CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20646

MEDICAL REVIEW(S)

REVIEW AND EVALUATION OF CLINICAL DATA
NDA 20-646-N(AZ)

Sponsor:	**Abbott Laboratories**
Drug:	**Tiagabine**
Proposed indication:	**partial seizures**
Material submitted:	**response to approvable letter**
Date received:	**4/1/97**

In response to the clinical efficacy section of the approvable letter, the sponsor has addressed the following issues:

1) Partial Seizures: The sponsor has reviewed the verbatims from the three pivotal trials regarding the incidence of incomplete reporting of partial seizures. They have also reviewed the number of seizures with documented partial onset. Finally, they have reanalyzed these adjusted data sets. The information provided is thorough and complete and does, indeed, provide a more accurate documentation of the number of partial onset seizures and the number of overall partial seizures. The actual change in numbers was small and the statistical reanalyses were reviewed by Dr. Sahlroot and found to "...not alter the statistical results contained in the original submission." [Statistical Review and Evaluation; Draft #2; J. Todd Sahlroot, Ph.D.]

3) Bioequivalence Study for 20 mg Tablet: The sponsor has submitted a new study demonstrating the bioequivalence between the Gabitril 20 mg and five of the 4 mg reference Gabitril tablets. This study has been reviewed by Dr. Iftekhar of the Division of Biopharmaceutics. He has found it to be adequate to allow for reintroduction of the 20 mg tablet into labeling.

Conclusions:

1) The indication for all partial seizures remains appropriate.

3) The sponsor may market the 20 mg tablet formulation.

Recommendations:

Appropriate changes should be made to the current labeling document to reflect the above conclusions.

Bob A. Rappaport, M.D.
Medical Reviewer
August 18, 1997

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REVIEW AND EVALUATION OF CLINICAL DATA

NDA	**20-646**
SPONSOR	**ABBOTT LABORATORIES**
BRAND NAME (GENERIC NAME)	**TIAGABINE HYDROCHLORIDE (GABATRIL™)**
INDICATION	**EPILEPSY**
NDA CLASSIFICATION	**1S**
ORIGINAL RECEIPT DATE	**NOVEMBER 6, 1995**
CLINICAL REVIEWER	**CYNTHIA G. MCCORMICK, MD**

Cynthia M. McCormick
7/26/96

SECTION 1.0 MATERIAL UTILIZED IN REVIEW

SECTION 1.1 MATERIAL FROM NDA

The following table lists specific volumes that were examined in reviewing this NDA. For the review of efficacy, the individual study reports data listings and CRFs when available were reviewed. The ISE was considered only as an overview document.

Table of NDA Volumes Reviewed for Clinical Evaluation of Tiagabine

CATEGORY	STUDY	DATE REC'D	VOLUME(S)
EFFICACY	Overview	11/6/1995	1.2, 1.101-104
	ISE	11/6/1995	1.476
Placebo-Controlled	M91-603	11/6/1995	1.167-190
	Data listings	11/6/1995	1.504-512
	M91-605	11/6/1995	1.191-212
	Data listings	11/6/1995	1.541-549
	M93-755	11/6/1995	1.213-225
Monotherapy	M93-090	11/6/1995	1.455-1.470
	Data listings	11/6/1995	1.581-587
	M90-511	11/6/1995	1.471
	Data listings	11/6/1995	1.503
Crossover	M90-481	11/6/1995	1.225-1.232
	M91-565	11/6/1995	1.233-1,240
CLINICAL PUBLICATIONS		11/6/1995	1.919-920

SECTION 1.2 REVIEW OF THE PUBLISHED LITERATURE

The sponsor provided a summary of published clinical literature accumulated during the development of tiagabine (NDA vol.1.919-920). This provided no additional information or insights not already found in the NDA.

SECTION 2.0 BACKGROUND

SECTION 2.1 INDICATION

This product has been developed for the treatment of partial onset epilepsy in adults, both as adjunctive and as monotherapy. In the past 4 years, three other

new molecular entities have been approved by the FDA for the same indication.

SECTION 2.2 IMPORTANT INFORMATION FROM RELATED INDS AND NDAS

There are no existing INDs or NDAs for chemically related compounds.

SECTION 2.3 ADMINISTRATIVE HISTORY

April 1, 1991	IND filed with the Division of Neuropharmacological Drug Products for investigation of tiagabine HCl in the treatment of epilepsy The development of this product proceeded without problems for the next four and a half years.
October 5, 1993	End of Phase II Meeting held with sponsor. Phase III program to evaluate tiagabine as monotherapy and for pediatric use (over the age of 6 years) was discussed.
June 14, 1995	PreNDA Meeting
November 6, 1995	NDA submitted to DNPDP

SECTION 2.4 DIRECTIONS FOR USE (from the text of proposed labeling)

The sponsor has recommended the following dosage and administration for tiagabine:

In adolescents the recommended dosage as adjunctive therapy is 4 mg /day increasing by 4 mg/week as needed for clinical response --up to 32 mg/day given in divided doses of 2 to 4 times/day.

In adults tiagabine may be added at a dose of 8 to 12 mg, day in divided doses of two to three times daily. The dose may be titrated at weekly intervals of 8-12 mg to a clinical response or maximum tolerated dose of 32-56 mg in divided doses.

Tiagabine is recommended for oral use with food.

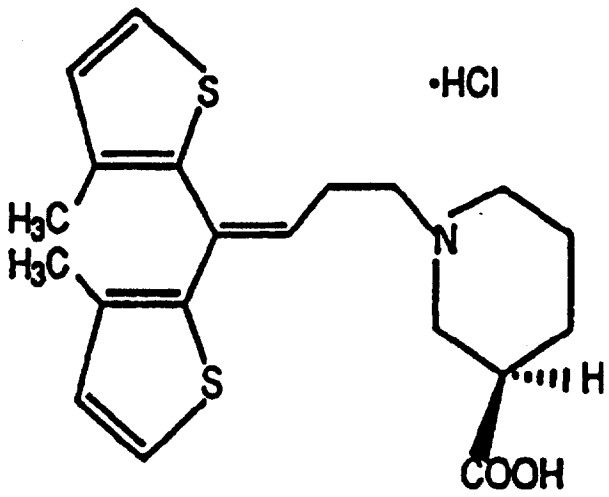
SECTION 2.5 FOREIGN MARKETING

As of October 12, 1995, tiagabine had not been approved for marketing in any foreign country.

SECTION 3.0 CHEMISTRY

Chemical Name:
CAS:
(R)-(-)-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]-3-piperinecarboxylic acid, HCl
INN:
(R)-(-)-[4,4-(3-methyl-2-thienyl)-3-butenyl]-3-piperinedicarboxylic acid, HCl

Chemical structure:



Molecular formula and weight:
$C_{20}H_{25}NO_2S_2 \cdot HCl$ **M.W.** 412.o (375.5 free base)

Physical and chemical characteristics:
This compound is soluble in aqueous base with decomposition; sparingly

soluble in water and isopropanol; slightly soluble in chloroform, acetone and tetrahydrofuran; very slightly soluble in aqueous acid. Its dissociation constants are pK_{a1}(acid)=3.3;pk_{a2}(amine)=9.4.

Stability: This compound is stable to heat in the presence of air when stored at 105°C for 91 hours. It is unstable in the presence of light in the solid state. It is also unstable in aqueous solutions when exposed to photo and oxidative stress conditions. The drug substance is stable for 24 months at 30°C showing no change in physical or purity parameters.

Please refer to Dr. Rzesotarski's review for chemistry review and deficiencies.

SECTION 4.0 ANIMAL PHARMACOLOGY

This section provides a summary of the preclinical efficacy profile of tiagabine HCl. Please refer to Dr.Fisher's review for details.

Tiagabine HCl is a member of a new class of pharmacologic agents - gamma-aminobutyric acid (GABA) uptake inhibitors which have been proposed to be of potential utility in the control of seizure activity by enhancing inhibitory synaptic transmission, and hence have application to the disease of epilepsy.

Tiagabine HCl exhibited both *in vivo and in vitro* pharmacologic activities which support its use in epilepsy. Tiagabine HCl potently inhibited the uptake of GABA into nerve endings, neurons and glia as demonstrated by direct measurement of GABA transport and of GABA levels in brain extracellular fluid, and it inhibited neuronal firing in electrophysiological experiments in a manner consistent with the enhancement of GABA inhibitory circuits. In a variety of models of convulsive seizures, including chemically-induced, sound-induced, light-induced and kindling-induced convulsions, tiagabine HCl exerted a protective effect. No significant tolerance to tiagabine HCl was observed in rodents after chronic administration for 30 days. TiagabineHCl enhanced the anticonvulsant efficacy of several clinically used antiepileptic drugs.

The efficacy of tiagabine HCl was decreased however, after prior administration of several antiepileptic drugs, an effect likely due to increased metabolism induced by the other drugs. In contrast, tiagabine HCl exacerbated absence-like spike discharges in rats exhibiting non-convulsive epilepsy. At high doses, tiagabine HC1 produced signs of central nervous system pharmacological effects in rats, mice and dogs, mostly on the motor system. Sedative effects were observed in the traction and rotarod tests, and cognitive impairing effects were seen in a conditioned avoidance test. However, effective doses for anticonvulsant effects were lower than those for these effects, giving rise to therapeutic indices in the range of 3-16 (i.p. dosing). Tolerance was observed to occur for the cognitive effects of tiagabine HCl.

In drug discrimination tests, tiagabine HCl did not substitute for direct and indirect benzodiazepine agonists or amphetamine. Tiagabine HCl was not self-

administered in rats and did not interact pharmacologically with barbiturates or ethanol. Tiagabine HCl at doses up to 30 mg/kg, p.o., did not affect the rat electroencephalogram.

SECTION 5.0DESCRIPTION OF CLINICAL DATA SOURCES

SECTION 5.1PRIMARY DEVELOPMENT PROGRAM

The Tiagabine clinical development program has consisted of a total of 62 studies. This includes studies performed by Abbott Laboratories and studies sponsored by of which 33 are clinical pharmacology, 3 are placebo controlled, parallel efficacy trials in epilepsy, 2 are monotherapy studies, and 2 are placebo controlled crossover design efficacy trials and the remainder are long term open label epilepsy studies.

5.1.1STUDY TYPE AND DESIGN/PATIENT ENUMERATION

Overview of studies and Number of Patients/Subjects included within each Group of Studies

Type	ID	Treatment Groups	Number of Patients		
			Abbott	Novo	Both
Phase 1: Clinical Pharmacology Studies[1]					
Single and Multiple dose	Abbott:M89-319;M89-398; M90-425;M90-426;M90-463;M90-496;M90-518;M91-560;M91-590;M92-792; M92-809;M92-809;M92-810;M93-083; M92-793;M93-009; M93-080;M93-081; M93-089; M94-155; M94-156;M94-157; M94-170;M94-171;M94-244	Single Tiagabine dose Subjects Patients Multiple dose Subjects Patients	 199 53 94 57	 61 0 82 8	 260 53 176 65
	M91-607; M91-712; M93-044; M93-066; M93-079; M93-087; M93-088; M94-188				
Phase 2: Clinical Efficacy Studies					

Placebo Controlled Parallel add-on	Abbott M91-603 Abbott M91-605 M92-775	Placebo Tiagabine	198 417	77 77	275 494
Low dose Medium dose Monotherapy			102	0	102

Phase 3:Clinical Safety Studies

Long-term epilepsy Studies	Abbott: M91-604[2] Abbott M92-813[3] M91-578; M91-595; M91-710; M92-873; M93-047; M93-065	Tiagabine	1414	725	2139
All Epilepsy	Abbott: M90-481;M90-511;M91-603; M91-604; M91-605; M92-813;M92-855; M93-090 M91-656; M91-578; M91-595; M91-710; M92-775 ; M92-873; M93-043; M93-047; M93-065	Tiagabine	1627	849[4]	2444

[1]This list does not include two phase 1 studies conducted in --a total of 24 subjects received tiagabine in these two studies, but their data are not in the safety database and were not included in the integrated summary provided by the sponsor

[2] Study M91-604 included patients who had participated in placebo-controlled add-on studies M91-603 and M91-605, monotherapy studies M92-855 and M93-090, and pediatric patients from M94-244.

[3]Study M 92-813 incorporated results from M 92-813 C which included 5 Canadian sites.

[4]Thirty-two patients had previously been enrolled in Abbott studies

SECTION 5.1.2 DEMOGRAPHICS

The demographic profile for each of the placebo-controlled epilepsy studies is discussed individually.

SECTION 6.0 HUMAN BIOPHARMACEUTICS

This section provides a summary of the biopharmaceutics profile of tiagabine HCl. Please refer to Dr. Mahmood's review for details.

•The pharmacokinetics of tiagabine involved linear processes of absorption and elimination.

•The average elimination half-life for tiagabine observed in most studies of healthy subjects ranges from 7 to 9 hours. Individual half-life values in healthy subjects exhibited a wide range of 2.6 to 16.7 hours. Half-life estimates appeared independent of dose, number of doses, route of administration, and formulation.

•Tiagabine is highly bound to plasma proteins in human subjects.

•Study M90-496 determined the relative bioavailability of tiagabine under fasting and nonfasting conditions. The results of this study showed that administration of tiagabine with food decreased the rate of tiagabine absorption by 65% and decreased the C_{max} by up to 44% but did not affect the extent of tiagabine absorption. Because taking tiagabine in the fed state reduces C_{max} without changing the extent of absorption, tiagabine was administered with food in the clinical trials.

•Study M89-398 was performed in epilepsy patients to determine the effect of concomitant administration of AED on the pharmacokinetics of tiagabine. Results of this study revealed that the elimination of tiagabine was two to four times more rapid, on average, in patients whose hepatic enzyme systems were induced by concomitant antiepileptic therapy, thus suggesting that tiagabine may be metabolized by the hepatic cytochrome P450 system. These results led to the use of induced patients only in the design of adequate and well-controlled add-on trials. This study and Study M93-009 showed linear pharmacokinetics and a half-life for tiagabine in induced patients of 4 to 7 hours.

•Study M92-855 was an open-label study that evaluated the maximum tolerated dose of tiagabine administered as monotherapy for the treatment of complex partial seizures. Tiagabine monotherapy was achieved in doses ranging from 25-54 mg/day (mean 38.4 mg/day), with a TID regimen being the most common. The initial dose of 0.25 mg/kg was tolerated by most patients.

•At least two metabolic pathways for tiagabine in humans have been tentatively identified, based on *in vivo or in vitro* studies: 1) thiophene ring oxidation leading to the formation of the (E) and (Z) isomers of 5-oxo-tiagabine; and 2) glucuronidation of tiagabine.

SECTION 7.0 EFFICACY FINDINGS

SECTION 7.1 OVERVIEW OF STUDIES PERTINENT TO EFFICACY

The sponsor has performed the following controlled trials designed to determine the efficacy of tiagabine HCl as an antiepileptic drug in patients with partial onset epilepsy.

ADJUNCTIVE THERAPY (DB PARALLEL)	STUDY M91-603	PBO/ TGB 16MG/ TGB 32MG/TGB 56MG
	STUDY M91-605	PBO/TGB 32MG
	STUDY M92-775	PBO/TGB 30 MG
ADJUNCTIVE THERAPY (CROSSOVER)	STUDY M90-481	PBO/TGB52 MG
	STUDY M91-565	PBO/TGB48 MG
MONOTHERAPY	STUDY M93-090	
	STUDY M90-511	NOT COMPLETED

All of the above studies were designed to evaluate tiagabine for the treatment of partial onset or complex partial seizures. The first five studies listed were intended to evaluate tiagabine as adjunctive therapy against a background of one or more concomitant antiepileptic medications. The remaining two were designed to evaluate tiagabine monotherapy. Study M90-511 was not carried to completion and study M93-090 was not considered positive by the sponsor. There were no formal study reports for these in the NDA.

The sponsor has submitted reports for the add-on trials only and considers the first three parallel trials as pivotal, the remaining two as supportive. The sponsor has presented a plethora of *post hoc* analyses and subanalyses (over 100 in some cases) for each one of these studies in addition to the prospective analyses outlined in the protocols. Some of these will be summarized for completeness. However, the approach to these in general will be to focus on (1) the planned primary analysis for each study and (2) the analyses which directly support the sponsor's claim. Thus, once the sponsor's primary analysis has been confirmed, the focus of the FDA's analysis of the sponsor's data will be on the more traditional evaluation of partial onset seizures and secondary generalization-- which are indeed what the sponsor has ultimately requested for labeling. Only the intent to treat datasets will be considered. Monotherapy will not be an issue here but studies M90-511 and M93-090 will be briefly summarized.

SECTION 7.2 SUMMARY OF STUDIES PERTINENT TO EFFICACY

SECTION 7.2.1 STUDY M91-603

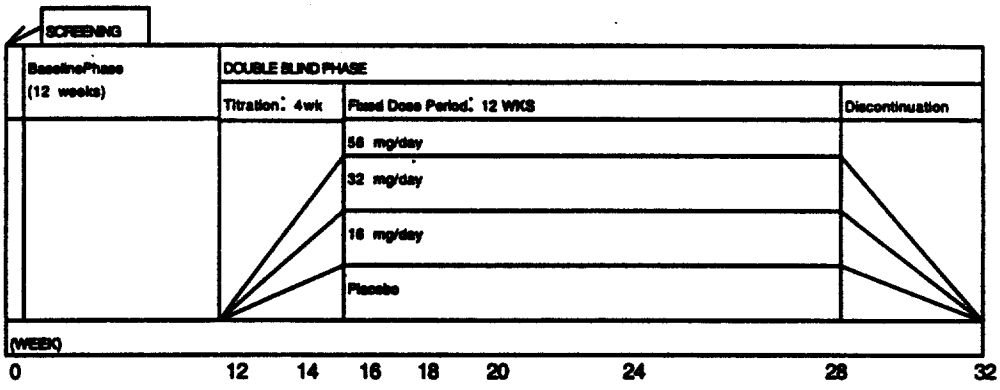
SECTION 7.2.1.1 PROTOCOL SYNOPSIS

TITLE Safety and Efficacy of three dose levels of Tiagabine HCl versus Placebo as Adjunctive Treatment for Complex Partial Seizures

OBJECTIVES: to determine the safety and efficacy of three dose levels of tiagabine HCl (16mg/ TGB 32mg/TGB 56mg) as add-on therapy for complex partial seizures.

STUDY DESIGN : a multicenter (21) randomized, double-blind, placebo-controlled, parallel group, add-on AED trial with multiple dose groups.

STUDY SCHEMATIC:



PROTOCOL

STUDY SCHEDULE:

Typical of epilepsy studies, this protocol has a Baseline Phase and a Double-Blind Phase. Patients meeting eligibility criteria at this screening visit would maintain a seizure diary throughout the study. Eligible patients entering the Double-Blind Phase would be randomized by a 3:2:3:2 ratio to one of four regimens: placebo, tiagabine 16 mg, tiagabine 32 mg, or tiagabine 56 mg divided four times a day. The Double-Blind Phase consists of three phases: (1) Titration (4 weeks), (2) Fixed Dose (12 weeks) and (3) Discontinuation (4 weeks). During Titration the study drug dosage would be gradually increased while during Fixed Dose the study drug would be kept constant. On completion of the Fixed-Dose Period all patients would enter Discontinuation as their dosage would be gradually reduced and then stopped.

Study Drug Titration and Tapering Schedule

		Titration Period				Discontinuation Period			
Ratio	Group	wk1 (mg)	wk2 (mg)	wk3 (mg)	wk4 (mg)	wk1 (mg)	wk2 (mg)	wk3 (mg)	wk4 (mg)
2	16 mg	8	8	16	16	8	8	0	0
3	32 mg	8	16	24	32	24	16	8	0
2	56 mg	8	24	40	56	40	24	8	0
3	Placebo	Placebo				Placebo			

The TDD of concomitant AEDs would be held constant throughout the study.

Enrollment

Key Inclusion Criteria

- Diagnosis of **complex partial epilepsy** supported by focal EEG in a patient having a complex partial seizure or an interictal EEG demonstrating asynchronous abnormalities consistent with complex partial seizures.
- Frequency of ≥six complex partial seizures, occurring alone or in combination with any other seizure type, within the 8-week period preceding the Screening Visit. Each of the two 4-week segments within the 8-week period contains at least one complex partial seizure.
- Stable regimen of one to three of the following AEDs: phenytoin, carbamazepine, valproate, phenobarbital or primidone. Valproate, if used, must be in combination with one of the above hepatic enzyme-inducing AEDs.

Key Exclusion Criteria

- Pseudoseizures.
- Active CNS infection, demyelinating disease, degenerative neurological disease, or any progressive CNS disease or those requiring frequent medication changes; Clinically significant psychiatric illness, psychological or behavioral problems, or history of psychosis severe enough to require hospitalization.
- A medical disease, either currently or within the previous three months, manifesting with signs and symptoms that could confound interpretation of the study results.
- Substance abuse
- Clinically relevant laboratory abnormality
- Administration of an investigational drug within 30 days prior to the Screening Visit.
- Pregnancy or lactation

EFFICACY VARIABLES

PRIMARY OUTCOME MEASURES

Two primary outcome measures are prospectively described for this study. The first is the change in **complex partial seizure** frequency (4-week rate) from baseline to the Titration and Fixed-dose period[1] for the **combined 32 and 56 mg** dosage groups compared to placebo. The second primary analysis described is a dose response analysis (pairwise analysis including all dosage groups) of change in complex partial seizure frequency from Baseline to Double Blind Period.

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[1] Revision Six - May 28, 1993: Revisions were made to the Statistical Methodology Section of the protocol. The seizure rate was revised to include the Titration Period in addition to the Fixed-Dose Period for the evaluable patient analysis and intent-to-treat analysis. This change reflected the communication between Abbott and FDA for another antiepilepsy drug. In addition, the seizure rates were expressed as 4-week rates instead of 12-week rates as originally planned. The primary efficacy variable for comparing the add-on tiagabine and add-on PBO treatment was the Experiment Period change from Baseline in the 4-week complex partial seizure rate. The Experiment Period was the combined interval of Titration Period and Fixed Dose Period in the Double-Blind Phase. No patients were enrolled under the original protocol and revision six was made after the end of the study but before the blind was broken and is not related to patient enrollment.

Seizure Rate Calculation

The baseline period 4-weeks complex partial seizure rate is calculated as the total number of complex partial seizures reported during the baseline phase multiplied by 28 days to the actual number of days in the baseline period.

$$\textbf{Baseline seizure rate} = \frac{28 \text{ days} \times \#CPS_{baseline}}{\text{actual } \#\ days_{baseline}}$$

Likewise, the experimental phase 4-weeks complex partial seizure rate is calculated as the total number of complex partial seizure reported during the experimental phase (titration and fixed dose period) multiplied by 28 days to the actual number of days in the experimental phase.

$$\textbf{Experiment Period Seizure Rate} = \frac{28 \text{ days} \times \#CPS_{experimental}}{\text{actual } \#\ days_{experimental}}$$

In the calculation of the rate complex partial seizures are counted if they are either occurring alone or in combination with any other seizure type. Specifically this includes:

- complex partial seizures occurring alone
- simple partial evolving to complex partial seizures
- simple partial evolving to complex partial to generalized tonic clonic seizures
- complex partial evolving to generalized tonic clonic seizures
- complex partial seizures occurring in any episode of partial complex status

Analysis Method:

PRIMARY OUTCOME MEASURES

The vanElteren test is the primary prospective method used to compare tiagabine (32 mg and 56 mg combined) versus placebo. The dose response effects of tiagabine HCl is assessed with the Jonkheere-Terpstra test using the three tiagabine HCl dose groups and the placebo group.

SECONDARY OUTCOME MEASURES

• **COMPLEX PARTIAL ONSET SECONDARILY GENERALIZED SEIZURES.** A subset analysis of the Fixed dose Period change from baseline in 4-week seizure rates was to be performed considering only **complex partial seizures** that progress to generalized tonic clonic seizures. This analysis would compare tiagabine HCl (32 and 56 mg combined) and placebo for patients who have experienced these seizures. Patients with partial onset seizures who experience secondary generalization during treatment and not during baseline are not included in this analysis.

• **Other Seizure types.** While these other seizure types are not specified, this analysis would be restricted to patients who report this seizure type during baseline and be performed if at least 10 patients in each treatment group experience this seizure type in baseline also. The analysis method would be the Wilcoxon two-sample test. Patients not experiencing these seizures during baseline and only during treatment would not be included in these analyses. All secondary analyses would compare the placebo to the combined 32 and 56 mg groups and the analysis methods would be the Wilcoxon two-sample test ignoring center effects.

SECTION 7.2.1.2 STUDY CONDUCT

Enrollment

A total of 297 patients were randomized in this study form 21 centers: 91, 61, 88, and 57 patients received placebo, tiagabine 16 mg, 32 mg and 56 mg, respectively. A total of 54 (18%) patients were prematurely discontinued from this study, leaving 243 (82%) patients who completed this study. The table below summarizes overall patient discontinuations. Thirteen (14%) patients were receiving placebo, 6 (10%) were receiving tiagabine 16 mg, 18 (20%) were receiving tiagabine 32 mg, and 17 (30%) were receiving tiagabine 56 mg. Of the 54 patients, 33 (11%) were discontinued because of adverse events, 14 (5%) were discontinued because of lack of efficacy, two(1%) because of personal reason, one (0.3%) was non-compliant, one (0.3%) was lost to follow-up, and three (1%) because of other reasons.

PATIENT DISPOSITION

Disposition	Placebo	Tiagabine			Total
		16 mg	32 mg	56 mg	
Randomized	91	61	88	57	297
Completed Study	78 (86%)	55 (90%)	70 (80%)	40 (70%)	243 (82%)
Total Prematurely discontinued	13 (14%)	6 (10%)	18 (20%)	17 (30%)	54 (18%)

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The table below summarizes patient demographics for all randomized patients by treatment groups. These variables include gender, race, age, weight, height, years with epilepsy and number of AEDs ever taken. No significant differences were seen.

Summary of Patient Demographics

	Placebo	Tiagabine			Overall	P-Values*
		16 mg	32 mg	56 mg		
N	91	61	88	57	297	
Gender						
Female	32 (35%)	30 (49%)	41 (47%)	22 (39%)	125 (42%)	0.254
Male	59 (65%)	31 (51%)	47 (53%)	35 (61%)	172 (58%)	
Age (mean)	34.4	32.5	34.5	34.4	34.0	0.748
min-max	12.0-77.0	13.0-51.0	12.0-72.0	13.0-58.0	12.0-77.0	
Median number of AEDs ever taken	6	7	7	7	7	0.879
Min-max	3.0-18.0	3.0-16.0	2.0-20.0	2.0-16.0	2.0-20.0	
Median years with epilepsy	21.1	21.5	24.6	24.5	22.9	0.14
min-max	1.8-58.6	3.4-42.8	1.4-65.8	5.2-54.5	1.4-65.8	
Race						
Caucasian	79 (87%)	55 (90%)	79 (90%)	48 (84%)	261 (88%)	0.663
Black	5 (5%)	5 (8%)	5 (6%)	5 (9%)	20 (7%)	
Other (Hispanic, Asian, etc.)	7 (8%)	1 (2%)	4 (5%)	4 (7%)	16 (5%)	

*Comparisons among all four treatment groups.

The mean age for all patients was 34.0 years (range=12-77). Most patients (88% (261/297)) were Caucasian, 7% Black (20)and 5%(16 patients) were of other races. Forty-two percent (125) were females. The patients were diagnosed with epilepsy for a mean of 23.6 years (median=22.9, range=1.4-65.8). The mean number of AEDs ever taken was 7.2 (median=7.0, range=2.0-20.0).

Patient Characteristics

A summary of patient characteristics including epilepsy etiologies, seizure types experienced within the 8-week period prior to Baseline and concomitant AEDs were summarized by the sponsor for each dose group and for the combined tiagabine 32 mg and 56 mg groups. The most common epilepsy etiologies were genetic propensity (31%), trauma (24%), unknown causes (44%), infections (16%), and ante/perinatal injury (12%). In addition to complex partial seizures, investigators reported that 54% of the patients experienced simple partial seizures and 30% experienced secondarily generalized tonic-clonic seizures within the 8-week period prior to Baseline. No statistically significant differences were found between the four treatment groups when compared for each epilepsy etiology and seizure type.

Comparisons of concomitant AEDs used by patients within the 8-week period preceding the Baseline did not show any significant differences among the treatment groups.

Concomitant AEDs Used by Patients Within 8 Weeks Preceding Baseline Phase

	Placebo	Tiagabine			Total	
Concomitant AED	N=91 N(%)	16 mg N=61 N(%)	32 mg N=88 N(%)	56 mg N=57 N(%)	N=297 N(%)	P-values
Carbamazepine	66 (73%)	39 (64%)	63 (72%)	37 (65%)	205 (69%)	0.576
CBZ Monotherapy	29 (32%)	16 (26%)	19 (22%)	13 (23%)	77 (26%)	0.419
Phenytoin	26 (29%)	26 (43%)	21 (24%)	21 (37%)	94 (32%)	0.073
PHT Monotherapy	6 (7%)	5 (8%)	6 (7%)	8 (14%)	25 (8%)	0.388
Valproate	22 (24%)	16 (26%)	31 (35%)	10 (18%)	79 (27%)	0.110
Primidone	10 (11%)	7 (11%)	13 (15%)	10 (18%)	40 (13%)	0.653
Phenobarbital	19 (21%)	14 (23%)	25 (28%)	18 (32%)	76 (26%)	0.436

Baseline Phase Comparability in 4-Weeks Seizure Rates

Baseline Phase 4-week seizure rates for each seizure type were tested for any difference among the four treatment groups and no statistically significant differences were observed in any comparison.

Median Baseline 4-Week Seizure Rates

		Tiagabine			
Seizure Types	Placebo	16 mg	32 mg	56 mg	P-Values*
Complex Partial					
N	91	61	88	57	
Median	7.4	8.5	9.6	9.1	0.711
Range					
Simple Partial					
N	49	37	50	32	
Median	9.2	10.5	14.1	9.2	0.783
Range					

Seizure Types	Placebo	Tiagabine 16 mg	Tiagabine 32 mg	Tiagabine 56 mg	p-Values*
Secondarily Generalized Tonic-Clonic					
N	32	24	27	23	
Median	2.1	1.8	2.8	1.7	0.814
Range					
Combined Partial					
N	91	61	88	57	
Median	10.9	10.5	12.6	10.9	0.588
Range					

* Overall comparison of all four treatment groups.

Similar comparability was seen for the 4-week Baseline seizure rates comparing the combined tiagabine 32 mg and 56 mg groups with the placebo group.

STUDY DRUG

Patients received mean daily doses of drug according to the dose to which they were randomized. In this study there were only two cases in which patients received either the incorrect dose or did not achieve the dose to which they were randomized. These two patients were given treatment out of randomization sequence (11104 and 11105). The sponsor does not explain how this happened or whether it was intentional or an error. Both patients received 56 mg of tiagabine.

Plasma concentrations were obtained at visit 8 (Fixed dose period) at trough, one-hour post dose and two-hours post dose. While the tiagabine trough and post-dose concentrations were highly variable among patients, mean values for the three dose groups generally increased proportionately with the dose of tiagabine. A summary of mean peak and trough tiagabine plasma concentrations is listed in the table below.

Summary of Mean Peak and Trough Tiagabine Plasma Concentrations

Samples	Tiagabine 16 mg		Tiagabine 32 mg		Tiagabine 56 mg	
	Mean ng/mL	SD	Mean ng/mL	SD	Mean ng/mL	SD
Trough	9.1	9.51	24.2	24.35	34.3	31.93
1 Hour post dose	34.4	19.80	70.5	44.47	141.9	61.96
2 Hour post dose	27.2	15.11	62.3	34.79	116.2	42.98

ERRORS IN RANDOMIZATION:

Patients 11104 and 11105 received medication out of their randomization sequence. In both cases they received the medication to which they would have been randomized if their numbers had not been swiched, that is 56 mg. [1]

[1]Sponsor's response to request for information. July 22, 1996 Telecon.

PROTOCOL VIOLATIONS

Adherence to the protocol was maintained in some areas, however there were some notable deviations, and innovative practices not described in the protocol or amendments that are worth noting. The sponsor has identified and enumerated the major protocol violations which occurred in the conduct of this trial.

PATIENTS WHO HAD THE STUDY BLIND BROKEN

Two patients had the blind broken during the study and these were during the Discontinuation Period:

Patient 11014 died from drowning in a bathtub full of water. The study blind was broken and the patient was found to have been receiving placebo.

Patient 11512 was hospitalized during the Fixed-Dose Period for irritability and verbal aggressiveness (hostile). Six days later, while in the hospital, the patient experienced four generalized tonic-clonic seizures within a 3 hour period. The blind was broken because of the increased seizures and the tiagabine 56 mg dose was tapered down to 40 mg/day.

PATIENTS WHO UNDERWENT CHANGES IN AED REGIMEN DURING THE STUDY INCLUDING THOSE WHO TOOK UNAPPROVED DRUGS

Approximately 15% of patients in this trial had changes made in the background concomitant drugs or had prn medications added when seizure counts rose too high. This practice was not allowed in the protocol, however may of these patients received clearance from the medical monitor to use these drugs. Because these medications were prn and used at home, this reviewer has no way to verify the extent of their use during the study.

The first group of these patients had changes in background drugs during this study.

Patients 11307, 11308, 11411, 11603, 11701, 11111, 11128, 10721, 10729, 11609, 11209, 11220, 11815, 11512 and 12009 had changes in their total daily doses of concomitant AEDs during the Double-Blind Phase either because of toxicity, adverse events or accident.

The following patients were given permission to use prn drugs (as indicated) for seizures that were increasing in frequency.

PROTOCOL VIOLATIONS INVOLVING CHANGES IN REGIMEN OF CONCOMITANT AEDS OR ADDITION OF PRN AEDS				
PID	RX	NUMBER OF VIOLATIONS/PERIOD		DRUG- DOSE
		BASELINE	EXP	
10501	32 MG	ONGOING PRN MED FOR SZ CLUSTERS		ATIVAN DOSE NS
10607	56 MG		1 X FOR SE	LORAZEPAM 2 MG IM
			1X	LORAZEPAM 1 MG
10818	32 MG	APPROVED FOR PRN "RESCUE" FOR ↑ SZ ACTIVITY		CLONAZEPAM 1 MG Q6H X2

10809	32 MG	APPROVED FOR PRN "RESCUE"		VALIUM10 MG PO
11305	PBO	1 X FOR PROLONGED CPS		LORAZEPAM 2 MG
12207	PBO	PRN SZ		ATIVAN DOSE NS
12004	PBO	USED ON PRN BASIS TO BREAK A REPETITIVE SEIZURE CYCLE		ATIVAN DOSE NS
12011	32 MG	2 DOSES TO PREVENT INCREASED SZ WITH ILLNESS		PHENOBARBITAL DOSE NS
10503	32MG	ONGOING AS A PRN MED		ATIVAN 2 MG
10505	56 MG	ONGOING AS A PRN MED		ATIVAN 1-2 MG PRN
10805	PBO	PRN		LORAZEPAM 1 MG
11408	32 MG	PRN		LORAZEPAM 1 MG
11012	16 MG	PRN		LORAZEPAM 2 MG BID
11307	PBO	PRN CLUSTERS		DIAZEPAM 10 MG
		PRN		LORAZEPAM 1 MG X2
		PRN		LORAZEPAM 2 MGX2
		PRN		LORAZEPAM 3 MG X2
11310	16 MG		1X FOR ↑ SEIZURES	LORAZEPAM 1 MG
10216	PBO	PRN		LORAZEPAM 1 MG
10219	PBO	PRN		LORAZEPAM 1-2 MG
10205	16 MG	PRN		LORAZEPAM 2 MG
10209	16 MG	GTC TREATED IN ER		VALIUM 5 MG IV
10213	56 MG	PRN		LORAZEPAM 2 MG
12004	PBO	PRN		LORAZEPAM 1-2 MG BID
11701	PBO		FOR ↑ SEIZURES	CLONAPIN 1.5 MG TID 1.5 MG X1
			1X	LORAZEPAM 3 MG IM
10908	PBO	PRN CLUSTERS		LORAZEPAM 1 MG
11802	56MG	PRN		LORAZEPAM 2 MG
11505	PBO	PRN		DIAZEPAM 10 MG

11503	16 MG	PRN		DIAZEPAM A5 MG
12207	PBO	PRN		LORAZEPAM 1 MG
10703	PBO		X1	LORAZEPAM 2.5 MG
10710	56 MG	PRN		LORAZEPAM 2 MG
10718	56 MG	PRN AFTER 2ND SEIZURE IN 24 HOURS		LORAZEPAM 1 MG
10726	56 MG	CLUSTERS	MULTIPLE SEIZURES	LORAZEPAM 1 MG

As the above table demonstrates, this practice of prn medication for increased seizures activity involved all treatment groups, and either or both periods of the study. There is no apparent trend.

PRACTICES NOT DESCRIBED IN THE PROTOCOL WHICH MAY HAVE INFLUENCED THE DATA

Counting Seizures: Generalized Seizures

In the final study report (not in the protocol or amendments) the sponsor indicates that in counting seizures, and in the final analysis the following assumption was made, "Since all patients included in the study had confirmed partial epilepsy, all generalized seizures were considered partial onset even if there was no clinical description of the seizure beginning focally"[1] Notably not all generalized seizures were treated in this manner. Only generalized convulsions (generalized tonic clonic seizures) were included in this paradigm. Atypical absence (as seen in Lennox Gastaut Syndrome), generalized tonic seizures, and myoclonic seizures which occurred not infrequently in this study in certain patients were not counted as "secondarily " generalized seizures. In this study there were with patients with evidence of primary generalized epilepsy-- for example 10704, "patient has primary generalized tonic clonic seizures (consistent with bilateral spike and polyspike and wave activity on EEG" , patient 11413 had an EEG which did not show a focal abnormality. None of the patients who experienced the above specific generalized seizure types reported tonic-clonic seizures, thus, where this paradigm might have been called into question it was not used.

In large measure patients with truly secondarily GTC described the type of partial seizure that then progressed to a generalized tonic clonic seizure and it was recorded as such in the overall seizure counts. For example, when a patient experienced a partial complex seizure that generalized, it was designated as PCGTC, or if a simple partial seizure was noted first the designation was SCPGTC and so on.

In this study when the SGTC in question were examined patient by patient to determine whether the assumption described above was justified or whether there might be any evidence for bias regarding the classification of the cases in question, there did not appear to be any trends, all five patients had a preponderance of partial onset seizures and for at least two to these patients the underlying etiology for their epilepsy would support the diagnosis of partial onset seizures. The next table enumerates those patients who reported "secondarily GTC seizures" (SGTC) where no antecedent partial

[1]NDA volume 1.167 (Clinical volume 066) p 43

seizure was witnessed.

PATIENTS WHO REPORTED SECONDARY GTC SEIZURES

ID	DOSAGE GROUP	PERIOD WHERE 2°GENERALIZED SEIZURES WERE ASSUMED	MEDICAL HISTORY OR ETIOLOGIC DIAGNOSIS
12209*	PBO	all periods	post traumatic
10716*	PBO	BL only	Familial
11503*	16 mg	all periods	Familial
12215*	32 mg	all periods	Familial
10402*	56 mg	BL only	Tuberose sclerosis

*Pt describes aura

In only five patients was a generalized convulsion not described in association with a particular type of partial seizure, and recorded as SGCT. These in fact were all associated with an aura, by description, likely a SPS. It is presumed also that the partial onset seizures to which these GTC were secondary are not included in the subanalyses for SPS. The combined partial onset seizures, however, should reflect their inclusion.

Estimated Seizure Counts

STATUS AND FLURRIES: One of the conventions used for quantifying status epilepticus probably resulted in an underestimate of seizure activity. The convention that was used (neither specified in the protocol nor in the amendments to the protocol) was that any episode of status epilepticus would be assigned a value of 1 + the maximum number of seizures on any given day[1]. The firm provided clarification that the maximum number of the seizure in question (eg. SP, CP, or CPGTC) occurring on any given day would be used to calculate the value for an episode of status epilepticus. There were four patients in M91-603 who reported status epilepticus. They are shown in the next table. Those patients who experienced status epilepticus were all in the tiagabine groups.

Other seizure estimates occurred in this study. The sponsor states that at each center patients were instructed to do the best they could at counting the number of seizures in a flurry. While flurries were not identified in the seizure tabulations, one can determine that they probably occurred when the record states "estimate". Surprisingly seizure flurries might conceivably receive more weight than episodes of status epilepticus across patients.

[1]NDA volume 1.167 p.073 (Clinical volume 066) p.36

ESTIMATED SEIZURE COUNTS STUDY M91-603
STATUS EPILEPTICUS/OR FLURRIES

PT ID	TREATMENT	BASELINE	DB PHASE
11306	PBO		9 episodes of PCGTC numbering 10 est (for each episode)
11308	16 mg		4 episodes of PC numbering 4 est (for each)
11310	16 mg		One episode CP (5 est)
10607	56 mg	Two episodes of SECP for which "UNK" was listed under number of sz, patient hospitalized.(Seizure counts) Also patient had clusters of seizure activity not able to quantify (General comments)	Admitted after 2nd day of confusion for EEG--It was determined that patient was in status epilepticus. Rx with Lorazepam
11123	32 mg	During the month of August patient had many CPS which she did not quantify est 15-20† A second entry of 5 CPS was commented with "estimate"	
12207	PBO	Patient had episode of status epilepticus (two episodes lasting 45 min each) not recorded	Pt lost record of SP seizures for 1 month. There were seizures of this type but number is unknown
12213	32 mg	SECP designated "1" under number of seizures. The highest number counted in this patient would have been 10, and the number for status should therefore have been "11"	
11122	56 mg	Repeated secondary GTC adm to hospital in status No seizure counts for one month. No coding for status in SAS data sets	
12109	32 mg	Patient in a state of confusion for 4 days--unable to quantify seizures not reflected in counts	
12107	16 mg	Funny feeling all day -thinks he had many small seizures--unable to count	Seizures at school-unable to count (2 episodes) Mother unaware of number of SPS
10710	56 mg	1 Episode of status epilepticus counted as 1 seizure. (Note: patient never returned seizure record, dates are estimates)	5 Episodes of status epilepticus counted as 1 seizure. (Note: patient never returned seizure record, dates are estimates)
11704	16 mg	Patient lost diary for two different two week periods. Center estimates approximately 60 sz/2 weeks (type NS)	
11103	PBO	Patient has mainly SPCP but , may have CPS. He records his seizures without such differentiation, Thus we are unable to differentiate the two types. All recorded as SPCP	

11706	32 mg	Pt lost calendar--estimates 12-13 SPCP since last visit. Late for appt. Calendar lost for remainder of time between visits	
10718	56 mg	Patient estimates 1 CP/week since 7/17 visit (did not keep diary)	Patient did not keep diary but estimates 2 CP per week (like baseline) and about 7 CP episodes about every 60-90 minutes††

In the raw data of daily seizure counts submitted by the sponsor on diskette, the sponsor lists each SE episode as consisting of one or unknown number of seizures. The four-week seizure rates submitted by the sponsor, however, incorporate the estimation procedure. This assurance is provided by the sponsor in Attachment I of the electronic submission and was verified by Dr.Sahlroot.

In cases where clusters of seizures occurred and there was no attempt to guess the number, the sponsor does not trace the steps taken in determining the actual seizure counts used. The estimated seizure counts seen in some patients with flurries appear to have been handled by a good effort on the part of the investigators and caretakers to enumerate difficult-to-count seizures. Yet in other cases it was not. This problem continues to plague antiepileptic drug trials. However, in this trial, the frequency of flurries for which there was no attempt at quantification was small and there did not appear to be any systematic error in favor of the drug. However, the inconsistent assignment of one paradigm for counting seizures in a flurry and a different one for counting seizures in an episode of status should have been corrected. While the underestimation of seizures in status however, would not be expected to bias the study in favor of the drug, it will be looked at further in FDA results section.

COUNTING SEIZURES: SIMPLE PARTIAL

Simple partial seizures were included among the subgroups analyzed by the sponsor. There are numerous examples of patients who did not begin to count simple partial seizures until after the study was underway, or patients who did not understand how to count simple partial seizures. Additionally there were the five patients with "secondarily generalized TC seizures" who described an aura with their typical seizures, for whom a SP seizure was likely not counted (because it was not identified by the sponsor). These inaccuracies undermine the sponsor's subgroup analysis for this seizure type. However this subgroup analysis was not considered a principal analysis by the sponsor. It must be noted however that the failure to count certain categories of partial seizures accurately does bear on the overall accuracy of the combined partial seizure analysis.

SECTION 7.2.1.3 SPONSOR'S EFFICACY RESULTS

The sponsor's efficacy results for this study will be summarized in the following format:

(1) PARTIAL COMPLEX SEIZURES, (2) ALL PARTIAL SEIZURES (3) SECONDARY GENERALIZED SEIZURES

A. CHANGE FROM BASELINE IN 4-WEEK SEIZURE RATE, COMPARING PLACEBO TO THE COMBINED 32 AND 56 MG DOSE GROUPS
B. PERCENT CHANGE (25 AND 50% REDUCTION IN SEIZURES COMPARING PLACEBO TO 32 AND 56 MG DOSE GROUPS
C. DOSE RESPONSE ANALYSIS: CHANGE FROM BASELINE IN THE 4 WEEK SEIZURE RATE
D. DOSE RESPONSE ANALYSIS OF PERCENT CHANGE

Analyses of simple partial seizures will not be summarized since they contribute little to the overall understanding of this drug's efficacy nor to the sponsor's claim. Those analyses which differ from that which was planned will be pointed out.

(I) PARTIAL COMPLEX SEIZURES

A. CHANGE FROM BL IN 4-WEEK SEIZURE RATE: COMPARING PLACEBO TO THE COMBINED 32+ 56 MG DOSAGE GROUPS

The primary efficacy variable for this study according to the protocol was the Change in the 4-week Complex Partial Seizure Rate from Baseline to the Experimental Phase for the combined 32 and 56 mg group compared to the placebo group. Tiagabine was statistically significantly superior to placebo for the combined groups 32 and 56 mg as specified in the protocol using the both the weighted (prospective) and non weighted vanElteren test.

COMPARISON OF CHANGE IN 4-WEEK SEIZURE RATES PLACEBO V. 32 AND 56 MG GROUPS COMBINED INTENT -TO - TREAT DATASET (COMPLEX PARTIAL SEIZURES)

	PLACEBO N=91			TIAGABINE 32/56 MG COMBINED GROUPS N=143		
VARIABLE	BL	EXP	CHANGE	BL	EXP	CHANGE
Mean	16.2	16.8	0.6	20.3	18.4	-1.9
SD	20.34	25.31	11.41	41.42	50.53	23.53
Median	7.4	7.8	-0.6	9.2	6.9	-2.6

TEST OF TREATMENT EFFECT

	Weighted Comparison	Unweighted comparison
Analysis Method	p-values	p-values
Nonparametric *	.007	.018
Parametric	.043	.019

*Van Elteren test (Non parametric test which blocks on center)--primary

While the difference between placebo and combined treatment groups is statistically significant, the clinical effect was very subtle, that is, the median seizure reduction in the treatment groups compared to Baseline was 2.6 CP seizures per month in the treated group and .6 CPS in the placebo group.

b. PERCENT CHANGE : Seizure reduction by 25% and 50%: Placebo compared to Combined 32 and 56 mg dose groups *(UNPLANNED ANALYSIS)*
This sponsor's unplanned analysis provides a more tangible comparison between the treatment and placebo and indicates that a clinically significant response is actually seen in a small group of patients. Continuing to focus on partial complex seizures in the intent-to-treat dataset for the combined dosage groups (32 and 56 mg) the sponsor has provided a comparison of the patients with 25% reduction and 50% reduction in both placebo and combined 32/56 mg dose groups.

COMPARISON OF %REDUCTION IN 4-WEEK SEIZURE RATES
PLACEBO V. TIAGABINE (32 AND 56 MG COMBINED)
INTENT-TO-TREAT DATASET/SEIZURE TYPE=COMPLEX PARTIAL

	---PATIENTS WITH---			
	25% OR MORE REDUCTION		50% OR MORE REDUCTION	
RX	PORTION (%)	P-VALUE†	PORTION (%)	P-VALUE†
PBO	28/91(31%)	.001	4/91 (4%)	<.001
TIAGABINE 32/56	76/143 (53%)		34/143 (24%)	

The reduction in seizures by 50% is experienced by a significantly greater number of patients in the combined treatment groups than in the placebo group. A 25% reduction is experienced by slightly more than 50% of patients, but when one looks at the median seizure rates, one can see that this 25% reduction is the marginally small 2 seizures per month noted above. The natural extension of this parameter is the percent change in seizures from clinical worsening (seizure increase) to 100 % improvement. This is shown in the following table.

COMPARISON OF % REDUCTION IN 4-WEEK SEIZURE RATES
PLACEBO V. TIAGABINE (32 AND 56 MG COMBINED)
INTENT-TO-TREAT DATASET
SEIZURE TYPE=COMPLEX PARTIAL

		PATIENT DISTRIBUTION OF % REDUCTION					
RX	N	INCR SEIZURES	0-24%	25-49%	50-74%	75-100%	MEDIAN
PLACEBO	91	40 (44%)	23 (25%)	24(26%)	3 (3%)	1 (1%)	9.3
TIAGABINE 32/56	143	39 (27%)	28 (20%)	42(29%)	19 (13%)	15 (10%)	29.2

The proportion of patients demonstrating increase in seizure frequency is somewhat less in the treatment group than the number showing improvement which is not unexpected and conforms with a modest placebo response normally seen in epilepsy trials.

The drawback with this and the previous analysis, planned and unplanned is that in combining dosage groups for comparison does not allow one to determine the minimum possible effective dose.

C. Dose Response Analysis: Change from Baseline in the 4-week Seizure Rate (Originally identified as a primary endpoint)

The sponsor assessed the dose-response relationship by using all four treatment groups and in addition, analyses were performed for all six possible pairwise comparisons. The pairwise comparisons included: tiagabine 16 mg versus placebo, tiagabine 32 mg versus placebo, tiagabine 56 mg versus placebo, tiagabine 32 mg versus 16 mg, tiagabine 56 mg versus 16 mg, and tiagabine 56 mg versus 32 mg. These analyses were performed to compare the change in 4-week seizure rates for complex partial seizures. These analyses were not done in a true intent-to-treat fashion since three patients from Dr. Brown's site were excluded from the comparison because there were no patients in the tiagabine 16 mg dose group. The results are shown in the next table.

Sponsor's Results: Comparison of Change in 4-week Seizure rates
Dose Response Analysis and all Pairwise Comparisons of Treatments
Intent to Treat Dataset \Seizure Type: Complex Partial

	Placebo N=90			Tiagabine 16 N=61			Tiagabine 32 N=86			Tiagabine 56 N=55		
Variable	BL	Exp	Change	BL	Exp	Change	BL	Exp	Change	BL	Exp	Change
Mean	15.8	16.3	0.4	21.8	19.3	-2.4	19.6	19.2	-.4	20.5	16.7	-3.8
(SD)	20.12	24.91	11.37	34.82	29.46	12.06	45.5	60.40	26.73	34.51	30.68	17.75
Median	7.4	7.6	-0.7	8.5	7.6	-0.8	9.6	7.0	-2.2	9.1	5.8	-2.8

P-values from pairwise comparisons of seizure rate changes

Weighted

Analysis	D-R* p-value	16 mg v Pbo.	32 mg v.Pbo	56 mg. v. Pbo	32 v 16 mg	56 v 16 mg	56 v 32 mg
†Non para-metric	.004	.436	.03	.028	.180	.158	.418
Para-metric	0.022	.629	.183	.018	.435	.156	.419

NON Weighted

Analysis	DR p-value*	16 mg v Pbo.	32 mg v. Pbo	56 mg. v. Pbo	32 v 16mg	56 v 16 mg	56 v 32 mg
†Non para-metric	.004	.462	.089	.05	.267	.074	.400
Para-metric	.022	.665	.117	.018	.314	.069	.330

*Dose response p-value
†Van Elteren test, primary analysis per protocol

The sponsor asserts that there was a statistically significant dose response in tiagabine antiepilepsy effect for complex partial seizures. The sponsor's dose response p-values were 0.004 and 0.022 from nonparametric and parametric analyses, respectively. During the Experimental Period, patients receiving either of the two higher doses experienced a somewhat greater decrease in **median** seizure rates when compared with Baseline Phase, compared to placebo or the 16 mg group, although the mean seizure decrease did not follow this rule. This difference between 16 mg and placebo was not clinically significant nor was the difference between 32 and 56 mg. The dose response was not

statistically significant when placebo patients were excluded from the analyses, the p-values were 0.108 and 0.138 for nonparametric and parametric analyses, respectively. The dose response relation with the placebo group excluded was not significant, but was actually stronger (based on steepness of the slope) than that with the placebo group included.

An alternative way of examining dose response is by pairwise comparisons among the four treatment groups. The sponsor's results were ambiguous. A statistically significant difference was seen in the tiagabine 32 mg when compared with placebo ($p = 0.030$) and tiagabine 56 mg when compared with placebo ($p = 0.028$). Of note, however is that the difference was not statistically significant when tiagabine 16 mg was compared to the placebo ($p = 0.436$), or when each of the tiagabine 32 mg and 56 mg dose groups were compared to 16 mg ($p = 0.180$ and 0.158), and when the tiagabine 56 mg was compared to the 32 mg dose group ($p = 0.418$).

D. DOSE RESPONSE ANALYSIS: PERCENT CHANGE

The sponsor again provides another view of this data in the Percent Change. This also was not a planned analysis. The number of patients with 25% or more reduction and 50% or more reduction are summarized in the next table.

Analyses of Percent Reduction from Baseline: Partial Complex Seizures (ITT)

Treatment	N	Median Percent Reduction	Proportion of Patients with Specified Reduction			
			>=25%	P-value	>=50%	P-value
Placebo	90	10.5	28 (31%)		4 (4%)	
Tiagabine 16 mg	61	12.6	17 (28%)	0.587	5 (8%)	0.418
Tiagabine 32 mg	86	24.6	43 (50%)	0.014*	17 (20%)	0.002*
Tiagabine 56 mg	55	32.9	31 (56%)	0.005*	16 (29%)	<0.001*

* Statistically significant when compared with placebo.

Clinical as well as statistical superiority of tiagabine 56 mg and to a lesser degree 32 mg over placebo was seen when the proportion of patients who has a 50% or greater reduction in the complex partial seizure rate was analyzed. The proportions of patients achieving a ≥ 50% reduction from Baseline when compared with placebo also exhibited a dose response.

(2) ALL PARTIAL SEIZURES

A.CHANGE FROM BASELINE IN 4-WEEK SEIZURE RATE COMPARING PLACEBO TO COMBINED 32 AND 56 MG DOSE GROUPS

Analyses for the change from Baseline in 4-week seizure rates were performed with all partial seizures combined but not as the primary analysis. Nevertheless it provides the basis for the labeling claim submitted by the sponsor. he analysis of this group uses the entire randomized population, and is traditionally the group studied in epilepsy trials, because it takes into consideration most l relevant seizure types suffered by the population in question, not just a subset of their seizures. The sponsor pointed out that in this analysis each seizure was counted only once regardless of the number of seizure

types occurring in a single event. The calculation for combined partial seizures included:

simple partial,
complex partial,
simple partial evolving to complex partial,
complex partial evolving to secondarily generalized tonic-clonic,
simple partial evolving to complex partial evolving to secondarily generalized tonic-clonic,
simple partial evolving to secondarily generalized tonic-clonic and
partial with secondary generalized tonic-clonic seizures were included.

As noted in the description of clinical trial, patients who experienced a generalized tonic-clonic seizure for whom an antecedent partial seizure was not witnessed were assumed to have had a partial onset secondarily generalized seizure. It is assumed that these were counted among the group of "all partial seizures combined".

During the Experimental Period, patients in the combined tiagabine 32 mg and 56 mg group experienced a median change of -2.9 in the 4-week combined partial seizure rate and the patients receiving placebo experienced a median change of -0.2 in the 4-week combined partial seizure rates.

Changes in Combined Partial Seizure Rate (ITT)

Dose Group	N	Median 4-Week Seizure Rates During		Median Change from Baseline	P-Value
		Baseline	Experiment		
Placebo	91	10.9	11.9	-0.2	
TGB 32 mg & 56 mg Combined	143	12	8.9	-2.9	<0.001*

* Statistically significant when compared to placebo

The treatment comparison favored the combined tiagabine 32 mg and 56 mg group with a statistically significant difference ($p < 0.001$).

B. Percent Change (25 and 50% Reduction in Seizures Comparing Placebo to 32 and 56 mg Dose Groups

When the 4-week combined partial seizure rate changes were expressed as a percent reduction from Baseline , the treatment comparison also favored the combined tiagabine 32 mg and 56 mg groups : 35 patients (24%) in the 32 mg and 56 mg combined group experienced 50% or greater seizure rate reduction as compared to four patients (4%) in the placebo group., $p < 0.001$). The 25% and 50% reduction in the 4-week combined partial seizure rates from baseline are presented in the following table.

Number and Proportion of Patients With at Least 25% or 50% Reduction in 4-week Combined Partial Seizure Rates (ITT)

	Placebo N = 91	Tiagabine 32 mg & 56 mg N = 143	P-Value
25% reduction	23 (25%)	79 (55%)	<0.001*
50% reduction	4 (4%)	35 (24%)	<0.001*

* Statistically significant when compared to placebo.

The proportion of patients experiencing worsening in combined partial seizure rates was 28% (40/143) for the combined 32 mg and 56 mg group, and 46% (42/91) for the placebo group using the ITT dataset. The following table shows the distribution of percent reduction in all partial seizures from baseline for the placebo compared to the combined 32 and 56 mg dose groups.

Sponsor's Results : Comparison of %Reduction in 4-week Seizure Rates
Placebo v. Tiagabine (32 and 56 mg combined)
Intent-to-treat Dataset
Seizure type=all Partial

		Patient Distribution of % Reduction					
Rx	N	Increased Seizures	0-24%	25-49%	50-74%	>75%	Median
Placebo	91	42 (46%)	26 (29%)	19 (21%)	4 (4%)	0	2.6
Tiagabine 32/56	143	40 (28%)	24 (17%)	44 (31%)	23 (16%)	12 (8%)	27.5

This demonstrates that a small group of patients (75% improvement by 8% in the combined treatment groups) had what might be considered a clinically significant response in the treatment groups compared to the placebo group.

The required subgroup analyses showed similar results as were seen for the combined partial seizures. The effects of tiagabine on the combined partial seizures were consistent regardless of patient's gender, age, weight, and use of single concomitant AED.

C. Dose Response Analysis: Change from Baseline in the 4 Week Seizure Rate

Dose response analyses were also performed for all partial seizures combined. During the Experiment al Period, patients receiving higher doses experienced a greater decrease in seizure rates. This effect was statistically significant for the 32 and 56 mg treatment groups when each was compared to placebo. The difference was not statistically significant when tiagabine 16 mg was compared to placebo (p = 0.237). A summary of reduction in seizure rate and comparison by treatment group is listed in the following table.

Sponsor's Results : Median 4-Week Combined Partial Seizure Rates and Changes

Dose Group	N	Baseline Period	Experiment Period	Change	P-Value
Placebo	90	10.8	11.7	-0.3	-
Tiagabine 16 mg	61	10.5	8.7	-1.2	0.237
Tiagabine 32 mg	88	12.6	10.6	-2.7	0.018*
Tiagabine 56 mg	55	10.5	7.8	-3.3	<0.001*

* Statistically significant when compared to placebo.

When tiagabine 56 mg dose group was compared to 16 mg the difference was statistically significant (p = 0.045). However, the differences were not statistically significant when the tiagabine 32 mg group was compared to 16 mg (p = 0.574) and tiagabine 56 mg was compared to 32 mg dose group (p = 0.212).

D. Dose Response Analysis of Percent Change

When the 4-week combined partial seizure rates were expressed as patients achieving ≥

25 or ≥ 50 percent reduction the proportion of tiagabine patients achieving the specified percent-reduction were favored when compared to placebo. The number of patients with 25% or more reduction and 50% or more reduction are summarized in the next table . These achieved statistical significance for the 32 and 56 mg groups compared to placebo.

Sponsor's Results : Median Changes in 4-week Combined Partial Seizure Rates by Percent Reduction

Treatment	N	Median	Patients with reduction of			
			>=25%	P-value	>=50%	P-value
Placebo	90	4.2	23 (26%)		4 (4%)	
Tiagabine 16 mg	61	11.7	19 (31%)	0.492	6 (10%)	0.210
Tiagabine 32 mg	86	23.5	42 (49%)	0.002*	17 (20%)	0.003*
Tiagabine 56 mg	55	37.0	35 (64%)	<0.001*	17 (31%)	<0.001*

* Statistically significant when compared with place

Only the 32 and 56 mg dose groups, however, demonstrated a statistically significant difference.

(3) SECONDARY GENERALIZED SEIZURES

A. CHANGE FROM BASELINE IN 4-WEEK SEIZURE RATE, COMPARING PLACEBO TO THE COMBINED 32 AND 56 MG DOSE GROUPS

An analysis of the change in 4-week seizure rates of "secondarily" generalized seizures was conducted. The protocol described this as an analysis of "partial complex seizures evolving to generalized tonic clonic seizures" . In actuality the analysis was much broader encompassing all partial onset seizures which evolved to GTC as well as GTC which were presumed to have had a partial onset. This was quite different from the original proposal.

In this analysis, only patients who experienced generalized tonic clonic seizures in baseline were included. Patients who experienced secondary generalization only after initiation of treatment were not included in this analysis. The sponsor provided no rationale for excluding these patients. There were 32 patients in the placebo group who experienced secondary generalized seizures during baseline and 50 patients in the tiagabine 32/56 mg group. If patients who had experienced generalized tonic clonic seizures during treatment had been included in this analysis, the N's would have been 35 and 63 for the placebo and combined treatment groups respectively[1].
The sponsor performed an analysis of change in 4 week generalized seizure rates for the groups in question, but did not consider the effect of overall reduction of partial seizures on the expression of secondary generalization in the treatment phase. The sponsor's

[1]Fifteen patients without secondarily generalized tonic-clonic seizures during Baseline Phase reported secondarily generalized tonic-clonic seizures during the Experiment Period. Of these 15 patients, three were receiving placebo (Patients 11413, 11701, 11805), four received tiagabine 16 mg (Patients 11604, 11909, 11808, 10506), five were receiving tiagabine 32 mg (Patients 11408, 11302, 12014, 11804, 10725) and three were receiving tiagabine 56 mg (10903, 12202, 10505). All of these patients had a history of experiencing secondarily generalized tonic-clonic seizures before starting the study.

results on face value are as follows:

Sponsor's Results : Comparison of Change in 4-week Seizure rates
Placebo v. 32 and 56 mg groups combined
Intent -to - treat Dataset
Secondary Generalized TC

	Placebo N= 32			Tiagabine 32/56 mg Combined Groups N= 50		
Variable	Baseline	Exp Phase	Change	Baseline	Exp Phase	Change
Mean	4.7	5.6	0.9	4.7	3.9	-0.8
SD	8.84	13.34	5.00	7.83	7.96	2.35
Median	2.1	1.8	-0.2	2.0	- 1.1	-0.5

Test of treatment Effect

Analysis Method	p-values
†Nonparametric	0.03
Parametric	0.036

†vanElteren test

The difference that is seen between the two dosage groups is statistically significant but clinically is based on a difference of merely less than one seizure per month. Because this analysis did not take into consideration those patients who did not have generalized tonic clonic seizures during baseline and because it did not incorporate the overall reduction in partial onset seizures it is incomplete. More will be said about this in summary.

B. Percent Change (25 and 50% reduction in seizures comparing placebo to 32 and 56 mg dose groups)

As before an analysis of 25% and 50% reduction in seizures was explored, comparing the placebo group with the combined 32/56mg treatment groups. The results are shown in the next table.

Sponsor's Results : Comparison of %Reduction in 4-week Seizure Rates
Placebo v. Tiagabine (32 and 56 mg combined)
Intent-to-treat Dataset
Seizure type=Partial Evolving to Generalized TC

—Patients with—			
25% or more reduction		50% or more reduction	
Portion (%)	p-value	Portion (%)	p-value
13/32 (41%)	0.174	10/32 (31%)	0.353
29/50 (58%)		22/32 (44%)	

The 25 and 50 percent reduction in secondary generalized seizures by the sponsor analysis does not appear to be statistically significantly greater in the combined treatment group than in the placebo group. The distribution of percent reduction of this seizure type is shown in the table below.

COMPARISON OF %REDUCTION IN 4-WEEK SEIZURE RATES
PLACEBO V. TIAGABINE (32 AND 56 MG COMBINED)
INTENT-TO-TREAT DATASET
SEIZURE TYPE=SECONDARY GENERALIZED TC

		PATIENT DISTRIBUTION OF % REDUCTION					
Rx	N	INCR SEIZURES	0-24%	25-49%	50-74%	75-100%	MEDIAN
PLACEBO	32	13(40%)	6(19%)	3(9%)	3(9%)	7(22%)	8.6
TIAGABINE 32/56	50	13(26%)	8(16%)	7(14%)	6(12%)	16(32%)	34.2

C. DOSE RESPONSE ANALYSIS: CHANGE FROM BASELINE IN THE 4-WEEK SEIZURE RATE

A dose-response analysis of **secondarily generalized tonic clonic seizures** for all dose groups including the 16 mg dose group was also performed. Only patients who experienced secondarily generalized tonic clonic seizures (and those that were *presumed* secondarily generalized) during Baseline were included in this analysis. Both parametric and nonparametric methods of analysis were used. The results are shown on the next table.

Comparison of Change in 4-week Seizure rates
Dose Response Analysis and all Pairwise Comparisons of Treatments
Intent to Treat Dataset
Seizure Type: Secondary Generalized TC

	Placebo N=32			Tiagabine 16 N=24			Tiagabine 32 N=27			Tiagabine 56 N=23		
Variable	BL	Exp	Chg	BL	Exp	Chang	BL	Exper	Chg	BL	Exp	Chg
Mean	4.7	5.6	0.9	2.7	1.4	-1.2	6.0	5.4	-0.6	3.1	2.1	-.9
(SD)	8.84	13.34	5.00	2.87	1.67	2.06	9.73	10.29	2.29	4.47	3.17	2.46
Median	2.1	1.8	-0.2	1.8	0.8	-0.6	2.8	1.3	-0.5	1.7	1.0	-0.7

P-values from pairwise comparisons of seizure rate changes

Analysis	Dose Response p-value#	16 mg v Pbo.	32 mg v. Pbo	56 mg. v. Pbo	32mg v.16 mg	56 mg v.16 mg	56 mg v.32 mg
Nonparametric	0.065	0.015	0.55	0.82	0.533	0.718	0.992
Parametric	0.072	0.008	0.133	0.03	0.235	0.665	0.465

Ironically none of the individual dosage groups were statistically significantly different from placebo except for the 16 mg group and the difference between these groups in terms of seizure reduction was clinically not significant (0.4 sz/month).

D. DOSE RESPONSE ANALYSIS OF PERCENT CHANGE

The table below incorporates the results of both efficacy variables, median 4-week change in seizure rate and 50% Reduction (Percent Change) in the dose response analysis. Neither analysis is capable of showing a significant dose response.

SECONDARILY GENERALIZED TONIC-CLONIC SEIZURES ANALYSES INCLUDING ALL FOUR TREATMENT GROUPS

Dose Group	N	Median 4-Week Seizure Rate During		Median Change from Baseline	P-Value	Patients Achieving ≥50% Reduction	
		Baseline Period	Experiment Period			No. (%) of Patients	P-Value
Placebo	32	2.1	1.8	-0.2		10 (31%)	
Tiagabine 16 mg	24	1.8	0.8	-0.6	0.015*	13 (54%)	0.105
Tiagabine 32 mg	27	2.8	1.3	-0.5	0.055	11 (41%)	0.586
Tiagabine 56 mg	23	1.7	1	-0.7	0.082	11 (48%)	0.266

* Statistically significant when compared to placebo.

None of the analyses of secondary generalization took into account the overall reduction in partial onset seizures with treatment. This will be discussed in the next sections, FDA analysis and Discussion.

OTHER ANALYSES:

WITHDRAWAL ANALYSIS

Utilizing the fact that all patients in this study were tapered off their medications during the termination phase while the blind was maintained, it was appropriate for the sponsor to have evaluated this phase for the presence of possible withdrawal seizures. The sponsor performed a dose response analysis to examine the withdrawal to study drug among patients who entered the discontinuation period. The comparisons in 4-week seizure rates of all seizure types were made between baseline and discontinuation phase.The table below summarizes the sponsor's findings for CPS, SPS, All partial seizures and secondarily generalized seizures.

SPONSOR'S RESULTS: CHANGE IN 4 WEEK SEIZURE RATES FROM BASELINE PHASE TO THE DISCONTINUATION PERIOD (ITT)

Dose Groups	Seizure Types							
	Complex Partial		Simple Partial		Secondarily Generalized Tonic-Clonic		Combined Partial	
	N	Median Change	N	Median Change	N	Median Change	N	Median Change
Placebo	84	-1.3	46	-1.9	29	-0.3	84	-1.4
Tiagabine 16 mg	58	1.0	36	-1.6	22	-0.3	58	-0.1
Tiagabine 32 mg	79	-1.3	44	-1.6	26	-0.4	79	-2.0
Tiagabine 56 mg	47	-0.5	28	-0.5	21	-0.3	47	-1.0
P-value (Dose Response)		0.452		0.997		0.222		0.86

The sponsor asserts that during the Discontinuation Period, no statistically significant difference was seen in 4-week rates of any seizure type, and that there was no evidence that withdrawal seizures occurred in the Discontinuation Period. When each of tiagabine 16 mg, 32 mg and 56 mg dose groups were compared with the placebo group, none of the pairwise comparisons showed statistically significant differences. However, patients who experienced secondary generalized seizures and simple partial seizures during withdrawal were not counted unless that seizure type was also present during baseline. Therefore patients who potentially had worsening of their seizures were not included. It will be recommended that these data be reanalyzed utilizing these patients who were

previously omitted. There are still some problems with the fact that the patients who were prematurely discontinued and who did not enter a formal termination phase were also not included in the analysis. The sponsor has identified these patients and provided a summary of these patients. Changes in 4-week seizure rates from the Baseline Phase to the Follow-up visit were calculated to determine whether there was any evidence that withdrawal seizures occurred upon abrupt discontinuation of the study drug. Because of the small number of patients in each treatment group, treatment- group comparisons were not performed, and the results should be interpreted cautiously. The table below shows the median changes in 4-week seizure rates during the Experiment Period when compared to Baseline 4-week seizure rates:

Sponsor's Results: 4-week Seizure Rate Changes for Patients who Prematurely Discontinued

	Seizure Types							
Dose Groups	Complex Partial		Simple Partial		Secondarily Generalized Tonic-Clonic		Combined Partial	
Placebo	5	0.0	2	-2.1	2	-4.0	5	-0.7
Tiagabine 16 mg	2	0.4	1	-5.7	2	2.0	2	0.4
Tiagabine 32 mg	6	-5.8	4	-0.7	2	0.2	6	-5.8
Tiagabine 56 mg	8	1.4	3	-3.3	2	0.4	8	1.4

Some consideration might be given to an analysis of all randomized patients using whatever data are available. The sponsor points out that there were not episodes of status epilepticus following abrupt withdrawal.

SECTION 7.2.1.4 FDA ANALYSIS

The sponsor's selection of complex partial seizures rather than all partial onset seizures as the primary focus in this study is somewhat restrictive. Furthermore, the Sponsor's claim for this drug is for [all] partial onset seizures, not merely for complex partial seizures. Indeed a more conventional approach in epilepsy studies has been the evaluation of all partial onset seizures with a secondary look at particular seizure types with an analysis of other seizure types in an effort to ascertain that a particular subgroup of seizures is not made worse by treatment, as one questions whether overall seizure control is achieved at the expense of a particular seizure type. Some sponsors choose to evaluate this with endpoints such as the appearance of new seizure types or increase or change in seizure type. This sponsor has actually done this but with an emphasis on a particular subgroup of the whole rather than on the whole. Rather than delve into areas which do not directly support this claim this review will focus on (1) the planned primary analyses and (2) the analyses which directly support the sponsor's claim. This will include the following:

I. The Sponsor's Primary Prospective Endpoints
   A. Partial Complex Seizures (Primary analyses, planned)
II. Endpoints Relevant to Requested Labeling Claims
   A. Partial Onset Seizures (All Partial)

B.Secondarily Generalized Seizures
C.Withdrawal Seizures

Before discussing the specific analyses of the seizure types in question, the seizure counts which were utilized for computing the efficacy variables were further confirmed with the sponsor. In those instances where seizure counts cannot be verified or data does not exist, an alternative approach will be discussed. The most problematic cases are those of status epilepticus. In these cases the SAS data sets provided by the sponsor either have no seizure counts or the entire episode of seizure activity was weighted as one seizure. In cases where no counts were supplied a rank analysis was performed assigning to those patients an extreme value consistent with a very high seizure count. Because the sponsor's "1+ " Rule was not prospectively identified, and because it made no clinical sense it was not pursued. In one case where an episode of *status epilepticus* presumed to be SECPTC rather than SECP an additional adjustment was made to the analysis of Partial Seizures with secondary generalization. No adjustments were made for estimated seizure counts within flurries, since no systematic bias was noted and it appeared that in nearly every case efforts were made to accurately describe the events numerically. No compensation was made for patients who had alterations in their concomitant medications during the trial, since these were equally distributed across all treatment groups and phases of the study.

The Sponsor's Primary Prospective Endpoints
A.Partial Complex Seizures (Primary analyses, planned)
Change in 4-week seizure rate from baseline to treatment--Comparing the Placebo to the Combined 32 and 56 mg dose groups

This parameter was evaluated critically as the primary prospective endpoint identified by the sponsor for this study. The problems with the primary data have been discussed. It was decided that at least in the case of status epilepticus it would be important to determine the effect of this method of estimating seizures on the outcome of the primary measure of efficacy.

A sensitivity analysis was performed to assess the degree of dependence of the analyses on the method for estimating episodes of SE, which clearly underestimated the actual number of seizures representative of such an event. With this in mind, patients were assigned seizure rates using the following paradigm. Defining 'Baseline-to-EP change in four-week seizure frequency' as the EP rate minus Baseline rate, a negative change indicates a reduction in four-week seizure frequency from Baseline, a positive change an increase in four-week seizure frequency from Baseline.

- Patients experiencing at least one episode of SE during Baseline but none during the EP were, considered to be highly responsive to the test drug. They were assigned an arbitrarily large (i.e., in absolute value) negative change.
- Patients experiencing at least one episode of SE during the EP but none during Baseline were considered to be highly unresponsive to the test drug. They were

assigned an arbitrarily large positive change.

- Patients experiencing one or more episodes of SE during Baseline and the EP were assigned a large negative change if placebo-treated or a large positive change if tiagabine-treated (worst-case analysis).
- Patients experiencing one or more episodes of SE during the Termination Phase only (i.e., after completion of the EP) were omitted from analyses.

The table below shows the number of patients falling into the first three categories.

PATIENTS REPORTED WITH STATUS EPILEPTICUS EPISODES DURING STUDY M91-603

Baseline Only		Experimental Phase Only		Baseline and Experimental Phase	
Type/No	Rx	Type/No	Rx	Type/No	Rx
SECP/ 1	32 mg	SECP/ 1	56 mg	unk/ 1	56 mg
SEGTC/1	56 mg				

Sensitivity analyses of CPS included only the SECP seizure type. Dr. Sahlroot performed sensitivity analyses using the sponsor's weighted and unweighted vanElteren test on the Baseline to EP change in 4-week seizure rate for the combined 32 and 56 mg combined treatment groups compared with placebo. The results were p-values of .004 for the weighted and 0.011 for the unweighted analysis. The differences were very small and the sponsor's values remain statistically significant.

Comparison of p-values from Sensitivity Analysis with Sponsor's p-values: Complex Partial Seizures (Corrected for Status Epilepticus) Intent to Treat

Treatment comparison	VanElteren p-values	
	Weighted	NonWeighted
Sensitivity Analysis	.004	.011
Sponsor's Analysis	.007	.018

Looking at the pairwise comparisons for the CPS using the primary outcome measure , none of the p-values was significant ($p \geq .028$, weighted vanElteren test) after Dunnett's correction for multiple comparisons with a control [1]. (please refer to Dr.Sahlroot's review).

[1]For two treated groups vs. control , $\alpha = .027$, for three treated groups vs a control, $\alpha = .019$

II. Endpoints Relevant to Requested Labeling Claims

A. Partial Onset Seizures (All Partial) CHANGE FROM BASELINE IN THE 4 WEEK SEIZURE RATE (PAIRWISE COMPARISONS OF INDIVIDUAL DOSE GROUPS WITH PLACEBO)

Because the sponsor desires labeling for patients with [all] partial onset seizures, this analysis was evaluated critically. Evaluation of this group is possible without compromising the original randomization, since partial complex seizures are a subset of all partial onset seizures and all patients in this study had partial complex seizures.

A sensitivity analysis was also performed using each type of SE listed by each of the 4 patients (including the patient with unstated SE and the other patient with SEGTC. Again the results remain highly statistically significant.

Comparison of p-values from Sensitivity Analysis with Sponsor's p-values: All Partial Onset Seizures (Corrected for Status Epilepticus)
Intent to Treat

Treatment comparison	VanElteren p-values	
	Weighted	NonWeighted
Sensitivity Analysis	.0007	.001
Sponsor's Analysis	<.001	<.001

Also, pairwise analyses of individual doses were examined in an effort to determine what the optimum dose should be. Looking at the pairwise comparisons for the POS using the primary outcome measure , only the 32 mg group was statistically significantly superior to placebo, (p=.018, weighted vanElteren test).

B. Secondarily Generalized Seizures

There are 4 main problems associated with he sponsor's analysis of secondary generalized seizures: 1) arbitrary assignment of all GTC seizures as secondarily generalized seizures (6 patients) 2) patients with secondarily generalization in the context of status not identified and counts not provided 3) omission of patients with 2° generalized seizure onset during treatment from the analysis and 4) failure to take into account the reduction in overall partial onset seizure rate into the equation of reduction in 2°generalized seizures. Of less importance is the sponsor's prospective plan to analyze patients with complex partial onset secondarily generalized seizures in contrast with the actual analysis which looked at all partial onset secondary generalized seizures.

As noted in the description of t he study the sponsor made the assumption that all generalized tonic clonic seizures were secondarily generalized. It is often postulated, perhaps reasonably so that when patients with predominantly partial onset seizures experience a generalized seizure the "partial seizure" from which these seizures derive may be simply unnoticed. Or, it may be argued equally, that they are what they appear to be. Short of running an EEG at the time of onset, there is no certainty. The firm has taken a stand on this issue, and whether correct or not, the number of patients for whom this assumption was made was indeed small, represented across all treatment groups and all periods, and does not appear to represent bias. In an effort to justify the sponsor's assumption, a look at the neurologic history, etiologic diagnosis was investigated for these patients. Unfortunately, the sponsor provided little of the necessary material to review in this regard. The other seizure types experienced by these patients were, indeed exclusively partial onset, and did not include other generalized seizure types.

Etiologic diagnoses were not provided in the many volumes of materials submitted, however from the medical histories that were submitted, some insight into the spectrum of disease could be gleaned patients, for example, with tuberose sclerosis, may have both focal and generalized manifestations of their disease, patients with Lennox Gastaut (for which the etiologies are numerous) may have both focal and generalized manifestations of their disease. There were patients who fell into these categories. The seizures reported in this study were, it is certain, largely partial onset. However there is no question that among these were patients who experienced truly generalized seizures as well. Cases in point include thirteen patients who manifested myoclonic, akinetic, tonic and/or absence seizures in addition to the partial onset seizures. These were coded as such-- recognized as generalized seizures. However six patients who had tonic clonic convulsions with no apparent focal onset, were treated differently. In other words this convention was not used for all generalized seizures--- only generalized tonic/clonic seizures were counted as secondary generalized seizures.

While there were only six examples that could be found of patients about whom this assumption was made and while there did appear to be some basis in these cases for making that assumption, it would not be unreasonable to see how this assumption affected the outcome of the study. These will be taken into account in the final analysis.

The second problem with the sponsor's evaluation of secondary generalized tonic clonic seizures arises when the patients who exhibited status epilepticus , including those which were hospitalized and treated, were not identified as having secondary generalization when they probably did. The sponsor was unable to determine in __ cases whether the patients developed secondary generalization in the course of their status epilepticus.

Thirdly, there were 15 patients who developed secondary generalized seizures during treatment who were not included in the analysis because they did not have this seizure type during baseline. Such an exclusion could bias the results in favor of treatment, since

the majority of these patients who were excluded were on drug when they experienced secondary generalization. This will be taken into account in the final analysis.

Fourth, the nature of the analysis should also be discussed here. The sponsor appears to have done a simple comparison of change in absolute secondarily generalized seizure rates between baseline and treatment for placebo and treatment groups. The rate of secondary generalization is in part a function of the overall rate of partial onset seizures, since they evolve from partial seizures. The sponsor's analysis should reflect a separation of the effects of secondary generalization from the overall effect on decreased partial onset seizures. The sponsor should show a decreased rate of generalization, given a partial seizure, after tiagabine treatment compared to placebo. In such an analysis, for example, the proportion o f partial seizures suffered could be calculated for the baseline period and the treatment period for each patient. Then the proportion of patients under each treatment arm exhibiting a decrease in the proportion of partial seizures with secondary generalization between baseline and treatment would be calculated. Efficacy would be demonstrated if the proportion of secondarily generalized seizures was significantly lower in the tiagabine treated patients than in the placebo group.

The analysis of Secondary Generalization will be deferred for sponsor to reevaluate.

Withdrawal:

Withdrawal seizures have been alluded to in the sponsor's proposed labeling. Since this trial does provide the capability to evaluate in some measure, seizures occurring in the setting of tiagabine withdrawal, every effort should be made to do this accurately. Such an analysis should include any seizure that occurs during baseline and during the withdrawal phase. The sponsor should undertake to reevaluate this issue with the intent-to - treat dataset, for all partial seizures and for secondarily generalized seizures including patients who had onset of secondarily generalized seizures during withdrawal.The analysis of withdrawal seizures will be deferred for sponsor to reevaluate

Summary: In summary , this study compared three total daily doses of tiagabine HCl with placebo in a parallel group add-on design. The results were positive for the primary prospective outcome measure, Change from Baseline to Experimental Period in the 4-week Complex Partial Seizure Rate) for the combined 32 and 56 mg dosage groups compared to placebo. The same was true for "all Partial seizures Combined" (POS). Sensitivity analyses performed due to inadequate seizure counts during episodes of status epilepticus did not alter the results of the primary comparisons for either complex partial seizures or all partial onset seizures. For the desired endpoint requested for labeling 32 mg (given on a QID schedule) was an effective dose for the adjunctive treatment of partial onset seizures. No statement can be made about the efficacy of this product in the treatment of partial onset generalized tonic clonic seizures until the appropriate analyses are performed.

SECTION 7.2.2 STUDY M91-605

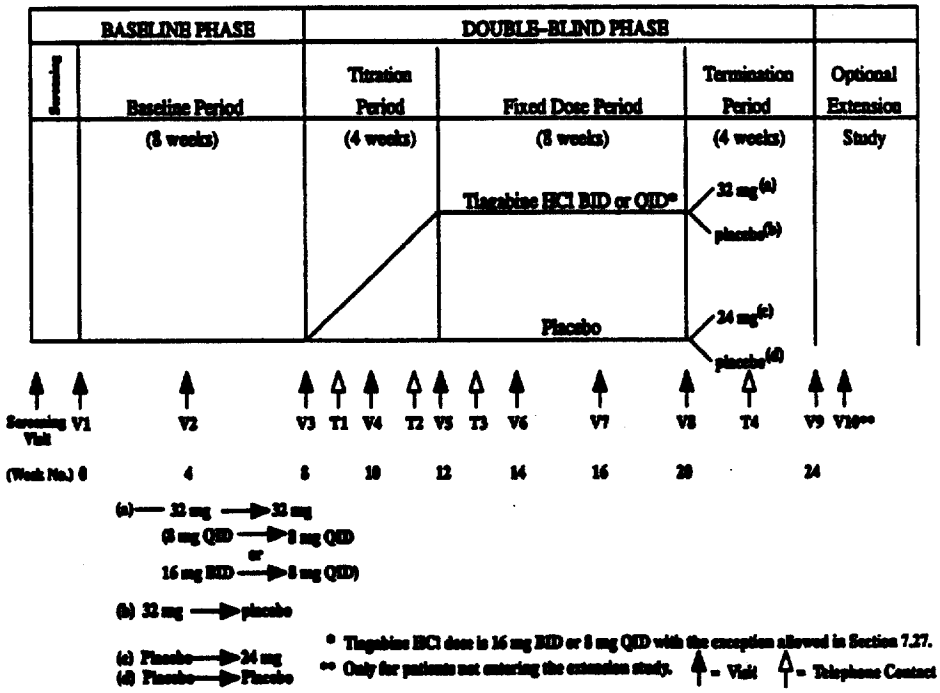
SECTION 7.2.2.1 PROTOCOL SYNOPSIS

TITLE: Safety and efficacy of BID and QID Dosing with Tiagabine HCl versus placebo as adjunctive Treatment for Partial Seizures

OBJECTIVES: to determine the safety and efficacy of BID and QID dosing with tiagabine HCl as add-on therapy for complex partial seizures.

STUDY DESIGN : a multicenter (26) randomized, double-blind, placebo-controlled, parallel group, add-on AED trial of two different regimens of Tiagabine(8 mg QID and 16 mg BID).

STUDY SCHEMATIC:



PROTOCOL

STUDY SCHEDULE: The study has an eight-week Baseline Phase, a four-week Titration Period, an eight-week Fixed-Dose Period, and a four-week Termination Period. The Titration Period and the Fixed-Dose Period combined are defined as the Experiment Period. Eligible patients carry the diagnosis of complex partial seizures, have focal EEG abnormalities and are maintained on a stable regimen of one to three antiepileptic drugs.

Patients entering the Double-Blind Phase are randomized to receive either placebo four times a day, 16 mg tiagabine HCl two times a day and placebo two times a day, or 8 mg

tiagabine HCl four times a day. During the four-week Titration Period, the dose of tiagabine HCl is increased in three steps to the final dosage level. The dosage is constant during the eight-week Fixed-Dose Period. Randomization to these treatment groups is done according to a 1:1:1 ratio in blocks of six patients, respectively, for each of the 26 centers.

Study Drug Titration Schedule					
Randomization Ratio	Group	Titration Period			
		Week 1	Week 2	Week 3	Week 4
1	16 mg BID	4 mg BID	8 mg BID	12 mg BID	16 mg BID
1	8 mg QID	2 mg QID	4 mg QID	6 mg QID	8 mg QID
1	Placebo	Placebo			

ENROLLMENT

key inclusion criteria

- Patients are required to have a diagnosis of **partial seizure with or without secondary generalization. The diagnosis must include complex partial seizures,** supported by observed ictal events consistent with complex partial seizures and documented by reliable observers such as family members, friends, or medical personnel. The diagnosis must also include one of the following: 1) an ictal electroencephalogram demonstrating a focal or localized ictal pattern in a patient clinically having a complex partial seizure, and/or 2) an interictal EEG demonstrating focal abnormalities (spikes, sharp waves, slowing) consistent with complex partial seizures.
- During the eight-week period preceding the Screening Visit, the patient must experience at least six complex partial seizures, occurring alone or in combination with any other seizure type. At least one complex partial seizure must occur within each of the two four-week segments within the eight-week period.
- Stable regimen of between one and three of the following AEDs: phenytoin, carbamazepine, valproate, phenobarbital, or primidone. Valproate could be used, but only in combination with one of the above hepatic enzyme-inducing AEDs.

Key exclusion criteria

- pseudoseizures.
- Active CNS infection, demyelinating disease, degenerative neurological disease, or any progressive CNS disease or those requiring frequent medication changes;
- Clinically significant psychiatric illness, psychological or behavioral problems, or history of psychosis severe enough to require hospitalization.
- A medical disease, either currently or within the previous three months, manifesting with signs and symptoms that could confound interpretation of

the study results.

- Substance abuse
- Clinically relevant laboratory abnormality
- Administration of an investigational drug within 30 days prior to the screening visit.
- Pregnancy or lactation

EFFICACY VARIABLES

PRIMARY OUTCOME MEASURES

The primary efficacy variable for this study for comparing treatment groups is the reduction from Baseline to the Experimental Phase (Combined interval of Titration Period and Fixed Dose Period) in 4-week **complex partial seizure rates.** Complex partial seizures occurring alone or in combination with other seizure types will be counted.

SEIZURE RATE CALCULATION

The baseline seizure rate 4-week seizure rate is calculated as the total number of complex partial seizures reported during the Baseline Phase multiplied by the ratio of 28 days to the actual number of days in the baseline period.

The Experiment Period 4-week complex partial seizure rate will be calculated as the total number of complex seizures reported during the Experiment Period Multiplied by the ratio of 28 days to the actual number of days in the Experiment Period. The actual number of days in the Experiment Period is defined as the duration from the days of randomization to the last day of treatment in the Experiment Period. The last day of treatment in the Experiment Period of the Study is defined as the date of the last seizure evaluation or the date of the last dose of treatment in the Experiment Period, whichever is earlier.

Analysis method:

For the primary outcome measure, the Van Elteren test, a nonparametric two-sample test to the multicenter case , is the primary method used for pairwise comparisons between treatment groups.

SECONDARY ANALYSES

Subset analyses are performed considering complex partial seizures that progress to secondarily generalized tonic-clonic seizures and for simple partial seizures. The analysis method for these subset analyses is pairwise treatment group comparisons using the Wilcoxon two-sample test ignoring center effects.

7.2.2.2 STUDY CONDUCT

ENROLLMENT

At total of 318 patients entered the Double-Blind Phase, 107, 106, and 105 patients were randomized to receive placebo, tiagabine 16 mg BID, and tiagabine 8 mg QID, respectively. A total of 271 (85%) patients completed the study, and 47 (15%) patients were prematurely discontinued from the study during the Double-Blind Phase. Twenty-nine (9%) patients discontinued during the Titration Period, fifteen (5%) patients discontinued during the Fixed-Dose Period, and three (1%) patients prematurely discontinued during the Termination Period. Patient disposition is summarized below.

Patient Disposition

	Placebo	Tiagabine		Total
		16 mg BID	8 mg QID	
Randomized	107	106	105	318
Completed	97 (91%)	90 (85%)	84 (80%)	271 (85%)
Prematurely Discontinued	10 (9%)	16 (15%)	21 (20%)	47 (15%)

Of those who prematurely discontinued during the Double-Blind Phase, ten patients were receiving placebo, 16 were receiving tiagabine 16 mg BID, and 21 were receiving tiagabine 8 mg QID.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

A summary of patient demographics for sex, race, age, weight, height, years with epilepsy, and number of AEDs ever taken for all randomized patients by treatment group is presented in the table below. There were no statistically significant differences among these groups at baseline.

Summary of Patient Demographics

	Placebo N=107	16 mg BID N=106	4 mg QID N=105	Overall N=318	P-Values*
Gender					
Female	53 (50%)	41(39%)	45 (43%)	139(44%)	.277
Male	54(50%)	65(61%)	60(57%)	179(56%)	
Age					
Mean(SD)	35.3(12.61)	33.4 (13.38)	32.6(11.36)	33.8(12.49)	
Median	34.0	32	32	33	.278
Min-max	13-71	12-67	12-66	12-71	
Median Number of AEDs ever taken	6	6	6	6	.129
Min-max	2-20	1-14	2-20	10-20	
Median years with epilepsy	24	17.9	22	22.8	.202
min-max	2.2-62.4	2.7-53.9	2-20	.9-62.4	
Race					
Caucasian	92(86%)	89(84%)	94(90%)	275(86%)	.760
Black	8(7%)	10(9%)	5(5%)	23(7%)	
Other (Hispanic, Asian, etc.)	8(7%)	7(7%)	6(6%)	20(6%)	

*For sex and race, from Fisher's exact test; for years with epilepsy, from Kruskall-Wallis Test, for Age and Number of AEDS, from One-way ANOVA

PATIENT CHARACTERISTICS

A summary of patient characteristics including epilepsy etiologies, seizure types experienced within the 8-week period prior to Baseline Visit 1 and concomitant AEDs were summarized by the sponsor for each group The most common epilepsy etiologies were idiopathic (52%), trauma (28%),infections (21%), genetic propensity (18%), unknown causes (44%), infections (16%), and ante/perinatal injury (16%). In addition to complex partial seizures, investigators reported that 44% of the patients experienced simple partial seizures and 39% experienced secondarily generalized tonic-clonic seizures within the 8-week period prior to Baseline Visit 1. There were no statistically significant differences between the three groups when compared for each epilepsy etiology and seizure type. Comparisons of concomitant AEDs used by patients within the 8-week period preceding the Baseline did not show any significant differences among

the treatment groups .

Concomitant AEDs
Used by Patients Within 8 Weeks Preceding

Concomitant AED	Placebo N=107 N(%)	Tiagabine 16 mg BID N=106 N(%)	Tiagabine 8 mg qid N=105 N(%)	Total N=318 N(%)	P-values (Fishers exact test)
Carbamazepine	72 (67%)	70(66%)	76(72%)	218(69%)	.576
Valproate	38(36%)	45(42%)	39(37%)	122(38%)	.554
Phenytoin	35(33%)	40(38%)	38(36%)	113(36%)	.737
Phenobarbital	11(10%)	5(5%)	10(10%)	26(8%)	.271
Primidone	12(11%)	10(9%)	4(4%)	26(8%)	.116
Chlorazepate	7(7%)	7(7%)	7(7%)	21(7%)	>.999
Acetazolamide	3(3%)	5(5%)	9(9%)	17(5%)	.164

BASELINE PHASE COMPARABILITY IN 4-WEEK SEIZURE RATES

Baseline Phase 4-week seizure rates for each seizure type were tested for any difference among the three treatment groups. No statistically significant differences were observed in any comparison. Median Baseline Phase 4-week seizure rates for all randomized patients by treatment group are summarized in the next table.

Median Baseline 4-Week Seizure Rates

Seizure Types	Placebo	Tiagabine 16mg BID	Tiagabine 8mg QID	P-Values*
Complex Partial				
N	107	106	105	.876
Median	8	8.4	7.9	
Range				
Simple Partial				
N	49	57	42	.973
Median	8	8.5	9.2	
Range				
Secondarily Generalized Tonic-Clonic				
N	37	43	44	.207
Median	3	2	2.5	
Range				
Combined Partial				
N	107	106	105	
Median	10.3	10.5	9.6	.725
Range	1.			

* Overall comparison of all four treatment groups.

STUDY DRUG

Study medication (tiagabine HCl 4 mg, tiagabine HCl 2 mg, and placebo tablets) was used. The daily dose was 16 tablets, 4 tablets to be taken four times a day.

PROTOCOL VIOLATIONS

PATIENTS WHO HAD THE STUDY BLIND BROKEN

Only one patient had study blind broken during the trial. This was done in reaction to a serious adverse event which occurred one week after starting on tiagabine (severe thrombocytopenia).

CONCOMITANT AEDS

Twenty patients (6%) of the patients enrolled in this study had changes in their concomitant AEDs one or more times during the study. These changes were made

either because of perceived toxicity (adverse events) or because of the need for additional seizure control not provided by their regimen. These changes were spread across all three treatment groups and occurred in both phases of the study. They are summarized in the table that follows.

PATIENTS WITH CHANGE IN DAILY DOSE OF CONCOMITANT AEDS

	Baseline AED Increased	Experimental AED Decreased	Baseline Decr	Experimental Increase
Placebo	1	0	3	1
TGB 16 mg BID	4	3	2	0
TGB 8 mg QID	4	3	3	2
Total	9	6	8	3

While many of these changes were ongoing (permanent) changes in regimen that could have potentially have affected the outcome of the study, the timing of these changes would most likely have resulted in a type 2 error. Note that no placebo patients had AED reduction during treatment and only two tiagabine patients had drugs increased during the experimental phase.

PLACEBO PATIENTS WHO RECEIVED TIAGABINE

Twenty four placebo patients (22%) in this study had documented Tiagabine levels during the experimental phase. This would be expected to result in a dilution of the drug's effect. The intent to treat analysis will be based on randomization assignment, regardless of this protocol violation.

ADJUSTMENT OF AEDS AND USE OF PRN BENZODIAZEPINES DURING THE STUDY

The practice of making adjustments to AED regimens and use of PRN benzodiazepines to achieve seizure control particularly in the setting of seizure clusters was widespread in this study.The following 21 (6%) patients were formally given leave to use PRN ativan and/or tranxene during the trial for seizures over a certain frequency or number.

Placebo	Tiagabine 16 mg BID	Tiagabine 8 mg QID
10102,10312, 10502,10607, 10805,11016, 11703,12111, 12602	12306,11906, 11009,10109, 10439	10207,10607, 11121,12105, 12107,12302, 10207

An additional 20 patients(6%) had changes in daily dose AED doses for >7 days during baseline or Experimental Phase (many more patients had shorter duration changes in their concomitant antiepileptic medication). These changes were made either for seizure control (bolded) or for adverse events.

Placebo	Tiagabine 16 mg BID	Tiagabine 8 mg QID
12210, 10204, 10804, 12403	10105,11106, 12119,10309, 10211,11809, 10801	10311,11371, 11811, 11117, 11807,11604, 11711,10802, 10409

Close inspection of these changes (increase or decrease) were balanced across periods and treatment assignments and did not appear to result in a systematic error.

PERFORMANCE OF SEIZURE SURGERY DURING THE STUDY

While this only involved one patient, a temporal lobectomy was performed during the Experimental phase of this study. This involved patient 11709 who had been randomized to the 8 mg QID group. During the study the patient was hospitalized for a WADA and Angiogram, had grid electrode placement and temporal lobectomy. While not strictly speaking a protocol violation, the outcome was expected to influence the primary efficacy measure, change in seizure rate from baseline. Data was collected on this patient throughout the study including the presurgical evaluation and until 2 days postop.

PRACTICES NOT DESCRIBED IN THE PROTOCOL WHICH MAY HAVE INFLUENCED THE DATA

COUNTING SEIZURES: GENERALIZED SEIZURES

As in Study M91-603, in the final study report for this trial (not in the protocol or amendments) the sponsor indicates that in counting seizures, and in the final analysis the following assumption was made, "Since all patients included in the study had confirmed partial epilepsy, all generalized seizures were considered partial onset even if there was no clinical description of the seizure beginning focally". As in study 603 there were patients who clearly had a mixture of what would be considered primary generalized seizures (myoclonic, atonic) and partial seizures that this convention may not always be reliable. It was not possible in this study to determine when this convention was invoked, and therefore to assess how appropriately it was used.

COUNTING SEIZURES: *STATUS EPILEPTICUS*

The convention for counting seizures during a seizure flurry or an episode of status epilepticus was not spelled out in the protocol. There were four individuals who experienced status epilepticus in this study of whom it can be said that their seizures were underestimated. They are enumerated in the next table.

Pt ID	Rx	Baseline	Exp phase
12505	TGB 16 mg BID	none	Day 18 SECP. One CP counted. Day 28 Patient taken to the ER and treated with lorazepam. Patient terminated on that day. No mention of SE on that day. No seizures counted.
10204	PBO	none	Day 9: Sz code T should have been SECP. One seizure counted as T. Day 20 SECP counted as 1 CP. Continued in study to day 83
10503	PBO	none	Day 73 Dilantin 1000, Pavulon 1.3 mcg/kg IV for muscle paralysis, valium 5 mg IV for seizure. Listed in seizure counts as SECP "ukn". No value assigned.
12119	TGB 16 mg BID	SEGTC was reported by sponsor This was given the value of 1 seizure	Another episode occurred, in the titration phase not specifically reported in the counts--between 5/7 and 5/13 when patient was said to have been seizure free, there wa s a notation: the patient's medication was held because of status epilepticus (CRF)

OTHER ESTIMATED SEIZURE COUNTS

Other seizure estimates occurred in this study and there were many examples of seizures reported that were not reflected in the data listings. The Sponsor states that at each center patients were instructed to do the best they could at counting the number of seizures in a flurry. While flurries were not identified in the seizure tabulations, one can determine that they probably occurred when the record states "estimate" and when the comments and telephone log indicates that such an episode took place. In some cases it

is difficult to determine whether the patient experienced a flurry or an episode of status.

ESTIMATED SEIZURE COUNTS STUDY M91-605
STATUS EPILEPTICUS/OR FLURRIES

PT ID	TREATMENT	BASELINE	DB PHASE
12505	TGB 16 mg BID	none	Day 18 SECP. One CP counted. Day 28 Patient taken to the ER and treated with lorazepam. Patient terminated on that day.
10204	PBO	none	Day 9: Sz code T should have been SECP. One seizure counted as T. Day 20 SECP counted as 1 CP. Continued in study to day 83
10503	PBO	none	Day 73 Dilantin 1000, Pavulon 1.3 mcg/kg IV for muscle paralysis, valium 5 mg IV for seizure. Listed in seizure counts as SECP "ukn". No value assigned.
12119	TGB 16 mg BID	SEGTC was reported by sponsor This was given the value of 1 seizure	Another episode occurred, in the titration phase not specifically reported in the counts–between 5/7 and 5/13 when patient was said to have been seizure free, there wa s a notation the patient's medication was held because of *status epilepticus* (CRF)
10820	TGB 16 BID	Comments: Patient had approximately 50 CP sz/day *these numbers specifically did not appear on the data sheets*	
10617	Tgb 16 BID		Comments:Patient experienced a flurry of SP and Possibly SPCP in 1 hour. They were unable to actually count these (day 53) Not recorded
11306	Tgb 16 BID		Comment : Patient had 12 seizures over the past weekend (day 61) and suffered 4 cracked ribs. *These do not appear in the data listings*
10307	Tgb 8BID	Medication listings: Day-11 to-12 D5W given for ER visit for seizure flurry. Narcan(same day) given for ER visit for unresponsiveness. *There was only 1 GPGTC recorded for that day*	
11312	Tgb 8 QID	Patient reported to OSU for seizures (day-8) *Counts not recorded*	
12801	Tgb 8 mg BID		Taken to ER on evening –given extra doses of AEDs Could not obtain ER report

In addition there are numerous examples of lost seizure diaries, counts not recorded during hospitalization or other reasons. The estimated seizure counts seen in patients with flurries does not appear to have been handled as carefully in this study as in M91-603. This problem continues to plague antiepileptic drug trials. In this trial, the frequency of flurries was relatively small and there did not appear to be any systematic error in favor of the drug. There were more episodes of inadequate record keeping or inability to quantify these seizures in the drug treated patients, however, these were balanced across baseline and treatment. As in the previous study, the inconsistent assignment of one paradigm for counting seizures in a flurry and a different one for counting seizures in an episode of status should have been corrected. While the

underestimation of seizures in status however, would not be expected to bias the study in favor of the drug, it will be looked at further in FDA results section.

In summary, the conduct of this trial and collection of data was notable for a host of activities which potentially affected the validity of the study. These included administration of drug to placebo patients, adjustment of concomitant AED during the study for the purpose of seizure control, administration of benzodiazepines for improvement in seizure control, seizure surgery for improvement in seizure control, inaccuracies in recording seizures and the use of a paradigm which gives inadequate weight to the seizures in question.

7.2.2.3 SPONSOR'S EFFICACY RESULTS

The sponsor's efficacy results for this study will be summarized in the following format:

(1) PARTIAL COMPLEX SEIZURES
- A.CHANGE FROM BASELINE IN 4-WEEK SEIZURE RATE, COMPARING PLACEBO TO THE 8 MG QID GROUP AND SEPARATELY TO 16 MG BID
- B.PERCENT CHANGE (25 AND 50% REDUCTION IN SEIZURES COMPARING PLACEBO TO HE 8 MG QID GROUP AND SEPARATELY TO 16 MG BID

(2) ALL PARTIAL SEIZURES
- A.CHANGE FROM BASELINE IN 4-WEEK SEIZURE RATE, COMPARING PLACEBO TO THE 8 MG QID GROUP AND SEPARATELY TO 16 MG BID
- B.PERCENT CHANGE (25 AND 50% REDUCTION IN SEIZURES COMPARING PLACEBO TO HE 8 MG QID GROUP AND SEPARATELY TO 16 MG BID

3) SECONDARY GENERALIZED SEIZURES,
- A.CHANGE FROM BASELINE IN 4-WEEK SEIZURE RATE, COMPARING PLACEBO TO THE 8 MG QID GROUP AND SEPARATELY TO 16 MG BID
- B.PERCENT CHANGE (25 AND 50% REDUCTION IN SEIZURES COMPARING PLACEBO TO HE 8 MG QID GROUP AND SEPARATELY TO 16 MG BID

Those analyses which differ from that which was planned will be pointed out.

(I) PARTIAL COMPLEX SEIZURES

A.CHANGE FROM BL IN 4-WEEK SEIZURE RATE: COMPARING PLACEBO TO 32 MG (SEPARATE ANALYSIS FOR 8 MG QID AND 16 MG BID)

The primary prospective efficacy variable for this study was the Change in the 4-week **Complex Partial Seizure Rate** from Baseline to the Experimental Phase (combined interval of Titration Period and Fixed-Dose Period) for each of the 32mg groups (tiagabine 16 mg BID and tiagabine 8 mg QID dose groups)compared to the placebo group. Complex partial seizures occurring alone or in combination with other seizure types were used to calculate this rate.

During the Experiment Period, patients in the tiagabine 16 mg BID and 8 mg QID treatment groups experienced a median decrease from Baseline of a mere 1.6 and 1.2 complex partial seizures per four weeks, respectively, while patients receiving placebo experienced a median decrease of 0.2 complex partial seizures per four weeks when compared to Baseline.

Change in Four-Week Complex Partial Seizure Rates (ITT)

Dose Group	N	Median Four-Week Seizure Rates During Baseline	Median Four-Week Seizure Rates During Experiment	Median Change From Baseline	P-value # vs. placebo
Placebo	105	8.0	8.1	-0.2	
Tiagabine 16 mg BID	106	8.4	6.1	-1.6	0.055
Tiagabine 8 mg QID	103	7.9	5.6	-1.2	0.018

#Van Elteren, nonparametric, weighted analysis

The change in four-week complex partial seizure rates was statistically significant in favor of tiagabine 8 mg QID when compared to placebo for the nonparametric weighted comparison, the prospective method of analysis (p=0.018) but not for tiagabine 16mg BID compared to placebo for the nonparametric weighted comparison (p=0.055).

B. PERCENT CHANGE (25 AND 50% REDUCTION IN SEIZURES COMPARING (NOT A PROSPECTIVE ANALYSIS)

This sponsor's unplanned analysis provides a more tangible comparison between the treatment and placebo and indicates that a response is actually seen in a small group of patients. Continuing to focus on partial complex seizures in the intent-to-treat dataset the sponsor has provided a comparison of the patients with 25% reduction and 50% reduction in both placebo and the 32 mg dose groups.

Number and Proportion of Patients With at Least 25% or 50% Reduction in Four-Week Complex Partial Seizure Rates (ITT)

	Placebo N=105	Tiagabine 16 mg BID N=106	p-Value vs. Placebo	Tiagabine 8 mg QID N=103	p-Value vs. Placebo
≥ 25% reduction	27 (26%)	52 (49%)	< 0.001	44 (43%)	0.006
≥ 50% reduction	10 (10%)	33 (31%)	< 0.001	28 (27%)	0.001

When the changes in four-week complex partial seizure rates were expressed as a percent reduction from Baseline to the Experiment Period, 33 patients (31%) in the tiagabine 16 mg BID group and 28 patients (27%) in the tiagabine 8 mg QID group experienced 50% or greater seizure rate reduction as compared to 10 placebo patients (10%) experiencing 50% or greater seizure rate reduction The difference in the proportion of the patients achieving 50% or more seizure rate reduction was statistically significant in favor of tiagabine 16 mg BID (p<0.001) and tiagabine 8 mg QID (p=0.001) when compared to placebo.

(2) ALL PARTIAL SEIZURES

A. CHANGE FROM BL IN 4-WEEK SEIZURE RATE: COMPARING PLACEBO TO 32 MG (SEPARATE ANALYSIS FOR 8 MG QID AND 16 MG BID)

Analyses for the Change from Baseline to Experimental phase in 4-week seizure rates were performed with all partial seizures combined but as a secondary analysis. Nevertheless they provide the basis for the labeling claim submitted by the sponsor. The analyses of this group use the entire randomized population, taking into consideration the whole spectrum of related seizure types suffered by the population in question, not

just a subset of their seizures. The sponsor pointed out that in this analysis each seizure was counted only once regardless of the number of seizure types occurring in a single event. The calculation for combined partial seizures included:

simple partial,
complex partial,
simple partial evolving to complex partial,
complex partial evolving to secondarily generalized tonic-clonic,
simple partial evolving to complex partial evolving to secondarily generalized tonic-clonic,
simple partial evolving to secondarily generalized tonic-clonic and
partial with secondary generalized tonic-clonic seizures were included.

As noted in the description of clinical trial, patients who experienced a generalized tonic-clonic seizure for whom an antecedent partial seizure was not witnessed were assumed to have had a partial onset secondarily generalized seizure. It is assumed that these were counted among the group of "all partial seizures combined".

During the Experiment Period, patients in the tiagabine 16 mg BID and tiagabine 8 mg QID treatment groups experienced a median decrease of 1.6 and 1.2 in the four-week combined partial seizure rate, respectively, whereas patients receiving placebo experienced a median decrease of 0.3 in the four-week combined partial seizure rates. These results are also not statistically significant and reflect a very small clinical change. The median four-week combined partial seizure rates and change from Baseline are summarized in the next table.

Four-Week Changes in Combined Partial Seizure Rates (ITT)

Dose Group	N	Median Four-Week Seizure Rates During		Median Change from Base-line	P-value† vs. Placebo
		Baseline	Experiment		
Placebo	105	10.3	11.3	-0.3	
Tiagabine 16 mg BID	106	10.5	8.2	-1.6	0.097
Tiagabine 8 mg QID	103	9.6	6.8	-1.2	0.056

†Van Elteren weighted test

B .PERCENT CHANGE (25 AND 50% REDUCTION IN SEIZURES COMPARING *(NOT A PROSPECTIVE ANALYSIS)*

The sponsor then chose to look at the data in terms of Percent Change in four-week combined partial seizure rate from Baseline to the Experiment Period. Again, this was not a planned analysis. The sponsor found that 30 patients (28%) in the tiagabine 16 mg BID and 24 patients (23%) in the tiagabine 8 mg QID treatment groups experienced 50% or greater seizure rate reduction as compared to eight patients (8%) in the placebo group. The difference in the proportion of patients achieving 50% or more seizure rate reduction was statistically significant in favor of both the tiagabine 16 mg BID and tiagabine 8 mg QID

treatment groups (p<0.001 and p=0.002, respectively).

Number and Proportion of Patients With at Least 25% or 50% Reduction in Four-Week Combined Partial Seizure Rates (ITT)					
	Placebo N=105	Tiagabine 16 mg BID N=106	P-value vs. Placebo	Tiagabine 8 mg QID N=103	P-value vs. Placebo
≥25% reduction	25 (24%)	48 (45%)	0.001	39 (38%)	0.028
≥50% reduction	8 (8%)	30 (28%)	<0.001	24 (23%)	0.002

(3) Secondary Generalized Seizures

A. Change from Baseline in 4-Week Seizure Rate, Comparing Placebo to the 8 mg QID Group and Separately to 16 mg BID

The sponsor analyzed the data to compare the effect of tiagabine 32 mg (either regimen) against placebo on the frequency of secondarily generalized tonic-clonic seizures to compare the change in four-week seizure rates from baseline. The calculation for secondarily generalized tonic-clonic seizure rate included: complex partial evolving to secondarily generalized tonic-clonic seizures, simple partial evolving to complex partial evolving to secondarily generalized tonic-clonic seizures, simple partial evolving to secondarily generalized tonic-clonic seizures, partial with secondarily generalized tonic-clonic and secondarily generalized tonic-clonic status epilepticus. The sponsor made the same assumption about generalized seizures without an antecedent partial seizure as was made in study M91-603. That is, since patients included in the study had confirmed focal epilepsy, all generalized tonic-clonic seizures were considered to have a partial onset even if there was no clinical description of the seizure beginning focally.

Four-Week Changes in Secondarily Generalized Tonic-Clonic Seizure Rates

Dose Group	N	Median Four-Week Seizure Rates in		Median Change from BL	P-value vs. Placebo	Patients with ≥50% Reduction	
		BL	EXP			EXP	p-value vs. Placebo
Placebo	37	3.0	2.8	-0.3		11 (30%)	
16 mg BID	43	2.0	1.6	-0.8	0.692	18 (42%)	0.351
8 mg QID	44	2.5	1.1	-0.7	0.483	21 (48%)	0.115

The results for secondarily generalized seizures do not achieve statistical significance for either regimen and therefore do not support the sponsor's labeling with regard to this aspect of seizure control.

B. Percent Change (25 and 50% Reduction in Seizures Comparing Placebo to he 8 mg QID Group and Separately to 16 mg BID (Unplanned Analysis)

The Change in the 4-week secondarily generalized tonic-clonic seizure rate expressed as a percent reduction from Baseline showed that the tiagabine 16 mg BID and 8 mg QID treatment groups had greater percentages of patients achieving a 50% or more reduction (42% and 48%, respectively) when compared to the placebo group (30%). However, the differences were not statistically significant (p=0.351 and 0.115, respectively). These changes in four-week secondarily generalized tonic-clonic seizure rates during the Experiment Period when compared to the Baseline Phase and numbers of patients experiencing 50% or more reduction are shown in the table above. These findings are consistent with the results for Tiagabine 32 mg/day compared to placebo in study M91-603.

As in the previous study patients who experienced secondarily generalized tonic clonic seizures during the treatment phase of the study were not included for analysis if they did not also have such a seizure during baseline, thus eliminating patients who got "worse " during treatment. In addition, the sponsor did not take into consideration in its analysis of secondarily generalized seizures the fact that the overall rates for partial seizures may have dropped (albeit minimally) in the treatment groups compared to placebo.

7.2.2.4 FDA ANALYSIS

As in Study M91-603, the sponsor's selection of complex partial seizures rather than all partial onset seizures as the primary focus in this study is not only unconventional, but also does not reflect the sponsor's desired labeling. . As before the focus of this review will be on (1) the planned primary analyses and (2) the analyses which directly support the sponsor's claim. This will include the following:

I. THE SPONSOR'S PRIMARY PROSPECTIVE ENDPOINTS
   A. PARTIAL COMPLEX SEIZURES (PRIMARY ANALYSES, PLANNED)

II. **Endpoints Relevant to Requested Labeling Claims**
   A. PARTIAL ONSET SEIZURES (ALL PARTIAL)
   B. Secondarily Generalized Seizures

THE SPONSOR'S PRIMARY PROSPECTIVE ENDPOINTS
A.PARTIAL COMPLEX SEIZURES (PRIMARY ANALYSES, PLANNED)
CHANGE IN 4-WEEK SEIZURE RATE FROM BASELINE TO TREATMENT--COMPARING THE PLACEBO TO EACH OF THE TIAGABINE 32 MG GROUPS (GIVEN AS QID OR BID)

The sponsor's primary outcome measure was the responsiveness of partial complex seizures to tiagabine 32 mg (as either of two regimens) compared to placebo. As pointed out, there were numerous methodological problems with the conduct of this study as well as the collection of data which, while they may not result in bias may affect the integrity of the outcome measures. One of the most obvious of the methodological flaws is in the counting of seizures (the principal efficacy variable), particularly in the counting of seizures within an episode of *status epilepticus.* As noted, an episode of status was assigned the numerical value of 1+ the maximum number of seizures counted of a given type. In some cases this resulted in a very small number of seizures. In an effort to determine whether this unusual paradigm affected the outcome of the study, a sensitivity analysis was performed to assess the degree of dependence of the analyses on the method for estimating seizures in episodes of SE in the same manner as in the previous study. The next table shows the number of patients experiencing at least one episode of SE during Baseline but none during the EP (considered to be highly responsive to the test drug and assigned an arbitrarily large (i.e., in absolute value) negative change), experiencing at least one episode of SE during the EP but none during Baseline (considered to be highly unresponsive to the test drug and assigned an arbitrarily large positive change) and experiencing one or more episodes of SE during Baseline and the EP (assigned a large negative change if placebo-treated or a large positive change if tiagabine-treated (worst-case analysis)).

PATIENTS REPORTED WITH STATUS EPILEPTICUS EPISODES DURING STUDY M91-605

BASELINE ONLY		EXPERIMENTAL PHASE ONLY		BASELINE AND EXPERIMENTAL PHASE	
TYPE/NO	RX	TYPE/NO	RX	TYPE/NO	RX
				SEGTC/ 1	16 MG BID
		SECP/2	PBO		
		SECP/1	16 MG BID		

Sensitivity analyses of CPS included only the SECP seizure type. Dr. Sahlroot performed sensitivity analyses using the sponsor's weighted and unweighted vanElteren test on the Baseline to EP change in 4-week seizure rate for the8 mg QID and 16 mg BID regimens compared with placebo. The results are shown in the next table. The differences were very small and the sponsor's values remain statistically significant for the 8 mg QID regimen only.

Comparison of p-values from Sensitivity Analysis with Sponsor's p-values: Complex Partial Seizures (Corrected for Status Epilepticus) Intent to Treat

Treatment comparison	VanElteren p-values	
	Weighted	NonWeighted
Tiagabine 8 mg QID vs Placebo		
Sensitivity Analysis	.018	.104
Sponsor's Analysis	.018	.104
Tiagabine 16 mg BID vs Placebo		
Sensitivity Analysis	0.035	0.184
Sponsor's Analysis	.055	.255

II. Endpoints Relevant to Requested Labeling Claims

A. Partial Onset Seizures (All Partial)

CHANGE FROM BASELINE IN THE 4 WEEK SEIZURE RATE (PAIRWISE COMPARISONS OF INDIVIDUAL DOSE GROUPS WITH PLACEBO)

While not the primary endpoint identified by the sponsor it is reasonable and useful to investigate the response in this group. Evaluation of this group is possible without compromising the original randomization, since partial complex seizures are a subset of all partial onset seizures and all patients in this study had partial complex seizures.

A sensitivity analysis of this group was also performed using each type of SE listed by each of the 4 patients (including the patient with unstated SE and the other patient with SEGTC. As before, the differences are not statistically significant for either regimen.

Comparison of p-values from Sensitivity Analysis with Sponsor's p-values: All Partial Onset Seizures (Corrected for Status Epilepticus) Intent to Treat

Treatment comparison	VanElteren p-values	
	Weighted	NonWeighted
Tiagabine 8 mg QID vs Placebo		
Sensitivity Analysis	.057	.173*
Sponsor's Analysis	.055	.168
Tiagabine 16 mg BID vs Placebo		
Sensitivity Analysis	.104	.172
Sponsor's Analysis	.097	.194

*Sensitivity p-valuesslighly different but no nonsignificant p-values becoming significant

B. Secondarily Generalized Seizures

The problems associated with the sponsor's evaluation of secondarily generalized seizures repeat themselves in this study. Again these include the 1) arbitrary assignment of all GTC seizures as secondarily generalized seizures (6 patients) 2) patients with secondarily generalization in the context of status not identified and counts not provided 3) omission of patients with 2° generalized seizure onset during treatment from the analysis and 4) failure to take into account the reduction in overall partial onset seizure rate into the equation of reduction in 2°generalized seizures. Of less importance is the sponsor's prospective plan to analyze patients with complex partial onset secondarily generalized seizures in contrast with the actual analysis which looked at all partial onset secondary generalized seizures. The analysis of Secondary Generalization will be deferred for sponsor to reevaluate if so desired.

Summary

The sponsor's primary endpoint Change in 4-week CPS seizure rate from Baseline to Experimental phase can be considered positive for Tiagabine 8 mg QID compared to placebo. The sponsor has requested labeling for "partial onset seizures with or without secondary generalization." It can be argued that the study demonstrates efficacy in the manner proposed for the treatment of partial onset seizures if treated with 16 mg BID only. In neither regimen is the claim for secondary generalization supported.

Since the sponsor requests a claim for secondary generalized seizures, more must be done in an effort to evaluate that subgroup (see discussion of study M90-603).

SECTION 7.2.3 STUDY M92-775

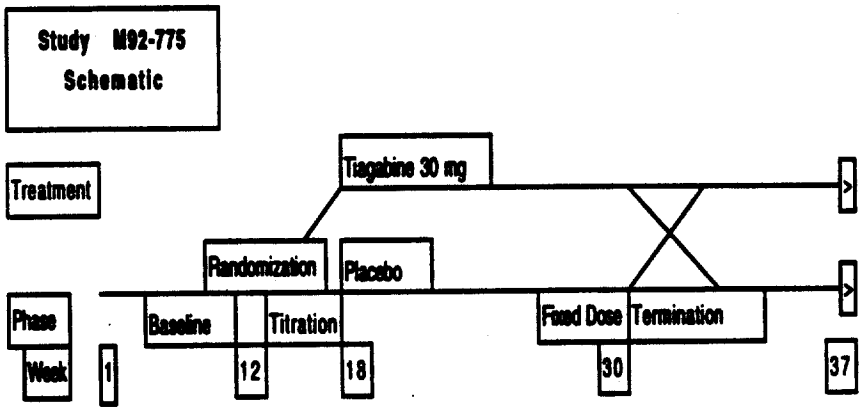
Reviewer's Summary: The design of this study should have been adequate. to demonstrate a difference between placebo and tiagabine for the treatment of partial onset seizures. It was performed and analyzed by and it is an acknowledged as a negative study. Reanalysis is by Abbot however has resulted in a statistically significant difference but with a clinical effect size of questionable significance. Because the Abbott analysis was done after the blind was broken and the negative results known, it will be presented for interest only. Furthermore, many of the methodological problems seen in the earlier two trials were incorporated by Abbott into its reanalysis. The original data and analysis will be presented followed by Abbott's reanalysis. It is the opinion of this reviewer this study overall should not be given the same importance as the previous two studies.

SECTION 7.2.3.1 PROTOCOL SYNOPSIS

TITLE Randomized, Double blind, Placebo-controlled, parallel-group Study of the Safety and Efficacy of Tiagabine Administered TID as Adjunctive Treatment for Partial Seizures.

OBJECTIVES: to determine the safety and efficacy of tiagabine HCl 30 mg when administered three times daily as s add-on therapy for complex partial seizures.

STUDY DESIGN : a multicenter (11) randomized, balanced, double-blind, placebo-controlled, parallel group, fixed dose (10 mg TID) , add-on AED trial following a prospective baseline and run-in (titration) period. Randomization for each center is separate.



PROTOCOL

STUDY SCHEDULE:

Typical of epilepsy studies, this protocol has a baseline phase and a double-blind phase. The study consists of a 12-week baseline period followed by a 22 week double blind phase. The double blind phase includes a 6 week titration period, a 12 week fixed dose and 4 week termination.

The study is initiated at visit 1 with initial screening at which time patients enter the 12-week prospective baseline period. By the end of Baseline, patients who fulfill the criteria for entering the double-blind phase are randomized to either add-on tiagabine or add-on

placebo. The patients then enter the six week run-in period, in which the patients who have been randomized to add-on tiagabine are titrated up to the 12 week fixed dose level of 10 mg tid.

MEDICATION AND DOSAGE REGIMEN

Tiagabine is dispensed in this study as 2 and 4 mg tablets and matched placebos. In the 6 week run-in period the dose levels are 4, 6, 10 mg tid, each for two weeks; in the 12 week fixed dose period the dose level is 10 mg tid. Study drug is taken three times a day (approximately every eight hours with food).

CONCOMITANT MEDICATION

Dose adjustment is discouraged. Dose adjustment during the Baseline Period will disqualify the patient from entering the Double-Blind Phase. In the Double-Blind Phase, dose adjustment will only be allowed, if a clinically significant and consistent change in plasma drug level should occur.

ENROLLMENT

In total, at least 120 patients were planned. No site was to enroll fewer than 10 patients.

Key Inclusion Criteria

- Diagnosis of **partial seizures with or without generalization** supported by observed ictal events consistent with partial seizures, an ictal l EEG demonstrating a focal abnormality or an interictal EEG demonstrating unilateral or bilateral asynchronous abnormalities consistent with partial seizures.
- Frequency of ≥six complex partial seizures, occurring alone or in combination with any other seizure type, within the 8-week period preceding the Screening Visit.
- Stable regimen of one to three of the following AEDs: phenytoin, acetazolamide, carbamazepine, phenobarbital, primidone, valproate, clonazepam, clobazam, lamotrigine, oxcarbazepine, vigabatrin or diazepam. (Vigabatrin, lamotrigine, and oxcarbazepine are only acceptable in countries where regulatory approval has been received. Diazepam is only acceptable for p.n. use.)

Key Exclusion Criteria

- Pseudoseizures.
- Active CNS infection, demyelinating disease, degenerative neurological disease, or any progressive CNS disease or those requiring frequent medication changes; Clinically significant psychiatric illness, psychological or behavioral problems, or history of psychosis severe enough to require hospitalization.
- A medical disease, either currently or within the previous three months, manifesting with signs and symptoms that could confound interpretation of the study results.
- Administration of an investigational drug within 30 days prior to the Screening Visit.

EFFICACY VARIABLES

PRIMARY OUTCOME MEASURES

The primary prospective outcome measure in this study was the proportion of **Responders**, that is , the percentage of patients achieving a 50% or greater reduction in the 4-week frequency of **all partial onset seizures** between baseline and fixed dose period and the Primary analysis dataset, the intent-to-treat dataset.

SEIZURE RATE CALCULATION

The Baseline seizure rate 4-week seizure rate would be calculated as the total

number of complex partial seizures reported during the Baseline Phase multiplied by the ratio of 28 days to the actual number of days in the baseline period.

The Experiment Period 4-week complex partial seizure rate would be calculated as the total number of complex seizures reported during the Experiment Period Multiplied by the ratio of 28 days to the actual number of days in the Experiment Period. The actual number of days in the Experiment Period would be defined as the duration from the days of randomization to the last day of treatment in the Experiment Period. The last day of treatment in the Experiment Period of the Study would be defined as the date of the last seizure evaluation or the date of the last dose of treatment in the Experiment Period, whichever is earlier.

ANALYSIS METHOD:
The primary efficacy analysis would be based on the set of 2 x 2 tables of percentages formed by classifying treatment versus ≥50 % seizure reduction, stratified by center. An exact test that the common odds ratio for these tables is unity would be performed. A secondary efficacy analysis would be based on the Fixed Dose Period change from Baseline Period in weekly seizure frequencies using the van Elteren test.

SEIZURE FREQUENCY CALCULATION
The weekly seizure frequency wouldbe calculated as the total number of seizures reported during an assessment period multiplied by the ratio of 7 days (one week) to the actual number of days in that period. For example, if a patient has 8 seizures in 28 days, then the estimated weekly seizure frequency wouldbe 2 (8 times 7/28). The actual number of days in an assessment period would normally be calculated from visit 1 to visit 4, and from visit 7 to visit 10, respectively.

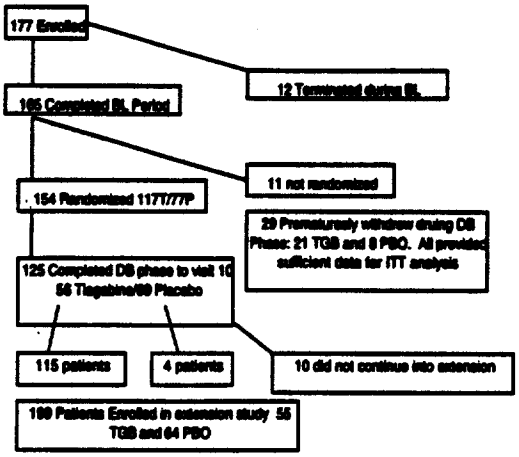
SECONDARY OUTCOME MEASURES
Efficacy analyses would also be performed for complex partial seizures and for simple partial seizures, considered separately. Additional efficacy analyses for other seizure types will also be performed. The analysis for a particular seizure type include patients who had at least one seizure of that type *during either the baseline or the fixed dose period.* Analysis methods will be similar to those described above except that the center effects will be ignored. This exception takes into consideration the small number of patients expected in each of these analyses. Comparisons of tiagabine and placebo in various subsets of patients such as those determined by the concomitant antiepileptics will also be performed with respect to the efficacy in partial seizures and other major seizure types.

SECTION 7.2.3.2 STUDY CONDUCT

ENROLLMENT
A total of 177 patients enrolled in the baseline phase of this study and of these 154 (87%) were randomized to treatment (1:1 ratio of Tiagabine 30 mg (77 pts) and Placebo (77 patients). Randomization occurred on a 1:1 basis within centers. There were 29 patients who withdrew during the double blind phase, leaving a total of 125 patients completed the trial as planned.

PATIENT DISPOSITION

The following schematic summarizes patient disposition:



Twenty nine patients (21 TGB and 8 PBO) withdrew prematurely from the double blind phase of the trial either by abrupt discontinuation or by premature entry into the termination phase. A total of 125 patients (81.2 % of those randomized) completed the study up to visit 10. Premature discontinuation after randomization (during the run-in or fixed dose phase) occurred because of adverse events (17 tiagabine and 2 placebo) , lack of efficacy (3 tiagabine and 4 placebo), non compliance (1 tiagabine), loss to follow-up (1 placebo) and other reasons.

DEMOGRAPHIC AND PATIENT CHARACTERISTICS AT BASELINE

Demographic and patient characteristics are summarized in the next table.

SUMMARY OF PATIENT CHARACTERISTICS

	Placebo (N=77)	Tiagabine (N=77)	p-value
AGE (YRS)			
MEAN	35	35.4	.866
RANGE	17.9-71.3	18.7-59.7	
GENDER			
FEMALE	30 (39%)	34 (44%)	.524
MALE	70 (61%)	66(86%)	
YEARS WITH EPILEPSY			
MEAN	23	24.9	.289
EPILEPSY ETIOLOGIES			
IDIOPATHIC	51%	39%	
PRE/PERINATAL	18%	28%	
TRAUMA	14%	18%	
INFECTION	8%	18%	

SEIZURE TYPES			
PARTIAL (POS)	100%	100%	
COMPLEX PARTIAL	97%	97%	
SIMPLE PARTIAL	68%	77%	
SGTC	62%	74%	
MEDIAN BL SEIZURE RATE (4WK)			
POS	10.5	12.2	.124
PCs	7.7	7.0	.514
SPS	12.5	10.9	.989
SGTC	1.3	2.0	.094
NUMBER AEDS EVER TAKEN			
MEAN	6.2	6.2	.876
RANGE	2-15	1-13	

There were no significant differences in patient characteristics including baseline phase comparability in 4-weeks seizure rates between treatment groups.

CONCOMITANT AEDS

Comparison of concomitant AED use at baseline between the two treatment groups also showed no significant differences:

Concomitant AED use During Baseline Period (All Randomized Patients

Principal Concomitant AED	Placebo (N=77)	Tiagabine 30 mg (N=77)
Carbamazepine	59	62
(monotherapy)	22	17
Valproic Acid	19	23
(Monotherapy)	2	3
Vigabatrin	14	15
(monotherapy)	2	0
Clonazepam	10	10
(monotherapy)	0	0
Phenobarbital	7	5
(monotherapy)	0	0
Lamotrigine	6	4
(monotherapy)	0	1
Clobazam	3	6
(monotherapy)	0	0

PROTOCOL VIOLATIONS

While it appeared that the trial was being conducted according to the protocol there were deviations from the protocol, which may have affected the outcome. These will be discussed next.

MEDICATIONS

During this study one patient incorrectly received tiagabine instead of placebo. Five other patients were given medication intended for other patients, but this did not result in the incorrect medication. They were all analyzed in the intent to treat group as randomized. This one patient would not be expected to bias the results in favor of the drug.

CONCOMITANT AEDS AND DEVICES

Patients were to have been on a stable regimen of 1-3 concomitant AEDs and changes to this regimen were not to have taken place. There was a widespread practice during this study of treatment of increased seizure activity with PRN benzodiazepines or one time doses of other antiepileptic drug. Fifteen randomized patients received intermittent diazepam for epilepsy during baseline and one patient received two doses of oxazepam for epilepsy during baseline. Numerous other patients also received diazepam, other benzodiazepines and other drugs for seizures during the baseline or treatment period. This practice involved over 20% of participants in study **M92-775.** In addition there were two patients who were implanted with vagal stimulators. Patients had these devices programmed before the start of the study and were instructed not to change the stimulation during the study (patients were told not to override the continuous voltage during the study. [1]) It is hoped that these patients were not actively involved in controlled trials for these devices at the time that they were enrolled in this study.

TABLE: SUMMARY OF PRN TREATMENT WITH AEDS (ESPECIALLY BENZODIAZEPINES) FOR ADDITIONAL SEIZURE CONTROL DURING STUDY M92-775

PID	PLACEBO	TIAGABINE 30 MG
11002		Clonazepam 1 mg prn seizures Diazepam 10 mg
11003	Diazepam 10 mg x3	
12002		Diazepam 5 mg IV
12006		Diazepam 5-10 mg
12008	Diazepam 20mg x3	
12011		Diazepam 12.5 mg (prn)
12013	Diazepam 5 mg prn (14 doses)	
13011		Diazepam 20 mg IV Phenytoin 250 mg IV
13021		Clobazam 30 mg Diazepam 5 mg PO * prn
13024	Diazepam 5-10 mg (5 doses)	
13028		Diazepam 2-4 mg (21 doses)
13029	Diazepam 20 mg IV	
13037	Diazepam 15 mg IV	

[1]Sponsor's response to specific questions about the use of vagal stimulators during this study, July 1,1996.

13042		Clonazepam 2 mg
14001	Diazepam (NS) prn	
14008		Diazepam 5-10 mg (16 doses)
14005		Diazepam Unk dose pr, prn
16001	Clobazam 10 mg (6 doses)	
17011	Diazepam 5 mg	
17012		Diazepam 20-30mg (81 doses)
19001		Diazepam 20 mg Lamotrigine 300-400 mgx2
19003		Diazepam 20 mg (2 doses)
19004	Diazepam 10-20 mg (4 doses)	
19006	Diazepam 20 mg(4 doses)	
19008	Lamotrigine 100-200 mg (2 doses)	
19009	Diazepam 20 mg (2 doses)	
19010	Diazepam 20-40 mg (6 doses) Midazolam 10 mg (2 doses)	
19013		Diazepam 20 mg (3 doses)
19019	Diazepam 10-20 mg (7 doses)	
19024		Diazepam 10 mg
20002		Diazepam 10 -30mg (27 doses)
21022		Vigabatrin 2000 mg x1
12004		Use of Vagal Stimulator
12006	Use of Vagal Stimulator	

*This patient was identified in the text as a patient who took prn diazepam during the study, but the data listings noted only clobazam.

Most of the patients who received these medications did so across study periods. No particular pattern could be ascertained.

PRACTICES NOT DESCRIBED IN THE PROTOCOL WHICH MAY HAVE INFLUENCED THE DATA

COUNTING SEIZURES: *STATUS EPILEPTICUS.* The convention for counting seizures during a seizure flurry or an episode of status epilepticus was not delineated in the protocol. The sponsor states that estimates by the investigator of the number of seizures occurring during an episode of status epilepticus for a patient were used without modification in the report, however, Abbott analyses reestimated these numbers as "one + the maximum number of seizures" of the given type that a patient had experienced in any day during the Baseline or Experimental Periods. In this study there were 6 patients who experienced status epilepticus, amny of whom experienced repeated episodes.They are enumerated in the next table. The original seizure counts are not identified in the report.

SUMMARY OF DATA LISTINGS OF STATUS EPILEPTICUS

PID	Period	Type of SE	Max # of Sz	Count in Data listings
15005 (Tgb)	Double Blind	SECP	7	1
	Double Blind	SECP	7	1
20002* (Tgb)	Double Blind	SECP	97	0
19007* (PBO)	Double Blind	not listed in data listings	unk	unk
15006 (PBO)	Baseline	SECP	20	1
	Baseline	SECP	20	1
	Double Blind	SECP	20	1
	Double Blind	SECP	20	1
	Double Blind	SECP	20	1
	Double Blind	SECP	20	1
	Double Blind	SECP	20	1
	Double Blind	SECP	20	1
	Double Blind	SECP	20	1
	Double Blind	SECP	20	1
19013 (TGB)	Baseline	SESP	6	1 (several hours status)
	Baseline	SESP	"	1 (several hours status)
	Baseline	SESP	"	1
	Baseline	SESP	"	1 (several hours status)
	Baseline	SESP	"	1 (several hours status)
	Baseline	SESP	"	1 (several hours status)
	Baseline	SESP	"	1 (several hours)
	Baseline	SESP	"	1 (several hours)
	Double Blind	SESP	"	1 (status)
	Double Blind	SESP	"	1
	Double Blind	SESP	"	1
21011 (PBO)	Double Blind	SECP	8	1

*This patient was listed in the text of the report, but no record of status epilepticus could be found in the data listings.

Certainly an episode of status epilepticus lasting for several hours should carry the value of more than just one seizure. The sponsor does not appear to have provided the original investigator estimates of the status data. It is not altogether clear what numerical value was given to these seizures for the (and for that matter, the Abbott analysis), however the data listings show only 1 seizure for each episode.

The sponsor was questioned about this and related issues and the following response was provided: (July 17, 1996)

> instructed the investigators to record precisely the number of seizures experienced by a given patient, by date and time. However, if the patients had episodes of prolonged seizures or clusters of seizures too numerous to count, these were recorded on the CRFs as status, and the investigators were instructed to record an "episode or count" of "1. The Abbott Laboratories Addendum to M92-775 (Clinical Volume 112, page 005), states that "Estimates by the investigator of the number of seizures occurring during an episode of status epilepticus for a patient were used without modification in the report analyses..." for the study. The statement is incorrect. did not instruct the investigators to collect seizure counts but only episode counts for status, as stated in the paragraph above.

COUNTING SEIZURES: GENERALIZED SEIZURES

It was the custom of Abbott Laboratories to make the assumption that a GTC with no antecedent seizure must have been a Secondarily Generalized Convulsion. Therefore in the analysis of secondary generalized seizures, all convulsions were included. In the data listings there was frequently a description of such seizures some were called secondarily generalized while others were not. The table below enumerates all of the occurrences of generalized seizures without an antecedent partial seizure which would have been included as "secondarily generalized" in the Abbott analysis. The analysis does not clearly detail how these are handled.

SUMMARY OF PATIENTS WHO EXPERIENCED GTC WITH NO ANTECEDENT SEIZURES

PID	Rx	No./ Description of SGTCS/Code	Seizure Etiology	EEG
11003	TGB	23/ "Nocturnal Generalized Convulsions"/SGTC	Post traumatic	Focal slow and paroxysmal abnormality
12003	PBO	12/"Typical Tonic Clonic Seizure"†/SGTC	Concussion as a child	Focal slow and paroxysmal abnormality
12006	TGB	12/ Generalized tonic clonic seizure†/SGTC	Meningitis at 11 yo	Focal slowing
12008	PBO	3 /Generalized tonic clonic seizure†/SGTC	Perinatal (Hemorrhage)	Generalized Slowing Focal paroxysmal
12009	PBO	4/ Generalized tonic clonic seizures†/SGTC	Astrocytoma	Generalized Paroxysmal abnormality
12013	PBO	1/Generalized tonic clonic seizure†/GTC	Oligodendroglioma	Focal slowing
13014	PBO	11/ Rapidly generalized tonic clonic seizure/SGTC	Idiopathic	Focal slow and paroxysmal abnormality

15005	TGB	2 /(SE) Generalized Convulsion not preceded by CP with incontinence of urine/CPGTC	Meningitis	Focal paroxysmal abnormality
15008	TGB	1 / No warning/eyes roll up/grunting/increased salivation/falls to ground/ both arms shake./CPGTC	Meningitis	Focal slow wave abnormality
17003	TGB	1/ Generalized rigidity followed by convulsions, occasionally sickness, usually exhausted afterward/SGTC	Idiopathic	Generalized and focal slow wave abnormality, Focal paroxysmal abnormality
17006	PBO	1/Generalized rigidity followed by shaking for all 4 limbs. Patient drowsy afterward/SGTC	Idiopathic	Generalized paroxysmal abnormality. Focal slow wave abnormality
17010	PBO	5 / Generalized rigidity followed by convulsion of all 4 limbs.Patient drowsy afterward/SGTC	Frontal Tumor	Generalized and focal slow wave abnormality, Generalized paroxysmal abnormality
18005	PBO	3/Begins to shake all over, followed by exhaustion and sleep for an hour/SGTC	Onset with febrile seizures	Focal paroxysmal abnormality
18013	TGB	7/Mainly tonic clonic seizures during sleep/CPGTC	Febrile Convulsions	Focal paroxysmal abnormality
18014	PBO	22/ Brief generalized convulsions/CPGTC	Idiopathic	Generalized slow wave abnormality
19008	PBO	1/No warning, stiffening of whole body-Falls-Jerking of body and limbs/ Small jerks, DRibbles, may bite tongue/CPGTC	Idiopathic --first fit after striking head and losing consciousness	Focal slow wave abnormality
19009	TGB	15/No warning, whole body stiffens, falls, irregular jerking of all 4 limbs. Last up to 15minutes/SGTC.	Idiopathic	focal slow wave abnormality Focal paroxysmal activity
19012	TGB	2/Starts to breathe heavily , falls, generalized convulsion, 90 seconds/CPGTC	Idiopathic	Focal paroxysmal abnormality
19019	PBO	120/Without warning falls, generalized convulsion, with injury, incontinence /SGTC	Trauma--history of major head injury	Focal slow wave abnormality

†Record makes a distinction between these and partial onset generalized tonic clonic

All of these patients had at least some partial onset seizures and most had some focal EEG findings. Nevertheless there are patients who also had generalized paroxysmal abnormalities, others who had generalized encephalopathies, and still others who have clearly generalized seizures as part of their seizure repertoire (absence, myoclonic, tonic). It is far less clear in this study that those seizures that had a clinical description of a typical grand mal seizure are of partial onset. The ambiguity in definition of these seizures affects the overall reliability of the counts that make up the Secondarily Generalized Seizure analyses but also affect the distribution of seizures called Simple Partial, Complex Partial and therefore All Partial Seizures as well

SECTION 7.2.3.3.0 SPONSOR'S EFFICACY RESULTS

SECTION 7.2.3.3.1 SPONSOR'S EFFICACY RESULTS (NOVO)

The sponsor's efficacy results for this study will be summarized in the following format:

(1) ALL PARTIAL ONSET SEIZURES: RESPONDER RATE (50% REDUCTION IN SEIZURES COMPARING PLACEBO TO THE TIAGABINE 30 MG GROUP)
(2) COMPLEX PARTIAL SEIZURES: RESPONDER RATE (50% REDUCTION IN SEIZURES COMPARING PLACEBO TO THE TIAGABINE 30 MG GROUP)
(3) SECONDARY GENERALIZED SEIZURES, : .RESPONDER RATE (50% REDUCTION IN SEIZURES COMPARING PLACEBO TO THE TIAGABINE 30 MG GROUP)

(1) ALL PARTIAL ONSET SEIZURES: RESPONDER RATE (50% REDUCTION IN SEIZURES COMPARING PLACEBO TO THE TIAGABINE 30 MG GROUP)

The primary prospective efficacy variable for this study was the proportion of patients in each treatment group experiencing a reduction from the baseline period of 50% or more in the 4-weekly partial seizure rate during the fixed dose period. Patients achieving this level of reduction were considered responders.

RESPONDER RATES† FOR ITT DATASET
SEIZURE TYPE : ALL PARTIAL ONSET

Seizure Type	Placebo		Tiagabine 30 mg		Test that common odds ratio‡ is unity (p-value)
	N	No (%) Responders	N	No (%) Responders	
All Partial	77	5 (6.5%)	77	11(14.3%)	.169

†Proportion of Patients experiencing 50% reduction in seizures
‡exact test that the common odds ratio for these tables is unity

Eleven of the 77 patients in the tiagabine group achieved a reduction in the 4-week seizure rate of 50% or more, compared with 5 of 77 patients in the placebo group. This indicates that a small proportion of patients in the tiagabine group (14.3%) had what was considered for this study a clinically apparent response and that proportion was also slightly greater than that seen in the placebo group (6.5%) . No statistically significant treatment effect was found (p=.169)

In addition to the above planned analysis many other analyses were done, including Median Partial 4-week Seizure Rate for baseline and fixed dose periods, comparing placebo to tiagabine groups (this will be discussed under Abbott results), reduction from baseline in square root transformed 4-week partial seizure rates, and comparison of percentage change (>50% increase) in all Partial seizure free days, and time to sixth seizure. There was evidence of a statistically significant treatment effect on some of these retrospective secondary variables, however for the primary prospective outcome measure, there was not.

2) PARTIAL COMPLEX SEIZURES

RESPONDER RATE (50% REDUCTION IN SEIZURES COMPARING PLACEBO TO THE TIAGABINE 30 MG GROUP)

As a secondary efficacy analysis, the Responder Rate was applied to complex partial seizure data in the intent to treat population (any patient who received treatment and experienced a complex partial seizure during the baseline and/or fixed dose period.) The results, now no longer reflect the original randomized group, but 96% of it.

RESPONDER RATES† FOR ITT DATASET
SEIZURE TYPE : COMPLEX PARTIAL SEIZURES

Seizure Type	Placebo		Tiagabine 30 mg		Test that common odds ratio is unity (p-value)
	N	No (%) Responders	N	No (%) Responders	
Complex Partial	75	11 (14.7%)	73	15 (20.6%)	.371

There were 15 responders in the treatment group (20.7%) and 11 responders from the placebo group (14.7%) , neither a large difference nor statistical effect.

3) SECONDARY GENERALIZED SEIZURES: RESPONDER RATE (50% REDUCTION IN SEIZURES COMPARING PLACEBO TO THE TIAGABINE 30 MG GROUP)

For patients with secondarily generalized tonic clonic seizures, the proportion of responders is shown below.

RESPONDER RATES† FOR ITT DATASET
SEIZURE TYPE : ALL PARTIAL ONSET

Seizure Type	Placebo		Tiagabine 30 mg		Test that common odds ratio is unity (p-value)
	N	No (%) Responders	N	No (%) Responders	
SGTC	35	9(25.7%)	38	12 (31.6%)	.399

†Proportion of Patients experiencing 50% reduction in seizures

Based on the data summaries provided by the sponsor, one recalls that many of these seizures were generalized tonic clonic seizures specifically with no antecedent partial seizure. Because the results are not statistically significantly different between the two groups, further reanalysis of this study may not need to be considered.

SECTION 7.2.3.3.2 SPONSOR'S EFFICACY RESULTS (ABBOTT)

Abbott Laboratories has undertaken a reanalysis of the data presented in this study report. This was done after the code had been revealed and the data was available for scrutiny. The differences between the prospective , analysis and the retrospective Abbott reanalysis can be summarized in the next table.

SUMMARY OF THE MAJOR DIFFERENCES BETWEEN
THE AND ABBOTT ANALYSES FOR STUDY M92-775

PARAMETER	ANALYSIS	ABBOTT ANALYSIS
Primary Outcome Variable	Responder Rate (50% Reduction) in POS	Change in 4-week Seizure Rate in PCS†
Statistical Test	Exact Test on the common odds ratio for by-center percentages	VanElteren Analysis weighted by center (for CPS and POS)

Period Analyzed	Fixed dose compared to Baseline	Experimental (Titration and Fixed dose Period) compared to Baseline
Patients Included in analyses of SPS, PCS and SGTC seizures	Patients who had this seizure type during baseline or treatment	Patients who had this seizure type during Baseline only
Primary Seizure type Analyzed	All Partial Onset Seizures	Partial Complex Seizures
Enumeration of Seizures during an episode of Status Epilepticus	Contemporaneous estimates used	Maximum plus 1 rule applied in lieu of generated counts
Enumeration of Complex Partial Seizures	Primary GTC and generalized status epilepticus counted separately from Secondarily Generalized TC seizures	All convulsions were counted as "secondarily generalized tonic clonic seizures", including those with no antecedent seizure
Seizure Counts	Two patients' seizure counts were enumerated differently by Abbott anc The sponsor did not clarify the etiology of this discrepancy or why counts were not used.	

†In this study the subset of patients with PCS were not the original randomized group, because of the nature of the entrance criteria, which was specific for all manifestations of partial onset seizures, not specifically partial complex seizures as in the other Abbott studies.

As one of many *post hoc* reanalyses, this reanalysis yielded highly statistically significant results in favor of the drug. However, it was not altogether an unreasonable approach to look at the data in this manner for consistency with the two previous trials, since the variables and the test statistics chosen for the reanalysis were those which had demonstrated efficacy for those.

COMPARISON OF THE AND ABBOTT RESULTS FOR STUDY M92-775

Seizure Type	Analysis‡ p-value	Abbott Analysis¥ p-value
All Partial Onset	0.169	0.019 (T)
Complex Partial	0.371	0.014 (T)
Secondarily Generalized Tonic Clonic	0.399	0.008 (T)

(T) statistically significant (at.05 level) treatment effect favoring tiagabine over placebo
‡ Analysis of Responder Rate
¥Analysis of Change in 4-week Seizure rates from baseline to Experimental Phase for tiagabine 30 mg vs. placebo.

The Abbott results for the variable Change in 4-week seizure rate from Baseline to Experimental Phase (Titration + Fixed Dose) for All Partial Onset (the group randomized), Partial Complex, Simple Partial and Secondarily Generalized Tonic Clonic Seizures is shown below, followed by a table of statistical tests on these variables with their p-values secondary analysis and Abbott Analysis).

COMPARISON OF CHANGE IN 4-WEEK SEIZURE RATES : ABBOTT'S ANALYSIS OF M92-775
"INTENT TO TREAT" DATASET

All Partial Onset Seizures

VARIABLE	PLACEBO N=77			TIAGABINE 30 MG N=77		
	Baseline	EXP	Change	Baseline	EXP	Change
Mean	17.3	19.0	1.7	22.6	22.2	-0.3
SD	20.4	28.7	14.6	23.7	27.5	18.3
Median	10.6	9.8	-0.5	12.7	11.0	-1.1

Nonparametric analysis, weighted, p=.014 , nonparametric , unweighted, p= .297
Parametric analysis, weighted p=0.194, Parametric , unweighted p=0.838

Partial Complex Seizures (Subset of ITT)*

VARIABLE	PLACEBO N=75			TIAGABINE 30 MG N=72		
	Baseline	EXP	Change	Baseline	EXP	Change
Mean	14.9	16.1	1.2	14.2	11.8	-2.4
SD	19.6	28.7	13.4	18.6	16.1	8.8
Median	7.8	7.5	-0.1	7.1	5.4	-1.3

Nonparametric analysis, weighted, p=.019 , nonparametric , unweighted, p= .396
Parametric analysis, weighted p=0.082, Parametric , unweighted p=0.448

Secondary Generalized Tonic Clonic Seizures (Subset of ITT)*

VARIABLE	PLACEBO N=77			TIAGABINE 30 MG N=77		
	Baseline	EXP	Change	Baseline	EXP	Change
Mean	5.5	6.5	1.1	4.3	3.7	-0.6
SD	18.9	25.4	7.1	6.4	6.2	4.0
Median	1.3	1.5	0.0	2.3	1.8	-0.6

Nonparametric analysis, p=.008
Parametric analysis p=0.146

* includes only those patients who experienced this seizure type in Baseline, not those patients who developed this seizure type during treatment

The results, although now highly statistically significant, continue to reflect a very small, almost insignificant change. For example, in the combined partial onset seizure group, the TGB treated patients had a median seizure reduction of 0.6 seizure/ month greater than placebo. This small change was statistically significant. However given the paroxysmal nature of the disease, a .6 seizure/per month change from baseline is almost negligible. The remainder of the subgroups also reflect this small difference clinically.

SECTION 7.2.3.3.3 FDA ANALYSIS

Study 775 compared Tiagabine 10 mg TID to placebo in a parallel group design. results were not statistically significant for the protocol determined primary outcome measure. Abbott reanalyses of the raw data using the same primary endpoint as in studies 603 and 605 provided statistically significant results.

ALL PARTIAL ONSET SEIZURES COMBINED

SENSITIVITY ANALYSIS FOR STATUS EPILEPTICUS

Because the original data on status epilepticus from the trial are not available, an additional sensitivity analysis using the SE data in the manner described for studies 603 and 605 was performed. The analysis for this study used the Abbott defined outcome measures and the Abbott defined statistical tests (since they are provided as an"answer to the negative results"). The following patients contributed to this analysis. While as the sponsor points out, there were 6 patients who developed status epilepticus during this study, only 4 had status during the baseline or experimental period. These are summarized below.

PATIENTS REPORTED WITH STATUS EPILEPTICUS EPISODES DURING STUDY M92-775

Baseline Only		Experimental Phase Only		Baseline and Experimental Phase	
Type/No	Rx	Type/No	Rx	Type/No	Rx
none	N/A	1 SECP	PBO	1 SECP	PBO
		1 SECP	TGB	1 SESP	TGB

Sensitivity analyses included both types of SE listed in the table and the p-values obtained by these reanalysis are shown below for All Partial Onset Seizures.

Comparison of p-values from Sensitivity Analysis with Sponsor's p-values: All Partial Onset Seizures (Corrected for Status Epilepticus) Intent to Treat

Treatment comparison	VanElteren p-values	
	Weighted	NonWeighted
[redacted]	.0465	.60
Sponsor's Analysis	.019	.396

The sensitivity analysis taking into account inadequate counts for status epilepticus, yielded a borderline statistically significant difference (p=.0465) .

ANALYSIS OF THE DIFFERENCE BETWEEN WEIGHTED AND UNWEIGHTED NONPARAMETRIC ANALYSES

In addition to the above, an analysis exploring the differences between the sponsor's weighted (by center) and unweighted van Elteren analysis was conducted by Dr. Sahlroot (please refer to his review). As he points out, the sponsor's results (p-values) for the weighted vanElteren were without exception smaller than those for the unweighted, indicating that the larger centers had greater treatment differences.

REANALYSIS OF ABBOTT'S DATA AFTER THE REMOVAL OF SMALL CENTERS
PARTIAL ONSET SEIZURES

	weighted VanElteren	Unweighted VanElteren
[redacted]	[redacted]	.40
[redacted]	[redacted]	.064

The results produced p-values of .013 (weighted vanElteren) and .064 (unweighted vanElteren) . The disparity between the weighted and unweighted analysis is reduced and Abbott's results continue to be statistically significant for partial onset seizures.

COMPLEX PARTIAL SEIZURES COMBINED

SENSITIVITY ANALYSIS FOR STATUS EPILEPTICUS

The p-values obtained in the sensitivity analysis for complex partial seizures taking into consideration patients with status epilepticus are shown below. The results using the VanElteren weighted analysis are significant at the .05 level.

COMPARISON OF P-VALUES FROM SENSITIVITY ANALYSIS FOR SE
WITH INTENT TO TREAT (CPS)

Treatment comparison	VanElteren p-values	
	Weighted	NonWeighted
[redacted]	[redacted]	[redacted]
Abbott's Analysis	0.014	.297

ANALYSIS OF THE DIFFERENCE BETWEEN WEIGHTED AND UNWEIGHTED NONPARAMETRIC ANALYSES

As above, an analysis exploring the differences between the sponsor's weighted (by center) and unweighted van Elteren analysis was conducted (please refer to Dr.Sahlroot's review). The sponsor's results (p-values) for the weighted vanElteren were again smaller than those for the unweighted, indicating that the larger centers had greater treatment differences. To assess the effect of smaller centers on the unweighted results, the three smallest centers (11 patients) were removed from the analysis. The 11 patients removed had higher baseline 4-week Partial onset seizure rates (median 24.5 vs. 11.0) The reanalysis did not alter the outcome of the study for the CPS.

REANALYSIS OF ABBOTT'S DATA AFTER THE REMOVAL OF SMALL
CENTERS (PARTIAL COMPLEX SEIZURES)

	weighted VanElteren	Unweighted VanElteren
Abbott's p-values	.014	.30
[redacted]	[redacted]	[redacted]

SECONDARILY GENERALIZED SEIZURES

This reviewer did not think that a reanalysis o f the protocol defined primary outcome measures was needed since these results were not statistically significant. The problems associated with the sponsor's analysis of secondarily generalized seizures were described in study M91-603 and will not be repeated here. Such a reanalysis would have to be undertaken by the sponsor if such an indication is desired.

Comments

There a re a host of problems which this study and its reanalysis by Abbott present. The initial study as performed by are unquestionably negative both from a statistical and a clinical standpoint. There is, as admits, no statistical significance for any of the effects seen. Furthermore the effect size is so small as to be almost negligible. For example for the primary outcome measure as defined by that is, the Responder Rate for all Partial onset seizures, the difference between treatment and placebo is only a few patients (5 patients (6.5%) responded in the placebo group and 11 (14.3%) responded in the treatment group) . This is hardly an important difference. The "response" in these patients is a 50% reduction in seizures distributed over a month. The average difference in this small cluster of patients (including those on placebo is from 8 to 4 seizures in a month. With knowledge of the underlying data , one must further question the authenticity of this effect. This drug must be considered a borderline statistical win and an even more borderline clinical success .

A conservative interpretation of the results of this study is that they do not contradict the results of M91-603, specifically that tiagabine at the dose of 32 mg may be effective in the adjunctive treatment of partial onset seizures. Nevertheless, due to the imbedded inaccuracies identified with this study and the lack of significance on the primary variable, this study cannot stand on its own as a pivotal trial, nor does it provide strong support for the clinical efficacy of this medication

SECTION 7.2.4 STUDY M91-565

SECTION 7.2.4 .1 PROTOCOL SYNOPSIS

TITLE Phase II Study of Tiagabine: Efficacy and Safety in Adjunctive Treatment of Partial Seizures

OBJECTIVES: An evaluation of the efficacy of tiagabine in the treatment of partial seizures when given in addition to other antiepileptic drugs.

STUDY DESIGN: The study is a European multicenter (6) , double-blind, placebo-controlled, fixed -dose, balanced two-period crossover antiepileptic add-on trial. The study will include an initial screening phase consisting of an open labelled titration phase and open labelled fixed dose period prior to the double-blind phase.

STUDY SCHEMATIC

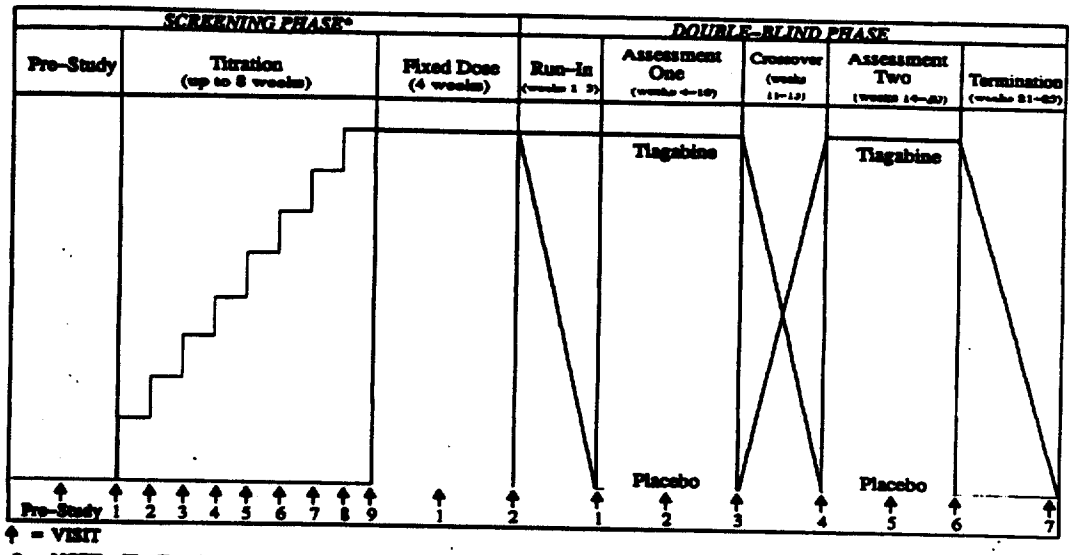


Figure 1. Study Schematic: Safety and Efficacy of Tiagabine HCl as Adjunctive Treatment for Complex Partial Seizures

PROTOCOL

PATIENT SELECTION

The population of interest is that with partial onset epilepsy manifested by **simple partial seizures with motor signs and/or complex partial seizures with or without secondary generalization.** Patients must have inadequate seizure control despite optimal doses/plasma concentrations of 1-3 established antiepileptic drugs. Projected enrollment for this study was 50 or more such patients.

Key Inclusion criteria

- Patients must have a diagnosis of either simple partial seizures with motor signs or complex partial seizures with or without secondary generalization. This diagnosis must be supported by the following:
- Observed ictal events consistent with simple partial seizures with motor signs or complex partial seizures that are documented by reliable observers.
  One of the next two:
- An ictal EEG demonstrating a focal abnormality in patients clinically having a simple partial seizure with motor signs or a complex partial seizure.
- An interictal EEG demonstrating unilateral or bilateral asynchronous activity consistent with the diagnosis.
  Or in the absence of a demonstrable EEG abnormality as defined above:
- CT or MRI evidence of a focal CNS lesion consistent with complex partial seizures or simple partial seizures with motor signs.
- Within the 8 week period preceding pre-study visit PI the patient must have experienced at least 6 partial seizures, partial seizures being defined here as simple partial seizures with motor signs and/or complex partial seizures. The seizures can have occurred alone or in combination with any other seizure type. If the seizures occur in clusters, only, the free intervals between clusters should not be more than 3 weeks.
- The patient must be on a stable regimen of between 1 and 3 of the following antiepileptic drugs: phenytoin, acetazolamide, flunarizine, carbamazepine, phenobarbital, primidone, valproate, clonazepam, clobazam, oxcarbazepine, or vigabatrin. (Vigabatrin, and oxcarbazepine are only acceptable in countries where regulatory approval has been received.)

Key Exclusion criteria

- Patients with a history of pseudo-seizures.
- Patients with an active CNS infection, demyelinating disease, degenerative neurologic disease, or any progressive CNS-disease that may confound interpretation of this study's result.
- Patients, who have had a clinical significant illness within the previous 3 months and/or who have

a medical or neurological disorder requiring frequent change in dose or medication.

- Patients with a disease manifesting with signs or symptoms that may confound interpretation of the study results.
- Patients taking concomitant non-epileptic medications which may confound interpretation of the study results,history of clinically significant psychiatric illness, psychological or behavioral problems, mentally retarded to such an extent that reliable recording of seizures and adverse events are impossible, and to such an extent that they cannot give informed content, have a confirmed diagnosis of a progressive cerebral tumor.
- Patients who have a history of substance abuse
- Patients who have taken investigational drugs (except tiagabine) within the last 2 months prior to the 8 week pre-study baseline period or any other anticonvulsant drugs than those allowed .

STUDY SCHEDULE The study consists of a Screening Phase and a Double-blind Phase. The e **Screening Phase** is divided into a pre-study, a titration and a fixed-dose period. Before entering the screening phase patients will give informed consent, provide a medical history, receive a physical examination and complete comprehensive laboratory tests . Eligible patients will then enter the titration period in which tiagabine will be administered on an open labelled basis in gradually increasing doses (12 - 64 mg/day). Dose escalation will continue until patients either show a clear reduction in seizure frequency or develop unacceptable adverse events. The dosage of tiagabine may be adjusted, if needed and thereafter held as constant as possible during the fixed dose period. The goal of the screening phase is to establish for each individual patient the dose of tiagabine at which there is a reduction in seizures from baseline or at which unacceptable adverse reactions develops. The dose range to explore is 12, 16, 20, 24, 32, 40, 52 and 64 mg per day.

Patients who experienced a reduction of at least 25 % in their total seizure frequency in the fixed dose period, who required no changes in their total daily dose of concomitant antiepileptic drugs, and who adequately tolerated tiagabine in the screening phase will enter the **Double-blind Phase**. When patients enter this phase they will be randomized (1:1) to two different sequences of drug administration: placebo-tiagabine or tiagabine-placebo. The dose of study drug will be selected by the investigator, individualized for each patient, and based on the safety and efficacy information collected for that patient during the screening phase. In the double-blind phase, study drug dosing will be held constant during the assessment periods.

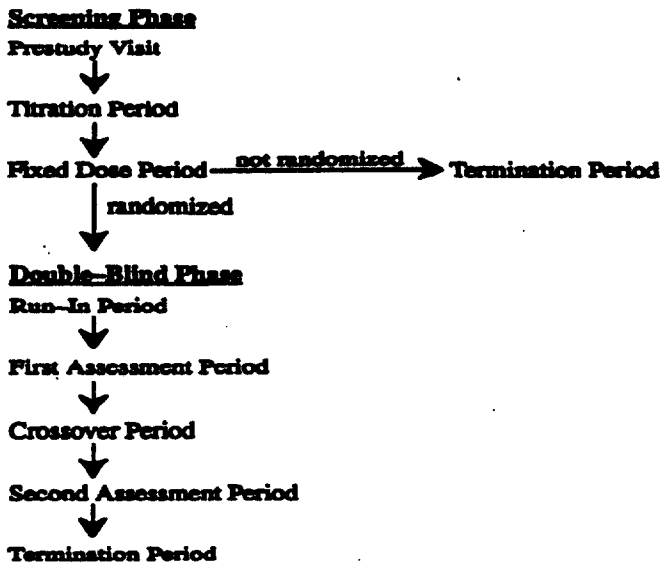
Treatment sequence: tiagabine-placebo

Patients assigned to the treatment sequence tiagabine-placebo will continue on the dose of tiagabine established during the screening phase until the end of assessment period one (i.e., through the run-in and assessment one periods). During the cross-over period the dose of study drug will be gradually reduced over 3 weeks to zero in 3 sequential steps. In assessment period two the patients will receive placebo.

Treatment sequence: placebo-tiagabine

For patients randomized to this treatment sequence the dose of study drug established during the screening phase will be gradually reduced to zero over 3 weeks. After assessment period one the dose of study drug will during the 2 week cross-over period be increased in 3 sequential steps to the dose level previously established during the screening phase.

Each assessment period is six weeks in duration



In summary, the Double-blind Phase of the study has a placebo controlled, fixed-dose, - two-period cross-over design, and consists of a run-in-period, two assessment periods separated by a cross-over period, and a termination period. Run-in, cross-over, and termination periods are included to permit gradual introduction and withdrawal of study drug .

MEDICATION AND DOSAGE REGIMEN

Tiagabine 2,3 and 4 gm tablets and matching placebos. Medication will be taken 4 times daily with food. The total daily dose of concurrent AEDs will remain unchanged, and if adjustments are needed patient will not be randomized.

EFFICACY VARIABLES

PRIMARY OUTCOME MEASURES

Seizure occurrences during the first and second assessment periods will be used for the efficacy analyses comparing add-on tiagabine and add-on placebo treatments. The primary efficacy variable will be the weekly partial seizure frequency calculated from seizures which occurred during an assessment period. Partial seizures occurring alone or progressing to secondarily generalized seizures will be included to calculate this seizure frequency. Additional analyses will be done considering complex partial and simple partial seizures separately.

All tests will be two-tailed and type 1 error rate of 0.05 will be used throughout.

SEIZURE RATE CALCULATION

The weekly seizure frequency will be calculated as the total number of partial seizures reported during an assessment period multiplied by the ratio of 7 days (one week to the actual number of days in that period. For example if a patient has 8 partial seizures in 28 days then be 2 (8x7/28) the estimated weekly seizure frequency will be normally calculated from visit 1 to visit 3 or from visit 4 to visit 6 (six weeks per period).

ANALYSIS METHOD:

The primary efficacy analysis will be a nonparametric analysis of the weekly partial seizure frequency based on the method proposed by Koch for two-period crossover studies and

application of it to multicenter studies using the van Elteren method.

SECONDARY ANALYSES

As a secondary analysis the weekly partial seizure frequency will be transformed to the square root scale and analyzed with an ANOVA which will include factors for sequence, center, patient, patient within center and period and for center and treatment.

Efficacy analyses will also be performed for complex partial seizures with or without secondary generalization and for simple partial seizures with motor signs, considered separately. Analysis of a particular seizure type will include patients who had at least one seizure of that type during **either the screening phase or the double blind phase.** Analysis methods will be similar to those used above, except that center effects will be ignored.

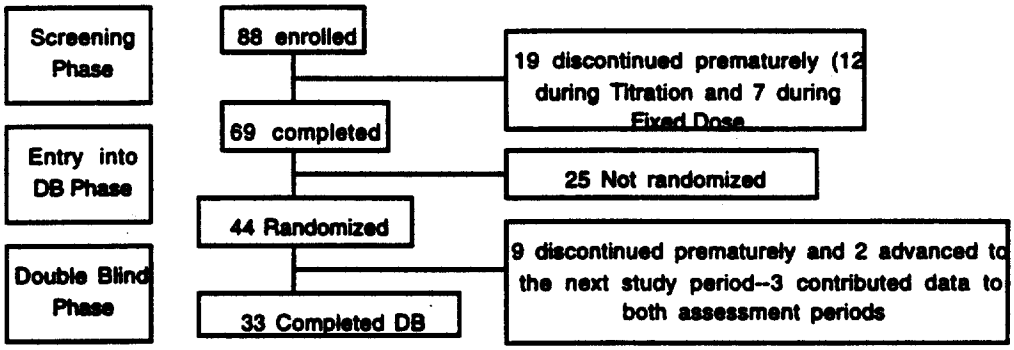
SECTION 7.2.4 .2 STUDY CONDUCT

ENROLLMENT

Eighty eight patients were enrolled in this study and all received tiagabine. Of these, 44 were randomized and entered the double blind phase.

PATIENT DISPOSITION

Forty four of the patients enrolled in the study were randomized and entered the double blind phase. One Dutch center used 5 clinics and randomization was carried out separately in these. Of those randomized 26 were randomized to the tiagabine-placebo sequence and 18 to the placebo-tiagabine sequence. Of these 24/26 and 12/18 completed both sequences. These 36 patients made up the sponsor's intent to treat dataset. The flow chart summarizes the disposition of patients in the study following randomization.



Nine patients discontinued prematurely during the double blind phase. Three (placebo) discontinued due to an adverse event, one (placebo) due to lack of efficacy. Five (tiagabine) were discontinued due to protocol violations.

Thus this study was meant to have a balanced crossover design but indeed it had a 2:1 (T/P:P/T) ratio for ITT.

PREMATURE CROSSOVER

In this study patients who had a clear, sustained increase in seizure frequency were

allowed to prematurely crossover from Assessment Period 1 to Assessment period 2. This practice only affected three patients, who had been randomized to the P/T sequence.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The following table summarizes patient characteristics and demographics (age, sex, race, etc) by sequence for all randomized patients in the intent to treat dataset.

Summary of Patient Characteristics (Intent to treat dataset)

	Tiagabine/Placebo N=24	Placebo/Tiagabine N=12	p-value
Age			
Mean	34.1	31.9	.501
range	20-49	20-51	
Gender			
female	7 (29%)	1(8%)	0.224
male	17 (61%)	11(92%)	
Years with Epilepsy			
Median	22.8	24.6	.763
Range	3.2-46.5	4.4-40.4	
Principal epilepsy etiologies			
Idiopathic	38%	33%	
Infectious	17%	25%	N/A
Trauma	21%	17%	
Ante/perinatal	17%	8%	
Seizure Types (Prestudy Screening)			
Partial	100%	100%	
Simple Partial	71%	25%	
Complex Partial	63%	92%	N/A
2° Generalized	42%	50%	
Other	4%	0%	
Number of AEDs ever Taken			
Median	7.5	6.0	.791
Range	1-14	2-19	

There were no significant differences between the groups on any variable analyzed. However, a higher proportion of patients in the tiagabine -placebo sequence had experienced simple partial seizures in the prestudy visit and a higher proportion of patients in the placebo tiagabine group experienced complex partial seizures in baseline.

STUDY DRUG ADMINISTRATION:

A summary of study drug administration during the double blind periods is presented in the table that follows. The mean TDD of tiagabine in the intent-to-treat dataset was 46.4

(range (16-64 mg) and the mean mg/kg TDD was 0.6 (range .23-1.16) mg/kg. The mean duration of tiagabine treatment was 84.4 days during the entire DB period for this group.

NUMBER OF PATIENTS PER DOSE LEVEL FOR EACH DATASET IN THE DOUBLE BLIND PHASE (N=44)

TDD OF TIAGABINE	RANDOMIZED	INTENT-TO-TREAT
12	0	0
16	3	2
20	2	1
24	3	3
32	4	3
40	8	8
52*	10	7
64	14	12

*Median dose achieved in this study was 52 mg

ERRORS IN RANDOMIZATION:
None were identified in this study.

CONCOMITANT AEDS AND DEVICES
Concomitant AEDs taken during the double blind phase was summarized by the sponsor. Thirty five (80%) of patients were taking CBZ prior to entering the study, 16 (36%) were on monotherapy and 19(43%) were on carbamazepine in combination with other drugs. The next most common AEDs were Valproic Acid (23%), vigabatrin (20%), Clobazam (14%) and phenytoin (14%). The most common AED combination was carbamazepine and valproate (7%). Concomitant AED plasma concentrations were obtained during the assessment periods, weeks 3 and 7. Concomitant AED concentrations are summarized below as tiagabine treatment period concentration expressed as % change from placebo.

CHANGE IN PLASMA CONCENTRATIONS OF MOST COMMONLY USED AEDS FROM PBO TO TGB TREATMENT PERIOD INTENT TO TREAT

AED	N	%Change in Concentration (mean±SD)	%Change in Distribution		
			>20% decrease	Within 20%	>20% increase
WEEK 3					
CBZ	22	3(18.4)	0	20	2
VPA	6	-7(25)	2	3	1
Phenytoin	5	-18(9.6)	3	2	0
Clobazam	3	-14(2.8)	0	3	0
WEEK 7					

AED	N	%Change in Concentration (mean±SD)	%Change in Distribution		
			>20% decrease	Within 20%	>20% increase
CBZ	24	2913.9)	0	22	2
VPA	6	18(47.1)	1	2	3
Phenytoin	6	4(14.7)	1	5	0
Clobazam	3	-16(35.8)	1	2	0

For most patients the plasma concentration s did not fluctuate more than 20%. No systematic increase or decrease could be seen for any AED.

PROTOCOL VIOLATIONS

CONCOMITANT AEDS AND DEVICES

Except for one patient, doses of concomitant AEDs remained constant throughout the study. Patient 7012 had his total daily dose of carbamazepine reduced during the placebo period of the double blind study. This patient was also unblinded during the study. This patient was excluded from all data analyses.

During this study there were several patients whose control of seizures could not be maintained even with 1-3 concomitant AEDs without the addition of additional drugs on a prn basis, most of which were benzodiazepines. The following summarizes the unapproved addition of medications to the existing AED regimen on a prn seizure basis:

USE OF PRN AEDS (ESPECIALLY BENZODIAZEPINES) DURING TRIAL 565

PT NUMBER	MEDICATION (DOSES)	TTEATMENT PERIOD
4004	Paraldehyde	TGB
	Clobazam 10-20 mg (9 doses)	7 doses TGB/2 doses PBO
4020	Clobazam 10-20 mg (2 doses)	TGB and PBO
4024	Clobazam 20 mg (6 doses)	TGB*
†7009	Diazepam 10 mg (1 dose	PBO
7011	Clonazepam 2.5 mg (1 dose)	TGB
†9002	Diazepam 10 mg (8 doses)	PBO
‡9012	Diazepam 10-20 mg (2 doses)	TGB
	Clobazam 30 mg (1 dose)	PBO
†9018	Diazepam 10 mg (2 doses)	PBO

† during placebo period
‡ during both periods
*this patinet was randomized to pbo-tgb sequence but it appears that he received only tiigabine, and not placebo first as scheduled.

There does not appear to have been any systematic error in favor of drug created by this pattern of medication, although the sponsor asserts that in most cases benzodiazepine use was most common during the placebo period.

COUNTING SEIZURES

There was some inconsistency in coding seizure types in this trial which could affect the efficacy responses for virtually all seizure types. This inconsistency was mainly in the area of generalized seizures. For example a number of patients experienced akinetic drop attacks in this study. These were coded inconsistently even though the clinical descriptions of the seizures were consistent. Center 9 appeared to have the most examples of coding primary akinetic seizures as complex partial. Those patients who experienced akinetic seizures in this study included the following: 9001, 9002, 9003, 9007, 9013, 9014 , 9015, 9018, 9019 . They were coded as CPAT and counted among all partial onset and partial complex seizures, presumably. Patient 4024 also experienced akinetic drop attacks, but this patients were coded as AT and not included with the others. One patient experienced myoclonus and was coded as SPMS (9019), while other patients who had simple partial with motor manifestations were also coded as SPMS. Another group included patients with generalized tonic clonic seizures. Clearly these fell into two categories, one in whom the seizure description included an antecedent seizure or aura and the other which did not. The former was appropriately coded with secondarily generalized tonic-clonic seizures. The latter in whom classical grand mal seizures were described, with no antecedent seizure were coded in a variety of ways. These are tabulated below.

VARIED CODING OF PATIENTS DESCRIBING CLASSICAL GTC WITH NO ANTECEDENT POS

PID	CODE	ANTECEDENT SZ	OTHER POS	DESCR	EEG/DX
4001	SPTC	No	Yes	Stiff/shakes	Focal slow/ Post meningitis
4006	CPCTC	No	No	No aura, GTC seizures with incontinence	Focal slow/ Idiopathic
4007	CPTC	No	No	Classical GTC	Focal Paroxysmal/ spina bifida HC
4008	SCTC	No	Prob	Tonic Clonic	Occasional L temporal slow/ temporal lobe atrophy
4012	SPTC	No	Poss	Tonic Clonic	Focal Paroxysmal/Post traumatic
4014	SPTC	No	Yes	No aura, TC sz	Mild x's theta rt parietooccipital/Familial epilepsy
4020	GTC	No	?*	TC sz no warning	Normal/ Idiopathic
4022	SPTC	No	yes	TC sz	Focal Paroxysmal/Posttraumatic
4024	CPTC	No	yes*	Stares, goes stiff	Focal paroxysmal/Idiopathic
5011	OTHS	No	yes	Tonic and clonic spasms with tongue bite	Focal paroxysmal/Rt frontal AVM
7009	CPTC	No	Yes	Infantile tonic clonic sz	Asymmetric/Neonatal insult and encephalitis
9001	CPTC	No	Yes*	GTC sz	Generalized and focal slow/Posttraumatic
9002	CPTC	No	Yes*	GTC sz	Focal slow and paroxysmal/Idiopathic
9016	SPTC	No	Yes*.	Falls to ground, body stiffens; arms and legs jerk. Few mins.	Focal paroxysmal/ Idiopathic

*other types of generalized seizures also described and recorded for this patient

Patients who experienced what were described as generalized tonic clonic seizures were all included in the overall analysis of all partial seizures and in the subgroup corresponding to the appropriate label. For example, patient 4014's GTC seizures would have been included in the analysis of secondarily generalized seizures as well as all partial seizures and simple partial seizures even though the seizures are described as having no aura. Patient 4020's GTC seizures (identical by description) might have been included in the secondarily generalized seizure category , perhaps in the combined partial onset category, but not in the subgroup analysis of complex partial seizures or simple partial seizures. The sponsor was pressed for more explanation of these scenarios. The response was as follows

> "It is true that the description of the generalized seizure for the patients you identify does not reflect the existence of an antecedent partial seizure and thus the description is inconsistent with the accompanying seizure code. However our colleagues at state that the seizure codes are correct. In some cases a seizure code may have been changed appropriately on the case report form to reflect a secondarily generalized seizure, but the corresponding description was not changed. "

The sponsor further indicates that only patient 4020 had both a GTC code and a seizure description that did not reflect a partial onset seizure. The sponsor also indicates that when a seizure was coded as a GTC, the presumed antecedent was counted among the Combined Partial Onset Seizures, Secondarily Generalized Seizures but not SPS or CPS.

STATUS EPILEPTICUS

In this study there were no patients who experienced status epilepticus, during an Assessment Period.

SECTION 7.2.4 .2 SPONSOR'S EFFICACY RESULTS

The sponsor's efficacy results for this study will be summarized in the following format:

(1) ALL PARTIAL ONSET SEIZURES:. WEEKLY PARTIAL SEIZURE RATE DURING AN ASSESSMENT PERIOD.
(2) COMPLEX PARTIAL SEIZURES: WEEKLY PARTIAL SEIZURE RATE DURING AN ASSESSMENT PERIOD
(3) SECONDARY GENERALIZED SEIZURES, : WEEKLY PARTIAL SEIZURE RATE DURING AN ASSESSMENT PERIOD.

Those analyses which differ from that which was planned will be pointed out. While the sponsor did other analyses, including an analysis for simple partial seizures, only those which are primary or are important in the sponsor's request for labeling will be discussed here.

(I) ALL PARTIAL ONSET SEIZURES : WEEKLY PARTIAL ONSET SEIZURE RATE DURING AN ASSESSMENT PERIOD

The weekly partial seizure rate on tiagabine was compared with placebo. The comparison is shown below.

WEEKLY PARTIAL SEIZURE RATES IN THE DOUBLE BLIND ASSESSMENT PERIODS INTENT-TO-TREAT GROUP PARTIAL ONSET SEIZURES N=36			
	TIAGABINE	PLACEBO	TIAGABINE MINUS PLACEBO : TREATMENT DIFFERENCE
Median	1.5	2.3	-0.6
Mean	2.4 (3.49)	3.7 (3.97)	-1.2 (2.31)
P-VALUES, VAN ELTEREN TEST			
WEIGHTED , .002			
NONWEIGHTED , .005			

The results show a statistically significant difference between treatment periods.

(2) PARTIAL COMPLEX SEIZURES: WEEKLY SEIZURE RATE DURING AN ASSESSMENT PERIOD. This analysis represents a subset of the original randomized group (28/44 patients). The weekly partial complex seizure rate during assessment periods was a secondary variable in this study. Comparisons of complex partial seizure rates for the intent to treat dataset are shown in the following table. There were only 28 of the 44 randomized patients who experienced at least one complex partial seizure in this study. These patients experienced a median of 0.7 fewer seizures per week (mean 1.1) while receiving tiagabine compared to placebo.

WEEKLY SEIZURE RATES IN THE DOUBLE BLIND ASSESSMENT PERIODS SUBSET OF "INTENT TO TREAT GROUP" COMPLEX PARTIAL SEIZURES N=28			
	TIAGABINE	PLACEBO	TIAGABINE MINUS PLACEBO : TREATMENT DIFFERENCE
Median	0.9	1.9	-0.7
Mean	1.5 (1.83)	2.6 (2.66)	-1.1 (1.99)
p-values, Van Elteren Test			
weighted , ≤.009			
nonweighted , ≤.009			

This difference was statistically significant in both the weighted and unweighted nonparametric analysis. (VanEleteren test).

(3) SECONDARY GENERALIZED SEIZURES : WEEKLY SEIZURE RATE DURING AN ASSESSMENT PERIOD.Another secondary efficacy variable was the weekly secondarily generalized TC seizure rate. This analysis also represents a subset of the original randomized group (18/44 patients). The weekly secondarily generalized TC seizure rate during assessment periods was a secondary variable in this study. Comparisons of secondarily

generalized TC seizure rates for the intent to treat dataset are shown in the following table. There were only 18 of the 44 randomized patients who experienced at least one secondarily generalized TC seizure in this study. These patients experienced a median of 0.4 fewer seizures per week (mean 0.6) while receiving tiagabine compared to placebo.

Weekly Secondary Generalized Seizures Rates In The Double Blind Assessment Periods
Intent-To-Treat Group
Secondary Generalized Seizures N=18

	Tiagabine	Placebo	Tiagabine minus Placebo : Treatment Difference
Median	0.6	0.8	-0.4
Mean	0.7(.75)	1.3 (1.43)	-0.6 (1.29)
p-values, Van Elteren Test			
weighted, 0.03			
nonweighted, 0.028			

This difference was statistically significant in both the weighted and unweighted nonparametric analysis. (VanEleteren test).

SECTION 7.2.4.4 FDA ANALYSIS

There are some theoretical problems associated with the design of this trial. This study combines an enrichment design with a crossover design, providing patients and investigators with two opportunities to become unblinded. The first of these is the long period of time on open label therapy , the enrichment phase during which time patients can optimize their dose titrating to "effect" and to adverse effects. Those who have a 25% reduction in seizures with this product are then randomized. This potential to recall side effects re-exposure may be heightened in this study as the period off drug and then on again (placebo/tiagabine sequence) or withdrawal after a long period on the product (tiagabine-placebo sequence) is conducted . Another opportunity for unblinding is created by the short titration periods of 2 weeks (compared to the initial 8 week titration period) between assessment periods and before Assessment Period 1. The third opportunity might occur with the patient who experiences an increase in seizures and is allowed to prematurely enter Assessment Period 2. This potential for unblinding is not addressed by the sponsor. Given the adverse event profile of tiagabine it may be assumed that the patients probably knew which treatment they were receiving.

The second problem with the design of this trial is that of the potential to experience withdrawal seizures or to have some carryover effect from the previous period. While the sponsor also did not address this potential in its analysis, Dr. Sahlroot performed an analysis of carryover effect. He found that for all partial seizures and partial complex seizures there was no statistically significant carryover effect in this study.

Significance tests for Carryover Effect in Crossover Trial M91-565
Parametric tests

All Partial Seizures	Complex Partial Seizures	Secondarily Generalized Seizures
p=0.87	p=0.55	p=ND

ANALYSIS OF MISSING DATA (Refer to Statistical Review for further details.)
Eight patients in this trial were randomized but did not contribute data to the ITT analysis due to missing data in one or more Assessment Periods. Two patients had missing data in both assessment periods.

Patients with Data missing during one or both Assessment Periods		
Patient	Assessment Period with missing data	Treatment
4015	1 (Analysis of all partial seizures only)	placebo
4016	2	tiagabine
4023	2	tiagabine
4024	1	placebo
4025	2	placebo
7012	2	placebo

These patients were incorporated into the analysis by imputing seizure rates for the missing Assessment Period. Patients with missing data in both Assessment periods were not used. The median seizure rate by seizure type during each Assessment period was determined using the set of all patients with data. The appropriate medians were then imputed for each patient with missing data . P-values for this trial were .041 for all partial seizures and 0.019 for complex partial seizures. Worst case analyses were also performed by imputing "0" for missing placebo seizure rates and imputing an arbitrarily large number for missing tiagabine rates. Results were not significant. (p>.25)

Comments The study on its face appears to demonstrate efficacy of tiagabine over placebo in the adjunctive treatment of Partial Onset Seizures with an effect size that is indeed small as noted in previous studies. The median seizure reduction with treatment is no more than .6 seizures per week or 2.4 seizures per month. When missing data is taken into account, this small difference may not even be statistically significant. The sponsor has not addressed the issue of blinding which is one of the real drawbacks of this trial, and for which reason it cannot be considered more than just a supportive trial.

Next, there is the problem of the raw data. Because the N for this study was so small and because there were so many patients with seizures that are of questionable categorization, this is an area that should be looked at more carefully by the sponsor and FDA together if the firm desires that this study should be relied upon.

Finally the problems discussed with secondarily generalized seizures in the previous studies must be addressed here by the sponsor.