other a washout (YTCE). Figure 2 shows that the combined population for both trials consisted of 190 subjects who were initially enrolled in the baseline phase; of these, 160 (mean age 27.2 years; age range 3-60 years) were randomized to the double-blind phase (81 placebo, 79 TOP). However, the actual intent-to-treat analysis of primary efficacy variables based on PGTC seizures encompassed 158 subjects (80 placebo, 78 TOP), since one placebo YTC subject (#161) and one YTCE TOP subject (#39) failed to experience PGTC seizures during baseline or the double-blind phase. All 160 subjects were included in the intent-to-treat analyses for all other efficacy variables.

Table 1 (v 53/168) summarizes features of the two trials, tables 2a and 2b review demographics, and Table 4 provides data on therapy discontinuation and study completion. 83 (52%) were male, 147 (92%) were white, and 32 (20%) were $\leq$16 years old (age range: 3-60). All subjects were required to have PGTC seizures. Most received treatment with at least 2 concomitant AEDs during the double-blind phase: 26% of YTC, and 19% of YTCE, subjects had >2 background AEDs. Valproate VPA), carbamazepine (CBZ), phenytoin (PHT), and lamotrigine (LTG) were the most commonly used background AEDs in both trials (VPA, PHT, and CBZ in YTC; VPA, CBZ, and LTG in YTCE). The median by-subject average TOP dosage over the entire double-blind treatment phase (titration and stabilization periods) was 3.7 mg/kg/day for YTC and 3.6 mg/kg/day for YTCE; the median average dosage during the stabilization period was 5.1 mg/kg/day for each trial. The median duration of double-blind therapy was within 2 days of the planned duration (140 days) for each trial; however, the mean duration was 10 days longer for YTC than YTCE (v 53/168, p 48).

Although both trials had identical designs, eligibility criteria, and total sample sizes, there were some differences, which, the sponsor claims, "may have reduced the power in Protocol YTCE, relative to that of Protocol YTC, especially when analyzed by standard, unadjusted, last-observation-carried-forward methods" (v 53/168, p 103). First, the mean duration of therapy in YTCE was about 10 days shorter than YTC, the result, according to the sponsor, of the larger percentage of patient withdrawals in the former (YTCE, 25%; YTC, 10%); the median duration was, however, identical for the two studies (see Table 7). Second, more subjects had seizure-related limiting adverse events (4 in YTCE, 3 in the placebo group; none in YTC): "Because of these efficacy-related discontinuations, predominantly in the placebo group, the last-observation-carried-forward approach, which implicitly assumes uninformative censoring, may be biased against TOP" (v 53/168, p 105). However, this scenario should, on the contrary, favor the placebo group, as pointed out by FDA statistician Dr. Sue-Jane Wang. Finally, there is the baseline PGTC seizure imbalance in favor of the placebo group in YTCE (as noted above), and baseline seizure rate was the only covariate that was found statistically significant ($p<0.05$) for the analysis of PGTC seizures in study YTCE (it had no important impact on the results of analyses based on YTC -- the positive study -- or the combined trials [v 53/168, p 49]). To emphasis his point, the sponsor cites a post hoc completer analysis, according to which the TOP vs placebo baseline PGTC seizure-rate imbalances even more pronounced, median of 6.2 PGTC seizures/month vs 3.0 PGTC seizures/month. Nevertheless, even analyses that compensated for the baseline imbalance were not statistically significant. A similar baseline imbalance can be found in the positive YTC study between TOP (median of 6.4 PGTC seizures/month) and placebo (4.0 PGTC seizures/month) subjects who experienced PGTC seizures and at least one other generalized seizure type; but this imbalance did not negatively affect the outcome. Additionally, for the pooled population (combined studies), the treatment effect based on percent seizure-rate reduction and treatment responders -- for the categories of PGTC seizures and all seizures -- showed no significant differences between subjects experiencing <4 seizures/months and those with $\geq$4 (or <17 and $\geq$17) seizures/month (see Table 22). According to the sponsor, "the results for the intent-to-treat population were generally consistent with those for subjects who completed the trials" (v 53/168, p 80).

In study YTC, TOP subjects had a median percent reduction from baseline in their average monthly PGTC seizure rate of 56.7%, compared to 9.0% in the placebo group ($p=0.019$; baseline PGTC seizure rate-adjusted p-value=0.020). TOP subjects in YTCE experienced a similar median percent reduction of 57.1%, but placebo subjects enjoyed a 33.2% reduction, or three times the amount the placebo cohort in YTC; the results were not statistically significant ($p=0.124$).

Nonetheless, the baseline PGTC seizure rate-adjusted analysis showed a statistical trend in favor of TOP (p=0.078); see Table 8. If both protocols are considered collectively, the median percent reduction was 56.9% for TOP subjects vs 27.1% for placebo, a statistically significant between-group comparison for both unadjusted (p=0.004) and baseline seizure rate-adjusted (p=0.003) analyses.

With respect to PGTC responder rates (≥50% reduction from baseline seizure rate), results from study YTC were statistically significant in favor of TOP, 56% TOP responders vs 20% placebo (p=0.001); this was not the case for YTCE, with 54% TOP responders vs 35% placebo (p=0.102). However, when adjusted for the baseline PGTC seizure rate imbalance, YTCE results were also statistically significant in favor of TOP (p=0.002). Collectively, for both protocols (see Table 9), 55% TOP vs 28% placebo subjects were treatment responders, a significant result in favor of TOP (p=0.001). If treatment response were defined as ≥75% median PGTC seizure-rate reduction (v 53/168, p 57), the results would be statistically significant in favor of TOP: 33% TOP vs 13% placebo in YTC (p=0.037), 36% TOP vs 15% placebo in YTCE (p=0.04), and, collectively, 35% TOP vs 14% placebo (p=0.003).

For all seizures, the intent-to-treat analysis showed a median percent seizure reduction from baseline during the double-blind phase of 42.1% TOP vs 0.9% placebo for YTC (p=0.003), 26.0% TOP vs 12.1% placebo for YTCE (p=0.212), and collectively for the combined trials 36.7% TOP vs 7.3% placebo (p=0.003). Treatment responders (≥50% seizure reduction) for all seizures showed percentages of 46% TOP vs 17% placebo for YTC (p=0.003), 43% TOP vs 19% placebo for YTCE (p=0.061), and overall, for the combined studies, 43% TOP vs 19% placebo (p=0.001). When treatment response is defined as ≥75% reduction, the percentages are 26% TOP vs 7% placebo for YTC (p=0.026), 30% TOP vs 5% placebo for YTCE (p=0.005), and overall, for the combined trials, 28% TOP vs 6% placebo (p<0.001).

Subgroup population analyses (age or gender) failed to demonstrate a statistically significant treatment difference with respect to PGTC seizures. There were too few non-white patients for definite conclusions TOP's effect in different racial subgroups. Table 20 reviews the data for the pooled population, grouped by PGTC seizures and all seizures. Median percent reduction and percent responders (≥50% seizure reduction) were reviewed by geographical location (see Table 21).

FDA biostatistician, Dr. Sue-Jane Wang, was asked to explore the possibility of differences between trials conducted in the US and Europe. YTC, the positive study, was an essentially US study (with a single center in Costa Rica), whereas YTCE contained centers in the US (39% of the patient population) and Europe (61%). Baseline seizure rates were similar between TOP and placebo arms in European centers (3.5 seizures/month vs 3.2), but not US ((8.8 vs 2.5). Nonetheless, when country subgroup data was submitted to protocol-defined primary efficacy analyses, percent reduction in PGTC seizures were not statistically significant (p >0.09) for TOP in either the US (48% TOP vs 37.9% placebo) or Europe (60% vs 31.4%); see p 8 of Dr. Wang's review.

The sponsor conducted several additional *post hoc* analyses to examine potential differences in treatment effect for PGTC and all seizures:

(1) *COMPLETERS*

CATEGORY OF PGTC SEIZURES: Table 11 reviews PGTC seizure data on subjects who completed the trials. Median percent reduction from baseline in average monthly PGTC seizure rates were 64.2% TOP vs 9.3% placebo in YTC (p=0.005), 60% TOP vs 33.8% placebo for YTCE (p=0.094), and, collectively, 60.7% TOP vs 27.1% placebo (p=0.002). Dr. Wang also found a numerical trend -- albeit not statistical significance -- in favor of TOP for percent reduction in PGTC seizures (60% TOP vs 33.8% placebo for study YTCE (see her review, p 9). In terms of *treatment response* for completers, results generally favor TOP for the categories of (a) ≥50% (a similar pattern showing statistical significance in favor of TOP for YTC and collective (combined study) analyses, and a numerical trend for YTCE; see Table 12), and (b) ≥75% (for YTC, 35% TOP vs 11% placebo [p=0.02], YTCE 39% TOP vs 10%

placebo [p=0.003], and, collectively (combined analysis), 37% TOP vs 11% placebo [p<0.001]); see Table 13 and Figure 5.

CATEGORY OF ALL SEIZURES: the percentages for completers were similar to the intent-to-treat population. Study YTC saw 50.8% TOP vs 5.2% placebo ($p \leq 0.001$); YTCE, 25.3% vs 12.6% (p=0.192); and the pooled population, 40.1% vs 11.5% ($p \leq 0.001$). In terms of *treatment response,* the percentages were again consistent with the intent-to-treat population. For ≥50% seizure reduction, study YTC had 50% TOP vs 18% placebo responders (p=0.001); YTCE, 35% TOP vs 17% responders (p=0.131); and, for the pooled population, 43% TOP vs 18% responders (p=0.001). When treatment response was defined as ≥75% seizure reduction, all groups demonstrated statistical significance in favor of TOP: 29% TOP vs 8% placebo for YTC ($p \leq 0.017$), 23% TOP vs 0% placebo for YTCE ($p \leq 0.017$), and 26% TOP vs 4% placebo for the combined studies ($p \leq 0.017$).

(2) *"SUBJECTS WHO EXPERIENCED PGTC SEIZURES WITH OTHER GENERALIZED SEIZURE TYPES":*

CATEGORY OF PGTC SEIZURES: In general, 82% of the combined populations of the two trials had PGTC seizures; the remainder "were believed to have PGTC seizures of unclear etiology" (v 53/168, p 61). (Data on subjects with only PGTC seizures were summarized, but the numbers were too few to conduct meaningful statistical analyses.) For subjects who experienced PGTC seizures with other generalized seizure types, the median percent reduction in baseline average monthly seizure rate trended in favor of TOP for YTC (56.7% vs 6.4%; p=0.066) and YTCE (48.5% vs 27.3%; p=0.065), but collectively was statistically significant (50.9% vs 21.4%; p=0.011). For subjects with only PGTC seizures, there was trend in favor of TOP (v 53/168, p 62). In term of *treatment response* for subjects who experienced PGTC seizures with other generalized seizure types was similar to results for the intent-to-treat population. In YTC, 52% TOP, compared to 21% placebo, subjects realized a ≥50% seizure reduction in their seizures (p=0.011). For YTCE, the percentages were 50% TOP vs 26% placebo (p=0.0004); and collectively, 51% TOP vs 23% placebo (p=0.002). For the category of ≥75% seizure reduction, the percentages were 31% TOP vs 12% placebo for YTC (p=0.060), 31% TOP vs 11% placebo for YTCE (p=0.063), and collectively 31% TOP vs 12% placebo (p=0.008); see 53/168, p 63.

CATEGORY OF ALL SEIZURES: statistical significance was shown for study YTC (40.1% TOP vs -3.3% placebo; p=0.005), but not for YTCE (17.3% vs -2.3%; p=0.368). No percentages were provided for the pooled population. With respect to treatment response for ≥50% seizure reduction, all groups demonstrated statistical significance: YTC (38% vs 18%; p<0.033), YTCE (31% vs 9%; p<0.033), and the pooled population (34% vs 13%; p<0.033). For ≥75% seizure reduction, all groups favored TOP: YTC (21% vs 6%; p=0.062), YTCE (22% vs 0%; $p \leq 0.006$), and the pooled population (21% vs 3%; $p \leq 0.006$).

Summaries of other seizure types, also classified as generalized, favor TOP, as shown by Table 17. Representative numbers were adequate for absence, myoclonic, and tonic seizures.

The subject's Global Evaluation of Improvement in Seizure Severity was a secondary efficacy parameter; see Table 18. In YTC, 62% TOP subjects vs 56% placebo patients (p=0.490) showed an improvement (minimal, moderate, or marked), though more TOP patients saw themselves as markedly improved (21% TOP vs 7% placebo). In YTCE, the percentages were statistically significant (48% TOP vs 33% placebo; p=0.026); and 33% TOP subjects registered as markedly improved vs 0% placebo (p=0.024). Overall, for the pooled population, the percentages were statistically significant (54% TOP vs 44% placebo; p=0.020); and more TOP patients described themselves as markedly improved (27% vs 4%; p=0.017). A similar pattern of results was seen when global evaluation scores were analyzed for completers (see Table 19): for YTC,

24% TOP vs 8% placebo (p=0.259); for YTCE, 39% vs 0% placebo (p=0.009); and, for the combined trial population, 62% TOP vs 49% placebo (p=0.005).

Despite the disparate results of studies YTC and YTCE, a case can nonetheless be made in support of TOP as adjunctive treatment for PGTC seizures. However, the reasoning to support this indication is based on a much lower standard of evidence than is traditionally offered:

(1) New FDAMA guidance document allows for proof of efficacy on the basis of a single study plus supportive data. In the case at hand, there is a positive trial, YTC, which is supported by corroborative data showing efficacy in partial-onset seizures in adults (an already approved indication) and children (see above).

(2) TOP efficacy was similar in both trials, 56.7% in YTC (which was strongly positive) and 57.1% in YTCE.

(3) TOP appears effective in the treatment of other generalized seizure types, such as tonic seizures and drop attacks. In study YTC, the median percent reduction from baseline in the average monthly tonic seizure rate numerically favored TOP over placebo (28% vs an increase of 1% in placebo) and, in the Lennox-Gastaut study (primarily pediatric subjects), the between-group difference with respect to drop attacks was statistically significant (14.8% median percent reduction in average monthly rate, as compared to an increase of 5.1% for placebo; p=0.041).

(4) Study YTCE's placebo rate of 33% was remarkably high. In most other trials, including epilepsy trials, the placebo rate hovers around 10-12%. The reason for the high placebo rate is unclear, although the sponsor suggests as possible causes (a) the high dropout rate of >20% (in YTC: 7% placebo vs 13%; in YTCE: 28% placebo vs 22% TOP), and (b) the imbalance in baseline seizure rate favoring the placebo group.

(5) In study YTC, 13% of TOP vs 5% placebo remained free of PGTC seizures (p=0.225), and 5% of TOP vs 0% placebo subjects free of all seizures (p=0.173) during the double-blind phase -- both categories (not protocol-defined endpoints), while not statistically significant, demonstrated a numerical trend in favor of TOP. Additionally, in YTCE,there is a statistically significant difference between groups for treatment response defined as ≥75% reduction in baseline seizure rate (p=0.04), unadjusted for baseline PGTC seizure rate.

(6) For study YTCE, *post-hoc* analyses by the sponsor, which adjusted for the substantial imbalance in baseline PGTC seizure rates, favor TOP more strongly, resulting in a p-value (0.078) for the primary variable (percent reduction from baseline in PGTC seizure rate), and a highly significant difference (p=0.016) for the comparison of treatment response based on PGTC seizures (p=0.002).

(7) In study YTCE, fewer patients in the TOP group (7 placebo vs 1 TOP) reported serious or limiting adverse events directly related to an increase in PGTC seizure rate or severity.

The serious reservations and weaknesses attached to data from unblinded trials notwithstanding, information derived from results of the unblinded extensions to YTC and YTCE are at least *suggestive* of -- that is, point in the direction of -- drug efficacy in the treatment of PGTC seizures. Table 9 in the Four-Month Safety Update (v 3/45, p 32) shows that rates for median percent seizure reduction from baseline for PGTC and all seizures jump dramatically once placebo patients are placed on drug and are consistent with rates obtained for treats in the controlled trials and unblinded extensions.

Table 9: Overall Summary of Topiramate's Efficacy in Protocols YTC/YTCE
(All Subjects Who Entered the Open-Label Extension Phase)

Variable	Double-Blind Placebo Subjects		Double-Blind Topiramate Subjects	
	Double-Blind Phase (N=66)	Open-Label Extension (N=66)	Double-Blind Phase (N=65)	Open-Label Extension (N=65)
Median Average Daily Dose, mg/kg/day	4.1	6.2	4.0	6.4
PGTC Seizures				
N	65[a]	65[a]	65	65
Median % reduction from baseline[b]	27.0	63.3	62.0	58.1
% treatment responders[c]	23	62	57	58
All Seizures				
N	66	66	65	65
Median % reduction from baseline[b]	9.4	42.1	40.1	32.6
% treatment responders[c]	17	45	43	42

[a] One of the 66 subjects did not experience a PGTC seizure.
[b] Monthly seizure rate = 28 x (no. seizures during period)/(no. days during period).
[c] Subjects with 50% or greater reduction from baseline seizure rate.

(According to the sponsor, most of the TOP subjects who completed the controlled segments of YTC and YTCE had their dosage slightly increased when they entered the unblinded extensions [see Table 3, Four-Month Safety Update, v 3/45, p 24]).

In order to provide additional support for the PGTC indication, the sponsor submitted a very late sNDA addition, dated 4/28/98 (nine months after the date of the original sNDA), in the form of a response to a March 1998 talk given by Dr. Russell Katz (Deputy Director, Neuropharmacological Drug Products, FDA) about the problems of approving a drug with two contradictory trials, one negative and one positive. The sponsor performed a subgroup analysis, using tonic-clonic seizure data from the Lennox-Gastaut trial. 38 (39%) of the 98 subjects (age range: 2-42; mean TOP age 11.9, mean placebo 13.8) in the trial had tonic-clonic seizures during baseline: 21 placebo and 17 TOP. Of these, 14 (37%) were ≤7 years old, 4 (11%) were 8-11, 9 (24%) were 12-16, and 11 (29%) were ≥17. TOP subjects realized a 34.8% median percent reduction from baseline in the average monthly seizure rate for tonic-clonic seizures, whereas placebo subjects experienced an increase of 4%, a between-group difference favoring TOP (p=0.034):

[redacted]

There are, however, several problems with the analysis. First, the data were derived from a small subgroup of the larger study population. [redacted] Third, "tonic-clonic seizures" may be generalized or of partial-onset in origin; the true nature of these seizures can only be determined on the basis of an EEG.

[redacted]

pediatric partial-onset seizures share the same mechanism of action as those in adults, there is no evidence to date that this is also true of PGTC seizures.

Lastly, there remains the question of TOP efficacy for PGTC seizures in the pediatric age group. Subgroup analyses detected no statistical difference between the response in pediatric and adult patients. The NDA PGTC pediatric population (YTC + YTCE) consisted of 17 TOP and 15 placebo subjects; and, of these, there were only 8 TOP patients in YTC, the positive study. On the basis of so small a sample, it would be very difficult to justify approval of TOP for PGTC seizures in the pediatric age group. Because of the associated neuropsychiatric side effects, TOP s not a benign drug.

In sum, TOP should be approved as an adjunctive agent to treat PGTC seizures in adults, but not children.

III. SAFETY

DATA BASE: The safety data base is comprised of:

(1) the three supplemental NDAs (with ISS centering on the pediatric experience new to the drug), which examine information from blinded, controlled trials plus some on-going open-label experience through 30 June 1996;

(2) the Four-Month Safety Update (through 2 April 1997); and

(3) additional more recent information through 11 March 1998, submitted 20 March 1998 by FDA request (this medical reviewer).

Safety parameters used in all studies included vitals, weight, EKG, physical and neurological examination, labs (hematology, chemistries, urinalysis), adverse events, and patient/caregiver global evaluations of mental status (compared to baseline and scored at the last double-blind visit as worse [0], no change [1], minimally improved [2], moderately improved [3], or markedly improved [4]; see v 13, p 33).

Adverse events were coded in accordance with the sponsor's "modified" WHOART dictionary ("an included term is the description most closely related to the investigator's terminology, the preferred term in a group of closely related included terms, and the body system is a broad category including related preferred terms" [v 13, p 39]). The Kaplan-Meier method was used to examine the relationship between time on study medication and occurrence of treatment-emergent adverse events. Other results, such as the patient/caregiver global evaluations of mental status, were summarized.

YTCE who completed the controlled trials, as well as those who elected to continue on to the open-label extensions after the completion of the controlled segment; a few additional subjects were recruited during the open-label extension. TOP has been approved as adjunctive treatment for partial-onset seizures in adults, and the safety profile in adults has been studied extensively and the

results can be found in labeling.

Unlike the adult indication, evidence to support safety in the pediatric population is new. The pediatric cohort (310 subjects in all) consists of subjects from the controlled trials, the open-label extensions, and nine additional open-label trials (EPPD-001, YOL, YOLE, YEP, YLT, YI, YJ, _____. Table 2 from the sNDA ISS (v 56/168) displays the patient population through 30 June 1996 and Table 1 (20 March 1998 submission), adding 7 patients, updates this information through 11 March 1998. The double-blind group contained 98 TOP pediatric subjects (YP, YTC, and YTCE); of the 101 placebo subjects, 96 entered the open-label extension, receiving study drug. Moreover, there were 116 pediatric subjects from other open-label trials (109 subjects as of the cut-off date of the sNDA + 7 additional subjects who enrolled subsequently in those trials and were included in the Four-Month Safety Update). There were nine additional open-label trials (EPPD-001, YOL, YOLE, YEP, YLT, YI, YJ, _____ YI and YJ were double-blind, placebo-controlled monotherapy trials in subjects ≥14 years with partial-onset seizures that also included open-label extensions (from which the safety-base subjects were taken); TOP was administered at one of two target dosages (100 or 1,000 mg/day) after gradual withdrawal of background AEDs. YEP and YLT were long-term open-label extensions for subjects with partial-onset seizures who completed open-label protocols (YKP/YKT and YCO2) or drug interaction protocols (M-215, M-216, M-218). EPPD-001 was an open-label pharmacokinetic study in which subjects (with any seizure type), aged 4-17, received TOP at four successive, increasing dosages (1, 3, 6, and 9 mg/kg/day; each for 7 days), after which they could enter a long-term extension (if <14 years, the dose could be increased to a maximum of 30 mg/kg/day, or ≤1600 mg/day; if ≥14, the dose could be increased to a maximum of 2,400 mg/day).

DEATHS: TOP labeling provides a SUDEP incidence of 0.0035 death per patient-year for the exposed adult population. The safety review for the original TOP NDA (partial-onset seizures in adults) consisted of 1446 individuals, of whom 20 were in the age 4-12, and 68 in the age 13-18, group. There were no pediatric deaths (the youngest was a 20 year old).

In the sNDA, Four-Month Safety Update, and recent 20 March 1998 submission, the combined safety base lists a total of 8 deaths, 6 of them in pediatric subjects. Three deaths form part of the clinical data base (1 adult, 2 children), another 3 are the result of voluntary spontaneous reports (all pediatric); 2 come from voluntary spontaneous European reports (1 adult, 1 pediatric). Following is a summary of available information (from the Four-Month Safety Update v 13/45, p 304, and v 21/45, p 337; 20 March 1998 submission, p 12; and clarification of the information via personal communication, 5/13/98, with Michael Kaufman and Catherine Glenkowski, RW Johnson):

(1) STUDY YTCE: 49-year-old, 75.9-kg female, with PGTC seizures, irregular menses, and depression, who died suddenly as a result of a seizure disorder after 152 days of double-blind placebo treatment in study YTCE. Concomitant AEDs included lamotrigine 300 mg/day, valproate 500 mg/day, sertraline, and estrogen/medroxyprogesterone as hormone replacement. Based on information available through day 126, she experienced two tonic-clonic seizures (one during the third trial week, or the titration period; and a second during the 17th, or the stabilization period). On day 152 she was found dead at home. An autopsy report concluded that the death was "as a result of a seizure disorder." The investigator assessed the relation of the death to study treatment as "unlikely."

(3) STUDY YP: 10-year-old girl, with partial-onset seizures who had been randomized to TOP in study YP at 9.4 mg/kg/day, dropped out of the trial after 441 days for lack of efficacy. More than 5 months after withdrawal, she was found dead. No autopsy was performed, and the cause of death is unknown; the relation to TOP was felt "to be doubtful" (SUDEP, per the sponsor).

(4) SPONTANEOUS REPORT (UK): 13-year-old boy with intractable epilepsy, associated with a hypothalamic hamartoma, congenital hydrocephalus, hypopituitarism, on nasogastric nutrition, was receiving TOP 600 mg/day adjunctive therapy. Concomitant AEDs were primidone 500 mg/day and CBZ 400 mg/day. On TOP for about 2 months, he was hospitalized "slightly dehydrated and severely constipated" and "essentially unconscious, flexing to pain, and vocalizing incoherently." The patient died suddenly; the cause of death was unknown.

(5) SPONTANEOUS REPORT (US): 9-year-old male, with undefined epilepsy, was receiving TOP 150 mg/day, along with PHT 275 mg/day and vigabatrin 1,500 mg/day. "He had a seizure, choked, and died in his sleep."

(6) SPONTANEOUS REPORT (US): 4-year-old male, receiving TOP 225 mg/day for 6 days was "found dead at home, face down on a pillow. Death was attributed to asphyxiation following a seizure and was considered unrelated to TOP therapy."

(7) SPONTANEOUS REPORT (AUSTRIA): 25-year-old female "with sudden death." No dosing information provided.

It is difficult to derive a suitable denominator for the experience encompassing the 6 pediatric patients described above. The most reliable information comes of course from the clinical data base, which consists of 310 children and represents an estimated 459 subject-years of exposure. There were two pediatric deaths in this population, yielding a SUDEP rate of 2/459, or 0.00436 deaths per patient-year; because one of the patients had been off medication for >5 months, this rate might therefore be construed as the worst-case scenario. Nevertheless, the rate appears to fall within the expected range, described in current labeling, for the incidence of SUDEP in epilepsy patients in general (from 0.0005 for the general epilepsy population, to 0.003 for a clinical trial population, to 0.005 for patients with refractory epilepsy).

SERIOUS ADVERSE EVENTS: A list of all serious adverse events in adults and children, and their incidence rates, can be found in the two tables in Appendix 4c. Similarities shared by many of these patients are (1) other concomitant serious medical problems, and (2) the severity of their underlying seizure disorder. Following are brief narratives of cases during the double-blind trials and selected cases from open-label extensions, which the sponsor provided in the 20 March 1998 submission:

KEY: db= double-blind phase op=open-label phase

Study	*Pt*	*Age/Sex/Group*	*Adverse Event*	*Onset*	*Resolved*	*Tx Related*
YP - db	13	5 F - placebo 25 mg/d	CONVULSIONS AGGRAVATED. Hosp on day 26 for prolonged postictal state; discharged day 27 and completed study. Concomitant drugs: VPA 1,125 mg/d, ethotoin 1,125 mg/d.	Day 26	Day 27	Possible

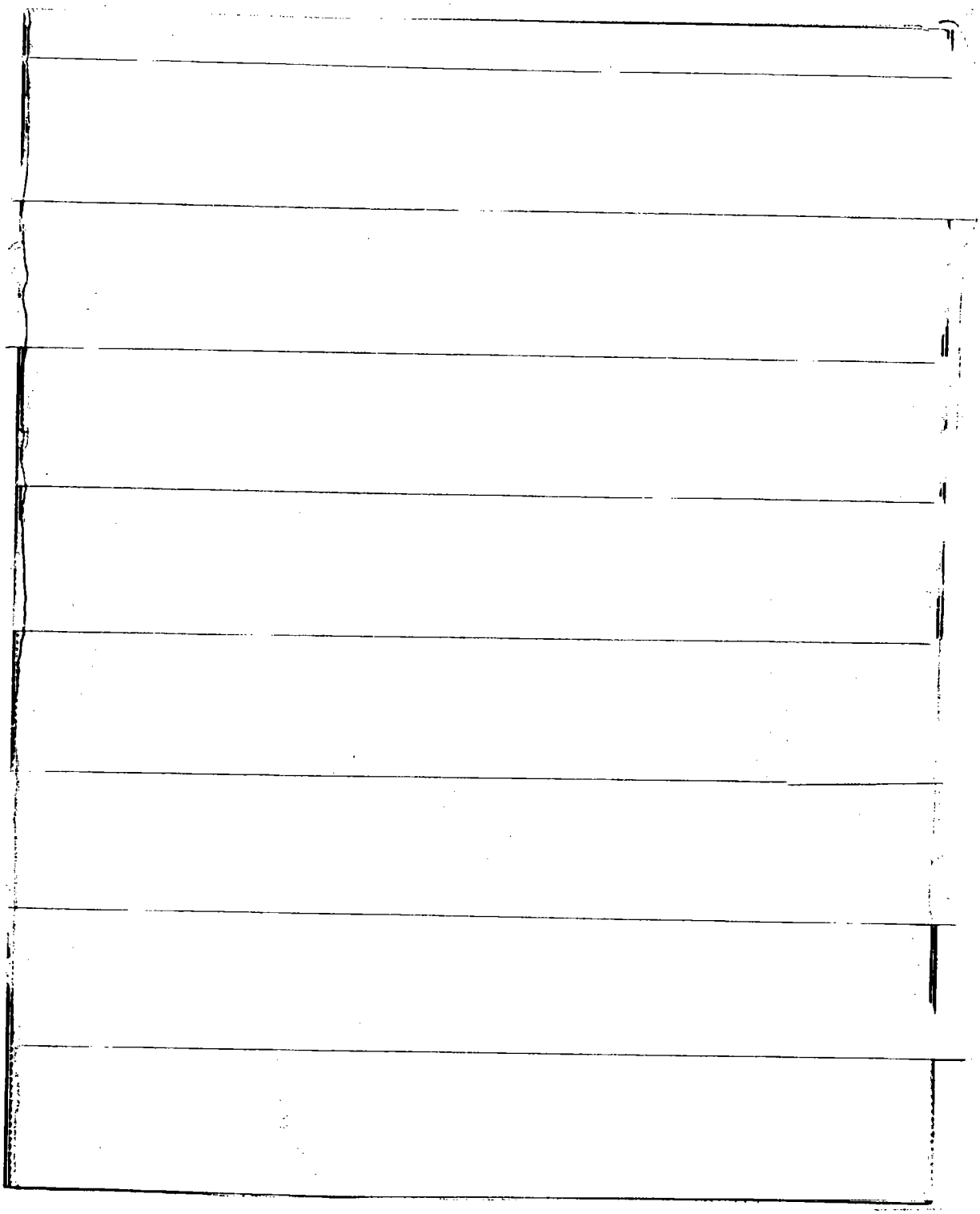
YP - db	74	9 M - placebo 175 mg/d	INFECTION VIRAL. Hosp with cough, sore throat, fever, vomiting (probably flu) day 66, given IV antibx. LP negative. Resolved 7 days later. Concomitant drugs: CBZ 600 mg/day.	Day 66	About Day 73	Unlikely
YP - db	116	5 M - placebo 100 mg/d	CONVULSIONS AGGRAVATED. Concomitant drugs: DPT 125 mg/d. Had 55-min seizure and elevated temp on day 104 after discontinuing AEDs x 2 days. Seizure cluster on day 105 led to hosp. PHT level 8.6. Loaded with IV PHT to give level 15.5 on day 106, at which time seizures stopped; temp reached 102.	104	Not available	Unlikely
YP - db	2	11 M - TOP 125 mg/d (5.2 mg/kg/d)	CONSTIPATION. Hydrocephalus, quadriparetic CP, constipation. Had sinusitis day 49, tx sulfa; then constipation day 50. Hosp on day 58 for fever, dehydration, anorexia, abd pain; was rehydrated and placed on antibx, laxatives. Prolonged PT treated with vit K. Discharged day 64. Still on TOP x 580 days.	49	64	Unlikely

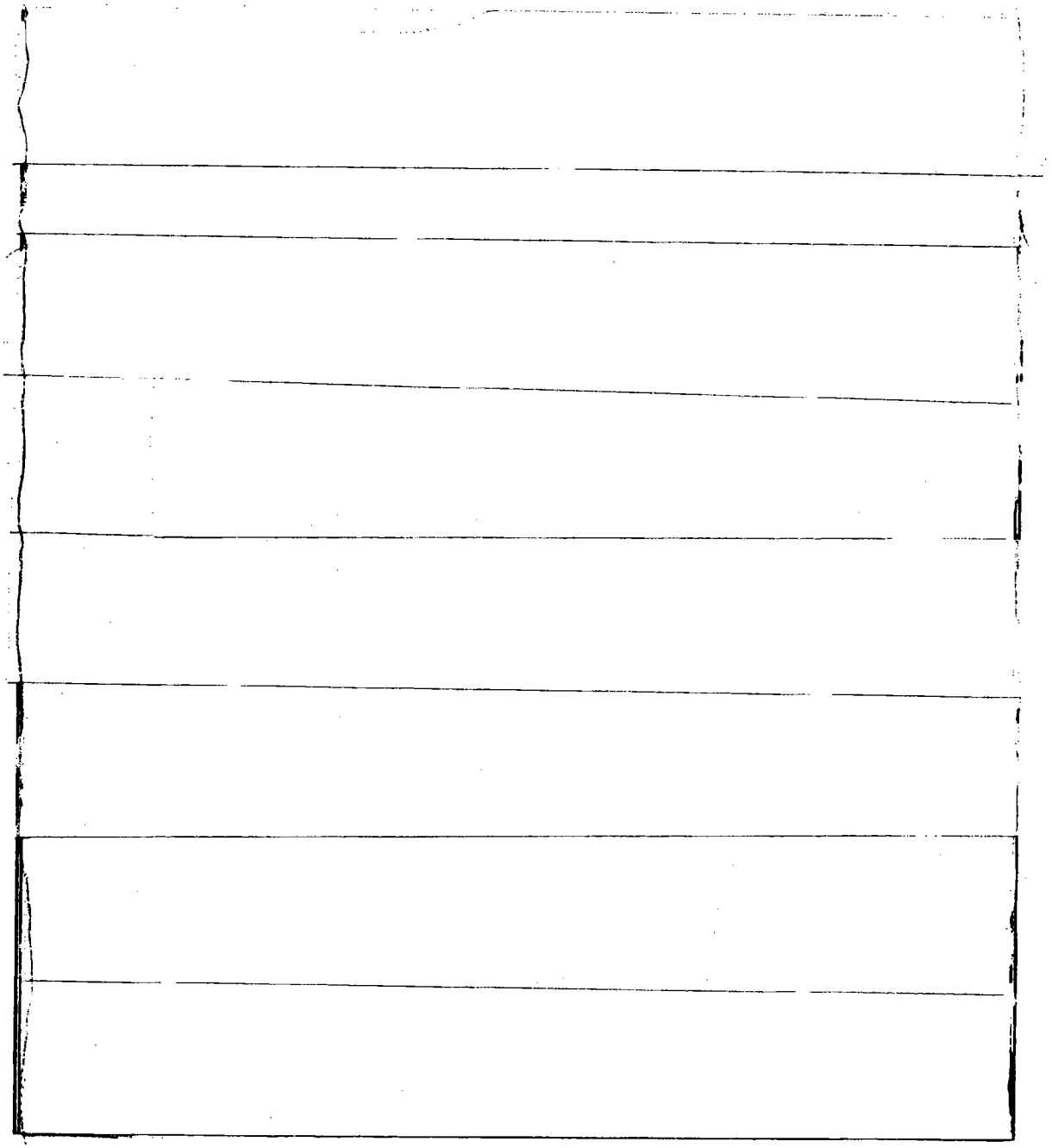
YTC - db	146	6 M - TOP 100 mg/d (3.9 mg/kg/d)	PNEUMONIA. PMH: MR, bowel/bladder incontinence, hypotonia, nonketotic hyperglycemia. Concomitant drugs: gabapentin 800 mg/d, phenobarb 120 mg/d, lorazepam 0.5 mg/d. Hosp on day 40 (during titration period, TOP dose 100 mg/d) for markedly severe pneumonia; discharged day 44, full resolution day 54.	40	54	Unlikely

YP - op	4	4 M - TOP open-label x 1 yr + pt's 22-month-old F cousin	OVERDOSE. Hosp after found asleep and difficult to arouse; found to have shallow resp, unresponsive except to pain. Tx lavage, charcoal, intubated, and hydrated. Discharged 2 days later; OD sxs resolved 3 days later, and TOP restarted. He received his last TOP dose 7 months later (8.7 mg/k/g/d). His TOP supply had run out, and his gave extra CBZ. As a result, his seizure activity increased; 3 days later, he became ataxic, fell, and blacked out -- sxs felt to be due to CBZ toxicity. The sxs resolved within 3 days, and he was withdrawn from the study due to noncompliance. The 22-month-old F was found "with a wild look in her eyes," then became unresponsive. On admission, she was irritable, combative when touched, had an arched back, extended legs, and questionable dystonic neck posture. Tx lavage, charcoal, and normal saline IV. 2 days post overdose, she was unresponsive, staring, and posturing bizarrely. The next day, she was asymptomatic and discharged.	~365	~367	Remotely related Likely
YP - op	45	2 M - TOP 29.3 mg/kg/d x 7 months	SEPSIS AND GASTROENTERITIS. PMH: frequent RSV infections, pneumonia, otitis. Concomitant AEDs: phenobarb 112.5 mg/d, lamotrigine 250 mg/d, diazepam. Hosp about 7 months into op extension when developed fever to 104, despite tx with ibuprofen and diazepam, and increased seizures. WBC 23,000; +blood cx. Tx antibx and discharged 11 days later. Then, 10 weeks later, hosp for gastroenteritis, tx with lorazepam; discharged 4 days later. Continued TOP.	~7 months	In 11 days	Remotely related

YP - op	47	3 M - placebo arm of the db trial, then on TOP 26.4 mg/kg/d during op x 8 months	AGGRAVATED CONVULSION AND VIRAL INFECTION. Concomitant AED: VPA 750 mg/d. Hosp after ~8 months on TOP for 2 prolonged episodes (5 hrs) of altered mental status and walking in circles. Dx: otitis, sinusitis, pneumonia, viral syndrome. Tx antibx. Continued TOP.	~8 months		Remotely related
YP - op	530	14 F - TOP 5.96 mg/kg/d	AGGRAVATED CONVULSION, DYSPHAGIA. Concomitant AEDs: clonazepam 0.525 mg/d, lamotrigine 50 mg/d. Hosp on day 82 after increased seizure activity, becoming "heavily sedated leading to difficulty swallowing. Events resolved (date unknown) and the pt was continued on TOP. Per sponsor: "This represents the first case of difficulty swallowing (dysphagia) submitted as an expedited report."	82	?	Definitely related
EPPD-001 - op	8	10 F - TOP 950 mg/d (23.1 mg/kg/d)	CONVULSIONS GRAND MAL. Concomitant AEDs: phenobarb 180 mg/d (Felbatol has just been discontinued). Day 2, and persisting throughout study, slowed mentation was observed. Erythema was noted after ~7 months (not TOP related). Hosp after 1 yr with partial complex status x 1 day; previously had up to 5 simple partial seizures/week. Still on TOP x 620 days.	2 ~210 ~365	Persist-ing	(Probably related) Not related Remotely related
YOL - op	22	13 M - TOP 1100 mg/d (10.1 mg/kg/d)	CONVULSIONS AGGRAVATED. PMH: multiple seizure types, encephalitis age 10, obesity, MR, multiple neurological abnormalities. Concomitant AEDs: CBZ 1200 mg/d, PHT 400 mg/d, chlorazepate 37.5 mg/d. Hosp on day 164 after "large seizure,'" for which received diazepam 5 mg, and increased seizure frequency over next 4 weeks. TOP was increased to 1300 mg/d and PHT discontinued. 4 weeks post discharge, again had serious aggravated convulsions; TOP increased to 1900 mg/d (17.5 mg/kg/d), before tapering due to ineffectiveness (off day 686).	164	686	Not related

YOL - op	181	14 M - TOP 300 mg/d (3.8 mg/kg/d) increasing to 1200 mg/d (15.2 mg/kg/d)	CONVULSIONS GRAND MAL, CONVULSIONS AGGRAVATED, EEG ABNORMAL. PMH: partial complex seizures 180/month + simple partial seizures 3/month. Concomitant AEDs: ethotoin, PHT 350 mg/d. Day 22, after discontinuation of ethotoin, had status; day 27 had serial seizures, resolving with IV PHT and lorazepam. ~5 months into enrollment had seizure surgery; TOP increased to 1300 mg/d, but then tapered because considered ineffective, eventually off on day 226.	22	226	Remotely related
YOLE - op	230	15 M - TOP 200 mg/d (3 mg/kg/d)	HALLUCINATIONS, APATHY, FATIGUE. PMH: gelastic seizures. Concomitant AEDs: CBZ, VPA, clonazepam. Hosp on day 59 with visual hallucinations and apathy (loss of contact with his environment). Tx diazepam with resolution. EEG showed no seizures. Also noted fatigue from day 57 to 68, when TOP discontinued. Follow-up 3 yrs later: fatigue resolved.	57	68	Probably related
YOLE - op	967	15 M - 200 mg/d (4.5 mg/kg/d)	CONVULSIONS AGGRAVATED. Concomitant AEDs: CBZ 1200 mg/d and VPA 1500 mg/d, reduced 1 month, then discontinued 4 months, after TOP began. ~6 months into study, breakthrough seizures occurred on 3 days, ~1 week apart. Hosp, tx diazepam; CBZ and VPA resumed with resolution of seizures. TOP continued.	~250		Probably related





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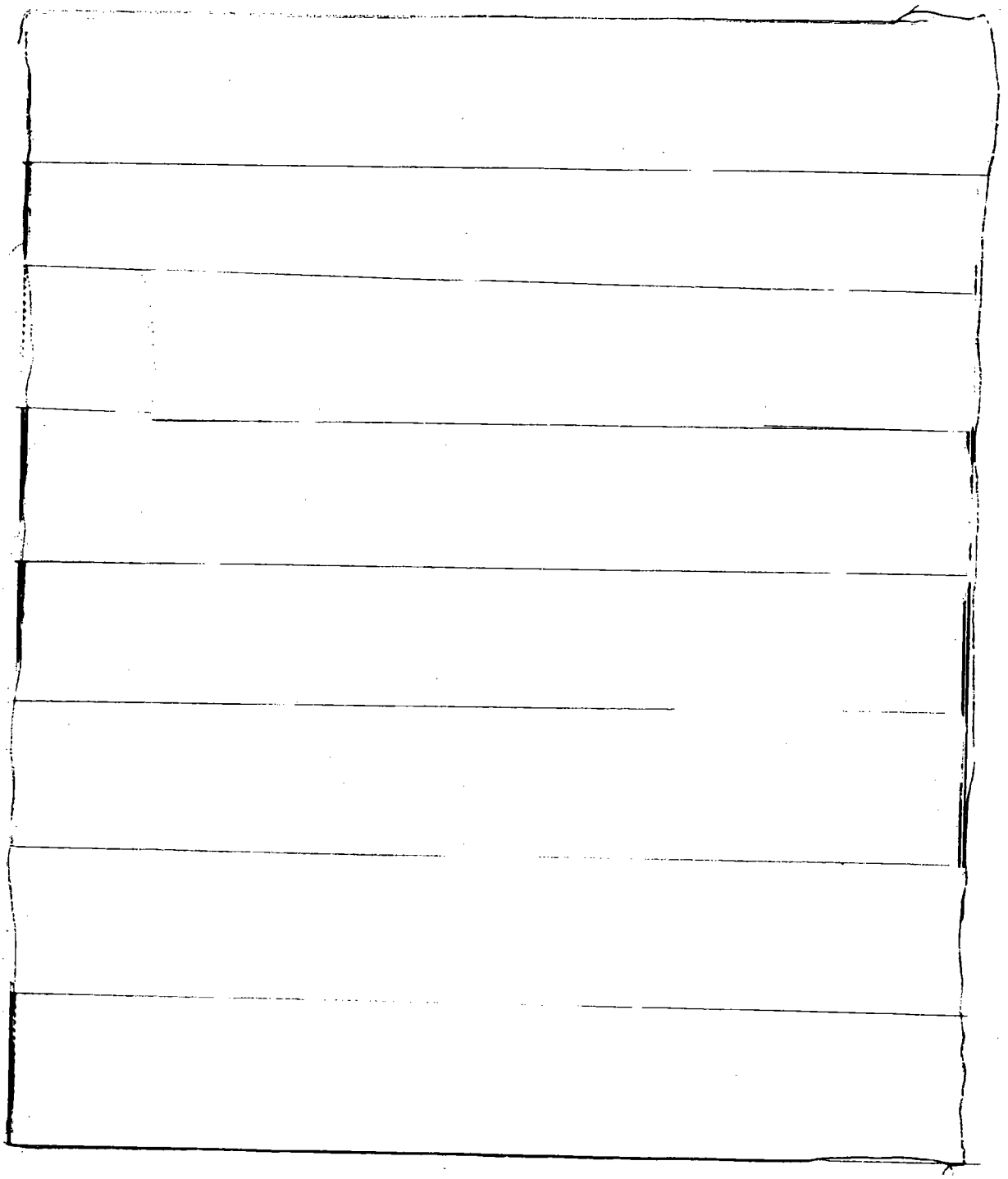

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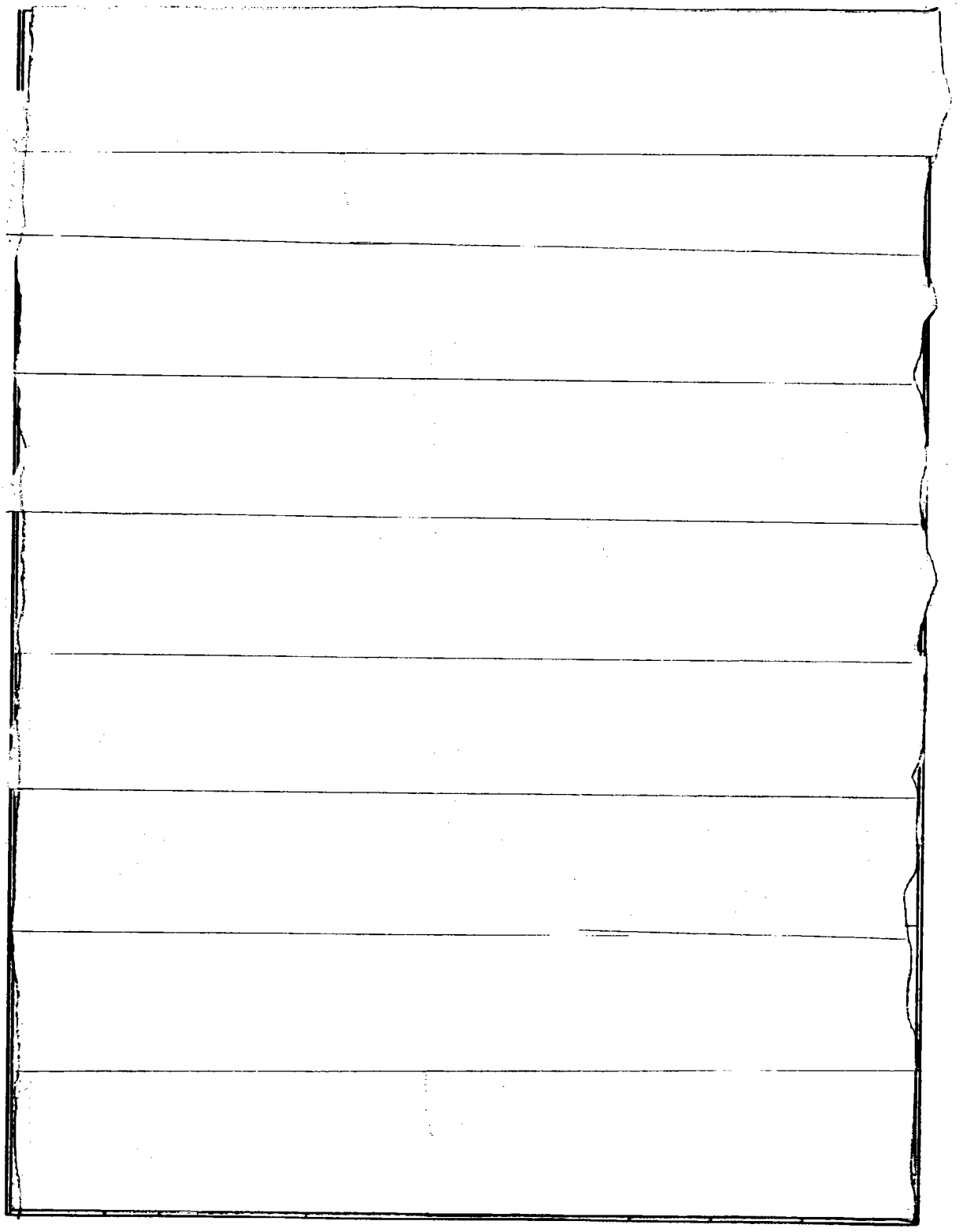

YTC - op	65	11 F - TOP 175 mg/d (5.3 mg/kg/d); randomized to TOP during db stage	FEVER, RASH, RESPIRATORY DISORDER, CONVULSIONS GRAND MAL,HALLUCINATIONS. Concomitant AED: VPA. Hosp day 163 with fever (103), rash, GTC seizure x 20 min; tx antibx, intubated x 1 day. Fever and rash resolved in 3 days. On day 165 had auditory (lasting 1 day) and visual (lasting 2 days) hallucination. Till on TOP x 663 days.	163	167	Possibly related: rash and hallucinations; remotely related: convulsions grand mal; not related: fever and respiratory disorder
YTC - db and op	146	6 M - 6.7 mg/kg/d; randomized to TOP during db stage	PNEUMONIA. PMH: gastrostomy tube, MR, nonketotic hyperglycemia. Concomitant AEDs: gabapentin 800 mg/d, phenobarb 120 mg/d, lorazepam 0.5 mg/d. Hosp on day 40 (titration phase) with pneumonia, tx antibx, discharged day 44, pneumonia resolved day 54. During op, on TOP 17.2 mg/kg/d (concomitant AED: phenobarb), hosp on day 303 due to increased seizure frequency, mild to moderate respiratory distress, fever; dx pneumonia, resolving in 7 days on antibx. Lamotrigine added, still on TOP.	40 303	54 310	Remotely related Remotely related
YTCE - op	218	15 M - TOP 4.6 mg/kg/d (db stage), increasing to 8.7 mg/kg/d (op stage)	PANCREATITIS. Concomitant AED: phenobarb 90 mg/d, PHT 500 mg/d, lorazepam 3-4 mg/d. Hosp on day 230 for bronchitis, hypovolemia, suspected pancreatitis (amylase 389, ref range <310; lipase 3566, ref range <208). Had cholecystectomy. TOP resumed.	310	?	Remotely related.

An examination of the table in Appendix 4a generally shows a comparable or lower percentage of similar complaints listed in current labeling. The side effect profiles for the pediatric and adult populations are compared below.

The adult experience with TOP has been examined in detail in the original NDA. More

extensive postmarketing experience has not turned up any additional serious problems with the drug to date (personal communication, April 1998, with Mary Mease, FDA Epidemiology, who provided a computer printout of the entire postmarketing experience to date).

The major side effects -- listed in current labeling with incidences >5% (in the order placebo, 200-400 mg, 600-1000 mg) -- have been disorders of the following systems:

neuropsychiatric (somnolence 10%, 30%, 26%; psychomotor slowing 2%, 17%, 25%; nervousness 7%, 16%, 21%; difficulty with memory 3%, 12%, 13%); confusion 5%, 10%, 15%; depression 6%, 8%, 13%; difficulty with concentration/attention 1%, 8%, 15%; anorexia 4%, 5%, 11%; mood problems 2,%, 4%, 10%)

GI (nausea 6%, 12%, 14%; dyspepsia 5%, 8%, 6%; abdominal pain 3%, 5%, 7%; constipation <1%, 5%, 3%)

central and peripheral nervous system (dizziness 14%, 28%, 32%; ataxia 7%, 21% 17%; speech disorders/related speech problems 3%, 17%, 14%; nystagmus 12%, 15%, 15%; paresthesia 3%, 15%, 15%; tremor 6%, 11%, 14%; language problems <1%, 6%, 12%; coordination abnormal 2%, 5%, 4%)

respiratory (URI 12%, 12%, 12%)

vision (diplopia 6%, 14%, 15%; vision abnormal 3%, 14%, 11%).

A comparison with figures in Appendix 4a generally shows lower percentages among the adult population of the sNDA.

WITHDRAWALS DUE TO ADVERSE EVENTS: There were relatively few withdrawals for adverse events in the controlled trials: none in YP[redacted]2 in YTC (1 in each arm; see Table 8 YTC), and 12 in YTCE (5 TOP, 7 placebo; see Table 8 YTCE). There were no real differences between the side effects experienced by the TOP and placebo patients.

OVERALL ADVERSE EVENT PROFILE: By request (20 March 1998 submission), the sponsor compared the incidence of adverse events in adults, occurring with a frequently ≥1%, from the original NDA (6 trials for partial-onset seizures in adults) with the profile obtained in the sNDAs and Four-Month Safety Update (adults with PGTC seizures [redacted] The results can be seen in Table 2 of that submission. No significant change in the overall adverse event profile was seen in adults.

In pediatric subjects, 7 neuropsychiatric events, along with weight decrease, occurred more frequently (≥5% difference) in TOP subjects than placebo, as follows:

--somnolence (26% vs 16%)
--anorexia (24% vs 15%)
--fatigue (16% vs 5%)
--nervousness (14% vs 7%)
--difficulty with concentration/attention (10% vs 2%)
--aggressive reaction (9% vs 4%)
--difficulty with memory (5% vs 0%)
--weight decrease (9% vs 1%).

With the exception of anorexia, mood problems, aggressive reaction, and personality disorder (behavior problems), neuropsychiatric adverse events were less often reported in pediatric than in adult patients. It may be true, as the sponsor suggests, that children are less likely to report adverse events: they may be less able to articulate their complaints or may be less willing to do so. But the incidence of mood problems and personality disorder (behavior problems) were similar between TOP and placebo groups. On the other hand, such adverse events as headache, vomiting, and diarrhea occurred more frequently among placebo subjects.

Furthermore, the incidence of common neuropsychiatric events reported in the sNDA ISS for the 303 pediatric subjects that formed its cohort did not increase appreciably (<5% increase for individual adverse events) in the total TOP group of 310 pediatric subjects in the Four-Month Safety Update over the sNDA population (303 subjects), despite a longer duration of exposure to study drug (12.5 months to 18 months). Somnolence (41%) and anorexia (38%) were the most frequently reported, followed by fatigue (25%), nervousness (21%), headache (20%), insomnia

(15%), mood problems (11%), difficulty with concentration/attention (11%), and personality disorder (11%).

The studies for all three indications each contained an assessment of patient mental status by means of a questionnaire completed by the subjects or caregiver at the first and final visits of the double-blind phase. In YP responses were scored on a scale from 0 (worsened) to 7 (marked improvement); YTC/YTCE, a 4-point scale was employed (from 0, or worsening of mental status, to 4, or marked improvement). For YP, comparison of the two questionnaires (before and after) showed that most subjects in both groups (the TOP and placebo) recognized no change from baseline, though numerically more TOP patients were seen as improved on each of the four scales. For and YTC/YTCE, comparison of the two questionnaires showed similar results for TOP and placebo groups YTC Table 22, and YTCE Table 22).

Weight loss occurred in 22% adult vs 11% pediatric subjects. According to the sponsor, anorexia is related to weight loss in both children and adults: subjects with weight loss reported as an adverse event were more likely to have also reported anorexia (26/34; 76%) compared with those who did not exhibit weight loss (84/274; 30%). The sponsor suggests that the slower titration rates and lower dosages in the sNDA studies may explain the differences in the adverse event profile, as well as the fact that children may not report certain types of subjective symptoms (depression) as readily as adults. The rate of discontinuation due to adverse events was also lower among children (0% in the double-blind trials among TOP subjects, 11% overall among TOP subjects) than adults (11% and >20%, respectively).

Another commonly reported adverse event in the original NDA adult population was paresthesia (15% for dosages of 200-400 mg/day, 18% for dosages up to 1000 mg/day), attributed by the sponsor to the drug's similarity to the carbonic anhydrase inhibitor group; the side effect led to drug discontinuation in 2% of the patients. In contrast, only 6% of the children and 8% of the adults in the sNDA or Four-Month Safety Update reported paresthesias, and none in either age group discontinued therapy due to the complaint.

As a result of its activity as a carbonic anhydrase inhibitor, TOP increased the incidence of kidney stones in adults in the original NDA population by 2-4 times that of a similar, untreated population (1.9% confirmed kidney stones). Three cases were found in the pediatric group:

(2) SPONTANEOUS REPORT: 23-month-old female, on TOP 50 mg/day for about 3 months, passed a kidney stone, considered "probably related to TOP." Concomitant medications included lamotrigine 200 mg/day and CBZ 300 mg/day; the patient was also on a ketogenic diet. The diet was stopped, but TOP was continued.

(3) SPONTANEOUS REPORT: 5-year-old male, with Menke's syndrome, passed a kidney stone while on TOP 25 mg/day, lamotrigine (dose unknown), and primidone (dose unknown). "The reporting physician felt that the patient's free water was decreased by 300 ml." Concomitant medications included ascorbic acid and antacids. No other information is available.

SAFETY LABS AND OTHER DATA: There were no abnormalities in adult or pediatric subjects not already mentioned in current labeling, and there were no significant differences between the two age groups. There were no noteworthy treatment-related changes from baseline at the start of the double-blind phase to the final visit at the end of the double-blind phase in mean vital-sign measurements in YP YTC/YTCE. Data in the sNDAs, Four Month Safety Update, and 20 March 1998 submission do not differ significantly from information found in current labeling.

There were no additional safety concerns or precautions.

IV. Dosing Recommendations

Based on the current package insert, the recommended dose in adults, as adjunctive treatment for partial-onset seizures, is 400 mg/day in 2 divided doses. In studies YTC and YTCE, which included pediatric as well as adult subjects, the daily target doses of 175, 225, and 400 mg were based on weight and intended to approximate 6 mg/kg/day (maximum: 9.3 mg/kg/day) for pediatric patients and 6 mg/kg/day for adults. The titration schedule as add-on for adults with PGTC seizures is identical to the regimen recommended in the labeling for partial-onset seizures: 50 mg/day as starting dose, with weekly increments of 50 mg/kg until the target dose of 400 mg/day is reached. Among pediatric subjects (98 total in the 4 double-blinded studies, YTC [redacted] YP), most received a target dose of 5-9 mg/kg/day (median: 6.1 mg/kg/day). The recommended titration schedule, reflecting the 4 double-blind trials, begins with a dose of 25 mg/kg/day (or less, based on a range of 1-3 mg/kg/day), with increases every 1-2 weeks, as tolerated, in increments of 1-3 mg/kg/day. Titration should be guided by response and side effects. In study YP, the starting dose for subjects <43 kg was 25-50 mg/day, increasing by 25, 50, or 75 mg/day every 1-2 weeks over a 6-week period until the target dose was reached. In studies YTC and YTCE (17 pediatric subjects total), subjects <43 kg started at 50 mg/day for the first 28 days, increasing the dose in increments of 25 to 75 mg/day every 2 weeks over an 8-week period, until the target dose was reached. In YL, a more rapid titration was employed, increasing the daily dosage by 2-3 mg/kg/day every week over a 3 week period. The sponsor, however, recommends a slower rate of titration for better tolerability. The sponsor states that maximum doses of 30 mg/kg/day (specified in the pediatric protocols) may be administered in adults and children, as tolerated, for optimal seizure control, but it should be noted that there is very little experience with such high doses (see Appendix 2 of the 20 March 1998 submission).

In subjects with renal impairment (creatinine clearance <70 ml/min/1.73 m^2), the dose should be halved. No dosage adjustment is suggested for patients with moderate hepatic impairment (about 30%). In both subsets of patients, titration should be guided by response and side effects, and a longer time period is required to reach steady state. (See v 53/198, pp 101-2.)

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V. Conclusion

Topamax (TOP) was approved as adjunctive therapy for the treatment of partial seizures in adults with epilepsy on December 24, 1997. The sponsor has submitted three supplemental NDAs to support its use as an adjunctive agent in the treatment of (1) pediatric partial-onset seizures [redacted] (3) primary generalized tonic-clonic seizures in adults.

The sponsor has provided adequate proof of efficacy and safety to support all three indications at the recommended doses.

VI. RECOMMENDATIONS

I recommend approval of topiramate, as an adjunctive agent, for the treatment of (1) pediatric partial-onset seizures (3) primary generalized tonic-clonic seizures in adults.

/S/

Richard M. Tresley MD
Medical Reviewer

NDA 20,505 (1) Supplements (Topamax: [a] pediatric partial-onset seizures [c] generalized tonic-clonic seizures); (2) Four-Month Safety Update; (3) 20 March 1998 (ISE update); (4) 28 April 1998 (additional analyses) div file/Katz R/Ware J/Tresley R/9 May 1998

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VII. TABLES

ATTACHMENT 1: International Classification of Seizures*

I. Partial (focal, local) seizures

A. Simple partial seizures (consciousness not impaired)
   1. With motor symptoms
   2. With somatosensory or special sensory symptoms
   3. With autonomic symptoms
   4. With psychic symptoms

B. Complex partial seizures (with impairment of consciousness)
   1. Beginning as simple partial seizures and progressing to impairment of consciousness
      a. With no features
      b. With features as in I.A.1-I.A.4
      c. With automatisms

C. Partial seizures evolving to secondarily generalized seizures
   1. Simple partial seizures evolving to generalized seizures
   2. Complex partial seizures evolving to generalized seizures
   3. Simple partial seizures evolving to complex partial seizures to generalized seizures

Generalized seizures (convulsive or nonconvulsive)

A. Absence seizures
   1. Absence seizures
   2. Atypical absence seizures

B. Myoclonic seizures

C. Clonic seizures

D. Tonic seizures

E. Tonic-clonic seizures

F. Atonic seizures (astatic seizures)

Unclassified epileptic seizures
Includes all seizures that cannot be classified because of inadequate o incomplete data and some that defy classification in hitherto describec categories. This includes some neonatal seizures, e.g., rhythmic eye movements, chewing, and swimming movements.
rom the International Classification of Epileptic Seizures. 1981

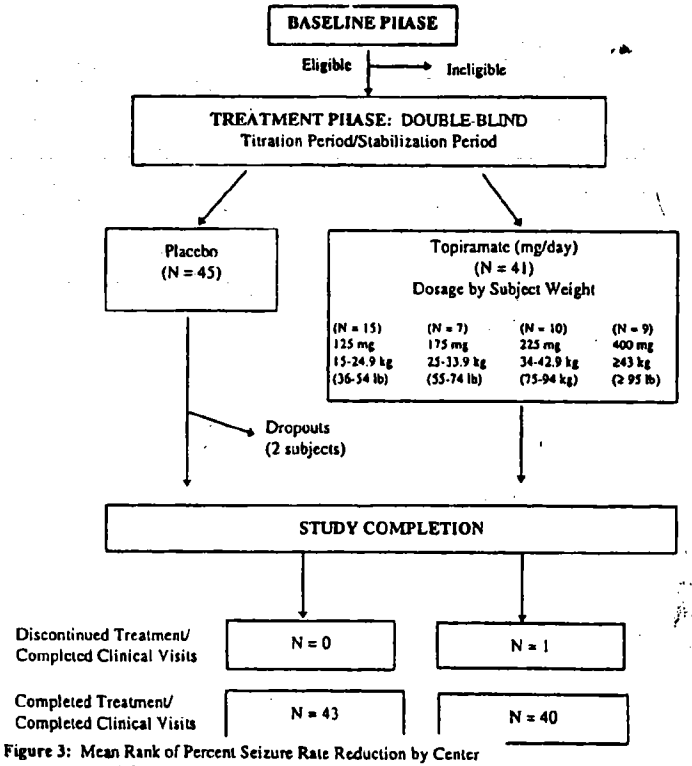

Figure 3: Mean Rank of Percent Seizure Rate Reduction by Center
(All Randomized Subjects; Protocol YP)

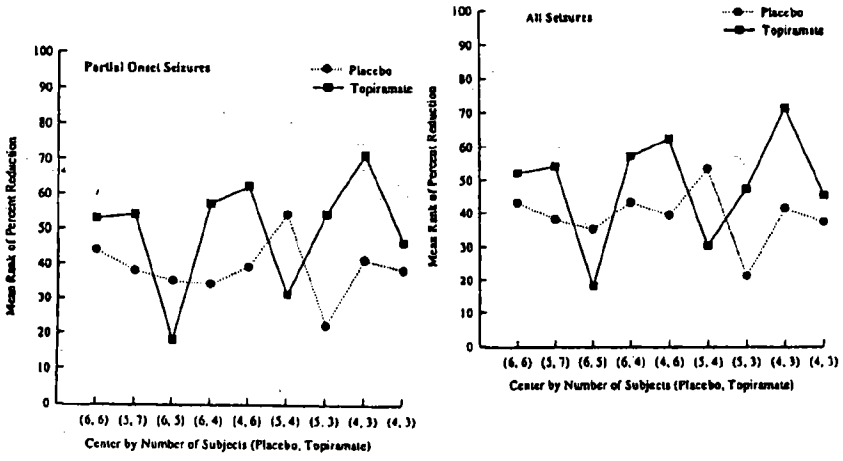

Table 1: Key Inclusion Criteria
(Protocol YP)

Male or female, one to 16 years of age, and, if female, premenarchal, or physically incapable of bearing children, or practicing an acceptable method of birth control.
Weight of at least 16 kg.
Partial onset seizures with or without secondarily generalized seizures.
Concomitant therapy with at least one, but no more than two, AEDs.
Experiencing six partial onset seizures during the 56-day baseline phase, with at least one partial onset seizure per each 28-day period.
EEG or CCTV/EEG before or during baseline phase consistent with partial epilepsy.
CT scan or MRI excluding potentially progressive neurologic diseases.
ECG during baseline phase without significant findings.

Table 2: Key Exclusion Criteria
(Protocol YP)

Treatable cause of seizures or progressive neurologic disorder.

Documented history of generalized status epilepticus within three months while complying with appropriate anticonvulsant therapy.
Seizures occurring only in clustered patterns defined as numerous seizures occurring in less than 30 min.
Significant recent history of medical disease (e.g., cardiovascular, hepatic, renal, gynecologic, musculoskeletal, gastrointestinal, metabolic, or endocrine diseases) which could impair reliable participation in the trial or necessitate the use of medication not allowed by protocol.
History of alcohol or drug abuse.
History (within the past six months) of a psychiatric or mood disorder requiring electroconvulsive therapy, major tranquilizers, or monoamine oxidase inhibitors or centrally-acting sympathomimetics.
Schizophrenic or history of exhibiting psychotic symptomatology.
History of poor compliance with therapy.
Taking benzodiazepines on more than an occasional basis, unless used as one of the two concomitant AEDs.
History of suicide attempt.
Current malignancy or history of malignancy within past five years.
Treatment with an experimental drug or used an experimental device within 60 days before admission.
Clinically significant ECG abnormalities.
History of nephrolithiasis.
Concurrent medications in past three months that included acetazolamide, zonisamide, triamterene, Vitamin C (in quantities greater than two grams per day), chronic use of antacids, or calcium supplements.
Taking felbamate.
Inability to take medication or maintain a seizure calendar, independently or with assistance.

ble 3: Topiramate Dosing Schedule
(Protocol YP)

Subject's Weight	Study Day: 1 through 14	15 through 28	29 through 42	43 through 56	57 through 113	Target Dosage Range* (mg/kg/day)
16-24.9 kg (36-54 lb)	(1) 25 mg tab PM	(1) 25 mg tab AM (1) 25 mg tab PM	(2) 25 mg tab AM (2) 25 mg tab PM	125 mg/day MAX (2) 25 mg tab AM (3) 25 mg tab PM	125 mg/day MAX (2) 25 mg tab AM (3) 25 mg tab PM	5.0 to 7.8
25-33.9 kg (55-74 lb)	(1) 25 mg tab PM	(1) 25 mg tab AM (2) 25 mg tab PM	(3) 25 mg tab AM (3) 25 mg tab PM	175 mg/day MAX (3) 25 mg tab AM (1) 100 mg tab PM	175 mg/day MAX (3) 25 mg tab AM (1) 100 mg tab PM	5.2 to 7.0
34-42.9 kg (75-94 lb)	(2) 25 mg tab PM	(2) 25 mg tab AM (2) 25 mg tab PM	(3) 25 mg tab AM (3) 25 mg tab PM	225 mg/day MAX (1) 100 mg tab AM (1) 100 mg + (1) 25 mg tab PM	225 mg/day MAX (1) 100 mg tab AM (1) 100 mg tab + (1) 25 mg tab PM	5.2 to 6.6
≥ 43 kg (≥ 95 lb)	(2) 25 mg tab PM	(3) 25 mg tab AM (3) 25 mg tab PM	(1) 100 mg tab + (2) 25 mg tab AM (1) 100 mg tab + (2) 25 mg tab PM	400 mg/day MAX (2) 100 mg tab AM (2) 100 mg tab PM	400 mg/day MAX (2) 100 mg tab AM (2) 100 mg tab PM	9.3

* Theoretical dosage range based on protocol-defined daily topiramate target dosages and subjects' weight.

Table 4: Schedule of Key Trial Procedures
(Protocol YP)

Procedure	Visit (Day)	Baseline 1 (-56)	Baseline 2 (-28)	Double-Blind Phase: Titration 3 (1)	Titration 4 (15)	Titration 5 (29)	Stabilization 6,7,8 (43,57,85)	Stabilization Final (113)
Baseline Procedure								
Seizure history		X						
Medical history		X		X[a]				
Inclusion/exclusion criteria		X	X	X				
Pregnancy test[b]			X	X				X
Efficacy Assessments								
Compile seizure diaries			X	X	X	X	X	X
Parental global evaluation[c]								X
Safety Assessments								
Adverse events					X	X	X	X
Clinical laboratory tests			X	X		X	X[d]	X
Neurological examination			X			X		X
Physical examination			X			X		X
Vital signs and weight		X	X	X	X	X	X	X
ECG			X					X
Parental global evaluations[e]								X
Pharmacokinetic assessments								
Topiramate plasma concentrations				X	X	X	X	X
AED(s) plasma concentrations		X	X	X	X	X	X	X
Administrative								
Dispense diary		X	X	X	X	X	X	X
Dispense study medication				X	X	X	X	X[f]
Collect and count unused study medication					X	X	X	X

[a] Medical history was updated to capture any adverse events that occurred during baseline.
[b] After Visit 3, serum/urine pregnancy test could be performed at the investigator's discretion, but always at the final visit. Pregnancy testing was performed before study drug was administered.
[c] Parental global evaluation of improvement in subject's seizure severity at the end of the double-blind phase relative to the beginning of the titration period.
[d] Visits 7 and 8 (Days 57 and 85 only).
[e] Parental global evaluations of improvement in subject's level of alertness, ability to perform activities of daily living, level of interaction, and response to verbal requests at the end of the double-blind phase relative to the beginning of the titration period.
[f] Subject evaluated for entry into extension phase or withdrawn from study.