAD trials consists of data for 14 patients still enrolled in open-label extension studies on the cutoff date for the original NDA. Twelve of these 14 patients experienced adverse events between the NDA and the Safety Update cutoff dates; all twelve had previously experienced adverse events that were reported with the original NDA data. In the appendix, I have included a table summarizing adverse events occurring in at least 2% of pregabalin-treated patients in the GAD controlled and uncontrolled studies, comparing data from the original NDA with updated data.

Integration of the new data did not substantially change any of the frequencies of the most common adverse events. New adverse events experienced during the period of time captured in the safety update were accidental injury (n=3), abnormal vision (n=2), infection (n=2), pain (n=2), insomnia (n=2), asthenia (n=1), back pain (n=1), neck rigidity (n=1), neck pain (n=1), nausea (n=1), headache (n=1), creatine phosphokinase increased (n=1), arthralgia (n=1), arthritis (n=1), dizziness (n=1), anxiety (n=1), sleep disorder (n=1), paresthesia (n=1), visual field defect (n=1), and retinal disorder (n=1).

4.6.5 Lab Results from the Integrated Database

In their analysis of lab data for the integrated safety database, Pfizer calculated mean changes from baseline for all analytes and based on those results provided additional discussion of platelet and CK outliers. The mean change analyses compared subjects' last lab result prior to initiating study medication in any study (baseline) to their last available non-follow up result (endpoint) (Summary of Safety, Appendix ALL.11, p.1158). Patients' data were excluded if the endpoint lab result was more than 14 days after last dose. Pfizer notes that for the changes by dose analyses, the dose represents the assigned dose and not necessarily the dose taken at the time of the lab collection (Summary of Safety, Appendix ALL.11, p.1159). Pfizer's platelet and CK outlier analyses (shifts outside normal range, clinically important) were based on the lab test result reference ranges for the four central labs that analyzed the samples.

Overall Mean Change from Baseline Lab Data, Controlled Trials

In Pfizer's table 25 (Summary of Safety p.65), they provided the results of mean change from baseline analyses of lab data from the controlled trials in the integrated safety database. This table provided the mean changes for the placebo and pregabalin (by dose and overall) treatment groups and identified the results that were statistically significantly different ($p<.05$, Wilcoxon rank sum test). In the following table I provide the mean changes results for analytes with statistically significant differences when comparing the overall pregabalin group to the placebo group.

FDA Table 29. Mean change from Baseline Results for Lab Analytes with Statistically Significant Differences when Comparing the Overall Pregabalin Group to the Placebo Group, Combined Controlled Trials, Integrated Safety Database

Analyte	Units	Placebo	Pregabalin
Hemoglobin	g/dL	-0.127	-0.193
Hematocrit	%	-0.411	-0.504
WBC	$x10^3/\mu L$	-0.102	-0.231

Differential/neutrophils	%	-0.482	-1.308
Absolute neutrophils	$x10^3/\mu L$	-0.078	-0.22
Differential/lymphs	%	0.3525	1.0332
Differential/eosinophils	%	0.0372	0.1581
Absolute eosinophils	$x10^3/\mu L$	0.0009	0.0032
Platelets	$x10^3/\mu L$	-0.333	-9.542
Glucose/nonfasting	mg/dL	10.178	-0.282
Creatine kinase	U/L	4.8228	9.6638
Uric acid	mg/dL	0.0205	0.1303
BUN	mg/dL	0.1358	0.5383
Albumin	g/dL	-0.041	-0.091
Total protein	g/dL	-0.052	-0.104
Alkaline phosphatase	U/L	-1.185	2.1067
AST	U/L	-0.016	0.9414
ALT	U/L	-0.023	0.9569
HDL Cholesterol	mg/dL	0.3883	-1.218
Sodium	mEq/L	-0.237	0.0459
Calcium	mg/dL	-0.06	-0.103
Amylase	U/L	-1.258	-1.384
Chloride	mEq/L	0.1823	0.5772
Urine protein	mg/dL	-1.833	-0.725

Data from Pfizer Table 25, Summary of Safety, p.65

A majority of the statistically significant differences included in the above table were small in magnitude. After reviewing the mean change results Pfizer concluded that "the mean decrease in platelets and the mean increase in creatine kinase were the only values that warranted additional assessment and discussion" (Summary of Safety, p.64).

Lab Outliers, Controlled Trials

While Pfizer provided results of outlier analyses in the Appendices, in their discussion of the lab data for the overall integrated safety database they reviewed only the outlier results for platelets and creatine kinase. I reviewed the outlier analysis for all analytes in Appendix tables ALL.90 (clinically important changes) and ALL.92 (Very High, High, Low and Very Low values at any time post baseline). With the exception of platelets and creatine kinase, there did not appear to be notable differences in risk for outliers in table ALL.90. Below, I summarize outlier risks for selected analytes included in ALL.90.

FDA Table 30. Potentially Clinically Important Changes, Overall Integrated Randomized Controlled Trials Database

Analyte	Outlier Criteria	Placebo	Pregabalin
Hemoglobin	? = 2g/dL	0.6% (13/2226)	0.6% (32/5158)
WBC	?= $2x10^3/\mu L$ and outside normal range	0.6% (13/2227)	0.9% (49/5158)
Platelets	20% below baseline and <150 $x10^3/\mu L$	1.6% (36/2224)	3.2% (162/5142)
Creatine kinase	>3xULN	0.5% (6/1332)	1% (34/3272)
Creatinine	>1.25xULN	1% (23/2249)	1.4% (72/5204)
BUN	>1.25xULN	2% (44/2249)	2.4% (72/5204)
Total Bilirubin	>1.25xULN	1.3% (30/2248)	1% (52/5201)
Alkaline phosphatase	>1.25xULN	0.6% (14/2248)	1.1% (56/5201)
AST	>3xULN	0.3% (7/2249)	0.5% (24/5202)

ALT	>3xULN	0.3% (6/2249)	0.5% (28/5202)

Data from Summary of Safety Appendix ALL.90

Except for creatine kinase and platelets, there did not appear to be notable differences in risk for outliers in table ALL.92. In many cases the very high/very low outlier category was unhelpful due to the extreme criteria used as a cutoff. Below I summarize outlier risks for selected analytes included in ALL.92.

FDA Table 31. Very High, High, Low and Very Low Values at any Time Post Baseline, Overall Integrated Randomized Controlled Trials Database

Analyte	Outlier Criteria	Placebo	Pregabalin
Hemoglobin	Low: M=11.5g/dL,F=9.5g/dL Very Low: =4.5g/dL	1% (23/2253) 0	1.3% (69/5229) 0
WBC	Low: =2.8 $x10^3/\mu L$ Very Low =0.5 $x10^3/\mu L$	0.8% (17/2254) 0	0.9% (49/5229) 0
Platelets	Low: =100 $x10^3/\mu L$ Very Low =10 $x10^3/\mu L$	0.4% (8/2252) 0	0.9% (46/5142) 0
Creatine kinase	High M=340U/L, F=180U/L Very High =1000U/L	8.1% (125/1544) 0.3% (5/1544)	10.5%(397/3781) 0.7% (28/3781)
Creatinine	High =2mg/dL Very High =6mg/dL	0.4% (8/2264) 0	0.4% (23/5253) 0
BUN	High =30mg/dL Very High =50mg/dL	2.6% (59/2264) 0.4% (9/2264)	2.8% (147/5251) 0.3% (17/5251)
Total Bilirubin	High =2mg/dL Very High =20mg/dL	0.3% (6/2264) 0	0.4% (22/5251) 0
Alkaline phosphatase	High =360U/L Very High =600U/L	0.9% (20/2264) 0.1% (2/2264)	0.8% (40/5251) 0.2% (11/5251)
AST	High =150U/L Very High =300U/L	0.2% (5/2264) 0% (1/2264)	0.1% (7/5251) 0.1% (5/5251)
ALT	High =165U/L Very High =300U/L	0.3% (6/2264) 0.1% (2/2264)	0.2% (12/5251) 0.1% (4/5251)

Data from Summary of Safety Appendix ALL.92

Platelets

Controlled trials

Pfizer reported that for the controlled trial data, all pregabalin dose groups had statistically significant differences in platelet change from baseline compared to placebo. These differences ranged from -5.3 $x10^3/\mu L$ for the 150mg/day pregabalin group to -12.3 $x10^3/\mu L$ for the 450mg/day pregabalin group (-11.5 $x10^3/\mu L$ for the highest pregabalin dose group, 600mg/day). Since the placebo group experienced a small mean change in platelet count (-0.333 $x10^3/\mu L$, N=2224), the observed differences compared to placebo were due to greater mean decreases in platelet counts from baseline in the pregabalin treatment groups (Summary of Safety, p.66).

Pfizer demonstrated an increased risk of low platelet count with pregabalin in the combined controlled trials using two different outlier criteria. Pfizer reported that 0.9% (46/5221) of pregabalin subjects and 0.4% (8/2252) of placebo subjects had a post baseline platelet count of $<100\ x10^3/mm^3$. Pfizer also noted that 3.2% (162/5142) of

pregabalin subjects and 1.6% (36/2224) of placebo subjects had a decrease in platelets of at least 20% and to a total count less than 150 $x10^3/mm^3$ (Summary of Safety, p.66).

Despite these differences in lab results, Pfizer did not find large differences in risk for associated adverse events between the pregabalin and placebo treated groups in the combined clinical trials database. Pfizer reported that thrombocytopenia was reported as an adverse event for 0.3% of pregabalin subjects and 0.1% of placebo subjects. Pfizer also noted that ecchymosis was reported as an adverse event for 0.5% of pregabalin subjects and 0.6% of placebo subjects (Summary of Safety, p.66).

Combined Controlled and Uncontrolled Trials

Pfizer identified 424 pregabalin treated subjects (5.4%, 424/7851) with a decrease in platelets of at least 20% and to a total count less than 150 $x10^3/mm^3$ in their combined controlled and uncontrolled trials database. One hundred and fourteen pregabalin subjects had a post baseline platelet count less than 100 $x10^3/mm^3$. Pfizer reported that one of the 114 subjects had an associated bleeding AE (epistaxis) and one had "thrombocytopenic purpura". Pfizer commented that for most of the other subjects, the low platelet counts were transient or below normal at baseline. Pfizer did not find consistent decreases in WBC counts, hemoglobin, or hematocrit (Summary of Safety, p.66).

In response to a request from the Division, Pfizer provided a listing of all pregabalin subjects with a platelet count <100,000 (March 19, 2004 submission). I reviewed this listing and summarized these data in an appendix. In the following table, I categorize these 120 pregabalin subjects by their lowest on-treatment platelet count.

FDA Table 32. Pregabalin Treated Subjects with Low Platelet Counts Classified by their Lowest On-Treatment Platelet Counts

Lowest Platelet Count	Number of Subjects
None =100,000 on-treatment*	7
100,000	6
90-99,000	36
80-89,000	21
70-79,000	14
60-69,000	9
50-59,000	8
40-49,000	6
30-39,000	4
20-29,000	2
10-19,000	4
0-9,000	3

*pts either had baseline or post-treatment values < 100,000

Sixteen of the 120 subjects had a baseline platelet count <100,000. For these sixteen subjects, eight had platelet count declines on-treatment, seven had their lowest platelet count at baseline, and one had no on-treatment platelet count measured.

Seven of 120 subjects had their only platelet count =100,000 either at baseline or post pregabalin treatment (no on-treatment platelet count <100,000). Of the 113 remaining patients with an on-treatment platelet count =100,000, 94 did not have a platelet count below 50,000. For the nine subjects with on-treatment platelet counts below 30,000, one had a baseline platelet count of 17,000. For the remaining eight subjects with on-treatment platelet counts below 30,000, this was a solitary event and none of these subjects had an additional on-treatment platelet count below 100,000. Three of these subjects had repeat normal platelet counts within days of their very low platelet counts.

To look for evidence of a treatment emergent persistent decline in platelet counts, I identified the subjects with a baseline platelet count =100,000 who had more than one on-treatment platelet count <100,000 or had their last on-treatment platelet count <100,000. Thirty-one subjects met these criteria. I summarize data for these 31 subjects below.

FDA Table 33. Summary Data for the Pregabalin Subjects with a Baseline Platelet Count =100,000 Who Had More Than One On-Treatment Platelet Count <100,000 or Had Their Last On-Treatment Platelet Count <100,000.

Subject	Age	Sex	Baseline PLT*	Lowest On-Treatment PLT	Baseline PLT - Lowest PLT
007-001003	26	Female	176,000	77,000	99,000
009-008015	26	Male	101,000	84,000	17,000
010-003106	58	Female	102,000	38,000	64,000
011-033004	48	Male	154,000	100,000	54,000
014-015013	61	Female	109,000	89,000	20,000
029-001013	56	Male	114,000	73,000	41,000
029-009005	61	Female	146,000	88,000	58,000
029-012010	68	Male	110,000	91,000	19,000
029-015001	70	Female	184,000	82,000	102,000
029-031012	52	Female	255,000	33,000	222,000
029-043014	72	Male	108,000	70,000	38,000
030-118014	73	Male	158,000	96,000	62,000
030-127030	81	Male	194,000	62,000	132,000
030-131014	81	Male	104,000	58,000	46,000
030-217007	76	Male	105,000	87,000	18,000
032-324002	31	Male	142,000	52,000	90,000
032-331005	65	Male	100,000	72,000	28,000
034-003001	28	Female	158,000	87,000	71,000
034-077003	58	Male	108,000	95,000	13,000
035-073108	42	Female	104,000	86,000	18,000
040-023001	67	Male	119,000	59,000	60,000
040-072021	64	Male	101,000	64,000	37,000
045-003003	65	Male	154,000	43,000	111,000
083-303012	35	Male	184,000	95,000	89,000
088-504035	46	Male	151,000	92,000	59,000
104-432005	35	Male	110,000	99,000	11,000
127-002007	75	Male	100,000	70,000	30,000
132-106014	64	Male	125,000	95,000	30,000
149-379002	45	Male	110,000	86,000	24,000
149-483009	66	Male	116,000	70,000	46,000
196-501002	69	Female	131,000	88,000	43,000

* The lowest platelet count prior to starting pregabalin treatment

Many of the subjects listed above had baseline platelet counts that were below the lower limit of normal (140,000 or 150,000) for the study laboratories that performed the analyses (Appendix ALL.82-85).

In addition to the platelet count information, we requested a listing of all AEs for the subjects with PLT <100,000 to determine if the low platelet counts were associated with bleeding events. Eleven of the subjects with low platelet counts had one or more AE terms suggestive of bleeding. I attempted to identify the platelet count near the time of the AE to assess the temporal relationship. I summarize those data below.

FDA Table 34. Subjects with Platelet Counts <100,000 and an AE Term Suggestive For Bleeding

Subject	AE	Study day of the AE	BL PLT	PLT near the time of the AE date
009-027007	Bloody stools	755	17,000	No on tx PLT until day 1037 (20,000)
009-045014	Bruises easily	628	114,000	Day 529 PLT 137,00 Day 620 PLT 122,000 Day 713 PLT 54,000
012-084102	Nose bleed	546	80,000	Day 512 PLT 65,000 Day 581 PLT 70,000
014-012016	Occult blood in stool	206	131,000	Day 127 PLT 122,000 Day 239 PLT 121,000
029-007005	Purpuric rash bilateral feet	53	153,000	Day 28 PLT 176,000 Day 80 PLT 125,000
	Epistaxis nasal hemorrhage	626	153,000	Day 553 PLT 183,000 Day 644 PLT 76,000
029-015001	Epistaxis	281	184,000	Day 197 PLT 100,000 Day 303 PLT 103,000
030-130007	Dark tarry stools	74	161,000	Day 72 PLT 178,000 Day 84 PLT 245,000
030-131014	Bruising multiple sites, petechiae multiple sites	74	104,000	Day 61 PLT 121,000 Day 75 PLT 13,000
031-216010	Nose bleeds	28	105,000	Day 21 PLT 106,000 Day 42 PLT 102,000
034-077003	Pigmented purpura legs	251	108,000	Day 251 PLT 125,000
035-056105	Bruising	374	152,000	Day 338 PLT 185,000 Day 429 PLT 171,000

For many of these events, the bleeding AE did not occur on days when platelet counts were checked. The platelet counts nearest to the bleeding AE did not suggest a relationship for most of these subjects. Subject 030-131014 had a strong temporal relationship between AE (bruising) and a treatment emergent very low platelet count (13,000). I summarize information about that subject below.

030-131014 This 81 year old male with post herpetic neuralgia, questionable mild idiopathic thrombocytopenia (stable platelet count around 110,000), hypothyroidism, heart murmur, and leg cramps, discontinued pregabalin treatment for worsening thrombocytopenia and PVCs. The subject participated in

an RCT where he received pregabalin and his baseline platelet count for that study was 123,000. His visit 4 platelet count was 105,000 and at the end of the RCT his platelet count was 87,000. On open label study day 14, his platelet count was 58,000. He was discontinued from the study on open label study day 25 and his platelet count was 121,000 that day. Thirteen days post treatment he developed bruising and swelling of the forearm, but refused to seek care. The next day he was seen at the study site and was found to have frequent PVCs, an arm and knee bruises, and petechiae on the arms, shoulder, shins, and knees. His platelet count that day was 13,000. He went to an emergency department and a repeat platelet count was 8,000. He was hospitalized and was treated with gamma globulin and recovered. Concomitant medications included aspirin, quinine, and amitriptyline. A consulting hematologist raised the possibility of a relationship of the decline in platelet count to quinine which the subject took on day 36. He had taken this medication as needed over the preceding four years without a similar associated event.

Creatine Kinase

Mean Changes

Pfizer noted that for the overall controlled trials data the mean change from baseline for creatine kinase (CK) among the pregabalin treated subjects was significantly increased compared to placebo for five of the six dose groups, and they considered these mean changes relative to placebo (9.6-26.3U/L) to be small. They also pointed to the statistically significant mean CK decrease relative to placebo for the 450mg/day pregabalin group (-9.5U/L). The mean change for CK was positive for the placebo group (4.82U/L) so that the observed differences compared to placebo were due to greater mean increases in CK from baseline in the pregabalin treatment groups (Appendix ALL.89).

The finding of a mean increase from baseline to end of study for pregabalin subjects was not consistent across the different study indication databases. The epilepsy and pain controlled studies but not the GAD controlled studies found higher mean increases in CK for pregabalin subjects compared to placebo subjects. The mean CK increase among pregabalin subjects in the GAD studies was similar to the mean increase in pregabalin subjects in other studies, but the placebo subjects in the GAD studies experienced a mean CK increase that was inconsistent (higher) with the placebo groups in other studies. A summary of the results by indication is provided in the table below.

FDA Table 35. CK Mean Change from Baseline to End of Study, Controlled Trials

Indication/Database	Placebo	Pregabalin
Overall	4.82	9.66
Diabetic Peripheral Neuropathy	-3.10	11.91
Post Herpetic Neuralgia	2.11	7.78
Epilepsy	-1.23	62.73
GAD	16.01	10.33

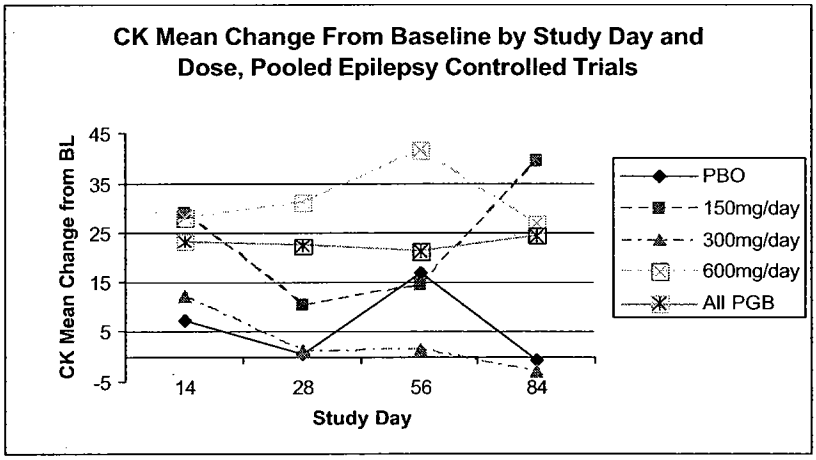
We requested CK mean change from maximum on-treatment value to baseline analyses for the overall pooled controlled trials group and for the individual treatment indication databases. Pfizer provided these analyses in a 3/31/04 submission. Pfizer cautioned that with different trial lengths some groups may have had more post baseline labs per patient making it difficult to interpret these results. We provide the results in the following table.

FDA Table 36. CK Mean Change from Baseline to Maximum On-Treatment Value, Controlled Trials

Indication/Database	Placebo	Pregabalin
Overall	27.90	60.13
Diabetic Peripheral Neuropathy	13.17	32.41
Post Herpetic Neuralgia	15.53	27.57
Epilepsy	45.77	107.79
GAD	19.41	64.10

The mean change from baseline to maximum analysis found a higher mean increase in CK for pregabalin subjects compared to placebo for all treatment indication groups.

To assess when the CK changes were occurring in the study, we requested analyses of mean CK change by study visit for the controlled trials. We selected the group of epilepsy trials for display because the trial durations and testing intervals were identical while for the other indications, the trial durations and testing intervals varied considerably making it more difficult to interpret the results. Below is a plot of the CK mean changes by study visit for the pooled epilepsy controlled trials. The mean CK increases from baseline relative to placebo were present early, varied over the course of the studies, and did not suggest an ordered dose response for the studied doses.



Outliers

Pfizer demonstrated an increased risk of high post baseline CK result with pregabalin in the combined controlled trials using three different outlier criteria. Pfizer reported that 1.7% (62/3742) of pregabalin subjects and 0.8% (12/1529) of placebo subjects had a post baseline CK greater than 3x ULN (Appendix ALL.93C). Pfizer found that 10.5% (397/3781) of pregabalin subjects and 8.1% (125/1544) of placebo subjects had a high CK lab result (=340U/L in males, =180U/L in females) at any time. Furthermore, 0.7%

(28/3781) of pregabalin subjects and 0.3% (5/1544) of placebo subjects had a very high CK result (=1000U/L) (Appendix ALL.092)*.

Since Pfizer's analyses could have included subjects with abnormal results at baseline, we asked for outlier analyses that included only subjects with normal CK results at baseline. Pfizer provided those results in a 4/27/04 submission and I summarize both the NDA analyses (all subjects) and the updated analyses (only those normal at baseline) in the following table.

FDA Table 37. Summary of CK Outlier Analyses Results, Overall and by Indication, Pregabalin Controlled Trials*

	NDA Analysis (All Subjects)		Updated Analysis (Subjects with Normal Baseline CK)	
Outlier Criterion	Pregabalin	Placebo	Pregabalin	Placebo
Overall Pooled Controlled Trials				
>3x ULN	1.7% (62/3742)	0.8% (12/1529)	0.9 (27/2944)	0.4% (5/1223)
=340U/L males, =180U/L females	10.5% (397/3781)	8.1% (125/1544)	6.7% (198/2944)	5.6% (69/1223)
=1000U/L	0.7% (28/3781)	0.3% (5/1544)	0.5% (16/2944)	0.2% (2/1223)
Diabetic Peripheral Neuropathy Pooled Controlled Trials				
>3x ULN	0.8% (5/595)	(0/289)	0.6% (3/517)	(0/252)
=340U/L males, =180U/L females	7% (45/647)	5.9% (18/307)	3.7% (19/517)	4% (10/252)
=1000U/L	0.3% (2/647)	0.3% (1/307)	0.2% (1/517)	(0/252)
Post Herpetic Neuralgia Controlled Trials				
>3x ULN	0.4% (2/562)	0.4% (1/259)	0.4% (2/500)	0.4% (1/240)
=340U/L males, =180U/L females	9.5% (57/598)	7% (19/273)	5.4% (27/500)	4.6% (11/240)
=1000U/L	(0/598)	(0/273)	(0/500)	(0/240)
Epilepsy Controlled Trials				
>3x ULN	2.3% (5/222)	(0/64)	2.4% (5/205)	(0/58)
=340U/L males, =180U/L females	12.4% (54/421)	9.5% (12/126)	14.1% (29/205)	6.9% (4/58)
=1000U/L	1.2% (5/421)	0.8% (1/126)	2% (4/205)	(0/58)
GAD Controlled Trials				
>3x ULN	0.8% (6/756)	0.7% (2/295)	0.4 (3/686)	0.4% (1/274)
=340U/L males, =180U/L females	7.1% (57/808)	7.3% (23/316)	2.9% (20/686)	5.8% (16/274)
=1000U/L	0.9% (7/808)	0.3% (1/316)	0.3% (2/686)	(0/276)

* In this analysis Pfizer classified subjects to a single category based on their most extreme result, so that the High (=340U/L males, =180U/L females) and Very High (=1000U/L) categories are mutually exclusive. In other words, subjects in the Very High category are not also included in the High category.

The epilepsy trials included the highest outlier risks among the different indication databases. With few exceptions, the pregabalin treated subjects had slightly higher outlier risks compared to the placebo treated subjects.

For the controlled trials, Pfizer provided CK outlier results stratified by multiples of the ULN. Those results are summarized below.

Pfizer Table ALL.093C Summary of Creatine Kinase Levels Stratified by Increase Over Upper Limit of Normal Controlled Studies - All Indications (Studies 009,011,014,017,021,022,025,026,029,030,031,032,034,040,045,080,081/153,083,085,087,092,094,104,105,127,131,132,149,173,196) - Combined Regimens

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

	Pregabalin Dose, mg/day (BID and/or TID)								
	Placebo	50	75	150	200	300	400	450	600
<=1X ULN	1319 (86.27%)	74 (92.50%)	55 (87.30%)	542 (86.17%)	104 (87.39%)	815 (81.34%)	233 (88.93%)	400 (85.47%)	903 (80.70%)
>1 to 2X ULN	177 (11.58%)	3 (3.75%)	6 (9.52%)	69 (10.97%)	9 (7.56%)	157 (15.67%)	24 (9.16%)	49 (10.47%)	159 (14.21%)
>2 to 3X ULN	21 (1.37%)	1 (1.25%)	2 (3.17%)	10 (1.59%)	3 (2.52%)	21 (2.10%)	2 (0.76%)	8 (1.71%)	31 (2.77%)
>3 to 4X ULN	6 (0.39%)	1 (1.25%)	0 (0.00%)	6 (0.95%)	1 (0.84%)	5 (0.50%)	1 (0.38%)	2 (0.43%)	15 (1.34%)
>4 to 5X ULN	3 (0.20%)	1 (1.25%)	0 (0.00%)	0 (0.00%)	1 (0.84%)	1 (0.10%)	1 (0.38%)	0 (0.00%)	4 (0.36%)
>5 to 10X ULN	1 (0.07%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.84%)	1 (0.10%)	1 (0.38%)	4 (0.85%)	3 (0.27%)
> 10X ULN	2 (0.13%)	0 (0.00%)	0 (0.00%)	2 (0.32%)	0 (0.00%)	2 (0.20%)	0 (0.00%)	5 (1.07%)	4 (0.36%)

For all pregabalin dose groups combined, the risk for CK greater than 5xULN was 0.6% (23/3742) compared to 0.2% (3/1529) for the placebo groups. The risk for CK greater than 5xULN in the 450mg/day and 600mg/day groups combined (1%, 16/1587) was three times higher than the risk in the remaining lower dose groups (0.32%, 7/2155).

For all pregabalin dose groups combined, the risk for CK greater than 10xULN was 0.35% (13/3742) compared to 0.13% (2/1529) for placebo. The risk for CK greater than 10xULN in the 450mg/day and 600mg/day groups combined (0.6%, 9/1587) was three times higher than the risk in the remaining lower dose groups (0.19%, 4/2155).

For the combined controlled and uncontrolled trials, Pfizer provided the following CK outlier table.

Pfizer Table Appendix FDA2004APR07 Summary of Creatine Kinase Levels Stratified by Increase Over Upper Limit of Normal
Combined Controlled and Uncontrolled Studies - All Indications
Pregabalin Summary of Clinical Safety: Neuropathic Pain, Adjunctive Therapy for Partial Seizures, and Generalized Anxiety Disorder

	All Pregabalin
<=1X ULN	5243 (77.4)
>1 to 2X ULN	1110 (16.4)
>2 to 3X ULN	232 (3.4)
>3 to 4X ULN	79 (1.2)
>4 to 5X ULN	31 (0.5)
>5 to 10X ULN	44 (0.6)
> 10X ULN	37 (0.5)

The Division asked Pfizer to determine if the subjects with CK >5x ULN also had recorded AEs suggestive of myopathy (ex. muscle weakness, muscle pain, etc.). In their 4/19/04 submission, Pfizer noted that 8/81 subjects with CK >5x ULN also had an AE possibly suggestive of myopathy. Pfizer provided the listings for these subjects that included the start and stop date for the AE and the date of the CK abnormality. For four of these subjects, the AE date was not temporally related to the lab abnormality date. For the remaining four subjects, the AE occurred near the time of the CK abnormality. One additional subject had an AE of rhabdomyolysis that was associated with a CK result of 4672 U/L but this result was from a local lab and therefore did not appear in the clinical trial database and was not identified in the analysis. Lastly, Subject 149-430001 who developed myopathy with elevated CK was not mentioned by Pfizer in this analysis. Following are the narrative summaries for the six subjects with AEs suggestive of myopathy associated with CK results >5x ULN.

Patient 010_008124, a 45-year-old man with seizures, developed rhabdomyolysis (COSTART preferred term myopathy) on Study Day 330 (creatine kinase at a local laboratory was 4672 U/L, normal range: 20-200 U/L), concurrent with new diagnoses of anemia, hepatitis C, Type II diabetes, hypokalemia (2.9 mmol/L, normal range: 3.5-5.3), hyponatremia, hypotension, and a serious adverse event of cellulitis, with a fever of 107°F. Creatinine was 1.4 mg/dL (normal: 0.35-0.93) at the onset of the event. The patient was receiving pregabalin 400 mg/day at the onset of the event. The investigator considered the rhabdomyolysis related to the concurrent serious adverse event of cellulitis. Neither the cellulitis nor the rhabdomyolysis was considered related to pregabalin. The rhabdomyolysis did not meet the criteria for a serious adverse event and was mild in intensity. The patient recovered from this event, with creatine kinase levels declining

to 614 U/L within a week and creatinine declining to normal within 2 weeks while the patient continued on pregabalin. The patient remained in the study.

Patient 032_306004, a 55-year-old man with chronic low back pain and a history of hypertension, hyperlipidemia, degenerative lumbar disc disease, and sigmoid colon polyps, developed cramps-leg (leg cramps) and cramps-stomach (abdominal pain) on Day 191 while on 300 mg/day pregabalin. The patient had previously received pregabalin 150 mg/day for 49 days in preceding double-blind Study 1008-032; hence total exposure to pregabalin at the time of onset of leg cramps and abdominal pain was 240 days. Other adverse events in this study included hypertonia and leg cramps on Day 160 while on 600 mg/day pregabalin, and CK, ALT, and AST elevations on Day 167. Study medication was interrupted from Day 180 to Day 189, resumed on Day 190, and permanently discontinued on Day 197 due to the adverse events of leg cramps and abdominal pain. The adverse events of leg cramps and abdominal pain resolved on Day 201. Creatine kinase was 1893 U/L on Day 169 and returned to 287 U/L on Day 206 (normal ranges 52-336 U/L). AST and ALT elevations were <2 X ULN when the elevations were reported. Concurrent medications included atenolol, hydrochlorothiazide, ibuprofen, and paracetamol. The investigator considered the adverse events of leg cramps and abdominal pain moderate in intensity and related to study medication.

Patient 032_322019 (Study 1008-032), a 39-year-old woman with chronic low-back pain and a history of gastroesophageal reflux disease, irritable bowel syndrome, asthma, ovarian cysts, obesity, and degenerative joint disease, had an increased creatine kinase value reported as an adverse event on Study Day 21 and fibromyalgia (myalgia) on Study Day 22. The patient received the fixed dose of pregabalin 600 mg/day through Study Day 22. On that day, the patient discontinued study medication and withdrew due to the adverse event of creatine kinase increased. The patient was also receiving premarin, medroxyprogesterone, serevent inhalation aerosol, albuterol sulfate 0.5% nebulizer, omeprazole, triamcinoline acetonide cream, Tylenol PM, Excedrin, ibuprofen, vicodin, diphenhydramine hydrochloride, and flovent. On Day 21, the creatine kinase value (1139 U/L) was above normal limits (38 – 176 U/L). There was no baseline or prior creatine kinase value available. On Study Day 29, 7 days after discontinuing pregabalin, the creatine kinase value of 108 U/L was within normal limits and the corresponding adverse event of creatine kinase increased was considered resolved. The patient reported the adverse event myalgia on Day 22, the last day of dosing with pregabalin 600 mg/day. The investigator considered the myalgia moderate and of unknown relationship to the study medication. At the last follow-up, the patient had not yet recovered from the myalgia.

Patient 080_112001, (Study 1008-080), a 30-year-old man with social phobia and a history of mitral valve prolapse, experienced rhabdomyolysis (myopathy) on Study Day 16 of treatment with pregabalin. At the time of the initial finding, the patient had received 3 days of treatment with 300 mg/day pregabalin (100 TID) followed by 13 days of treatment with 450 mg/day pregabalin (150 mg TID). At screening the patient's creatine kinase (CK) = 94 U/L (normal 52-226), alanine aminotransferase (ALT) = 22 U/L (normal 10-45), and aspartate aminotransferase (AST) = 24 U/L (normal 12-31) were within the normal range. The study investigator saw the patient for his Week 2 study visit on Day 16. The routine clinical labs drawn at this visit revealed an elevated values for CK = 30,700 U/L, ALT = 142 U/L and AST = 507 U/L with potassium (K) levels remaining normal. The labs were repeated on Day 17 with CK, ALT and AST continuing to be elevated 44,700 U/L, 170 U/L, and 787 U/L, respectively. Additionally, K was elevated on Day 17 with a value of 8.4 mEq/L (normal = 3.6-4.8). The patient complained of sore muscles, which he attributed to recent weight-lifting workouts, but was otherwise asymptomatic. On Study Day 19, the drug was stopped and the patient was instructed to go to the emergency room for evaluation and was admitted at that time with a diagnosis of rhabdomyolysis. Clinical labs conducted on Day 19 were CK = 39,743, AST = 762, and K = 3.3. An electrocardiogram showed non- specific ST segment and T wave abnormalities. He was treated with intravenous hydration and alkalinization of his urine. The patient was discharged from the hospital 2 days later on Day 21 without complications or sequelae. Clinical labs were done upon discharge on Day 21 showed CK= 13,996 and K = 3.7. Final clinical labs were completed at the withdrawal visit on Day 32 and showed all laboratory values had returned to normal. Concomitant medication included propranolol hydrochloride. The patient recovered from the event of rhabdomyolysis on Day 30. The investigator considered the event severe and probably related to pregabalin.

Patient 085_416002 (Study 1008-085), a 24 year-old white man with generalized anxiety, reported muscle ache (myalgia) on Study Day 40 of the double blind study (Study 1008-085). The patient received the fixed dose of pregabalin 450 mg/day through Study Day 49, when he completed the study. The patient had no medical history relevant to the adverse event of myalgia. At the onset of myalgia, concurrent medications were sumatriptan succinate, ibuprofen, and pseudoephedrine hydrochloride. On Study Day 40, the patient was treated with naproxen for the myalgia. The patient recovered from the myalgia on Study Day 43. The investigator commented that the myalgia was secondary to exercise, and considered it moderate and definitely not related to pregabalin. On Study Day 43, while receiving pregabalin 450 mg/day, the patient had a creatine kinase value (12,310 U/L) above normal limits (52 – 336 U/L), which was also reported as an adverse event (elevated CK). The laboratory test was repeated on Study Day 45, with the creatine kinase value (2642 U/L) less elevated but still above normal limits. The investigator commented that the elevated creatine kinase was also related to exercise; at both Day 43 and Day 45, the source of the elevated creatine kinase was the muscles (creatine kinase isoenzyme MM). At Study Day 49, while the patient was still receiving pregabalin 450 mg/day, the creatine kinase value (340 U/L) was close to the upper limit of normal and the adverse event was considered resolved. After completing Study 1008-085, the patient entered the open label study (Study 1008-084). Excluding the 3-day titration period, the patient received pregabalin 300 mg/day through Study Day 30 and began receiving pregabalin 600 mg/day at Study Day 31. The creatine kinase value had been elevated at the last measurement in the double blind study, and was also above normal limits at the first measurement in the open-label study, on Day 22 of Study 1008-084 (816 U/L). However, the value was within normal limits on Study Day 30 (154 U/L). On Study Day 99, the patient withdrew consent and discontinued study medication. On Day 100 of Study 1008-084, the patient had a creatine kinase value of 5146 U/L; the source the source of the elevated creatine kinase was the muscles (creatine kinase isoenzyme MM). The increased creatine kinase was reported as an adverse event on Study Day 101. The investigator considered the event severe and unlikely related to pregabalin. There were no subsequent measurements of creatine kinase in the study.

Patient 149_430001, a 31 year old female with a history of diabetes mellitus, neuropathy, nephrotic syndrome, gastroparesis, retinopathy, recurrent UTIs, and hypertension developed acute renal failure, rhabdomyolysis, and pneumonia. The study drug was stopped on study day 59 for the adverse events of pneumonia, rhabdomyolysis, acute renal failure, and fever. The narrative reported that this subject was admitted to a hospital on study day 60 with acute renal failure, fever, lethargy, shortness of breath, cough, dehydration, and painful swelling and weakness in her legs. The patient profile submitted by Pfizer included lab values from study day 59 and at that time her CK was 79 U/L and her creatinine was 2.7mg/dL (baseline creatinine 1.4 mg/dL). While hospitalized she was diagnosed with pneumonia and myopathy. On study day 60, her CK rose to 4504 U/L, and her creatinine was 5.6mg/dL. She was treated with antibiotics, insulin, heparin, and intravenous fluids. Her creatinine improved to 2 mg/dL and creatinine kinase to 124 U/L. and she was discharged on study day 72.

To put the CK abnormalities in perspective, I read the review of CK for rosuvastatin, a recently approved treatment for elevated cholesterol. Rosuvastatin was associated with CK elevations and the development program included cases of rhabdomyolysis that resulted in limi ting the maximum recommended dose (80mg dose was not approved). In the rosuvastatin NDA, the risk for CK elevations >5x the ULN in the combined controlled and uncontrolled data lower dose groups (5-40mg) was 0.5% (30/5544) compared to 2.4% (32/1314) in the 80mg group. The risk for CK elevations >10x the ULN in the combined controlled and uncontrolled data lower dose groups (5-40mg) was 0.2% (11/5544) compared to 1.3% (17/1314) in the 80mg group. The reviewer reported that the risk for CK elevations >5x ULN associated with symptoms of myopathy was 0.09% (5/5544) in the combined lower dose groups compared to 1.1% (14/1314) in the 80mg group. There were no cases of rhabdomyolysis in the lower dose groups while the risk for rhabdomyolysis in the 80mg group was 0.5% (6/1314)

To further examine instances of extreme CK elevation with pregabalin, I reviewed the summary of the CK data for the 28 subjects from controlled trials with a CK=1,000 (see outlier table above). The group includes 12 subjects (first 12 in the table below) with a CK elevation that appeared to decrease or resolve with continued pregabalin treatment. For the remaining 16 subjects, the CK=1,000 was either the only on-treatment CK measurement for the subject or the CK was increasing at the time of the last on-treatment measurement.

FDA Table 38. Summary of the CK Data for the 28 Pregabalin Subjects from Controlled Trials with a CK=1,000

Subject ID	Highest CK on PGB	Baseline CK*	CK ULN†	Comments
CK elevation resolved or improved while continuing pregabalin treatment				
029-041007	8404		336	Day 6 CK 113, Day 27 CK 8404, Day 34 CK 90 (last on tx) no post tx
031-227005	1255	213	336	Day 8 CK 1255 (first on tx), Day 22 CK 518, Day 43 CK 396, Day 56 CK 194 (last on tx) no post tx
034-036005	1471	84	336	Day 13 CK 83 (first on tx), Day 32 CK 1471, Day 55 CK 90, Day 87 CK 80 (last on tx), no post tx
080-105024	1062	165	336	Day 14 CK 1062 (first on tx), Day 28 CK 233, Day 68 CK 300 (last on tx) no post tx
080-107019	2632	15860	336	Day 6 CK 2632 (first on tx), Day 19 CK 311, Day 29 CK 317 (last on tx), Day 98 CK 184 (post tx)
080-107033	15920	1139	336	Day 8 CK 486 (first on tx), Day 13 CK 15920, Day 15 CK 10280, Day 27 CP 575, Day 32 CK 478, Day 55 CK 713, Day 69 CK 507 (last on tx) no post tx
081-210009	1499	156	336	Day 14 CK 258 (first on tx), Day 28 CK 1499, Day 42 CK 895, Day 56 CK 254 (last on tx), no post tx
085-416002	12310	102	336	Day 43 CK 12310 (first on tx), Day 45 CK 2642, Day 49 CK 340 (last on tx) no post tx
104-416016	1128	1824	336	Day 30 CK 1128 (first on tx), Day 38 CK 395 (last on tx), Day 66 CK 925 (post tx)
104-439007	1049	175	176	Day 21 CK 1049 (first on tx). Day 27 CK 233, Day 56 CK 307 (last on tx) no post tx
105-519005	1312	1493	176	Day 22 CK 1312 (first on tx), Day 30 CK 645, Day 59 CK 630 (last on tx) no post tx
149-418020	1107	10	80	Day 9 CK 13 (first on tx), Day 30 CK 22, Day 58 CK 1107, Day 60 CK 11 (last on tx), Day 86 CK 13 (post tx)
Abnormal CK was the only on-treatment result or was present at the last on-treatment result				
009-008016	4722		336	Day 14 CK 150 (first on tx), Day 28 CK 187, Day 56 CK 193, Day 84 CK 4722, Day 86 CK 1031 (post tx), Day 91 CK 244 (post treatment)
026-003042	1112		336	Day 36 CK 1112 (first/only on tx), Day 47 CK 1101 (post tx)
032-307029	1097		336	Day 54 CK 1097 (only available CK)
032-322019	1139		176	Day 21 CK 1139 (first/only on tx), Day 29 CK 108 (post tx), Day 35 CK 80

034-045004	1100	80	336	Day 14 CK 110 (first on tx), Day 29 CK 98, Day 55 CK 78, Day 83 CK 1100 (last on tx) no post tx
034-053002	1241	242	336	Day 15 CK 461 (first on tx), Day 30 CK 309, Day 59 CK 229, Day 79 CK 1241 (last on tx), no post tx
034-060005	8735	94	176	Day 13 CK 105 (first on tx), Day 27 CK 81, Day 55 CK 96, Day 79 CK 8735 (last on tx) no post tx
080-111029	1207	162	336	Day 13 CK 484 (first on tx), Day 69 CK 1207 (last on tx), Day 79 CK 153 (post tx)
080-112001	44700	94	336	Day 16 CK 30700 (first on tx), Day 17 CK 44700 (last on tx), Day 33 CK 144 (post tx)
083-301019	4925	198	176	Day 28 CK 4925 (first/only on tx) Day 35 CK 249 (post tx), Day 42 CK 178 (post tx), Day 49 CK 339 (post tx), Day 56 CK 509 (post tx), Day 70 CK 169 (post tx)
083-305010	1102	736	336	Day 25 CK 1102 (first/only on tx) no post tx
083-305047	19510	99	336	Day 31 CK 19510 (first/only on tx) Day 38 CK 508 (post tx), Day 45 CK 196 (post tx), Day 59 CK 120 (post tx)
083-307017		2061	336	No on tx values, Day 25 CK 1788 (post tx)
085-401018	3936	970	336	Day 49 CK 3936 (first/only on tx), Day 58 CK 537 (post tx), Day 110 CK 326 (post tx)
094-804001	1093	80	170	Day 20 CK 1093 (first/only on tx), Day 27 CK 745 (post tx)
104-419028	5735	146	336	Day 21 CK 1243 (first on tx), Day 27 CK 3749, Day 29 CK 5735 (last on tx), no post tx

*For subjects with more than one baseline CK, the highest baseline is displayed
†ULN from Appendix ALL.096 and from lab data sets

In addition to the pregabalin subjects above, the sponsor identified five placebo subjects from controlled trials who had a CK=1,000. I summarize those results below.

FDA Table 39. Summary of the CK Data for the Five Placebo Subjects from Controlled Trials with a CK=1,000

Subject ID	Highest CK	Baseline CK*	CK ULN†	Comments
026-003052	4052	1043	336	Day 6 CK 1092, Day 20 CK 886, Day 25 CK 4054
029-007017	1006		336	Day 6 CK 1112 (first on tx), Day 20 CK 1006, Day 35 CK 473
034-050008	1350	778	336	Day 16 CK 854, Day 28 CK 602, Day 58 CK 1350, Day 84 CK 775
080-101024	1042	72	336	Day 15 CK 1042, Day 71 CK 92
080-104004	11415	74	336	Day 15 CK 11415, Day 23 CK 397, Day 84 CK 60

In the controlled trials, the risk for CK=1,000 was higher for pregabalin (0.7% 28/3781) compared to placebo (0.3%, 5/1544). These tables illustrate that for some subjects the CK abnormalities were present at baseline and that CK elevations were present in the placebo

treated subjects supporting that these events occur in the background. In addition, there were subjects who developed marked CK elevations on pregabalin that resolved with continued treatment. A number of subjects had their marked CK abnormality for their only on-treatment test or at their last on-treatment test.

Elevated CK and Creatinine

Pfizer reported that among the pregabalin treated subjects with an elevated creatine kinase result, four had evidence of renal dysfunction defined as an increase in creatinine >0.2mg/dL (Summary of Safety, p. 67). Pfizer noted that three of these four subjects (149 375009, 149 430001, and 014 017005) had evidence of renal dysfunction at baseline and experienced further increase in creatinine that were temporally associated with the increase in creatine kinase. The fourth subject (131 104008) had an elevated creatine kinase at baseline and both creatine kinase and creatinine increased during the study (both analytes returned to normal after stopping pregabalin). Pfizer identified an additional subject (010 008124) who had elevations in creatine kinase and creatinine but these lab values were from a local laboratory and were not included in the lab database so this subject did not appear in the above analysis. This subject's narrative is included above (Summary of Safety pp.67-68.).

Pfizer concluded that pregabalin appears to elevate creatinine kinase in some patients but they did not feel that this finding was associated with a clinically important risk of renal dysfunction (Summary of Safety p.68).

Patients with Total Bilirubin=2mg/dL and with ALT and/or AST>3x ULN

I requested a table that included all total bilirubin, AST and ALT results for pregabalin subjects who had a total bilirubin result =2mg/dL. The purpose of the request was to identify all pregabalin subjects with a total bilirubin =2mg/dL and AST and/or ALT>3 times ULN. In a 3/19/04 submission, Pfizer provided a table that included information for 56 pregabalin subjects with a total bilirubin result =2mg/dL. Six of the subjects who had a total bilirubin =2mg/dl also had an AST and or ALT >3x ULN. I summarize the lab data for those six subjects below.

FDA Table 40. Summary of Data for the Six Pregabalin Subjects who had a Total Bilirubin =2mg/dl and had an AST and or ALT >3x ULN

Subject ID	High T bili on PGB	Baseline T bili*	Comments
014-021004	3.7	1.5	BL ALT 78, AST 52, Day 14 ALT 107, AST 56 T bili 1.3 (first on tx), Day 71 ALT 1234, AST 824, T bili 3.7(first on tx=2), Day 78 ALT 902, AST 590, T bili 2.5, Day 84 ALT 378, AST 192, T bili 2.3, Day 127 ALT 19, AST 17, T bili 1, remaining on-tx T bili<2 (through day 700)
034-036006	5.8	1.1	BL ALT 78, AST 93, Day 172 ALT 117, AST 260, T bili 0.9, Day 256 ALT 135, AST 190, T bili 5.8, Day 333 ALT 33, AST 34, T bili 0.5 (last on tx) Day 438 ALT 22, AST 26, T bili 0.3 (post tx)

132-106011	4.9	0.5	BL ALT 30, BL AST 28, Day 10 ALT 29, AST 30, T bili 0.5, Day 31 ALT 638, AST 395, T bili 4.9 (last on tx), Day 37 ALT 438, AST 246, T bili 1.8 (post tx), Day 58 ALT 34, AST 29, T bili 0.7 (post tx)
149-371002	5.1	0.4	BL ALT 8, AST 8, Day 92 ALT 136, AST 84, T bili 5.1 (first on tx >2), Day 178 ALT 13, AST 9, T bili 0.4, no other on tx T bili=2
149-415019		0.7	BL ALT 6, AST 6, No on tx results, Day 14 ALT 141, AST 203, T bili 6.9 (post tx)
173-328015	0.7	1.2	BL ALT 37, AST 79, Day 8 ALT 30, AST 71 T bili 0.7 (first/only on tx), Day 29 ALT 62, AST 179 T bili 2.3 (post tx), Day 31 ALT 73, AST 203, T bili 1.7(post tx)

* For subjects with more than one baseline value, highest T bili selected

Below, I summarize information from the narratives and/or patient profiles for the subjects identified in the above table. Two of the cases were likely related to cholelithiasis, one case occurred in a subject with a history of alcohol abuse and hospitalizations for pancreatitis; one subject was re-challenged with pregabalin following the event without recurrence; one event was noted eight days after a subject had discontinued from a trial, following a GI bleed (on day 6); and the last event occurred in a subject who had slightly elevated AST and total bilirubin at baseline.

014 021004 This 44 year old female with diabetes mellitus, and neuropathy developed elevated liver function test results. The narrative reported that this subject was diagnosed with hyperthyroidism and started on propylthiouracil. Approximately two weeks later she entered a pregabalin trial and was randomized to placebo. Baseline LFTs for this study included ALT 20 U/L, AST 21 U/L, ALP 201 U/L, and total bilirubin 0.9mg/dL. On study day 15, while receiving placebo, she had the following results: ALT 81 U/L, AST 55 U/L, ALP 222 U/L, and total bilirubin 1.1mg/dL. On study day 28, the transaminases and ALP decreased slightly while the total bilirubin increased to 1.5mg/dL. At the termination visit for this study, she had the following results: ALT 42 U/L, AST 43 U/L, ALP 230 U/L, and total bilirubin 1.1mg/dL. She then enrolled in the open label study and began pregabalin treatment. The narrative reported negative results for Hepatitis A, B, and C, and a positive test for CMV. On study day 71 her ALT was 1234U/L, her AST was 824U/L and her total bilirubin was 3.7mg/dL with an ALP of 824U/L. Pregabalin was held on day 71, and propylthiouracil was stopped on day 77. She was treated with radioactive iodine on day 85. Lab tests on day 127 included an ALT of 19 U/L, AST U/L, and a total bilirubin of 1 mg/dL. Pregabalin was re-started on day 136 and LFTs remained normal on pregabalin.

034 036006 This 41 year old male with a history of alcohol abuse was admitted to a hospital for pancreatitis on study day 173. He presented with nausea and vomiting. An abdominal ultrasound demonstrated fatty liver. Labs included lipase 400IU/L, amylase 96 U/L, total bilirubin 3.5mg/dL, ALP 252 U/L, AST 455 U/L, and blood alcohol 243mg/dL. He was treated with IV fluids, recovered, and continued in the study. Concomitant medications at the time of the event were doxazosin, potassium, omeprazole, fluoxetine, allopurinol, and diclofenac. He had a second admission for pancreatitis on study day 324. This event occurred after several days of alcohol use. He was discontinued from the study at that time.

132 106011 This 86 year old male with a history of post herpetic neuralgia, hypertension, prostate cancer, and hypercholesterolemia withdrew from a study on day 32 for elevated alkaline phosphatase. On day 31 he had the following test results: ALT 638 U/L, AST 395 U/L, total bilirubin 4.9 mg/dL, and ALP 1115 U/L and pregabalin was stopped. On day 37 (off treatment) his ALT was 438 U/L, AST was 246 U/L, total bilirubin was 1.8mg/dL, but his ALP rose to 1366 U/L and his amylase (623 U/L) and WBC count ($13,900/mm^3$) were elevated. He underwent an ultrasound on day 37 and the narrative reported that he passed a gallstone that same day. On day 58, his ALP was 316 U/L, and his transaminases and total bilirubin were normal.

149 371002 This 70 year old female with a history of peripheral neuropathy, hypertension, osteoporosis, and diabetes mellitus, developed worsening cholelithiasis on study day 325 of open label pregabalin. This subject was initially diagnosed with cholelithiasis on study day 92 and underwent papillotomy extraction of choledochous stones on study day 294. On study day 325, she was hospitalized with sharp epigastric pain, fever, and vomiting. She was treated with an unspecified antibiotic and improved. She was told that a cholecystectomy would be necessary. Her only study total bilirubin result >2 mg/dL occurred on day 92 when she was initially diagnosed with cholelithiasis.

149 415019 This 66 year old female with diabetes mellitus, neuropathy, hypertension, recent myocardial infarction, angina, cholelithiasis, hypercholesterolemia, and cataracts developed a GI bleed, jaundice, myocardial infarction, and died. Study medication was stopped on day six, after the subject experienced bleeding from the alimentary tract and black tarry stools. She received a transfusion and endoscopy documented two esophageal erosions, fresh clots in the stomach, and a duodenal ulcer. On day 14 she developed jaundice and an ultrasound documented cholelithiasis. On day 18 she experienced an MI and died. Concomitant medications at the time of the event were atenolol, cilazapril, potassium, amlodipine, lovastatin, hydrochlorothiazide, insulin, and gliclazide.

173-328015 This 43 year old male with neuropathy and diabetes mellitus participated in this study and received pregabalin for 23 days when the study was terminated. During the study, this subject had no adverse events. Baseline ALT was 37 U/L (ULN 45 U/L) AST was 79 U/L (ULN 31 U/L) and total bilirubin was 1.2 mg/dL (ULN 1 mg/dL). On day 8, when his only on-treatment LFTs were measured, his ALT was 30 U/L, AST was 71 U/L and total bilirubin was 0.7mg/dL. On day 29, six day after stopping pregabalin, his ALT was 62 U/L, AST was 179 U/L and total bilirubin was 2.3mg/dL. Follow up labs on day 31 included ALT 73 U/L, AST 203 U/L, and total bilirubin 1.7 mg/dL. Medications taken during the study included glipizide, ibuprofen

Epilepsy Laboratory Data

Controlled Epilepsy trials

Mean Change from Baseline Data

Pfizer provided a table listing the laboratory result mean changes from baseline with statistically significant differences compared to placebo from epilepsy trials. In the following table I provide the mean change results for the analytes where there were statistically significant differences for the overall pregabalin group compared to placebo.

FDA Table 41. Mean Change from Baseline for Analytes where there were Statistically Significant Differences for the Pregabalin Group Compared to the Placebo Group, Controlled Epilepsy Trials

Test	Units	Placebo	All PGB
Differential-Neutrophils	%	0.0267	-0.964
Platelets	x^{103}/μ^{L}	6.0103	-4.974
CK-Creatine Kinase	U/L	-1.234	62.725
Albumin	g/dL	-0.005	-0.043
Sodium	mEq/L	-0.366	-0.029
Potassium	mEq/L	-0.002	0.0495
Chloride	mEq/L	-0.086	0.6671

From Pfizer Table 105, Summary of Safety p.191.

The results of this analysis were similar to the mean change from baseline results for the overall controlled trial database. With the exception of CK and platelets, the mean changes for the pregabalin group were similar to the mean changes for the placebo group.

Pfizer noted that the mean CK increase among pregabalin subjects was greatly influenced by a single subject who had CK of 8656 U/L. To demonstrate the influence of this outlier, Pfizer noted that the median CK increase for the overall pregabalin group was 9U/L (Summary of Safety p.191).

Outlier Results

Pfizer provided results of outlier analyses as appendices. I reviewed the outlier analysis for all analytes in Appendix tables Epilepsy.72 (clinically important changes) and Epilepsy.74 (Very High, High, Low and Very Low values at any time post baseline). As in the overall population, pregabalin subjects had higher risks for low platelet and high creatine kinase outliers. Below, I summarize outlier risks for selected analytes included in Appendix Epilepsy.72.

FDA Table 42. Potentially Clinically Important Changes, Epilepsy Controlled Trials Database

Analyte	Outlier Criteria	Placebo	Pregabalin
Hemoglobin	? = 2g/dL	1% (3/292)	0.7% (5/735)
WBC	?= 2x10^3/μL and outside normal range	1.4% (4/292)	1.8% (13/735)
Platelets	20% below baseline and <150 x10^3/μL	3.4% (10/291)	4.9% (36/733)
Creatine kinase	>3xULN	0% (0/64)	2.3% (5/222)
Creatinine	>1.25xULN	0.7% (2/292)	0.3% (2/736)
BUN	>1.25xULN	0% (0/292)	0.4% (3/736)
Total Bilirubin	>1.25xULN	0% (0/292)	0.3% (2/736)
Alkaline phosphatase	>1.25xULN	0.7% (2/292)	2.6% (19/736)
AST	>3xULN	0.7% (2/292)	0.7% (5/736)
ALT	>3xULN	0.7% (2/292)	0.5% (4/736)

Data from Appendix Epilepsy.72

Except for creatine kinase and platelets, there did not appear to be notable differences in risk for outliers in table Epilepsy.74. As in the overall database analysis, in many cases the very high/very low outlier category was unhelpful due to the extreme criteria used as a cutoff. Below I summarize outlier risks for selected analytes included in Epilepsy.74.

FDA Table 43. Very High, High, Low and Very Low Values at any Time Post Baseline, Overall Integrated Randomized Controlled Trials Database

Analyte	Outlier Criteria	Placebo	Pregabalin
Hemoglobin	Low: M=11.5g/dL,F=9.5g/dL Very Low: =4.5g/dL	1.4% (4/293) (0/293)	1.5% (11/745) (0/745)
WBC	Low: =2.8 x10^3/μL Very Low =0.5 x10^3/μL	3.1% (9/293) (0/293)	3.6% (27/745) (0/745)
Platelets	Low: =100 x10^3/μL Very Low =10 x10^3/μL	0.7% (2/293) (0/293)	1.1% (8/743) (0/743)
Creatine kinase	High M=340U/L, F=180U/L Very High =1000U/L	9.5% (12/126) 0.8% (1/126)	12.4% (52/421) 1.2% (5/421)
Creatinine	High =2mg/dL Very High =6mg/dL	(0/292) (0/292)	0.1% (1/744) (0/744)
BUN	High =30mg/dL Very High =50mg/dL	0.3% (1/292) (0/292)	0.3% (2/744) 0.1% (1/744)
Total Bilirubin	High =2mg/dL	(0/292)	0.1% (1/744)

	Very High =20mg/dL	(0/292)	(0/744)
Alkaline phosphatase	High =360U/L Very High =600U/L	4.1% (12/292) 0.3% (1/292)	3.2% (24/744) 1.1% (8/744)
AST	High =150U/L Very High =300U/L	(0/292) (0/292)	0.1% (1/744) 0.1% (1/744)
ALT	High =165U/L Very High =300U/L	(0/292) (0/292)	0.4% (3/744) 0.1% (1/744)

Data from Appendix Epilepsy.74

GAD Laboratory Data

Controlled GAD Trials

There were no deaths or serious adverse events involving laboratory abnormalities in the controlled GAD studies. Only one pregabalin-treated patient withdrew from a controlled GAD study due to a laboratory abnormality. Patient 083_301019 withdrew from study 83 due to a creatine kinase increase to 4935 U/L (from a baseline value of 198 U/L) while receiving pregabalin 450 mg/day during a taper from her assigned dose of 600 mg/day (see "Discontinuations" section). One patient treated with a comparator withdrew from a controlled GAD study due to a laboratory abnormality; this alprazolam-treated patient developed liver function test abnormalities that led to withdrawal.

Mean Changes from Baseline to Final on Therapy Values

Pfizer provided the mean changes from baseline to endpoint for the laboratory values in which there was a statistically significant difference between pregabalin and placebo. The following table summarizes the mean change results for the laboratory values for which there were statistically significant differences between the overall pregabalin group and the placebo group.

FDA Table 44. Mean Change from Baseline to Endpoint Values for Laboratory Parameters with a Statistically Significant Difference between Pregabalin and Placebo in Controlled GAD Trials

Laboratory test	Units	Placebo	Pregabalin All doses
Differential—neutrophils	%	0.4903	-0.564
Differential—lymphocytes	%	-0.695	1.0855
Platelets	$X10^3/\mu L$	-4.105	-8.178
Creatine Kinase	U/L	16.007	10.325
Uric acid	mg/dL	-0.031	0.153
Albumin	g/dL	-0.081	-0.113
AST	U/L	0.1904	1.3617
ALT	U/L	-0.12	1.9697
Sodium	mEq/L	-0.164	0.1359
Amylase	U/L	-0.374	-1.449

From Pfizer table 125, Summary of Safety p. 219.

A majority of the statistically significant differences that were noted were small in magnitude. Both ALT and AST increased from baseline over the course of pregabalin

treatment (compared to negligible changes from baseline in these parameters for placebo-treated patients), although the changes observed were very small. The greatest changes from baseline in pregabalin-treated patients were evident for creatine kinase and platelet count. Pfizer noted that the mean decrease in platelet count in pregabalin-treated patients was similar to the decrease observed in the overall population of pregabalin-treated patients. The difference in mean change from baseline in platelet count between pregabalin-treated patients and placebo-treated patients in the GAD population was smaller than in the overall population, however, because placebo-treated GAD patients had a more substantial decrease in platelet count than was evident in the overall population. Pfizer also noted that while pregabalin-treated GAD patients had a mean increase in creatine kinase that was similar to the increase observed in the other indications, this increase was smaller in magnitude than the increase that was observed in placebo-treated GAD patients.

Appendix table GAD.071 (Summary of Safety, p. 14359) summarizes mean changes from baseline by pregabalin dosage for all clinical laboratory values measured. A relationship between pregabalin dosage and decrease in platelet count is evident at the lower dosage ranges, with a progressively larger decrease in mean platelet count seen at doses from 150 mg to 300 mg. Platelet count did not appear to decrease substantially more at doses above 300 mg/day. A consistent dose-response relationship for mean creatine kinase increase was not evident. The following table summarizes mean changes from baseline for creatine kinase and platelet count:

FDA Table 45. Mean Change from Baseline for Creatine Kinase and Platelet Count by Dosage in Controlled GAD Trials

Dose (mg/day)	Creatine Kinase (U/L)	Platelet count ($x10^3/\mu L$)
placebo	16.007 (n=295)	-4.105 (n=409)
150	11.778 (n=54)	-2.839 (n=186)
200	8.4032 (n=62)	-4.097 (n=62)
300	13.037 (n=81)	-10.67 (n=81)
400	12.194 (n=170)	-9.313 (n=166)
450	4.8365 (n=159)	-11.97 (n=156)
600	11.961 (n=230)	-8.916 (n=359)

From Pfizer table 2.7.4 Appendix GAD.071, Summary of Safety, p. 14359,

Mean changes from Baseline to Minimum and Maximum Values Observed at any Time on Therapy

In response to the Division's request for additional data analyses, Pfizer also provided the mean changes from baseline to maximum and minimum values measured at any time on therapy for placebo-and pregabalin-treated patients in the GAD controlled trials. In the table below, I summarize these data for selected laboratory values:

FDA Table 46. Mean Changes from Baseline to Minimum and Maximum Values Observed at Any Time on Therapy in Controlled GAD Trials

Laboratory	Units	Minimum or	Placebo	Pregabalin;

Value		Maximum Value[24]			all doses and regimens	
			n	mean change	n	mean change
Hemoglobin	g/dL	Minimum	409	-0.278	1012	-0.237
WBC	$x10^3/\mu L$	Minimum	409	-0.196	1012	-0.294
Platelets	$x10^3/\mu L$	Minimum	409	-4.257	1010	-8.588
Creatine kinase	U/L	Maximum	295	19.41	756	64.098
Creatinine	mg/dL	Maximum	415	0.0015	1023	0.0062
BUN	mg/dL	Maximum	415	0.141	1023	0.5036
Total Bilirubin	mg/dL	Maximum	415	-0.01	1023	-0.003
Alkaline phosphatase	U/L	Maximum	415	-0.843	1023	1.2278
AST	U/L	Maximum	415	0.3494	1023	2.7468
ALT	U/L	Maximum	415	0.0169	1023	2.8886

From 2004MAR16 Request: Table 1.MAX.GAD and 2004MAR16 Request: Table 1.MIN.GAD (in Pfizer submission dated 3/31/04).

The most substantial difference in change from baseline to maximum or minimum value at any time on therapy between pregabalin- and placebo-treated patients was observed for creatine kinase. When values measured at any time on therapy were considered, in contrast to when final on therapy values alone were considered, pregabalin-treated patients had a substantially greater mean change from baseline to maximum observed creatine kinase value than did placebo-treated patients. Pregabalin-treated patients also had a greater mean change from baseline to minimum platelet count measured at any time on therapy than did placebo-treated patients, although the difference was not nearly as marked as for creatine kinase. Moreover, in contrast to creatine kinase, the relationship between pregabalin and placebo with respect to mean change in platelet count from baseline to minimum value observed at any time on therapy was consistent with the relationship observed when only final on therapy values were considered. Mean changes in other laboratory parameters that were observed in the analysis using minimum and maximum values measured at any time on therapy were small, unlikely to be clinically significant, and largely consistent with the earlier analysis examining changes to final on therapy values only.

Given that the most substantial difference between pregabalin- and placebo-treated patients in mean change to maximum or minimum value was observed for creatine kinase, I examined the dose response relationship for this parameter. No clear dose-response relationship emerged. The following table summarizes mean change from baseline to maximum creatine kinase value observed at any time on therapy for placebo and each pregabalin dose group:

FDA Table 47. Mean Change from Baseline to Maximum Creatine Kinase at any Time on Therapy by Dosage in Controlled GAD Trials

Dose (mg/day)	n	Mean change in creatine kinase (U/L)

[24] Although Pfizer provided changes from baseline to both minimum and maximum values for all laboratory parameters (see Pfizer submission dated 3/31/04), I have selected the most clinically relevant direction of change to summarize in this table.

placebo	295	19.41
150	54	12.556
200	62	8.6452
300	81	16.728
400	170	12.847
450	159	223.76[25]
600	230	35.335

Outlier Results

Pfizer provided results of outlier analyses as appendices. I reviewed the outlier analyses for all analytes in Appendix tables GAD.072 (clinically important changes). The following table summarizes outlier risk for selected laboratory values included in GAD.072:

FDA Table 48. Potentially Clinically Important Changes, GAD Controlled Trials Database

Laboratory Value	Outlier Criteria	Placebo	Pregabalin; all doses and regimens
Hemoglobin	? = 2g/dL	0.5% (2/409)	0.2% (2/1012)
WBC	?= $2x10^3/\mu L$ and outside normal range	0% (0/409)	0.4% (4/1012)
Platelets	20% below baseline and <150 $x10^3/\mu L$	0% (0/409)	0.6% (6/1010)
Creatine kinase	>3xULN	0.7% (2/295)	0.8% (6/756)
Creatinine	>1.25xULN	0% (0/415)	0.4% (4/1023)
BUN	>1.25xULN	0% (0/415)	0.2% (2/1023)
Total Bilirubin	>1.25xULN	1.2% (5/415)	1.5% (15/1023)
Alkaline phosphatase	>1.25xULN	0.2% (1/415)	0.4% (4/1023)
AST	>3xULN	0% (0/415)	0.5% (5/1023)
ALT	>3xULN	0% (0/415)	0.6% (6/1023)

The risk for having a laboratory value defined by the sponsor as being potentially clinically important was at least two times greater in pregabalin-treated patients than in placebo-treated patients for white blood cell count decrease, platelet count decrease, creatinine increase, BUN increase, alkaline phosphatase increase, AST increase, and ALT increase. The overall risks for being an outlier for all of these laboratory parameters were small, however. Of note, the risks for creatine kinase elevation to greater than three times the upper limit of normal were comparable for pregabalin- and placebo-treated patients, unlike in the combined controlled trials database and the epilepsy and diabetic peripheral neuropathy controlled trials, in which pregabalin-treated patients had a substantially higher risk than placebo-treated patients for developing creatine kinase elevations considered potentially clinically important. The risk among pregabalin-treated patients for developing a platelet count decrease considered potentially clinically important was lower than in the combined controlled trials database, but demonstrated a similar

[25] Maximum change from baseline in this dosage group was 19,411 U/L. Median change from baseline to maximum creatine kinase value in this dosage group was 6 U/L.

relationship to the risk among placebo-treated patients as was seen in the overall controlled trials database.

Pfizer submitted additional analyses of changes in laboratory values deemed clinically important in which they excluded patients with abnormal baseline values from the analysis.[26] The risks for clinically important changes were very similar in this analysis compared with the more inclusive analysis for most laboratory parameters. Of note, the risk for clinically important creatine kinase elevation in pregabalin-treated patients was 0.4% (3/686). This risk, which was exactly the same as the risk evident in placebo-treated patients with normal baseline creatine kinase values, was slightly lower than the risk in the analysis that also included patients with abnormal baseline values. The risk for clinically important platelet count decrease was 0.6% (6/976), the same absolute risk and risk relative to placebo as in the analysis that included patients with abnormal baseline values. The highest risk for development of a clinically important laboratory value was again observed for total bilirubin, in which 1.5% (13/979) of pregabalin-treated patients developed an increase deemed clinically important compared with 0.8% (3/396) of placebo-treated patients. This risk was comparable to the risk in the analysis that included patients with abnormal baseline values.

I also reviewed the risks of very high, high, low, and very low laboratory values at any time post-baseline as summarized in appendix table GAD.074. The following table summarizes these outlier risks for selected laboratory values included in appendix GAD.074:

FDA Table 49. Very High, High, Low and Very Low Values at any Time Post Baseline, GAD Controlled Trials Database[27]

Analyte	Outlier Criteria	Placebo	Pregabalin
Hemoglobin	Low: M=11.5g/dL,F=9.5g/dL Very Low: =4.5g/dL	0.5% (2/417) 0% (0/417)	0.1% (1/1022) 0% (0/1022)
WBC	Low: =2.8 x10^3/μL Very Low =0.5 x10^3/μL	0.2% (1/417) 0% (0/417)	0.2% (2/1022) 0% (0/1022)
Platelets	Low: =100 x10^3/μL Very Low =10 x10^3/μL	0% (0/417) 0% (0/417)	0.2% (2/1020) 0% (0/1020)
Creatine kinase	High M=340U/L, F=180U/L Very High =1000U/L	7.3% (23/316) 0.3% (1/316)	7.1% (57/808) 0.9% (7/808)
Creatinine	High =2mg/dL Very High =6mg/dL	0.2% (1/420) 0% (0/420)	0% (0/1029) 0% (0/1029)
BUN	High =30mg/dL Very High =50mg/dL	0% (0/420) 0.2% (1/420)	0.1% (1/1029) 0% (0/1029)
Total Bilirubin	High =2mg/dL Very High =20mg/dL	0.5% (2/420) 0% (0/420)	0.3% (3/1029) 0% (0/1029)

[26] See 2004MAR16 Request: Table 2.CIMP.GAD in submission dated 3/31/04.

[27] In Pfizer Appendix GAD.074, from which this table is adapted, patients with laboratory values meeting the criteria for very high were counted only in the very high category rather than in both the high and very high categories, despite meeting criteria for both categories. The same rules were applied by Pfizer to patients with laboratory values meeting the criteria for very low; they were counted only once in the more severe category rather in both the low and very low categories. These rules are explained by Pfizer in Appendix ALL.11 (Summary of Safety, p. 1160) and in a footnote to Appendix GAD.074 on page 14385 of the Summary of Clinical Safety.

Alkaline phosphatase	High =360U/L Very High =600U/L	0.2% (1/420) 0% (0/420)	0.1% (1/1029) 0% (0/1029)
AST	High =150U/L Very High =300U/L	0% (0/420) 0% (0/420)	0.1% (1/1029) 0.2% (2/1029)
ALT	High =165U/L Very High 300U/L	0.2% (1/420) 0% (0/420)	0.3% (3/1029) 0% (0/1029)

From Pfizer Appendix GAD.074 (Summary of Safety, pp. 14385-14392).

Pregabalin-treated patients and placebo-treated patients had similar outlier risks for most laboratory parameters with the exception of very high creatine kinase (defined by the sponsor as creatine kinase =1000 U/L) occurring at any time on therapy. While risks of high creatine kinase (=180 in females and =340 in females) were similar in pregabalin- and placebo-treated patients, the risk of very high creatine kinase was three times higher in pregabalin-treated patients than in placebo-treated patients, which was the highest risk ratio observed for any of the laboratory parameters.

The risk of experiencing platelet count <100 $x10^3/\mu L$ at any time during therapy was very low among pregabalin-treated patients with GAD.

I reviewed additional data submitted by Pfizer in which the risks of developing very high, high, low, and very low laboratory values at any time post-baseline were calculated excluding patients with abnormal laboratory results for the relevant parameter prior to treatment.[28] The most notable differences in outlier risks in this analysis compared with the analysis in which all patients were included regardless of baseline values were evident for creatine kinase. The risks of developing high and very high creatine kinase values were 2.9% (20/685) and 0.3% (2/685) respectively, substantially smaller risks than were evident for the more inclusive analysis. The risk of developing high creatine kinase values that was observed in pregabalin-treated patients was lower than the risk observed in placebo-treated patients, for whom the risks of developing high and very high creatine kinase values were 5.8% (16/276)) and 0% (0/276) respectively. These risks were also smaller than the risks evident for placebo-treated patients in the more inclusive analysis.

4.6.6 Vital Signs

Vital Signs from the Integrated Database

Pfizer reported that during the controlled trials pregabalin had no significant effect on heart rate, blood pressure, or respiratory rate (Summary of Safety, p.68).

Overall Mean Change from Baseline Vital Sign Data

Controlled Trials

[28] See 2004MAR16 Request: Table 2.HILO.GAD in submission dated 3/31/04.

Pfizer's mean change vital sign analyses results were provided as appendix tables. Pfizer calculated mean changes at termination from baseline for supine and sitting systolic and diastolic blood pressure. There were no mean change analyses for heart rate or respiratory rate. The pregabalin group appeared to have slightly greater decreases in blood pressure compared to the placebo group. The following table summarizes the blood pressure mean change results.

FDA Table 50. Summary of Blood Pressure Changes from Baseline, Pooled Controlled Trial Data, All Indications

Mean Change at Termination from Baseline		
	Placebo (n=1153)	Pregabalin (n=2641)
Supine Systolic Blood Pressure	-2.8	-4.3
Supine Diastolic Blood Pressure	-1.2	-2.4
Sitting Systolic Blood Pressure	-0.2	-1.8
Sitting Diastolic Blood Pressure	0.1	-1.0

From Tables Appendix All.113, All.114.

Pfizer reported that during controlled trials, the mean change in weight among pregabalin subjects was +1.6kg compared to +0.3kg among the placebo subjects (Summary of Safety, p.68). Noting the difficulties with the dose response analyses, Pfizer found that the mean increases in weight generally ordered by increasing pregabalin dose categories with the greatest mean increase in weight (+2.0kg) among those pregabalin subjects assigned to in the highest pregabalin dose group, 600mg/day (Appendix ALL.121).

Vital Sign Outlier Results

Controlled Trials

Pfizer provided analyses of vital sign outliers. Pregabalin subjects had a 4.5 fold increased risk of 7% weight gain compared to placebo subjects. Pregabalin subjects appeared to have a slightly increased risk of blood pressure declines when compared to placebo subjects. For the remaining vital sign parameters there appeared to be little difference between the outlier risks when comparing pregabalin subjects to placebo subjects although there are limitations with this analysis. The outlier criteria were generally extreme and could have overlooked less severe but important changes. The termination vital sign results that were examined in the analysis could have occurred up to 14 days after last dose of study medication (Summary of Safety, p.1156). Pfizer presented their outlier results stratified by dose but they note that the classification of dose was made according to the randomized dose and may not reflect the dose taken at the time of the vital sign measurement (Summary of Safety, p.1157). Below I summarize the results of Pfizer's outlier analyses comparing risks for placebo subjects to risks for all pregabalin subjects.

FDA Table 51. Vital Sign Clinically Important Changes from Baseline to Termination, Pooled Controlled Trial Data, All Indications

Parameter	Criteria	Placebo	Pregabalin
Weight	Decrease 7% from BL	1.5% (33/2233)	0.9% (46/5181)

	Increase 7% from BL	1.7% (38/2233)	7.7% (401/5181)
Heart Rate (supine)	<50 and ? from BL =30 bpm	0.1% (1/1160)	0.0% (1/2645)
	>120 and ? from BL=30 bpm	0.1% (1/1160)	0.0% (0/2645)
SBP (supine)	<90 and ? from BL of =30	0.0% (0/1153)	0.1% (3/2641)
	>180 and ? from BL of =40	0.3% (3/1153)	0.2% (5/2641)
DBP (supine)	<50 and ? from BL of =20	0.1% (1/1153)	0.2% (4/2641)
	>105 and ? from BL of =30	0.1% (1/1153)	0.1% (2/2641)
SBP (standing)	<90 and ? from BL of =30	0.0% (0/1280)	0.1% (2/2845)
	>180 and ? from BL of =40	0.6% (8/1280)	0.3% (8/2845)
DBP (standing)	<50 and ? from BL of =20	0.1% (1/1280)	0.1% (3/2844)
	>105 and ? from BL of =30	0.2% (2/1280)	0.1% (3/2844)
Heart Rate (sitting)	<50 and ? from BL =30 bpm	0.0% (0/1175)	0.1% (2/2748)
	>120 and ? from BL=30 bpm	0.0% (0/1175)	0.0% (0/2748)
SBP (sitting)	<90 and ? from BL of =30	0.1% (0/1175)	0.1% (3/2748)
	>180 and ? from BL of =40	0.1% (0/1175)	0.0% (0/2748)
DBP (sitting)	<50 and ? from BL of =20	0.2% (2/1175)	0.0% (1/2748)
	>105 and ? from BL of =30	0.0% (0/1175)	0.0% (0/2748)
Respiratory Rate	<10 OR ? from BL of =10	1.1% (10/950)	1% (23/2319)
	>30 OR ? from BL of =10	0.5% (5/950)	0.4% (9/2314)

From Table Appendix ALL.110

Blood Pressure

In separate analyses, Pfizer characterized the distribution of blood pressure changes at termination by determining the percentage of patients with increases and decreases in five mm Hg increments (ex. 0-5mm change, >5 to 10mm change, >10 to 15mm change etc.). These analyses appeared to demonstrate slightly greater risks for some of the decrease in blood pressure change categories when comparing pregabalin subjects compared to placebo subjects. I summarize the results from the sitting SBP and DBP decreases in the table below.

FDA Table 52. Distribution of Decreases in SBP and DBP at Termination Compared to Baseline, Pooled Controlled Trial Data, All Indications

Decrease in sitting SBP	Placebo N=1175	Pregabalin N=2748	Decrease in sitting DBP	Placebo N=1175	Pregabalin N=2748
>0 to 5mm	13.4% (158)	13.2% (362)	>0 to 5mm	15.9% (187)	17.3% (475)
>5 to 10mm	14.5% (170)	17.2% (472)	>5 to 10mm	17.4% (205)	18.3% (502)
>10 to 15mm	5.6% (66)	6.5% (179)	>10 to 15mm	4.4% (52)	6.1% (169)
>15 to 20mm	6.0% (70)	6.9% (190)	>15 to 20mm	3.3% (39)	4.3% (117)
>20 to 25mm	2.0% (24)	2.3% (64)	>20 to 25mm	0.8% (9)	0.7% (18)
>25 to 30mm	1.9% (22)	1.9% (51)	>25 to 30mm	0.3% (3)	0.3% (9)
>30 to 35mm	0.4% (5)	0.7% (19)	>30 to 35mm	0.1% (1)	0.1% (3)
>35 to 40mm	0.3% (4)	0.5% (15)	>35 to 40mm	0% (0)	0% (0)
>40 to 45mm	0.2% (2)	0.1% (3)	>40 to 45mm	0% (0)	0% (1)
>45 to 50mm	0% (0)	0.1% (4)	>45 to 50mm	0% (0)	0% (0)
>50mm	0% (0)	0.1% (3)	>50mm	0% (0)	0% (0)

From Pfizer Tables Appendix ALL.111A and Appendix ALL.112A

Orthostatic Hypotension analyses

Pfizer collected orthostatic blood pressures only in the neuropathic pain studies. In their methods section of the NDA, they explained that subjects had their supine blood pressure measured, then after three minutes standing, had their standing blood pressure measured (Appendix ALL.11). For their analyses of these blood pressure results, Pfizer considered termination systolic blood pressure decreases =20mmHg or systolic blood pressure <100mm Hg on standing as meeting criteria for orthostatic hypotension. The following table summarizes, by dose, the incidences of orthostatic hypotension in the neuropathic pain controlled trials. There did not appear to be notable differences in orthostatic hypotension risk among the individual pregabalin dose groups or among the individual pregabalin dose groups compared to placebo.

FDA Table 53. Percentage of Subjects who Met Orthostatic Hypotension Criteria, Neuropathic Pain Controlled Trials

Treatment Group	Orthostatic Hypotension
Placebo	5.5% (43/783)
Pregabalin 75mg	6.5% (9/139)
Pregabalin 150mg	6% (28/464)
Pregabalin 300mg	5.7% (32/566)
Pregabalin 600mg	4.8% (23/480)

Data from Appendix NeP.096

Weight Increase

Controlled Studies

In addition to examining mean weight changes and considering weight gain as an adverse event, Pfizer provided a separate set of special analyses that examined the incidence of =7% weight gain for each indication and in all controlled studies pooled. The following table summarizes the incidence of weight gain of =7% from baseline to last observation for each indication and in all controlled studies (including other non-neuropathic pain and psychiatry studies for which Pfizer is not seeking approval):

Pfizer Table 30. Summary of ≥7% Weight Gain (Baseline to Last Observation) by Indication: Controlled Studies

[n (%)of Patients With ≥7% Weight Gain]

Indication	Pregabalin Total Daily Dose in mg/day (BID and/or TID)							
	Placebo	150	200	300	400	450	600	Any Dose[b]
All Studies[c]	N=2233	N=1122	N=175	N=1158	N=320	N=470	N=1701	N=5181
	38 (1.7)	53* (4.7)	4 (2.3)	81* (7.0)	22* (6.9)	33* (7.0)	198* (11.6)	401* (7.7)
NeP	N=831	N=505	--	N=612	--	--	N=507	N=1775
	13 (1.6)	18* (3.6)	--	40* (6.5)	--	--	41* (8.1)	105* (5.9)
DPN	N=444	N=207	--	N=309	--	--	N=358	N=947
	6 (1.4)	7 (3.4)	--	12* (3.9)	--	--	27* (7.5)	49* (5.2)
PHN	N=387	N=298	--	N=303	--	--	N=149	N=828
	7 (1.8)	11 (3.7)	--	28* (9.2)	--	--	14* (9.4)	56* (6.8)

Epilepsy	N=292	N=181	--	N=87	--	--	N=385	N=737
	6 (2.1)	15* (8.3)	--	12* (13.8)	--	--	102* (26.5)	133* (18.0)
GAD	N=428	N=195	N=64	N=79	N=170	N=162	N=374	N=1044
	6 (1.4)	2 (1.0)	0 (0.0)	1 (1.3)	12* (7.1)	5 (3.1)	22* (5.9)	42* (4.0)

* Significantly different from placebo based on odds ratio

[a] N at risk = the number of patients with both baseline and termination/LOCF weight.

[b] Includes all other doses of pregabalin (i.e., 50 and 75 mg/day).

[c] Includes other nonneuropathic pain and other psychiatry studies.

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In all controlled studies pooled (which includes data from non-neuropathic pain and other psychiatry studies) and in the controlled studies for each indication pooled, pregabalin-treated patients had a higher incidence of weight gain of at least 7% than did placebo-treated patients. The incidence of weight gain of at least 7% was markedly higher in the epilepsy controlled studies than in the controlled studies for the other indications. To adequately interpret these data, however, one must consider that weight gain requires time to manifest and that when comparing across indications, the epilepsy controlled trials were all 12 weeks in duration while the neuropathic pain controlled trials varied in duration between 5-13 weeks and that the GAD controlled studies were 4-6 weeks in duration. The relative risk associated with pregabalin for weight gain of at least 7% was 8.8 (18.0% [133/737] of pregabalin-treated patients experienced a weight gain of at least 7% compared with 2.1% [6/292] of placebo-treated patients) in the epilepsy studies compared with 4.5 (7.7% [401/5181] of pregabalin-treated patients experienced a weight gain of at least 7% compared with 1.7% [38/2233] of placebo-treated patients) for all controlled studies pooled and 2.9-3.8 for the other indications individually. The lowest incidence of weight gain of at least 7% was observed in the GAD studies. In the GAD studies, the relative risk associated with pregabalin for a weight gain of at least 7% was 2.9 (4.0% [42/1044] of pregabalin-treated patients experienced a weight gain of at least 7% compared with 1.4% [6/428] of placebo-treated patients). Focusing on weight data from epilepsy controlled trials through study week six (closest to the duration of the other trials), the risk for 7% weight gain from baseline among pregabalin subjects was 6% (26/758), similar to the risks observed in the pregabalin subjects from the trials for other indications (July 7, 2004 submission).

Pfizer's analyses provided evidence of dose response for pregabalin associated weight gain. The subjects assigned to the 600 mg/day dose group had the highest incidence of weight gain of at least 7% in all studies pooled and in the epilepsy, DPN, and PHN trials. This effect was most marked in the epilepsy trials; the 600 mg/day dose group had a relative risk of weight gain of at least 7% associated with pregabalin of 12.6 (26.5% [102/385] of pregabalin-treated epilepsy patients in the 600 mg/day dose group experienced a weight gain of at least 7% compared with 2.1% [6/292] of placebo-treated epilepsy patients), which was twice the risk observed in the next lower dose group, 300 mg/day (in this dose group, 13.8% [12/87] of pregabalin-treated patients experienced a weight gain of at least 7% compared with 2.1% [6/292] of placebo-treated patients; relative risk associated with pregabalin treatment=6.6). With the exception of the GAD studies, the incidence of weight gain of at least 7% generally increased with increasing dose at pregabalin doses lower than 600 mg/day. In the GAD trials, the dose-response

relationship observed was more variable. The pregabalin 400 mg/day dose group had the highest incidence of weight gain of at least 7%.

Pfizer presents a cumulative distribution of weight gain by dose for all controlled studies in Table 31 (Summary of Safety, p. 82) and for each indication in Appendices ALL.134-ALL.138 (Summary of Safety, pp. 7365-7369). 2.6% (134/5181) of pregabalin-treated patients from all controlled studies had a weight gain of at least 10% compared with 0.6% (13/2233) of placebo-treated patients.[29] The 600 mg/day dose group had the highest percentage of patients with a weight gain of at least 10%, as was observed for a weight gain of at least 7%. 0.6% (33/5181) of pregabalin-treated patients had a weight gain of at least 15% (compared with 0.1% [2/2233] of placebo-treated patients) and 0.2% (11/5508) had a weight gain of at least 20% from baseline (compared with 0.0% [1/2233] of placebo-treated patients). The 600 mg/day dose group had the highest proportion of patients with a weight gain of at least 15%. The 400 mg/day dose group had the highest proportion of patients with a weight gain of at least 20%; 0.6% (2/320) of patients in this dose group experienced this degree of weight gain. One of these patients gained =30% and the other gained =35% of his or her baseline body weight. The 400 mg/day dose group was the only pregabalin dose group in which any patient gained =25% of his or her baseline body weight.

The epilepsy studies had a substantially greater percentage of patients with weight gain =10% than was observed for the other indications. In the epilepsy studies, 8.1% (60/737) of patients had a weight gain =10% (compared with 0.3% [1/292] of placebo-treated patients), 2.3% (17/737) of patients had a weight gain =15% (compared with zero placebo-treated patients), and 0.5% (4/737) of patients had a weight gain =20% (compared with zero placebo-treated patients). The percentage of patients experiencing each of these weight gain increments was highest in the 600 mg/day dose group. No patients in epilepsy studies had a weight gain of =25%. In other study groupings, the percentage of patients with a weight gain of at least 10% from baseline was smaller and very similar, ranging from 1.1% (12/1044) in the controlled GAD studies (compared with 0.5% [2/428] in placebo-treated patients) to 2.1% (17/828) in the controlled post-herpetic neuralgia studies (compared with 0.8% [3/387] of placebo-treated patients). The percentage of pregabalin-treated patients with a weight gain =15% was <1% in all indications other than epilepsy, ranging from 0.1% (1/1044) in the controlled GAD studies (compared with zero placebo-treated patients) to 0.4% (3/828) in the controlled post-herpetic neuralgia studies (compared with 0.3% [1/387] of placebo-treated patients).

Pfizer examined age, body mass index <28 or =28, and gender as potential risk factors for the development of weight gain =7% (see Appendices ALL.140-ALL.153, Summary of Safety, pp. 7371-7391,). They also examined use of concurrent anti-epileptic drugs as a potential risk factor in the controlled epilepsy studies. It did not appear that gender modified the risk for weight gain of =7% for either the controlled studies combined or the controlled studies for individual indications. The largest difference between men and women in the risk for weight gain =7% was observed in the epilepsy studies, in which

[29] Number of patients at risk (e.g., the denominator) in both groups included those patients who had both baseline and termination (or last observation carried forward) weights recorded.

women treated with pregabalin appeared to be at greater risk than men for weight gain of at least 7%. In the epilepsy studies, the relative risk for weight gain associated with pregabalin was 7.9 for men (15.0% [53/353] of pregabalin-treated men experienced a weight gain of at least 7% compared with 1.9% [3/154] of placebo-treated men) and 9.4 for women (20.8% [80/384] of pregabalin-treated women experienced a weight gain of at least 7% compared with 2.2% [3/138] of placebo-treated women).

Pfizer presented data comparing by treatment group the frequency of weight gain of at least 7% among patients with baseline BMI <28 and =28 (see Appendices ALL.144 and ALL.146, Summary of Safety, pp. 7377 and 7380). Pfizer concluded that baseline BMI did not affect the risk of developing weight gain of at least 7%. I calculated the pregabalin-associated relative risk for weight gain of at least 7% for each study grouping, comparing the relative risk in all patients, those with baseline BMI <28, and those with baseline BMI =28. Baseline BMI did not appear to have a consistent, strong association with the risk for weight gain of at least 7%.

Pfizer examined the interaction between age and the development of weight gain =7%, presenting by trial and dosage groups the percentage of pregabalin- and placebo-treated patients who experienced a weight gain of at least 7% in the following age categories—18-64, 65-74, and =75. These data are presented in Appendices ALL.148, ALL.160, and ALL.152 (Summary of Safety, pp. 7383, 7386, and 7389). Age did not appear to be a substantial or consistent modifier of risk for weight gain of at least 7%, although the impact of age was difficult to assess for the GAD and epilepsy studies, in which there were relatively few patients =65. Age =75 did appear to substantially increase the risk for weight gain of at least 7% associated with pregabalin in the post-herpetic neuralgia studies. In these studies, 3.3% (6/181) of pregabalin-treated patients aged 18-64 experienced a weight gain of at least 7% (compared with 0% [0/72] of placebo-treated patients in this age group; approximate relative risk associated with pregabalin treatment=1.4).[30] In the 65-74 year age group, 7.6% (21/278) of pregabalin-treated patients experienced a weight gain of at least 7% (compared with 4.0% [6/151] of placebo-treated patients; approximate relative risk associated with pregabalin treatment=1.9). In the =75 year age group, 7.9% (29/369) of pregabalin-treated patients experienced a weight gain of at least 7% (compared with 0.6% [1/164] of placebo-treated patients; approximate relative risk associated with pregabalin treatment=13.2). In all controlled studies, patients in the =75 year age group had a greater relative risk of =7% weight gain associated with pregabalin treatment than did patients in either of the younger age groups. Patients in the 65-74 year age group demonstrated the lowest overall relative risk of weight gain of at least 7% associated with pregabalin treatment. Relative risk was 4.8 in the 18-64 year age group (8.1% [323/3992] of pregabalin-treated patients experienced a weight gain =7% compared with 1.7% [28/1644] of placebo treated patients), 2.7 in the 65-74 years age group (6.0% [42/702] of pregabalin-treated patients experienced a weight gain =7% compared with 2.2% [8/361] of placebo treated

[30] In order to perform a relative risk calculation I assigned one event of weight gain of at least 7% to the placebo group of this age category. One event in this group would be consistent with a risk of 1.4%, which I used in the relative risk calculation. The result is an underestimation of the relative risk associated with pregabalin.

patients), and 7.8 in the =75 year age group (7.0% [33/474] of pregabalin-treated patients experienced a weight gain =7% compared with 0.9% [2/222] of placebo treated patients).

Pfizer examined the interaction between weight gain and concurrent use of valproate and topiramate, noting that use of concurrent anti-epileptic drugs was allowed in the controlled studies and that weight gain is a recognized side effect of valproate treatment. Weight loss, in contrast, is a recognized side effect of topiramate.[31] In Appendix ALL.155 (Summary of Safety, p. 7393), they present the percentage of patients who were concurrently using valproate or topiramate in each dose group in the epilepsy controlled trials; they also present the proportion of patients who gained =7% who were concurrently using either valproate or topiramate. Separate data are presented for each drug. They conclude that the majority of pregabalin-treated patients who experienced weight gain of =7% were not valproate users and that valproate use was not greater among patients who had a weight gain of =7% than among the overall epilepsy population. They base these conclusions on their findings that 18.0% (24/133) of pregabalin-treated patients who gained =7% were concurrently using valproate and that 19.7% (149/758) of pregabalin-treated patients were concurrently using valproate.

Based on the data they provided in Appendix ALL.155, I performed the following analysis to further examine potential risk modification by concurrent topiramate or valproate use:

FDA Table 54. Relative Risks of Weight Gain =7% by Use of Concurrent Anti-Epileptic Drugs (AED); Controlled Epilepsy Trials

Concurrent anti-epileptic drug	Placebo no. (%) of patients with weight gain =7% from baseline	No. of concurrent users of relevant AED in placebo group	Pregabalin; all doses no. (%) of patients with weight gain =7% from baseline	No. of concurrent users of relevant AED in pregabalin group	Excess risk	Relative risk
Valproate	2 (3.4%)	59	24 (16.1%)	149	12.7%	4.7
Topiramate	2 (3.2%)	63	45 (33.1%)	136	29.9%	10.3

Compared with the overall relative risk associated with pregabalin for weight gain of =7% in epilepsy trials (8.6), the risk among concurrent users of valproate was slightly lower and the risk among concurrent users of topiramate was slightly higher. These data suggest that concurrent valproate or topiramate use does not explain the observed increased risk for weight gain among pregabalin subjects compared to placebo subjects in the epilepsy trials.

Weight Gain and Clinical Events in Controlled Studies

[31] According to topiramate labeling, weight decrease consistently occurred more frequently in topiramate-treated patients than in placebo-treated patients in clinical trials of topiramate for epilepsy in adult and pediatric patients.

Pfizer investigated the association between weight gain =7% and selected cardiorespiratory adverse events, changes in laboratory values, and changes from baseline systolic and diastolic blood pressure. They presented changes in mean and median supine and sitting systolic and diastolic blood pressure in those patients who sustained a weight gain of at least 7% by dose and treatment groups in Tables ALL.157 Corrected and ALL.158 Corrected.[32] Patients who sustained a weight gain of at least 7% did not appear to have substantial mean changes in supine or sitting systolic or diastolic blood pressure, either considered independently or compared with changes observed in the overall population. The following table summarizes changes from baseline in systolic and diastolic blood pressure by treatment group for the overall group of pregabalin-treated patients and those patients who gained at least 7% of their baseline body weight:

FDA Table 55. Changes from Baseline to Termination in Mean Systolic and Diastolic Supine and Sitting Blood Pressure for Overall Population and Patients With Weight Gain =7% by Treatment Group; Controlled Studies (All Indications)

Blood pressure Parameter		Mean Blood Pressure [mm Hg] (SD) in Overall population				Mean Blood Pressure [mm Hg] (SD) in Patients With Weight Gain =7%			
		Placebo		Pregabalin; all doses and regimens		Placebo		Pregabalin; all doses and regimens	
	No. of patients	*2384*		*5508*		*39*		*399*	
	No. of patients with BP measurements	*1153*	*1175*	*2641*	*2748*	*18*	*21*	*166*	*232*
		supine	sitting	supine	sitting	supine	sitting	supine	sitting
Systolic	Change from baseline	-2.9 (15.68)	-0.2 (12.62)	-4.3 (16.56)	-1.8 (12.60)	-3.9 (15.06)	-0.0 (11.62)	-1.6 (16.54)	-0.1 (12.61)
Diastolic	Change from baseline	-1.2 (9.63)	0.1 (9.01)	-2.4 (9.85)	-1.0 (8.98)	-3.2 (10.62)	0.7 (9.03)	-0.7 (9.50)	-0.2 (10.31)

From Pfizer Appendices ALL.113 and ALL.114 (Summary of Safety, pp. 7169-7176) and ALL.157 CORRECTED and ALL.158 CORRECTED (May 17, 2004 submission to NDA).

In the overall group, patients treated with both pregabalin and placebo had small mean changes in systolic and diastolic pressure in both the supine and sitting positions ranging from a decrease of 4.3 mm Hg (mean supine systolic blood pressure change observed in pregabalin-treated patients) to an increase of 0.1 mm Hg (mean sitting diastolic blood pressure change observed in placebo-treated patients). In the group of patients who experienced a weight gain of =7%, pregabalin-treated patients had small declines in their mean supine and sitting systolic and diastolic blood pressures ranging from 0.1 (mean sitting systolic blood pressure decline) to 1.6 mm Hg (mean supine systolic blood

[32] See submission to NDA dated May 17, 2004.

pressure decline). In contrast, placebo-treated patients with a weight gain of at least 7% had changes in supine and sitting systolic and diastolic blood pressure ranging from no change (observed for mean sitting systolic blood pressure) to an increase of 3.2 mm Hg (observed for mean supine diastolic blood pressure). There appeared to be no clear relationship between pregabalin dose group and mean changes in sitting systolic or diastolic blood pressure in patients with a weight gain of at least 7%. Modest increases in mean supine systolic and diastolic blood pressure were observed in the 600 mg dose group; this was the only pregabalin dose group in which an increase in a mean blood pressure parameter was observed in patients with a weight gain of at least 7%. In the 600 mg dose group,[33] mean supine systolic blood pressure increased from 134.0 mm Hg at baseline (SD 16.09 mm Hg) to 136.9 mm Hg (SD 18.56 mm Hg); mean change observed was 2.9 mm Hg (SD 16.07 mm Hg). In the same dose group, mean diastolic blood pressure increased from 79.3 mm Hg at baseline (SD 9.33 mm Hg) to 80.3 mm Hg (SD 9.12 mm Hg); mean change observed was 0.9 mm Hg (SD 9.49 mm Hg).

Pfizer presented the frequencies of selected cardiorespiratory adverse events in patients with and without weight gain of =7% by dose group in Appendices ALL.159 and ALL.160 (Summary of Safety pp. 7410-7411). I calculated the relative risks associated with pregabalin for these events by weight gain category. The following table summarizes these data:[34]

FDA Table 56. Relative Risks for Selected Cardiorespiratory Adverse Events in Patients With and Without Weight Gain =7%; Controlled Trials (All Indications)

Adverse Event	Patients With Weight Gain; Treatment Assignments		RR_{WG}	Patients Without Weight Gain; Treatment Assignments		RR_{NWG}
	Pregabalin N=401	Placebo N=38		Pregabalin N=4780	Placebo N=2195	
Hypertension	2.5% (10)	0% (0)	*	0.5% (26)	1.1% (24)	0.45
Hypotension	0.5% (2)	0% (0)	*	0.2% (11)	0.1% (3)	2.0
Palpitation	0.7% (3)	2.6% (1)	0.27	0.6% (14)	0.5% (24)	1.2
Dyspnea	0.7% (3)	0% (0)	*	1.0% (47)	0.8% (18)	1.25
Tachycardia	0.7% (3)	2.6% (1)	0.27	0.2% (10)	0.5% (10)	0.4

From Pfizer Appendices ALL.159 and ALL.160 (Summary of Safety, pp. 7410-7411).

* Relative risk associated with pregabalin could not be calculated for these events given that there were no events in the placebo group.

Compared with placebo-treated patients who experienced weight gains of =7%, pregabalin-treated patients with the same degree of weight gain were more likely to experience hypertension, hypotension, and dyspnea. None of the 38 placebo-treated patients who gained at least 7% of their baseline body weight experienced any of these

[33] In this dose group, baseline and termination supine blood pressure measurements were available for 47/196 patients who experienced a weight gain of at least 7%.

[34] In addition to the selected cardiorespiratory events presented in the table below, Pfizer also presents data by treatment group and weight gain category for arrhythmia, atrial arrhythmia, atrial fibrillation, cardiovascular disorder, and congestive heart failure. I have not presented these in my table above since no pregabalin-treated patients with weight gain of at least 7% experienced any of these events.

adverse events. Compared with the overall population of pregabalin-treated patients and the pregabalin-treated patients who did not experience a weight gain of =7%, pregabalin-treated patients who experienced a weight gain of =7% were more likely to experience hypertension (experienced by 0.7% [39/5508] of pregabalin-treated patients overall), hypotension (experienced by 0.2% [13/5508] of pregabalin-treated patients overall), and tachycardia (experienced by 0.3% [14/5508] of pregabalin-treated patients overall). This analysis is limited by the unknown nature of the temporal relationship between weight gain and these cardiorespiratory events. It might have been more illuminating to restrict the analysis only to those patients experiencing the new onset of these events after the weight gain of =7%, although the number of events involved would likely have been too small to form the basis of any meaningful conclusions.

Pfizer also examined the association between weight gain of at least 7% and changes in clinical laboratory parameters over the course of the controlled studies, concluding that weight gain of =7% had no apparent impact on clinical laboratory values including glycosylated hemoglobin. They performed the same laboratory data analyses as they had for the entire controlled trial population for those patients who experienced a weight gain of at least 7%. I observed several notable differences in this population compared with the overall pregabalin-treated population pertaining to changes in platelet count and creatine kinase. Compared with the overall pregabalin-treated population, patients who experienced a weight gain of at least 7% experienced a greater mean increase in creatine kinase (23.9 U/L; n=233). This increase was smaller, however, than the mean creatine kinase increase that was observed among placebo-treated patients who experienced a weight gain of at least 7% (31.6 U/L; n=19). A slightly higher percentage of pregabalin-treated patients who experienced a weight gain of at least 7% had creatine kinase values that changed to high at the endpoint of the study compared with the overall population of pregabalin-treated patients (8.6% [19/22] compared with 23.5% [4/17] of placebo-treated patients with a weight gain of at least 7% and 6.5% [194/2990] of pregabalin-treated patients overall). Pregabalin-treated patients with a weight gain of at least 7% did not, however, have a higher proportion of patients with a change in creatine kinase that was considered clinically important compared to the overall pregabalin-treated population, nor did they have a higher proportion of patients with high or very high creatine kinase values at any time post-baseline compared with the overall population of pregabalin-treated patients.

Patients with weight gain of at least 7% had a slightly greater mean decrease in platelet count compared with the overall pregabalin-treated population. Mean decrease in platelet count was 12.6 $x10^3/\mu L$ (n=394) for the pregabalin-treated patients with =7% weight gain. The mean decrease in platelet count was 1.2 $x10^3/\mu L$ for placebo-treated patients with =7% weight gain and 9.5 $x10^3/\mu L$ for the overall pregabalin-treated population. Pregabalin-treated patients with =7% weight gain also had a slightly higher percentage of patients with low platelet counts at any time post-baseline (1.5% [6/401]) compared to the overall population of pregabalin-treated patients (0.9% [46/5508]). None of the 38 placebo-treated patients with =7% weight gain experienced a low or very low platelet count at any time post-baseline. The proportion of patients weight gain of at least 7% who experienced platelet counts considered clinically important and the proportion of

patients with weight gain of at least 7% whose platelet count changed to low or very low from baseline to endpoint did not differ substantially from the corresponding proportions in the overall population of pregabalin-treated patients.

I also examined changes in lipid profiles, fasting plasma glucose, and glycosylated hemoglobin in patients with weight gain of at least 7%, since weight gain has the potential to affect these parameters. I was not able to draw any conclusions regarding pregabalin's effect on these parameters due to the limitations of the available analyses. Pfizer's analyses for these laboratory values were based on a small proportion of the total number of patients who experienced a weight gain of at least 7%. Data from 48 pregabalin-treated patients and six placebo-treated patients who experienced a =7% weight increase were available for the hemoglobin A_1C mean change analyses. Data from one placebo-treated patient and 11 pregabalin-treated patients were available for analysis of the percentage of patients in each treatment and dose group who had a change in their hemoglobin A_1C to high over the course of the study; these patients represent fractions of the total number of patients in their treatment group with weight gain of =7% that are far too small on which to base any conclusions. The number of patients with evaluable data for the lipid parameters was similarly low. Moreover, since hemoglobin A_1C reflects glucose control over the preceding two to three months, it might not adequately reflect changes occurring over the course of a short-term controlled study, particularly for those patients who discontinued early from the study. Changes in lipid parameters as a result of weight change may also not become apparent over the course of a short-term controlled trial, requiring longer person-time to become manifest.

Combined Controlled and Uncontrolled Studies

In controlled and uncontrolled studies combined for all indications, mean weight change from baseline was 2.8 kg. 20.2% (1598/7928) of pregabalin-treated patients experienced a weight gain of at least 7%. This is a substantially higher percentage than was observed in the controlled studies alone; this difference compared to the controlled studies is not unexpected given that weight gain takes time to become manifest and the controlled studies were shorter. As was observed in the controlled studies, weight gain of at least 7% was most frequent in the epilepsy trials and least frequent in the GAD trials. The following table summarizes the proportion of pregabalin-treated patients that experienced a weight gain of at least 7% by indication:

Pfizer Table 32. Summary of ≥7% Weight Gain: Combined Controlled and Uncontrolled Studies All Indications

Indication (N at Risk[a])	Any Pregabalin [n (%)]
All Combined Controlled and Uncontrolled Studies (N=7928)	1598 (20.2)
Combined Controlled and Uncontrolled NeP (N=2438)	462 (18.9)
Combined Controlled and Uncontrolled DPN (N=1374)	296 (21.5)
Combined Controlled and Uncontrolled PHN (N=1064)	166 (15.6)
Combined Controlled and Uncontrolled Epilepsy (N=1530)	615 (40.2)

Combined Controlled and Uncontrolled GAD (N=1703)	185 (10.9)

[a]N at risk = the number of patients with both baseline and termination/LOCF weight recorded.
Pfizer Table 32, page 83, Summary of Clinical Safety

Pfizer compared the frequencies of selected cardiorespiratory adverse events in patients who experienced a weight gain of at least 7% in all controlled and uncontrolled studies combined with the corresponding frequencies in patients who did not experience weight gain of at least 7%. Relative to patients without weight gain of at least 7%, patients with weight gain of at least 7% had slightly higher frequencies of hypertension (3.1% [49/1598] compared to 1.8% [113/6331]), tachycardia (1.4% [22/1598] compared to 0.5% [33/6331]), and dyspnea (3.1% [49/1598] compared to 2.4% [150/6331]). Other selected cardiorespiratory adverse events occurred with very similar frequencies in the two weight groups.

Pfizer also provided the cumulative distribution of weight gain by indication. The following table demonstrates that patients in the epilepsy trials experienced greater degrees of weight gain than patients in trials for any of the other indications:

Pfizer Table 34. Cumulative Distribution of Weight Gain by Indication: Combined Controlled and Uncontrolled Studies All Indications

% Increase	DPN N=1413	PHN N=1111	NeP N=2524	Epilepsy N=1613	GAD N=1962	All Studies[a] N=8666
N at Risk[b]	1374	1064	2438	1530	1703	7928
≥7	296 (21.5)	166 (15.6)	462 (18.9)	615 (40.2)	185 (10.9)	1598 (20.2)
≥10	161 (11.7)	83 (7.8)	244 (10.0)	416 (27.2)	73 (4.3)	891 (11.2)
≥15	59 (4.3)	19 (1.8)	78 (3.2)	208 (13.6)	16 (0.9)	353 (4.5)
≥20	22 (1.6)	9 (0.8)	31 (1.3)	98 (6.4)	4 (0.2)	154 (1.9)
≥25	10 (0.7)	3 (0.3)	13 (0.5)	57 (3.7)	1 (0.1)	79[c] (1.0)
≥30	8 (0.6)	1 (0.1)	9 (0.4)	29 (1.9)	0 (0.0)	40[c] (0.5)
≥35	3 (0.2)	0 (0.0)	3 (0.1)	17 (1.1)	--	22[c] (0.3)
≥40	0 (0.0)	--	0 (0.0)	12 (0.8)	--	14[c] (0.2)
≥45	--	--	--	10 (0.7)	--	11[c] (0.1)
≥50	--	--	--	5 (0.3)	--	6[c] (0.1)
≥55	--	--	--	4 (0.3)	--	5[c] (0.1)
≥60	--	--	--	2 (0.1)	--	3[c] (0.0)
≥65	--	--	--	0 (0.0)	--	1[c] (0.0)

[a]Includes other nonneuropathic pain studies and other psychiatry studies.
[b]N at risk = the number of patients with both baseline and termination/LOCF weights recorded.
[c]Database error: Patient 105_519007, height was entered for weight.
Pfizer Table 34, page 85, Summary of Clinical Safety

Pfizer examined the association between weight gain and the common adverse events of somnolence, increased appetite, dry mouth, hyperglycemia, and diabetes mellitus in the controlled and uncontrolled studies combined by comparing the frequencies of these events in those patients with and without weight gain of at least 7%. Patients with a weight gain of at least 7% reported the adverse events of increased appetite, hyperglycemia, and diabetes mellitus more frequently than those patients without a weight gain of at least 7%. The following table summarizes these data:

FDA Table 57. Selected Adverse Events in Patients With and Without =7% Weight Gain; Combined Controlled and Uncontrolled Studies (All Indications)

Preferred term	Patients With =7% Weight Gain % (no.) n=1598	Patients Without =7% Weight Gain % (no.) n=6331
Somnolence	27.2% (434)	27.2% (1720)
Increased appetite	5.3% (84)	2.9% (181)
Dry mouth	7.5% (120)	10.0% (636)
Hyperglycemia	1.6% (26)	0.9% (58)
Diabetes mellitus	0.9% (15)	0.3% (17)

From Pfizer table 35, Summary of Safety, page 86.

Although increased appetite was more frequently reported in those patients who gained at least 7% of their body weight, this degree of weight gain was not limited to those patients who reported increased appetite. The extent of underreporting of increased appetite as an adverse event could be quite large, however, and the true nature of the association between increased appetite and weight gain is thus difficult to determine. It also should be noted that the events of hyperglycemia and diabetes mellitus are not likely to be fully captured by adverse event forms and the data as presented above are not very helpful in determining the true nature of the association between these events and weight gain in the controlled and uncontrolled studies. Actual blood glucose measurements have the potential to be more useful. Although these data are not provided for the patients who experienced a weight gain of at least 7% in the controlled and uncontrolled studies combined, they are provided for the controlled trials alone. These data are difficult to assess, however, for several reasons. Although Pfizer provided data regarding fasting plasma glucose changes for patients who sustained a weight gain of at least 7%, they cautioned that blood glucose data labeled fasting should generally be considered to be nonfasting (page 64, Summary of Clinical Safety). Comparing changes in random nonfasting blood glucose measurements in patients with weight gain to the corresponding changes in the overall population may be of limited usefulness. Moreover, the number of patients with weight gain contributing assessable glucose data is relatively small, and the usefulness of assessments made using isolated plasma glucose measurements is uncertain.

Pfizer assessed the post-treatment course of patients who experienced a weight gain of at least 7% by examining weight changes occurring after the cessation of pregabalin treatment in 22 patients from three studies who experienced this degree of weight gain (see Appendix ALL.199, Summary of Safety, pp. 7488-7499).[35] Mean weight loss after the last dose of pregabalin in these patients was 1.7 kg. Follow-up measurements were collected from eight to =36 days after the last dose of pregabalin. Mean percentage decrease in weight after the last dose of pregabalin was 2.3%. Mean increase from their weight baseline in these patients was 4.1 kg at their follow-up measurement after pregabalin cessation; mean percentage increase from baseline was 5.3%. It appears that

[35] These three studies were Study 72, a controlled study of reproductive function in healthy male volunteers, Study 82, a randomized withdrawal design relapse-prevention study in patients with social phobia, and Study 88, another randomized withdrawal design relapse-prevention study conducted in patients with GAD.

weight loss did occur after the cessation of pregabalin treatment in these patients who had gained at least 7% of their body weight but that weight had not returned to baseline in the time interval examined. Given that this analysis is based on very few patients from three disparate study populations, it would be unwise to draw conclusions from these data.

Epilepsy Vital Sign Data

Controlled Epilepsy trials

Mean Change from Baseline Data

Pfizer reported that pregabalin had no clinically significant effect on heart rate, blood pressure, or respiratory rate during controlled epilepsy trials (Summary of Safety, p.192). The data from epilepsy controlled trials demonstrated a slight decline in systolic and diastolic blood pressure for pregabalin subjects compared to placebo subjects. Those data are summarized below. Pfizer did not present mean change results for heart rate or respiratory rate from the epilepsy controlled trials.

FDA Table 58. Summary of Blood Pressure Changes from Baseline, Epilepsy Controlled Trials

Mean Change at Termination from Baseline		
	Placebo (n=294)	Pregabalin (n=752)
Systolic Blood Pressure (sitting)	1.0	-1.6
Diastolic Blood Pressure (sitting)	0.8	-0.7

From Table Appendix Epilepsy.090

Pfizer reported that during epilepsy controlled trials, the mean change in weight among pregabalin subjects was +2.1kg compared to no change among the placebo subjects (Summary of Safety, p.192). Although this mean weight gain was greater than that observed for the controlled trials for neuropathic pain and GAD indications, this is not an appropriate comparison since the epilepsy controlled trials had the longest duration. If one limits the mean change analysis to the first six weeks of the epilepsy controlled trials (similar to the duration of the controlled trials for other indications) the mean weight gain was 1.4kg for pregabalin subjects and 0kg for placebo while the mean weigh gain for pregabalin subjects in the GAD trials was 1.4kg and for placebo subjects was 0.4kg, and in the neuropathic pain trials the mean weight gain for pregabalin subjects was 1.5kg and 0.2kg for placebo subjects (July 7, 2004 Submission, Summary of Safety p.163, Summary of Safety p.220).

Outlier Results

Pfizer presented the results of their outlier analyses in appendix tables. In these trials, pregabalin subjects had an almost nine fold increased risk of weight gain compared to placebo subjects. There was a slightly increased risk for SBP decrease but not DBP decrease among pregabalin subjects compared to placebo subjects. Pregabalin subjects also had an increased risk of declines in respiratory rate compared to placebo subjects.

For the remaining vital sign parameters, there did not appear to be notable differences in outlier risks when comparing pregabalin subjects to placebo subjects, with the same caveats noted above. Below, I summarize the results from Pfizer's outlier analyses of epilepsy controlled trial vital sign data.

FDA Table 59. Vital Sign Clinically Important Changes from Baseline to Termination, Epilepsy Controlled Studies

Parameter	Criteria	Placebo	Pregabalin
Weight	Decrease 7% from BL	2.4% (7/292)	1.2% (9/737)
	Increase 7% from BL	2.1% (6/292)	18% (133/737)
Heart Rate (sitting)	<50 and ? from BL =30 bpm	0.0% (0/294)	0.1% (1/752)
	>120 and ? from BL=30 bpm	0.0% (0/294)	0.0% (0/752)
SBP (sitting)	<90 and ? from BL of =30	0.0% (0/294)	0.3% (2/752)
	>180 and ? from BL of =40	0.3% (1/294)	0.0% (0/752)
DBP (sitting)	<50 and ? from BL of =20	0.0% (0/294)	0.0% (0/752)
	>105 and ? from BL of =30	0.0% (0/294)	0.0% (0/752)
Respiratory Rate	<10 OR ? from BL of =10	1.0% (3/293)	1.9% (14/752)
	>30 OR ? from BL of =10	1.0% (3/293)	0.4% (3/752)

From Table Appendix Epilepsy.087

GAD Vital Sign Data

Controlled Trials

Pfizer reported that pregabalin had no clinically significant effect on blood pressure, heart rate, or respiratory rate in the controlled trials for GAD. In appendix tables, they presented several analyses of vital sign changes in GAD controlled trials. The following table summarizes data regarding means change in systolic and diastolic sitting blood pressure by treatment group:

FDA Table 60. Summary of Blood Pressure Changes from Baseline; Controlled GAD Trials[36]

Mean Change from Baseline to Termination [mm Hg] (SD)		
Blood pressure parameter	Placebo (n=467)	Pregabalin (n=1110)
Systolic Blood pressure (sitting)	-0.5 (11.27)	-1.4 (11.63)
Diastolic blood pressure (sitting)	0.2 (8.48)	-0.9 (8.42)

From Pfizer Appendix GAD.090 (Summary of Safety, pp. 14480-14481).

Pregabalin-treated patients had slight declines in systolic and diastolic blood pressure from baseline to termination. Placebo-treated patients had a negligible increase in diastolic blood pressure from baseline to termination and a slight decrease in systolic blood pressure that was smaller than the decrease observed in pregabalin-treated patients. The difference in change observed between pregabalin- and placebo-treated patients was 0.9 mm Hg for systolic blood pressure and 1.2 mm Hg for diastolic blood pressure.

[36] This table includes data from patients with blood pressure measurements available at both baseline and termination.

Pfizer reported that the mean weight change in controlled trials for GAD was 1.4 kg in pregabalin-treated patients and 0.4 kg in placebo-treated patients. This weight increase was similar to the change observed in pregabalin-treated patients in controlled trials for postherpetic neuralgia and diabetic peripheral neuropathy and slightly smaller than the increase observed in pregabalin-treated patients in controlled trials for epilepsy.

Pfizer also presented outlier analyses, comparing pregabalin- and placebo-treated patients with respect to the development of clinically important changes in vital signs over the course of the controlled studies. The following table summarizes these data:

FDA Table 61. Clinically Important Changes in Vital Signs from Baseline to Termination; Controlled GAD Studies

Parameter	Criteria	Placebo	Pregabalin
Weight	Decrease 7% from BL	0.5% (2/428)	0.4% (4/1044)
	Increase 7% from BL	1.4% (6/428)	4.0% (42/1044)
Heart Rate (sitting)	<50 and ? from BL =30 bpm	0.0% (0/467)	0.0% (0/1110)
	>120 and ? from BL=30 bpm	0.0% (0/467)	0.0% (0/1110)
SBP (sitting)	<90 and ? from BL of=30	0.2% (1/467)	0.0% (0/1110)
	>180 and ? from BL of=40	0.0% (0/467)	0.1% (1/1110)
DBP (sitting)	<50 and ? from BL of=20	0.4% (2/467)	0.0% (0/1110)
	>105 and ? from BL of=30	0.0% (0/467)	0.0% (0/1110)
SBP (standing)	<90 and ? from BL of=30	0.0% (0/100)	0.0% (0/200)
	>180 and ? from BL of=40	0.0% (0/100)	0.5% (1/200)
DBP (standing)	<50 and ? from BL of=20	0.0% (0/100)	0.0% (0/200)
	>105 and ? from BL of=30	0.0% (0/100)	0.0% (0/200)
Respiratory Rate	<10 OR ? from BL of=10	0.3% (1/366)	0.3% (3/910)
	>30 OR ? from BL of=10	0.0% (0/366)	0.2% (2/910)

From Pfizer Appendix GAD.087 (Summary of Safety, pp. 14472-14475).

There did not appear to be any notable differences between pregabalin- and placebo-treated patients in outlier risks for any of the vital sign parameters delineated in the table above with the exception of weight. Pregabalin-treated patients had a risk relative to placebo-treated patients of 2.9 for a weight gain of at least 7%. There were also slightly increased risks among pregabalin-treated patients compared to placebo-treated patients for standing and sitting systolic blood pressure increases considered clinically important. This slight difference in risk was not evident for diastolic blood pressure. Pregabalin-treated patients also appeared to have a slightly greater risk for respiratory rate increases considered clinically important than was evident for placebo-treated patients.

Controlled and Uncontrolled Trials

Pfizer presents data regarding the percentage of patients who experienced clinically important changes in vital signs in the combined controlled and uncontrolled GAD studies in Appendix GAD.095 (Summary of Safety, p. 14500). Data through the Safety

Update are presented in Appendix GAD.22 (Safety Update, pp. 3219-3220). Through the safety update, 13.3% (226/1703) of patients experienced a weight gain of at least 7% at some point during a trial. 1.9% (32/1703) of patients experienced a weight loss of at least 7%. Without a comparator, it is difficult to interpret the data regarding the percentage of patients experiencing vital sign changes considered clinically important.

4.6.7 ECG Analyses

Overview

In two separate memos (MEMO 720-04340, MEMO 720-30165), Pfizer summarized ECG results from phase II/III studies from the pregabalin development program. MEMO 720-04340 summarized ECG results by indication for eighteen randomized controlled trials that studied pregabalin in pain, epilepsy, and psychiatry indications (4745 subjects). MEMO 720-30165 summarized ECG results from ten randomized controlled trials in GAD, new psychiatry studies not included in the previous memo, and two sustained efficacy (relapse prevention) studies (2757 subjects).

MEMO 720-04340

Methods

Pfizer's summary of ECG data focused on results of analyses that pooled ECG data from double blind placebo controlled clinical trials and one double blind active controlled trial. The pooled studies were grouped by treatment indications. The following table identifies the pooled studies and the groupings used in the analyses.

FDA Table 62. Pooled Studies Included in the Pregabalin ECG Data Analyses

Indication/Pool	Studies included	Number treated
Pain (diabetic neuropathy, post herpetic neuralgia, osteoarthritis, fibromyalgia)	014, 029, 040, 131, 030, 032, 104, 031, 105, 127	Pregabalin 1867 Placebo 913 Amitriptyline 87
Diabetic Neuropathy	014, 029, 040, 131	Pregabalin 560 Placebo 332 Amitriptyline 75
Epilepsy	007, 009, 034	Pregabalin 605 Placebo 197 Gabapentin 48
Psychiatry (generalized anxiety disorder, social phobia, [redacted])	021, 025, 026, 017, 022	Pregabalin 533 Placebo 282 Lorazepam 204

From RR Memo 720-04340, p.7

In addition to these results for the pooled analyses, Pfizer provided results from the individual studies in an appendix to their memo.

Interval Measurement and Heart Rate Correction

Pfizer noted that the included pooled studies captured twelve-lead ECGs at baseline and at least once on-treatment. Timing of ECGs with respect to dose varied from study to study. ECGs were read by a core laboratory [redacted]. Readers were blinded with respect to treatment. Interval measurements were made using a calibrated 7 power magnifying loupe. Readers preferentially measured the QT in lead II but used lead V5 when the end of the T wave was not clearly identified in lead II. If the end of the T wave was not identifiable in either lead II or lead V5, then the lead with the best T wave offset was selected for measurement. Readers used the same lead to measure QT for an individual patient. Pfizer's mean change presentations analyzed QT corrected for heart rate using a linear correction derived from baseline data from individual studies (RR Memo 720-04340, p. 8-9). Pfizer reported that the slopes from the individual studies ranged from 0.11433 to 0.17690 (RR Memo 720-04340, p. 8033). QTc outlier analyses were based on corrections using Bazett's method (RR Memo 720-04340, p. 8032).

Changes from Baseline

Pfizer compared changes from baseline (last ECG prior to study treatment) for the maximum double blind value for PR, QRS, QTc, and VR and to the minimum double blind VR. For individual studies, Pfizer analyzed data using an ANCOVA model that included treatment, center, and baseline ECG. For the pooled by indication analyses protocol was substituted in place of center in each model. Treatment interactions with prognostic factors, namely age, sex, race, and creatinine clearance were also investigated using ANCOVA methods with data pooled by indication. Pfizer performed these analyses using separate models for each prognostic factor and the models included treatment, prognostic factor, treatment by prognostic factor interaction terms, and the baseline ECG parameter for the interval being evaluated. (RR Memo 720-04340, p. 9-10)

Outlier analyses

Pfizer used the following criteria to assess ECG results for potentially clinically significant changes:

FDA Table 63. Criteria for Clinical Significance for ECG Parameters

Parameter	Criteria for Clinically Significant Change	Criteria for Significant Value*	Source
PR Interval	=25% Increase from BL	<120 or >200msec	Expert Consultant, published guidelines
QRS Duration	=25% Increase from BL	<60 or >100msec	Expert Consultant, published guidelines
Ventricular rate	---	<60 or >100 bpm	Expert Consultant, published guidelines
QTc	=30 msec increase from BL	=500 msec	Expert Consultant, published guidelines

*regardless of baseline value

Demographics

Pfizer provided the demographics by indication and I summarize those results in the following table.

FDA Table 64. Demographics by indication, ECG Analyses

Indication	Age (range of means from pooled studies)	Sex	Race	Cr clearance (range of means from pooled studies)
Pooled pain	49 to 67 years	56% F	91% white	80 to 101 mL/min
Diabetic neuropathy	56 to 61 years	41% F	90% white	95 to 110 mL/min
Epilepsy	36 to 40 years	50% F	86% white	103 to 112 mL/min
Psychiatry	35 to 37 years	53% F	83% white	101 to 103 mL/min

ECG Results

Effect of Pregabalin on PR Interval

PR Mean Maximum Change from Baseline

In their overview of results, Pfizer notes that pregabalin increased the PR interval at doses =300mg/day, but that the mean effect on the PR interval was small (3-6msec increase compared to placebo) and not clinically meaningful. In the only indication it was studied (pain), the 450mg/day dose has a significant effect on the PR interval. Pregabalin 300mg/day was associated with a significant effect on the PR interval in the pooled pain studies but not in the pooled epilepsy studies. The following table summarizes the mean maximum change from baseline for PR interval for the pooled analyses.

FDA Table 65. ANCOVA LS Mean Maximum Change from Baseline, PR Interval

Treatment (n)	LS PR mean change from baseline (ms)	Estimated difference from placebo (95%CI)
Pooled Pain Studies		
Placebo (n=773)	3.03	--
PGB 75 mg/day TID (n=151)	5.04	2.01 (-0.72, 4.74)
PGB 150 mg/day TID (n=312)	4.91	1.89 (-0.10, 3.87)
PGB 300 mg/day TID (n=385)	6.06	3.03 (1.20, 4.85)
PGB 450 mg/day TID (n=171)	6.29	3.26 (0.70, 5.82)
PGB 600 mg/day TID (n=484)	6.42	3.40 (1.76, 5.03)
Pooled Diabetic Neuropathic Pain Studies		
Placebo (n=294)	4.22	--
PGB 75 mg/day TID (n=73)	5.86	1.64 (-2.20, 5.48)
PGB 150 mg/day TID (n=73)	4.16	-0.06 (-4.11, 4.00)
PGB 300 mg/day TID (n=127)	5.30	1.08 (-2.06, 4.21)
PGB 600 mg/day TID (n=213)	7.78	3.56 (1.05, 6.07)
Pooled Epilepsy Studies		
Placebo (n=190)	3.57	--

PGB 50 mg/day BID (n=80)	3.86	0.30 (-3.24, 3.84)
PGB 150 mg/day BID (n=82)	5.69	2.13 (-1.39, 5.65)
PGB 300 mg/day BID (n=79)	3.63	0.06 (-3.49, 3.62)
PGB 600 mg/day BID (n=160)	8.70	5.14 (2.48, 7.80)
PGB 600 mg/day TID (n=95)	7.37	3.81 (0.42, 7.20)
Pooled Psychiatry Studies		
Placebo (n=201)	0.59	--
PGB 150 mg/day TID (n=200)	1.49	0.90 (-1.64, 3.44)
PGB 600 mg/day TID (n=196)	3.65	3.06 (0.54, 5.58)

From Memo 720-04340 Tables 11, 14, 17, and 20

PR Outliers

Pfizer outlier analyses for PR prolongation by indication groups appeared to demonstrate slight increases in risk for PR increase =25% from baseline and for on-treatment PR >200msec, although their dose response analyses did not appear to support linear relationships. I provide those results in the following table.

FDA Table 66. PR Interval Outlier Risks by Pooled Indications

Pooled Pain Studies							
		Pregabalin Dose (mg/day)					
	Placebo	75	150	300	450	600	All PGB
=25% ? from baseline	2% (15/769)	2.6% (4/151)	2.2% (7/312)	3.1% (12/385)	4.1% (7/171)	1.7% (8/478)	2.5% (38/1497)
>200msec on treatment	7.4% (57/773)	17.2% (26/151)	8% (25/313)	7.3% (28/385)	3.5% (6/171)	12.2% (59/484)	9.6% (144/1504)
Pooled Diabetic Neuropathy Studies							
		Pregabalin Dose (mg/day)					
	Placebo	75	150	300		600	All PGB
=25% ? from baseline	1.8% (5/280)	1.4% (1/73)	0% (0/74)	2.4% (3/127)		2.4% (5/207)	1.9% (9/480)
>200msec on treatment	8.5% (24/284)	11% (8/73)	18.9% (14/74)	10.2% (13/127)		15.6% (33/212)	14% (68/486)
Pooled Epilepsy Studies							
		Pregabalin Dose (mg/day)					
	Placebo	50 BID	150 BID	300 BID	600 BID	600 TID	All PGB
=25% ? from baseline	2.6% (5/190)	1.3% (1/80)	3.7% (3/82)	1.3% (1/90)	2.5% (4/160)	3% (4/132)	2.4% (13/533)
>200msec on treatment	5.3% (10/190)	6.3% (5/80)	3.7% (3/82)	6.3% (5/79)	8.1% (13/160)	1.5% (2/132)	5.3% (28/533)
Pooled Psychiatry Studies							
		Pregabalin Dose (mg/day)					
	Placebo	150			600		All PGB
=25% ? from baseline	1% (2/201)	1% (2/200)			2.6% (5/196)		1.8% (7/396)
>200msec on treatment	2.5% (5/201)	4.5% (9/200)			2% (4/196)		3.3% (13/396)

From Tables 12, 15, 18, and 21, Memo 720-04340

Pfizer noted that the percentage of pregabalin subjects with a PR =220msec and a =40msec increase from baseline was 0.25% (6/2426) compared to 0.5% (6/1160) for placebo. The following table summarizes these PR outliers by dose.

FDA Table 67. Summary of Patients Who Had a Post Baseline PR Interval =220msec and a =40msec increase in PR Interval during Double Blind, Controlled Trials of Pregabalin

Treatment Group							
	Pregabalin (mg/day)						AMT
Placebo	50	75	150	300	450	600	75mg/day
N=1160	N=80	N=151	N=594	N=464	N=171	N=966	N=70
6 (0.005)	1 (0.01)	0	0	0	0	5 (0.005)	1 (0.01)

AMT=Amitriptyline
From Pfizer Table 4, Memo 720-04340, p.17

PR Prolongation Related Adverse Events

Pfizer found no meaningful differences between pregabalin and placebo subjects for adverse events coded to terms related to AV block, based on a small number of such events. Below, I summarize the results of this analysis.

FDA Table 68. AV Block Related Adverse Events in Controlled Trials of Pregabalin

Adverse Event Preferred Term	Placebo N=1579	Pregabalin N=3336
AV Block	0	0.0% (1)
AV Block First Degree	0.1% (1)	0.1% (5)
AV Block Second Degree	0	0.1% (2)

From Pfizer Table 5, Memo 720-04340, p.18

Four of the five pregabalin subjects with First Degree AV block AEs were in the highest pregabalin dose group (600mg/day). One of the pregabalin subjects with second degree heart block (011 083004) had first degree heart block at baseline and returned to first degree heart block while continuing pregabalin. The second pregabalin patient with second degree heart block (014 024 02413) was considered to have second degree heart block at baseline by a cardiology consultant (not identified by investigator). Pfizer identified one pregabalin subject (029 036008) from an open label trial with complete heart block that occurred in the setting of an acute myocardial infarction.

Effect of Pregabalin on QRS Interval

QRS Mean Maximum Change from Baseline

Pfizer reported that the maximum increases in QRS from baseline for pregabalin subjects were not consistently different for pregabalin subjects compared to placebo (Memo 720-0430, p.20).

QRS Outliers

Pfizer's summary of QRS outliers (=25% increase, <60msec, >100msec) did not suggest differences between pregabalin and placebo treated subjects (Memo 720-0430, Tables 12, 15, 18, and 21).

Effect of Pregabalin on QTc

QTc Mean Maximum Change from Baseline

In appendix tables B02, B07, D02, and F02, Pfizer reported the summary statistics for ECG parameters that included the mean maximum QTc changes from baseline for pregabalin and placebo and there was little difference when comparing treatments for any of the different indication groups. The following table summarizes the mean maximum QTc changes from baseline for the treatment indication groups.

FDA Table 69. Unadjusted Mean Maximum Change from Baseline, QTc* Interval

Treatment (n)	QTc mean max change from baseline (ms)	Difference from placebo
Pooled Pain Studies		
Placebo (n=782)	2.8	--
Pregabalin (n=1510)	2.3	-0.5
Pooled Diabetic Neuropathic Pain Studies		
Placebo (n=291)	3.6	--
Pregabalin (n=483)	3.8	0.2
Pooled Epilepsy Studies		
Placebo (n=190)	7.9	--
Pregabalin (n=534)	4.1	-3.8
Pooled Psychiatry Studies		
Placebo (n=201)	3.1	--
Pregabalin (n=396)	-0.1	-3.2

*linear correction for heart rate

Pfizer reported that their ANCOVA analysis of maximum increases in QTc from baseline for pregabalin subjects did not find consistent differences for pregabalin subjects compared to placebo. I provide the results from Pfizer's ANCOVA analysis results of mean maximum QTc change from baseline in the following table.

FDA Table 70. ANCOVA LS Mean Maximum Change from Baseline, QTc* Interval

Treatment (n)	LS QTc mean change from baseline (ms)	Estimated difference from placebo (95%CI)
Pooled Pain Studies		
Placebo (n=786)	2.69	--
PGB 75 mg/day TID (n=153)	3.24	0.55 (-2.06, 3.17)
PGB 150 mg/day TID (n=319)	4.14	1.45 (-0.45, 3.34)
PGB 300 mg/day TID (n=384)	2.16	-0.53 (-2.29, 1.23)
PGB 450 mg/day TID (n=172)	2.76	0.07 (-2.39, 2.53)

PGB 600 mg/day TID (n=494)	1.62	-1.07 (-2.64, 0.49)
Pooled Diabetic Neuropathic Pain Studies		
Placebo (n=293)	2.57	--
PGB 75 mg/day TID (n=72)	2.71	0.14 (-3.60, 3.88)
PGB 150 mg/day TID (n=74)	4.55	1.98 (-1.91, 5.87)
PGB 300 mg/day TID (n=125)	3.42	0.85 (-2.20, 3.90)
PGB 600 mg/day TID (n=220)	1.82	-0.75 (-3.15, 1.65)
Pooled Epilepsy Studies		
Placebo (n=190)	5.31	--
PGB 50 mg/day BID (n=80)	2.26	-3.05 (-6.69, 0.59)
PGB 150 mg/day BID (n=82)	2.87	-2.45 (-6.06, 1.16)
PGB 300 mg/day BID (n=80)	0.76	-4.56 (-8.20, -0.92)
PGB 600 mg/day BID (n=160)	3.76	-1.56 (-4.29, 1.17)
PGB 600 mg/day TID (n=96)	3.96	-1.36 (-4.83, 2.12)
Pooled Psychiatry Studies		
Placebo (n=201)	-0.41	--
PGB 150 mg/day TID (n=201)	-0.98	-0.57 (-3.39, 2.24)
PGB 600 mg/day TID (n=196)	-3.79	-3.38 (-6.17, -0.57)

*linear correction for heart rate
From Memo 720-04340 Tables 11, 14, 17, and 20

QTc Outliers

There did not appear to be notable differences in risk between pregabalin and placebo subjects for the QTc outliers examined by Pfizer. In the following table I summarize the QTc outlier risks from the pooled studies.

FDA Table 71. QTc Outlier Risks by Pooled Indications

Pooled Pain Studies							
		Pregabalin Dose (mg/day)					
	Placebo	75	150	300	450	600	All PGB
30= Max change<60	5.9% (46/782)	3.3% (5/151)	6% (9/316)	4.2% (16/382)	6.4% (11/172)	7.2% (35/489)	5.7% (86/1510)
60= Max change<90	0% (0/782)	0% (0/151)	0.6% (2/316)	0.3% (1/382)	0.6% (1/172)	0% (0/484)	0.3% (4/1510)
Max change =90	0% (0/782)	0% (0/151)	0% (0/316)	0% (0/382)	0% (0/172)	0.2% (1/484)	0.1% (1/1510)
=500msec	0.1% (1/790)	0% (0/153)	0% (0/322)	0% (0/390)	0% (0/174)	0.4% (2/484)	0.1% (2/1543)
Pooled Diabetic Neuropathy Studies							
		Pregabalin Dose (mg/day)					
	Placebo	75	150	300		600	All PGB
30= Max change<60	5.5% (16/291)	5.7% (4/70)	9.5% (7/74)	4.9% (6/123)		7.9% (17/216)	7% (34/483)
60= Max change<90	0% (0/291)	0% (0/70)	0% (0/74)	0% (0/123)		0% (0/216)	0% (0/483)
Max change =90	0% (0/291)	0% (0/70)	0% (0/74)	0% (0/123)		0.5% (1/216)	0.2% (1/483)
=500msec	0.3% (1/295)	0% (0/72)	0% (0/75)	0% (0/130)		0% (0/227)	0% (0/504)

Pooled Epilepsy Studies							
		Pregabalin Dose (mg/day)					
	Placebo	50 BID	150 BID	300 BID	600 BID	600 TID	All PGB
30= Max change<60	10% (19/190)	8.8% (7/80)	4.9% (4/82)	8.8% (7/80)	8.8% (14/160)	7.6% (10/132)	7.9% (42/534)
60= Max change<90	0.5% (1/190)	0% (0/80)	0% (0/82)	0% (0/80)	0% (0/160)	0.8% (1/132)	0.2% (1/534)
Max change =90	0% (0/190)	0% (0/80)	0% (0/82)	0% (0/80)	0% (0/160)	0.8% (1/132)	0.2% (1/534)
=500msec	0% (0/192)	0% (0/84)	0% (0/83)	0% (0/80)	0% (0/160)	0% (0/136)	0% (0/543)
Pooled Psychiatry Studies							
		Pregabalin Dose (mg/day)					
	Placebo	150			600		All PGB
30= Max change<60	8.5% (17/201)	8.5% (17/201)			7.2% (14/195)		7.8% (31/396)
60= Max change<90	0% (0/201)	0% (0/201)			0% (0/195)		0% (0/396)
Max change =90	0% (0/201)	0% (0/201)			0% (0/195)		0% (0/396)
=500msec	0% (0/202)	0% (0/202)			0% (0/199)		0% (0/401)

From Tables 13, 16, 19, and 22, Memo 720-04340

Effect of Pregabalin on Ventricular Rate

Ventricular Rate Mean Maximum Increase and Decrease Change from Baseline

Pfizer reported that neither the mean maximum increase nor decrease in ventricular rate from baseline for pregabalin subjects were consistently different for pregabalin subjects compared to placebo (Memo 720-0430, pp.24-25).

Ventricular Rate Outliers

Pfizer's summary of ventricular rate outliers (<60, >100) did not suggest differences between pregabalin and placebo treated subjects (Memo 720-0430, Tables 12, 15, 18, and 21).

MEMO 720-30165
Methods
Pfizer's summary of ECG data focused on results of analyses that pooled ECG data from double blind placebo controlled clinical trials. Pfizer analyzed the pooled data for the GAD studies, the pooled data for new psychiatry studies, and separately, the data from the sustained efficacy studies. The following table identifies the pooled studies and the groupings used in the analyses.

FDA Table 72. Pooled Studies Included in the Pregabalin ECG Data Analyses

Indication/Pool	Studies included	Number treated
Generalized Anxiety	021*, 025*, 026*, 083,	Pregabalin 941

Disorder	085	Placebo 382 Lorazepam 204
New Short Term Psychiatry Studies	080, 083, 085, 092, 094	Pregabalin 929 Placebo 338 Alprazolam 93, Paroxetine 77
Sustained Efficacy (relapse prevention)	082	Pregabalin 80 Placebo 73
	088	Pregabalin 168 Placebo 170

From RR Memo 720-04340, p.7
*Data from these studies were included in the analyses in MEMO 720-0430

Pfizer's approach to analyzing the ECG data in this memo was similar to the approach outlined above. Due to the unique design of the sustained efficacy (relapse prevention) studies, Pfizer used a slightly different analysis approach for studies 082 and 088. These studies included an open label treatment phase that was followed by randomization to placebo or pregabalin. Pfizer provided ECG analyses that used the pre-open label baseline ECG and separate analyses that used the pre double blind baseline ECG. Since there was no washout period between the open label phase and the double blind phase in these studies, the pre-double blind phase ECG is actually an on-treatment ECG and not a true baseline ECG.

Demographics

Pfizer provided the demographics by indication and I summarize those results in the following table

FDA Table 73. Demographics by Study Grouping, Memo 720-30165 Analyses

Indication	Age (range of means from pooled studies)	Sex	Race	Cr clearance (range of means from pooled studies)
GAD	37 to 40 years	59% F	80% white	100 to 107 mL/min
New Psychiatry	33 to 40 years	56% F	78% white	101 to 135 mL/min
082	34 to 37 years	41% F	80% white	104 to 105 mL/min
088	39 years	57% F	85% white	101 to 104 mL/min

ECG Results

Effect of Pregabalin on PR Interval

PR Mean Maximum Change from Baseline

In their overview of results, Pfizer notes that pregabalin increased the PR interval with a mean effect compared to placebo of 4-6msec that they considered not clinically meaningful. The following table summarizes the mean maximum change from baseline for PR interval for these analyses.

FDA Table 74. ANCOVA LS Mean Maximum Change from Baseline, PR Interval

Treatment (n)	LS PR mean change from baseline (ms)	Estimated difference from placebo (95%CI)
Pooled GAD Studies		
Placebo (n=250)	-0.52	--
PGB 150 mg/day TID (n=164)	0.38	0.90 (-1.81, 3.62)
PGB 200 mg/day BID (n=47)	3.20	3.72 (-0.86, 8.31)
PGB 300 mg/day TID (n=68)	0.28	0.80 (-3.00, 4.60)
PGB 400 mg/day BID (n=57)	-0.99	-0.47 (-4.80, 3.86)
PGB 450 mg/day TID (n=125)	3.23	3.75 (0.72, 6.79)
PGB 600mg/day TID (n=215)	3.94	4.47 (2.08, 6.85)
Pooled New Psychiatry Studies		
Placebo (n=219)	0.13	--
PGB 200 mg/day BID (n=70)	4.02	3.89 (-0.10, 7.87)
PGB 300 mg/day TID (n=128)	1.84	1.71 (-1.38, 4.80)
PGB 400 mg/day BID (n=97)	1.97	1. 83 (-1.70, 5.37)
PGB 450 mg/day TID (n=200)	5.27	5.14 (2.55, 7.73)
PGB 600 mg/day BID (n=17)	4.00	3.87 (-3.91, 11.65)
PGB 600 mg/day TID (n=133)	4.71	4.58 (1.52, 7.64)
Study 082		
Placebo (n=36)*	0.62	--
PGB 450 mg/day TID (n=36)*	-1.29	-1.91 (-9.56, 5.75)
Placebo (n=36) ‡	-7.26	--
PGB 450 mg/day TID (n=34)‡	-1.94	5.32 (-4.73, 15.36)
Study 088		
Placebo (n=125) *	0.05	--
PGB 450 mg/day TID (n=114)*	3.78	3.73 (0.48, 6.99)
Placebo (n=122) ‡	-4.42	--
PGB 450 mg/day TID (n=113) ‡	-0.69	3.73 (0.49, 6.97)

Compiled from Tables 9, 10, 11, 12, 13, and 14, MEMO 720-30165
*Uses open label baseline
‡Uses double blind baseline

PR Outliers

Pfizer outlier analyses for PR prolongation by indication groups appeared to demonstrate slight increases in risk for PR increase =25% from baseline and PR >200msec, although their dose response analyses did not appear to support linear relationships. I provide those results in the following table.

FDA Table 75. PR Interval Outlier Risks by Pooled Indications

GAD Studies								
		Pregabalin Dose (mg/day)						
	PBO	150	200	300	400	450	600	All PGB
=25% ? from baseline	1.2% 3/250	0.6% 1/164	6.4% 3/47	1.5% 1/68	0% 0/57	0.8% 1/125	2.3% 5/215	1.6% 11/676
>200msec on	2.4%	4.3%	2.1%	2.9%	7%	3.2%	2.3%	3.4%

treatment	6/250	7/164	1/47	2/68	4/57	4/125	5/215	23/676
New Psychiatry Studies								
		Pregabalin Dose (mg/day)						
	PBO	200	300	400	450	600*	600‡	All PGB
=25% ? from baseline	0.9% 2/219	4.3% 3/70	2.3% 2/128	1.0% 1/97	2.0% 4/200	0% 0/17	1.5% 2/133	2.0% 13/645
>200msec on treatment	1.4% 3/219	2.9% 2/70	3.1% 4/128	4.1% 4/97	4.5% 9/200	0% 0/17	3.0% 4/133	3.6% 23/645
Study 082								
		Pregabalin Dose (mg/day)						
	Placebo	450 TID						
=25% ? from open baseline	5.6% 4/72	1.3% 1/80						
=25% ? from db baseline	0% 0/71	2.6% 2/77						
>200msec on treatment	4.2% 3/72	7.5% 6/80						
Study 088								
		Pregabalin Dose (mg/day)						
	Placebo	450 TID						
=25% ? from open baseline	3.5% 6/170	1.8% 3/169						
=25% ? from db baseline	0.6% 1/167	0% 0/168						
>200msec on treatment	2.9% (5/170)	4.7% (8/169)						

From Tables B02, C02, D02, and D11, Memo 720-04340
*BID dosing regimen
‡TID dosing regimen

Pfizer reported that there were 3 patients from the GAD and New Psychiatry groups (1 placebo, 2 pregabalin) with a post baseline PR=220msec and a maximum increase of =40msec. One subject from study 082 had a post baseline PR=220msec and a maximum increase of =40msec when compared with the double blind baseline but not when compared to the open label baseline (MEMO 720-30165, pp. 25-6).

PR Prolongation Related Adverse Events
Pfizer reported that there were no subjects in the analyzed trials with adverse events coded to terms related to AV block.

Effect of Pregabalin on QRS Interval

QRS Mean Maximum Change from Baseline

Pfizer reported that the maximum increases in QRS from baseline for pregabalin subjects were not consistently different for pregabalin subjects compared to placebo (Memo 720-30165, p.26).

QRS Outliers

Pfizer's summary of QRS outliers (=25% increase, <60msec, >100msec) did not suggest differences between pregabalin and placebo treated subjects (Memo 720-30165, Tables B02, C02, D02, and D11).

Effect of Pregabalin on QTc

QTc Mean Maximum Change from Baseline

In appendix tables B04, C04, D04, D05, D13 and D14, Pfizer reported the unadjusted mean maximum QTc changes from baseline for pregabalin and placebo and there was little difference when comparing treatments for any of the different indication groups. The following table summarizes the mean maximum QTc changes from baseline for the treatment indication groups.

FDA Table 76. Unadjusted Mean Maximum Change from Baseline, QTc* Interval

Treatment (n)	QTc mean max change from baseline (ms)	Difference from placebo
Pooled GAD Studies		
Placebo (n=250)	3.8	--
Pregabalin (n=676)	-0.9	-4.7
Pooled New Psychiatry Studies		
Placebo (n=219)	4.1	--
Pregabalin (n=645)	0.4	-3.7
Study 082		
Placebo (n=36)*	-2.9	--
Pregabalin (n=36)*	0.8	3.7
Placebo (36) ‡	1.0	--
Pregabalin (34) ‡	-1.4	-2.4
Study 088		
Placebo (n=125)*	-1.7	--
Pregabalin (n=114)*	-3.5	-1.8
Placebo (n=122) ‡	-0.2	--
Pregabalin (n=113) ‡	-2.1	-1.9

*linear correction for heart rate
*Uses open label baseline
‡Uses double blind baseline

Pfizer reported that their ANCOVA analysis of maximum increases in QTc from baseline for pregabalin subjects did not find consistent differences for pregabalin subjects compared to placebo. I provide the results from Pfizer's ANCOVA analysis results of mean maximum QTc change from baseline in the following table.

FDA Table 77. ANCOVA LS Mean Maximum Change from Baseline, QTc

Treatment (n)	LS QTc mean change from baseline (ms)	Estimated difference from placebo (95%CI)
Pooled GAD Studies		

Placebo (n=250)	1.16	--
PGB 150 mg/day TID (n=165)	-0.46	-1.62 (-4.48, 1.23)
PGB 200 mg/day BID (n=48)	-1.74	-2.90 (-7.69, 1.89)
PGB 300 mg/day TID (n=68)	-2.87	-4.03 (-8.02, -0.03)
PGB 400 mg/day BID (n=56)	-2.37	-3.53 (-8.11, 1.04)
PGB 450 mg/day TID (n=125)	-0.43	-1.59 (-4.79, 1.60)
PGB 600mg/day TID (n=215)	-2.64	-3.80 (-6.31, -1.29)
Pooled New Psychiatry Studies		
Placebo (n=219)	1.20	--
PGB 200 mg/day BID (n=71)	0.09	-1.11 (-4.98, 2.76)
PGB 300 mg/day TID (n=129)	-0.80	-2.00 (-5.01, 1.01)
PGB 400 mg/day BID (n=96)	-0.74	-1.94 (-5.40, 1.52)
PGB 450 mg/day TID (n=200)	-0.51	-1.71 (-4.24, 0.82)
PGB 600 mg/day BID (n=17)	-2.76	-3.96 (-11.54, 3.62)
PGB 600 mg/day TID (n=133)	-0.87	-2.07 (-5.06, 0.91)
Study 082		
Placebo (n=36)*	-1.80	--
PGB 450 mg/day TID (n=36)*	5.98	7.78 (1.03, 14.53)
Placebo (n=36) ‡	0.58	--
PGB 450 mg/day TID (n=34)‡	7.69	7.11 (0.75, 13.48)
Study 088		
Placebo (n=125) *	-1.44	--
PGB 450 mg/day TID (n=114)*	-6.77	-5.33 (-8.64, -2.02)
Placebo (n=122) ‡	1.19	--
PGB 450 mg/day TID (n=113)‡	-3.35	-4.54 (-7.84, -1.25)

Compiled from Tables 9, 10, 11, 12, 13, and 14, MEMO 720-30165
*Uses open label baseline
‡Uses double blind baseline

QTc Outliers

There did not appear to be notable differences in risk between pregabalin and placebo subjects for the QTc outliers examined by Pfizer. In the following table I summarize the QTc outlier risks from the pooled studies.

FDA Table 78. QTc Outlier Risks by Pooled Indications

GAD Studies								
		Pregabalin Dose (mg/day)						
	PBO	150	200	300	400	450	600	All PGB
30= Max change<60	8.4% 21/250	4.8% 8/165	8.3% 4/48	0% 0/67	3.5% 2/57	6.4% 8/125	7.9% 17/214	5.8% 39/676
60= Max change<90	0% 0/250	0% 0/165	0% 0/48	0% 0/67	0% 0/57	0% 0/125	0% 0/214	0% 0/676
Max change =90	0% 0/250	0% 0/165	0% 0/48	0% 0/67	0% 0/57	0% 0/125	0% 0/214	0% 0/676
=500msec	0% 0/252	0% 0/166	0% 0/49	0% 0/67	0% 0/57	0% 0/125	0% 0/216	0% 0/681
New Psychiatry Studies								

		Pregabalin Dose (mg/day)						
	PBO	200	300	400	450	600*	600‡	All PGB
30= Max change<60	5.9% 13/219	8.6% 6/70	2.3% 3/128	3.1% 3/97	5% 10/200	5.9% 1/17	7.5% 10/133	5.1% 33/645
60= Max change<90	0% 0/219	0% 0/70	0% 0/128	0% 0/97	0% 0/200	0% 0/17	0% 0/133	0% 0/645
Max change =90	0% 0/219	0% 0/70	0% 0/128	0% 0/97	0% 0/200	0% 0/17	0% 0/133	0% 0/645
=500msec	0% 0/222	0% 0/72	0% 0/128	0% 0/97	0% 0/201	0% 0/17	0% 0/133	0% 0/648

Study 082

		Pregabalin Dose (mg/day)
	Placebo	450 TID
30= Max change<60 open baseline	2.8% 1/36	5.6% 2/36
60= Max change<90 open baseline	0% 0/36	0% 0/36
Max change =90 open baseline	0% 0/36	0% 0/36
30= Max change<60 db baseline	5.6% 2/36	2.9% 1/34
60= Max change<90 db baseline	0% 0/36	0% 0/34
Max change =90 db baseline	0% 0/36	0% 0/34
=500msec	0% 0/36	0% 0/36

Study 088

		Pregabalin Dose (mg/day)
	Placebo	450 TID
30= Max change<60 open baseline	7.2% 9/125	0.9% 1/114
60= Max change<90 open baseline	0% 0/125	0% 0/168
Max change =90 open baseline	0% 0/125	0% 0/168
30= Max change<60 db baseline	4.9% 6/122	2.7% 3/113
60= Max change<90 db baseline	0% 0/122	0% 0/113
Max change =90 db baseline	0% 0/122	0% 0/113
=500msec	0% 0/125	0% 0/114

From Tables B03, C03, D03, and D12, Memo 720-04340
*BID dosing regimen
‡TID dosing regimen

Effect of Pregabalin on Ventricular Rate

Ventricular Rate Mean Maximum Increase and Decrease Change from Baseline

Pfizer reported that neither the mean maximum increase nor decrease in ventricular rate from baseline for pregabalin subjects were consistently different for pregabalin subjects compared to placebo (Memo 720-30165, pp.28-30).

Ventricular Rate Outliers

Pfizer's summary of ventricular rate outliers (<60, >100) did not suggest consistent differences between pregabalin and placebo treated subjects (Memo 720-0430, Tables B02, C02, D02, and D11).

4.7 Special Safety Topics

4.7.1 Accidental Injury

Pfizer examined the relationship between selected CNS AEs and accidental injury AEs (Summary of Safety, p.96). For this analysis, Pfizer considered AEs coded to the preferred term accidental injury and the following CNS AE preferred terms that could predispose an individual to injury: dizziness, somnolence, asthenia, amblyopia, diplopia, nystagmus, ataxia, abnormal gait, amnesia, confusion, speech disorder, thinking abnormal, euphoria and incoordination. The potential limitations of this analysis include lack of consideration of the temporal association between the CNS AEs and the accidental injury AEs, and the possibility that the pooling of CNS events could obscure a relationship between accidents and a particular CNS event or a subset of the CNS events considered by Pfizer.

Pfizer demonstrated that the risk for CNS events alone, accidental injuries alone and CNS events plus accidental injuries together, were higher for pregabalin subjects compared to placebo subjects. In the controlled trials, accidental injury was reported as an AE by 4.2% (233/5508) of pregabalin subjects and 2.9% (69/2384) of placebo subjects. Furthermore, Pfizer reported that 53.2% (2930/5508) of pregabalin subjects and 22.3% (531/2384) reported one or more of the CNS AEs listed above. The risk of co-occurrence of accidental injury and one or more CNS AEs was 1.7% (96/5508) for pregabalin and 0.7% (17/2384) for placebo.

Pfizer intended to examine whether the observed increased risk of accidental injury in pregabalin subjects is related to the increased risk of CNS AEs. Although Pfizer's analysis cannot directly answer that question, it explores the relationship between CNS events and accidental injury for pregabalin and placebo subjects. Pfizer reported that 3.3% (96/2930) of the pregabalin subjects with the selected CNS events described above also had an accidental injury AE compared to 3.2% (17/531) of placebo subjects with CNS AEs. If one assumes a causal relationship between the presence of these CNS events and accidental injury risk, these data suggest that although pregabalin was associated with an increased risk of CNS events, it did not alter the relationship between CNS events and accidental injuries when compared to placebo. Interestingly, among pregabalin subjects who did not experience one or more of the selected CNS AEs, the risk for

accidental injury was 5.3% (137/2578) compared to an accidental injury risk of 2.8% (52/1853) for placebo subjects who did not experience one or more of the selected CNS AEs. Focusing on those subjects who experienced accidental injury AEs, the risk of one or more of the CNS AEs of interest was 41% (96/233) for pregabalin subjects compared to 25% (17/69) for placebo subjects. For those who did not experience an accidental injury AE, the risk of a CNS event was 54% (2834/5275) for pregabalin subjects compared to 22% (514/2315) for placebo subjects. Unfortunately, without knowing the temporal relationship between these CNS events and the accidental injury AEs one cannot completely understand the relationship between these events.

In their analysis, Pfizer also noted that for the combined controlled and uncontrolled trials database, epilepsy subjects experienced the highest risks for the pooled CNS AEs, accidental injury AEs and concurrent CNS and accidental injury AEs. Pfizer suggested that this finding might be due to concurrent AEDs that epilepsy subjects were taking.

4.7.2 CNS Adverse Events

Pfizer provided separate discussions of selected CNS AE risks where they addressed the following CNS AE groupings:

- Motor function: ataxia, incoordination, abnormal gait, and speech disorder
- Mental status: thinking abnormal, amnesia, confusion, and stupor
- Neuropsychiatric disorders: euphoria, depression, suicide attempt, psychotic depression, depersonalization, agitation, emotional lability, personality disorder, hallucinations, psychosis, and hostility
- CNS events of convulsions, twitching, and myoclonus

In most cases Pfizer simply restated the overall and indication specific AE risks for the selected CNS AEs. For the Thinking abnormal AEs, they reclassified events using more clinically descriptive terms.

Motor function

Pfizer commented that ataxia and abnormal gait risks were highest among pregabalin subjects in the epilepsy trials while incoordination risk was highest in pregabalin subjects in GAD trials. Focusing on the relative risks reveals that GAD subjects had the highest relative risk for ataxia, that the relative risk for abnormal gait was similar for the neuropathic pain and epilepsy indications (not defined for GAD), and that the neuropathic pain group had the highest relative risk for incoordination. In the following table, I summarize the risks and relative risks for these motor related AEs, by indication.

FDA Table 79. Motor Related CNS AE Risks and Relative Risks, by Indication, NDA Controlled Trials

Adverse Event	Indication	Pregabalin	Placebo	RR
Ataxia	Neuropathic pain	3.7% (68/1831)	0.9% (8/857)	4.1
	Epilepsy	13.2% (100/758)	4.1% (12/294)	3.2

	GAD	2.9% (33/1149)	0.2% (1/484)	14.5
Abnormal gait	Neuropathic pain	2.3% (43/1831)	0.2% (2/857)	11.5
	Epilepsy	3.4% (26/758)	0.3% (1/294)	11.3
	GAD	0.3% (4/1149)	(0/484)	-
Incoordination	Neuropathic pain	1.6% (30/1831)	0.2% (2/857)	8
	Epilepsy	4.1% (26/758)	1% (3/294)	4.1
	GAD	7.1% (4/1149)	1% (5/484)	7.1

Data from Appendices ALL.272, ALL.273, and ALL.274

Based on a review of verbatim terms, Pfizer also considered most of the speech disorder verbatim terms suggestive of motor deficits (articulation) rather than cognition problems (Summary of Safety, p.98).

Mental Status

Pfizer reclassified the thinking abnormal verbatim terms to what they felt were more clinically descriptive terms, namely difficulty with concentration/attention, cognition problems, language problems, and slowed thinking. I provide the risks and relative risks following the re-coding of verbatim terms to the preferred terms listed above.

FDA Table 80. Risks and Relative Risks for Thinking abnormal AEs following re-coding, by Indication, NDA Controlled Trials

Adverse Event	Indication	Pregabalin	Placebo	RR
Cognition problems	**Overall**	**0.8% (46/5508)**	**0.3% (6/2384)**	**2.7**
	Neuropathic pain	0.4% (7/1831)	0/857	-
	Epilepsy	1.2% (9/758)	0.3% (1/294)	4
	GAD	0.9% (10/1149)	0.6% (3/484)	1.5
Difficulty With Concentration\ Attention	**Overall**	**4% (218/5508)**	**1.2% (28/2384)**	**3.3**
	Neuropathic pain	1% (18/1831)	0.7% (6/857)	1.4
	Epilepsy	3.2% (24/758)	0.7% (2/294)	4.6
	GAD	4.7% (54/1149)	1.7% (8/484)	2.8
Language problems	**Overall**	**0.4% (24/5508)**	**0.1% (2/2384)**	**4**
	Neuropathic pain	0.3% (5/1831)	(0/857)	-
	Epilepsy	1.6% (12/758)	0.3% (1/294)	4.1
	GAD	0.3% (3/1149)	(0/484)	-
Slowed Thinking	**Overall**	**0.4% (24/5508)**	**0.1% (2/2384)**	**4**
	Neuropathic pain	0.3% (5/1831)	(0/857)	-
	Epilepsy	1.7% (13/758)	0.7% (2/294)	2.4
	GAD	0.4% (5/1149)	(0/484)	-

Data from Appendices ALL.277, ALL.280, and ALL.281, All.282

The above table supports that the highest risks and relative risks for these CNS AEs were generally observed in the epilepsy controlled trials.

Pfizer felt that the coding of terms to the preferred terms amnesia, confusion and stupor were appropriate. They felt these events were infrequent and not clinically significant.

Neuropsychiatric disorders

Pfizer noted that euphoria occurred more commonly among pregabalin subjects (3.7%, 205/5508) than placebo subjects (0.5%, 11/2384). The risk varied by indication with the highest risk in the pregabalin GAD subjects (4.5%) and the lowest risk among epilepsy subjects (0.8%).

Depression was reported as an AE for 1.4% (75/5508) of pregabalin subjects and 1.1% (26/2384) placebo subjects in pregabalin controlled trials. In the overall combined controlled and uncontrolled trials database, depression was reported as an AE for 4.6% (395/8666) of subjects and as an SAE for 0.2% (16/8666) of subjects. The NDA included eleven pregabalin subjects who attempted suicide (0.1%, 11/8666). No placebo subjects (0/2384) and one active comparator subject (amitriptyline, 1.1%, 1/87) had an AE of suicide attempt. See section 4.7.4 for more details.

Pfizer felt that the AEs of depersonalization (1.5%, 81/5508), agitation (0.5%, 30/5508), emotional lability (0.7%, 36/5508), personality disorder (0.3%, 14/5508), hallucinations (0.3%, 16/5508) and hostility (0.2%, 11/5508) were uncommon among pregabalin subjects in the controlled trials. They noted that the risks for these events among placebo subjects ranged from 0.1% (2/2384) for hallucinations to 0.5% (13/2384) for emotional lability. Psychosis was reported only during uncontrolled epilepsy studies (0.6%, 9/1613), and six of the nine AEs were post ictal and/or were reported in the patients' medical history. AE risks for hostility, agitation, hallucinations, and personality disorder among pregabalin subjects were similar in the controlled trials across indications (all less than 0.9%). Pregabalin GAD subjects had the highest risk for depersonalization (2.7% compared to 0.6% for placebo) and pregabalin epilepsy subjects had the highest risk for emotional lability (1.6% compared to 1.4 for placebo).

Convulsions, myoclonus, twitching

In the entire pregabalin safety database, including phase I and dental pain studies, nineteen subjects (0.2%, 19/9373) had convulsion AEs. Thirteen of these subjects had a prior history of epilepsy. Of the remaining six subjects, two were from diabetic peripheral neuropathy studies, one from an acute dental pain study, one from a chronic osteoarthritis study, and two from a GAD study. Pfizer stated that four of these six subjects either had a history of seizures (although not diagnosed with or treated for epilepsy) or had clear precipitating factors for seizure (although they did not detail those factors). The fifth subject was diagnosed as having epilepsy during the trial and the remaining subject had no previous diagnosis of or treatment for epilepsy (Summary of Safety, p.104).

In the combined controlled and uncontrolled studies safety database, 0.8% (65/8666) of pregabalin subjects had myoclonus AEs. Sixty of the sixty-five subjects with myoclonus AEs were from epilepsy studies (forty-five during uncontrolled epilepsy trials). Pfizer stated that in the small number of patients with myoclonus who underwent EEG testing, there was no evidence that the myoclonus events were epileptic (Summary of Safety,

p.104). In controlled trials, the risk for myoclonus in pregabalin subjects was 0.3% (17/5508) compared to <0.1% (1/2384) for placebo subjects.

In the combined controlled and uncontrolled trials database, 2% (176/8666) of pregabalin subjects had twitching AEs and 81 of these subjects were from epilepsy trials. In controlled trials, the risk for twitching in pregabalin subjects was 1.2% (68/5508) compared to 0.5% (12/2384) for placebo subjects. Pfizer also noted that 40 of the 68 pregabalin subjects with twitching AEs from controlled trials were randomized to the 600mg/day dose (Summary of Safety, p.104).

4.7.3 Skin Adverse Events

The preclinical studies included a finding of tail dermatopathy of rats and monkeys that ranged from erythema to necrosis and that were characterized histologically by hyperkeratosis, acanthosis, fibrosis, and/or necrosis (mentioned above). In order to look for evidence of correlated events in humans, we reviews the controlled trials AEs looking specifically at skin and oral mucous membrane events in pregabalin and placebo subjects. The following table summarizes the reported AE risks for these events. There did not appear to be evidence of pregabalin related dermatopathy in humans based on the AE data from the controlled trials.

FDA Table 81. Skin and Oral Mucous Membrane AEs, Controlled Trials, Integrated Database

AE	Placebo (n=2384)	Pregabalin (n=5508)
Body as a Whole		
Cellulitis	0.1% (2)	0.2% (11)
Cyst	0.2% (4)	0.2% (10)
Mucous membrane d/o	0	0.04% (2)
Vasculitis	0.0% (1)	0
Skin		
Rash	2% (47)	1.7% (92)
Skin d/o	0.1% (2)	0.3% (14)
Contact dermatitis	0.1% (3)	0.2% (9)
Skin ulcer	0.1% (2)	0.1% (3)
Gastrointestinal		
Stomatitis	0.2% (4)	0.1% (6)
Ulcerative stomatitis	0.0% (1)	0.1% (3)
Aphthous stomatitis	0.0% (1)	0
Mouth ulceration	0.1% (3)	0.2% (12)

4.7.4 Suicides and Depression

Given recent concerns over a possible relationship between gabapentin and suicide, I provide a more detailed review of depression and suicide AEs in the pregabalin NDA and Safety Update Databases.

Suicide Deaths
There was one pregabalin death in the NDA and Safety Update databases attributed to suicide. This event was reported for a male with a history of depression who committed

suicide (self inflicted GSW) 42 days after stopping pregabalin, which he took for two days during a GAD trial. Concomitant medications included gabapentin and venlafaxine. Pfizer reported in the Safety Update a second suicide in a subject (ID # 145-4) receiving blinded therapy (narrative in 6/4/04 submission). This subject had a history of seizure disorder, depression, headaches, cystic fibrosis, head injury/fractured skull, osteoporosis, chest infections related to cystic fibrosis, horizontal unsustained bilateral nystagmus, and bilateral mild congenital anomaly of optic disc. He committed suicide by helium anoxia/plastic bag suffocation. The subject had no history of alcohol or drug abuse and no prior history of suicide attempts. The subject's depression was considered stable at the time of death, and there was no change in the subject's anticonvulsant medications within the two weeks prior to death. The subject was reportedly compliant in taking his study medication, and therefore, it was assumed that he was also compliant in taking his other medications including venlafaxine hydrochloride.

Depression/Suicide SAEs
Controlled trials
Through the Safety Update, the risk for suicide attempt SAEs in controlled trials was 0.1% (3/5781) for pregabalin subjects and was 0 (0/2449) for placebo subjects. I read through the narratives for the three pregabalin subjects with suicide attempt SAEs and summarize the events below.

011-021001 This 29 year old female had a history of seizure disorder and depression. The narrative mentioned a life threatening suicide attempt on day 19 of pregabalin treatment but did not identify the method of the attempt. The narrative noted that the subject had an elevated Phenobarbital level (68.9 mg/L). Concomitant medications were listed as topiramate, barbiturate, clobazam, and fluoxetine.
080-106018 This 26 year old female had a history of social phobia and attempted suicide on study day 16. The subject overdosed on 45 Sominex (salicylamide/methapyrilene hydrochloride/scopolamine aminoxide hydrobromide) tablets. She attributed the suicide attempt to interpersonal stressors that were not detailed in the narrative.
081-127007 This 19 year old male had a history of social phobia and attempted suicide on study day 29. The subject reported feeling depressed earlier in the study. He was discontinued from the study and started on fluoxetine and zolpidem. He agreed to return for follow up a week later but apparently returned home and ingested 25 pregabalin capsules (100mg).

Through the Safety Update, the risk for depression SAEs was 0 (0/5781) for pregabalin subjects and <0.1% (2/2449) for placebo subjects.

Combined Controlled and Uncontrolled Trials

Pfizer reported that through the Safety Update, there were 11 suicide attempt SAEs. Four of the events were summarized above (three SAEs, one death)[37]. I read through seven additional narratives for subjects with suicide attempts. This group of seven subjects (029 017029, 029 030006, 009 008019, 012 055106, 034 064001, 032 331001, 009 028003) included four males and three females and the age range was from 29 to 75 years old. Five of these seven subjects who attempted suicide had either a history of depression,

[37] The suicide from the safety update mentioned above is in a patient receiving blinded therapy and is not included in this total.

previous suicide attempts, or were taking an antidepressant. Two subjects were enrolled in DPN studies, four in epilepsy studies, and one in a chronic pain study.

Through the Safety Update, the risk for depression SAEs was 0.2% (17/9278) in the combined controlled and uncontrolled trials database.

Depression/Suicide Overall AEs
Controlled trials
There were three suicide attempts in pregabalin subjects (all SAEs) and none in placebo subjects in the controlled trials.

Pfizer reported that the risk for depression in the controlled trials was 1.3% (75/5781) among pregabalin subjects compared to 1.1% (26/2449) among placebo subjects.

Combined Controlled and Uncontrolled Trials
Pfizer reported that through the safety Update, there were 12 suicide attempt AEs. Through the Safety Update, the risk for depression AEs was 4.6% (428/9278) in the combined controlled and uncontrolled trials database.

4.7.5 Ophthalmology Findings

The pregabalin development program included ophthalmologic testing, which Pfizer states was prompted by the Canadian Health Protection Branch following reports of visual field changes reported with vigabatrin, a GABA transaminase inhibitor. Ophthalmologic testing included monitoring of visual fields/peripheral vision, visual acuity, and fundoscopy. Dr. Wiley Chambers of the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products reviewed the pregabalin ophthalmologic test result data and presented his findings in a memo dated 3/31/04.

Dr. Chambers concluded that visual acuity and visual field changes but not fundoscopic changes were seen more commonly in pregabalin subjects compared to placebo subjects. He pointed to visual field changes at the 300mg dose and visual acuity changes at the 600mg dose. He did not detect a specific pattern of visual acuity or visual field defects and he commented that few of the observed visual changes would significantly affect typical activities of daily living.

Dr. Chambers did not think that the ophthalmologic findings with pregabalin should preclude approval, but he did recommend labeling to describe the findings of the development program. In addition, Dr. Chambers recommended additional studies that could be performed as part of a Phase IV commitment.

4.7.6 Effects on Male Fertility

Because of pregabalin effects on sperm parameters and fertility in male Wistar rats, Pfizer studied the effect of pregabalin on sperm motility in humans. In their review of the

results, Pfizer concluded that pregabalin did not appear to provide risk to human male reproductive function at the maximum dose of 600mg/day.

HFD-170 requested that HFD-580 review these results. Dr. Olivia Johnson reviewed the results of the animal and human male reproductive studies in a memo dated 5/3/04. We were provided a copy of this consult review.

HFD-580 noted the animal findings of male rat reproductive toxicity at doses 4x the expected maximal human dose. These findings included adverse effects on sperm parameters and reproductive organ histology. HFD-580 described the monkey study results as disparate. They noted that in a short term study Pfizer reported small testes, and low testicular weight while long term studies did not support this effect.

In the human study, 072, HFD-580 felt that the study did not provide reasonable assurance of no effect on human sperm. They concluded that the trial did not demonstrate clinically meaningful changes in seminal fluid parameters, but was not powered to detect a significant effect in sperm concentration. 580 also noted that an excess of pregabalin subjects (5/30 v. 1/16) had FSH values normal at baseline that dropped to below normal at end of treatment.

HFD-580 felt that if pregabalin will be prescribed to men of reproductive age, an additional clinical trial should be performed (as a phase IV commitment) powered to examine the effect of pregabalin on sperm concentration. They describe such a study as a parallel group placebo controlled trial with a primary endpoint of either percentage of patients with a 50% reduction from baseline in sperm concentration or percentage of patients with lower than normal ($20x10^6$/mL) sperm concentration compared to placebo. In the proposed study, HFD-580 recommends that drug or placebo should be given for 3 months with semen analysis at baseline, month 3, and month 6. The sponsor should also measure FSH and testosterone at baseline, month 3 and month 6. These studies usually require 100 patients per group. 580 also provided labeling recommendations and they will be provided in the labeling section of the review.

4.7.7 Sexual Side Effects

Pfizer reported that in controlled trials, pregabalin was associated with an increased risk of adverse sexual side effects including impotence, libido decreased, anorgasmia, and abnormal ejaculation compared to placebo (Summary of Safety, p.107). The following table summarizes risks for sexual side effects for the overall controlled trials safety database. It should be noted that adverse sexual side effects were not solicited by a structured questionnaire.

FDA Table 82. Adverse Events Related to Sexual Dysfunction, Pregabalin Controlled Studies

	Placebo		All PGB	
	Male	Female	Male	Female
All Indications[a]	N=1139	N=1245	N=2557	N=2951
Impotence	8(0.7)	0(0.0)	73(2.9)	3 (0.1)

Libido Decreased	6(0.5)	1(0.1)	58(2.3)	21 (0.7)
Anorgasmia	0(0.0)	1(0.1)	21(0.8)	17 (0.6)
Abnormal Ejaculation	1(0.1)	0(0.0)	36(1.4)	0 (0.0)

From Pfizer Table 46, Summary of Safety p.108

Pfizer noted that the incidences of adverse sexual side effects were higher in men and in subjects enrolled in GAD studies.

4.7.8 Impairment of Mental Ability, Ability to Operate Machinery

Pfizer performed a study (097) intended to examine the effect of pregabalin on psychomotor function, driving ability, and sleep. This randomized crossover study enrolled 24 healthy subjects and exposed them to pregabalin 150mg TID, placebo, and alprazolam 1 mg TID. This study included tests of psychomotor function (critical flicker fusion, Hick's choice reaction time, compensatory tracking task, Sternberg memory scanning test, rapid visual information processing, and line analogue rating scales), sleep tests (sleep EEG, wrist actigraphy, and Leeds sleep evaluation questionnaire), and driving skills (brake reaction time).

Pfizer noted that dizziness and somnolence were frequently reported events with pregabalin, but that test results suggest that these events did not impair the subjects' ability to function. Pfizer reported that pregabalin resulted in mild information processing and sensory-motor coordination impairment, but not psychomotor impairment. Pfizer noted that the effect of pregabalin on each of these parameters was less than the effect observed with alprazolam. Pfizer reported that alprazolam but not pregabalin was associated with memory impairment. Pregabalin and alprazolam were associated with increased subjective reports of sedation and incoordination. Both alprazolam and pregabalin were associated with improved latency to sleep onset, total sleep time, and number of awakenings and both were associated with decreased REM sleep. Alprazolam resulted in increases of Stage 2 sleep, whereas pregabalin resulted in increases in slow wave sleep (Summary of Safety, pp.79-80).

4.7.9 Peripheral Edema and Weight Gain

Pfizer presented a separate discussion regarding peripheral edema in the safety database and conducted special analyses to further assess the risk of peripheral edema associated with pregabalin and investigate a possible association between the development of peripheral edema and weight gain.

The overall incidence of peripheral edema AEs in controlled studies was 6.1% (336/5508) in pregabalin-treated patients compared with 1.8% (42/2384) in placebo-treated patients. The highest incidence of peripheral edema was in the neuropathic pain studies; similar incidences and relative risks were observed in the diabetic peripheral neuropathy and post-herpetic neuralgia studies, which comprised the neuropathic pain studies. Pregabalin-treated patients in the GAD studies had the lowest frequency of peripheral edema; placebo-treated patients in GAD studies also had the lowest incidence observed among placebo-treated patients. Thus the pregabalin-associated relative risk

was higher for GAD than any other indication. This calculation was based on relatively few events, however, and must be interpreted with caution. Neither the pregabalin-treated patients in the GAD studies nor the pregabalin-treated patients in the epilepsy studies had an incidence of peripheral edema that was statistically significantly greater than that observed in the placebo group for the relevant indication. The table below summarizes Pfizer's data regarding frequencies of peripheral edema across dose groups and indications and the corresponding relative risks for peripheral edema that I calculated. Shaded cells indicate that the frequency of peripheral edema in that pregabalin dose group was statistically significantly greater than the frequency in the placebo group for the same indication:

FDA Table 83. Incidence of Peripheral Edema by Dose Group and Indication; Controlled Studies

Study Group	Placebo	Pre-gabalin; 150 mg/d	Pre-gabalin; 200 mg/day	Pre-gabalin; 300 mg/day	Pre-gabalin; 400 mg/day	Pre-gabalin; 450 mg/day	Pre-gabalin; 600 mg/day	Pre-gabalin; all doses and regimens	Relative risk (frequency [%] in all pregabalin-treated patients/ frequency [%] in placebo-treated patients)
All	1.8% (42/2384)	4.8% (56/1164)	1.9% (4/208)	8.9% (109/1224)	1.9% (7/360)	5.0% (25/501)	7.3% (131/1802)	6.1% (336/5508)	3.4
Neuro-pathic pain	2.9% (25/857)	7.2% (37/514)		12.5% (79/633)			13.6% (71/523)	10.4% (190/1831)	3.6
DPN	2.4% (11/459)	6.1% (13/212)		9.3% (30/321)			12.5% (46/369)	9.4% (92/979)	3.9
PHN	3.5% (14/398)	7.9% (24/302)		15.7% (49/312)			16.2% (25/154)	11.5% (98/852)	3.3
Epilepsy	2.0% (6/294)	3.2% (6/185)		3.3% (3/90)			5.6% (22/395)	4.2% (32/758)	2.1
GAD	0.4% (2/484)	1.4% (3/210)	2.6% (2/78)	1.1% (1/91)	2.7% (5/186)	2.8% (5/178)	1.5% (6/406)	1.9% (22/1149)	4.7

From Pfizer Table 36 (Summary of Safety, p. 88).

In the neuropathic pain and epilepsy studies, increased pregabalin doses appeared to be associated with an increased frequency of peripheral edema. This dose-response relationship was not evident for the GAD studies.

Since Pfizer coded investigator terms for edema to more than one preferred term without obvious reasons for making such distinctions, they examined the incidence of edema adverse events that were coded as either edema, generalized edema, or peripheral edema.