CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20646

STATISTICAL REVIEW(S)

DCTIRN

SEP 12 1996

Statistical Review and Evaluation

SEP 6 1996

NDA#: 20-646

Applicant: Abbott Laboratories

Drug: Gabatril™ (tiagabine)

Indication: Adjunctive therapy for partial onset seizures

Documents reviewed: Vols. 1.592, 1.616, 1.638, 1.650 and 1.658

Medical Reviewer: Cynthia McCormick, M.D. (HFD-120)

Background

The sponsor has submitted data for five randomized double-blind placebo-controlled clinical trials of tiagabine as add-on therapy (M91-603, M91-605, M92-775, M90-481, M91-565) (See Table 0). All trials were conducted by Abbott Laboratories except Trials 775 and 565 which were conducted by Three trials were parallel group (603, 605, 775) and two had a crossover design (481, 565). Protocol-specified (or protocol-revised) primary endpoints were: change from Baseline to Experiment Period in four-week complex partial seizure (CPS) rate (603, 605), proportion of patients with ≥50% reduction from Baseline to Fixed Dose Period in weekly partial onset seizure (PS) rate (775), difference in four-week CPS rate between placebo and tiagabine treatment periods (481), and difference in weekly PS rate between placebo and tiagabine treatment periods (565).

The sponsor conducted two monotherapy trials, M93-090 and M90-511, but chose not to submit individual study reports. Summary results were available from the Integrated Summary of Efficacy. Trial 090 failed to show a statistically significant difference -- no p-value was presented -- between high and low dose tiagabine on the primary endpoint, change from Baseline to the Experiment Period in four-week CPS rate. Trial 511 discontinued early, enrolling just 11 patients.

The sponsor has conducted a plethora of analyses for each add-on trial involving various combinations of patient dataset (intent-to-treat (ITT), evaluable, completers), seizure type (CPS, PS, simple partial (SPS), secondarily generalized tonic-clonic (SGTC)) and statistical analysis methodology (parametric or nonparametric, weighted or unweighted[1]). This review will focus on the sponsor's results for (1) protocol-specified primary endpoints using the primary analysis

[1] Weighted and unweighted analyses are explained in greater detail in the "FDA Analysis" section of this review.

methodology. Other analysis results will be cited as needed. This review will consider only ITT analyses.

Appendix 1 lists all seizure types that occurred during the trials. To calculate seizure rates for one of the "analysis" seizure types (PS, CPS, SPS or SGTC), the sponsor used all seizures of that type occurring alone or in combination with other seizure types. For example, analysis of CPS included complex partial seizures occurring alone, simple partial evolving to complex partial, simple partial evolving to complex partial evolving to secondarily generalized tonic-clonic, and complex partial evolving to secondarily generalized tonic-clonic. Thus, a seizure could be included in several different analyses, e.g., a complex partial seizure evolving to a secondarily generalized tonic-clonic seizure was analyzed as a CPS, PS and SGTC seizure. For each of the four seizure type categories, analysis of data from Trials 603 and 605 included patients *with at least one seizure of that type during the Baseline Period.* For Trial 775, included all patients *with at least one seizure of that type during Baseline or the Fixed Dose Period.* For crossover Trials 481 and 565, analyses included patients who had *at least one seizure of the given type during either one of the Assessment Periods.*

This reviewer did not examine the sponsor's analyses of SGTC seizures or conduct any independent analysis of this seizure type. According to Dr. McCormick, the sponsor's seizure classification effort reflected an uncertainty in diagnosis between primary and secondary generalized seizures. For this reason, the sponsor's analysis of SGTC seziures is probably flawed, as would be any statistical analysis of these data. In consultation with Dr. McCormick, this reviewer also did not examine the sponsor's analyses of or conduct any independent analysis of SPS since the sponsor does not want a claim for this indication.

Sponsor's Results

Trial 603

This trial was a randomized, double-blind placebo-controlled parallel group add-on trial conducted at 21 U.S. centers. The trial compared three dose levels of tiagabine (16, 32, 56 mg/day all administered as qid doses) to placebo. Study phases included an eight-week Baseline Phase and 20-week Double-Blind Phase, the latter consisting of a four-week Titration Period, 12-week Fixed Dose Period and four-week Discontinuation Period. The Titration and Fixed Dose Periods constituted the Experiment Period (EP). The protocol-specified primary endpoint was the change from Baseline to Fixed Dose Period in the 12-week CPS rate. The primary endpoint was revised via protocol amendment to the Baseline-to-EP change in the four-week CPS rate. The protocol-specified primary comparison was the combined tiagabine 32 mg/day and 56 mg/day treatment groups ('tiagabine (32+56) mg') vs placebo.

Two hundred ninety seven (297) patients were randomized to receive tiagabine or placebo. Ninety one (91), 61, 88 and 57 patients were randomized in ratios 3:2:3:2 within centers to placebo and tiagabine 16 mg, 32 mg and 56 mg, respectively. Minimum Baseline seizure rates

required for randomization were eight CPS per 12 weeks and one CPS during two of three four-week blocks. No changes were allowed to the total daily doses of concomitant antiepileptic drugs. Table 1 shows patient demographics by treatment group. A significant difference was seen for 'years with epilepsy' between placebo and tiagabine (32+56) mg (p=.040, not shown in Table 1 which lists p-values across all four treatment groups only). There were no other significant differences between groups in any other demographic variables. Baseline four-week CPS rates were comparable between groups (**medians:** placebo 7.4, tiagabine 16mg 8.5, tiagabine 32mg 9.6, tiagabine 56mg 9.1; p.=71) and as well as for tiagabine (32+56) mg (median 9.2) vs placebo. Two hundred forty three (243) patients (83%) completed the trial. Table 2 lists reasons for premature discontinuation by treatment group.

Three patients experienced complex partial status epilepticus (SECP) (one tiagabine 32mg, two tiagabine 56mg). A fourth patient receiving tiagabine 56 mg experienced generalized tonic-clonic status epilepticus (SEGTC)[2]. Three of these patients experienced a total of nine episodes of SE, the other patient an unknown number of episodes. Because estimates for the number of seizures in each SE were not generally available, the sponsor used a post-hoc method to assign each SE episode a seizure count equal to n+1, where n was the maximum daily number of seizures of that type during the Baseline or EP.

The ITT dataset consisted of all randomized patients with at least one 'interval seizure history' during the EP (n=295). (Two randomized patients were excluded from the ITT analyses due to the absence of seizure data during the Double-Blind Phase.) The primary analysis method per-protocol was the van Elteren test, a nonparametric test which blocks on center.

Results for the primary endpoint (four-week CPS rate) and primary treatment comparison are shown in Table 3A. Results for PS are shown in Table 3B. Table 4 shows results of pairwise comparisons of each treatment group with placebo. Results for the change in four-week seizure rate across all seizure types and analysis methods are shown in Table 5. Patients in the tiagabine (32+56) mg group experienced a median decrease of 2.6 CPS per four weeks relative to Baseline. Placebo patients experienced a median decrease of 0.6 CPS. The difference was statistically significant for weighted and unweighted van Elteren analyses (p=.007 and .018, respectively). Thirty four (34) patients in the tiagabine (32+56) mg group (24%) experienced ≥50% reduction in CPS from Baseline compared to four patients (4%) in the placebo group (p<.001). No significant interactions of treatment with sex, age or race were observed (p>.10).

Trial 605

This trial was a randomized, double-blind placebo-controlled parallel group add-on trial conducted at 26 U.S. centers. The trial compared two regimens of tiagabine (16 mg bid and 8 mg

---

[2] The sponsor's Final Report puts the number of patients with SE at four. The raw data (electronic data supplied by the sponsor) show only three patients with SE during the trial. Dr. McCormick identified the fourth SE patient from the CRFs.

qid) to placebo. Study phases included an eight-week Baseline Phase and 20-week Double-Blind Phase, the latter consisting of a four-week Titration Period, eight-week Fixed Dose Period and four-week Discontinuation Period. The Titration and Fixed Dose Periods constituted the EP. The protocol-specified primary endpoint was the change from BP to Double-Blind Phase in the eight-week CPS rate. The primary endoint was revised via protocol amendment to the Baseline-to-EP change in four-week CPS rate. The objective of the trial was to compare each of the two tiagabine dosing regimens to placebo.

Three hundred eighteen (318) patients were randomized to receive tiagabine or placebo. One hundred seven (107), 106 and 105 patients were randomized in ratios 1:1:1 within centers to placebo, tiagabine 16 mg bid and tiagabine 8 mg qid, respectively. Minimum Baseline seizure rates required for randomization were six CPS per eight weeks and one CPS during each successive four-week block. No changes were allowed to the total daily doses of concomitant antiepileptic drugs. Table 6 shows patient demographics by treatment group. There were no significant differences between groups in any variables. Baseline four-week CPS rates were comparable between groups (**medians:** placebo 8.0, tiagabine 8mg qid 7.9, tiagabine 16mg bid 8.4). Two hundred seventy one (271) patients (85%) completed the trial. Table 7 lists reasons for premature discontinuation by treatment group.

Four patients experienced SE (two placebo, two tiagabine 16mg bid). Three patients each experienced one episode of SE and the other patient experienced an unknown number of episodes. Three patients experienced SECP (two placebo, one tiagabine 16mg bid) and the fourth experienced SEGTC. As in Trial 603, each SE episode was assigned a seizure count equal to n+1, where n was the maximum daily number of seizures of that type during the Baseline or EP.

The ITT dataset consisted of all randomized patients with at least one 'interval seizure history' during the EP (n=317). (One patient was excluded from the ITT dataset for this reason.) The primary analysis method was per-protocol the van Elteren test. The sponsor also excluded all three patients at center 6117 (#10501, 10502, 10503) for **all** pairwise comparisons because there were no patients in the tiagabine 16 mg bid group to permit the **particular** comparison with placebo. Thus, 314 patients contributed to analyses involving pairwise comparisons of tiagabine 16 mg bid and 8 mg qid with placebo.

Results for the primary endpoint (four-week CPS rate) and primary treatment comparisons are shown in Table 8A. Results for PS are shown in Table 8B. Results for the change in four-week seizure rate across all seizure types and analysis methods are shown in Table 9. Twenty-four (24) patients randomized to placebo had tiagabine in their plasma at one or more visits. These patients were analyzed according to their assigned randomization. Patients in the placebo, tiagabine 16 mg bid and tiagabine 8 mg qid treatment groups experienced median decreases of 0.2, 1.6 and 1.2 CPS per four weeks compared to Baseline, respectively. The difference was statistically significant for tiagabine 8 mg qid vs placebo ($p=.018$) after Dunnett's correction ($\alpha=.027$) but not for tiagabine 16 mg bid vs placebo ($p=.055$). Thirty three (33) patients (31%) in

the tiagabine 16 mg bid mg group and 28 patients (27%) in the tiagabine 8 mg qid mg group experienced ≥50% reduction compared to ten patients (10%) in the placebo group (p<.001 and p=.001, respectively). There was a significant interaction of treatment with age (p=.009) for age categories 12-18, 19-50 and >50 with larger treatment differences observed in the 12-18 age category compared to the other categories. No significant interaction was found between treatment and sex. The sponsor did not examine race.

Trial 775: Novo Nordisk analysis

This trial was a randomized, double-blind placebo-controlled parallel group add-on trial conducted at 11 European centers. The trial compared tiagabine 10 mg tid to placebo. Study phases included a 12-week Baseline Phase and 22-week Double-Blind Phase, the latter consisting of a six-week Run-in Period, 12-week Fixed Dose Period and four-week Termination Period. The protocol-specified primary endpoint was the proportion of patients with ≥50% reduction from Baseline in weekly PS rate during the Fixed Dose Period. Four-week rates were used in the actual analyses for purposes of comparability with other trials and did not affect trial results.

One hundred fifty four (154) patients were randomized in a 1:1 ratio within centers to tiagabine or placebo. Seventy seven (77) patients were randomized to tiagabine and the same number to placebo. Six patients incorrectly received medication that had been allotted to other patients. Only one mistake involved a patient receiving the wrong test drug. This patient, randomized to placebo, received tiagabine for four weeks. All six patients were included in the ITT dataset and analyzed according to the randomized treatment assignment. Minimum Baseline seziure rates required for randomization were eight PS during Baseline and one PS during two of three four-week blocks. No changes were allowed to the total daily doses of concomitant antiepileptic drugs. Table 10 shows patient demographics by randomized group. There were no significant differences between groups in any variables. Baseline four-week PS rates were comparable between groups (**medians:** tiagabine 12.2, placebo 10.5; p=.12). One hundred twenty five (125) patients (81%) completed the trial. Table 11 lists reasons for premature discontinuation by treatment group.

Six patients experienced SE (three placebo, three tiagabine) during the trial for a total of 35 episodes. The table below summarizes SE episodes from the raw data:

Patient	Baseline	Titration	Fixed Dose	Termination	Total
15005	0	0	1	1	2
15006	2	1	4	3	10
19007	0	0	0	1	1
19013	9	11	0	0	20
20002	0	0	0	1	1

21011	0	1	0	0	1
total	11	13	5	6	35

Three patients experienced SECP (two placebo, one tiagabine), two experienced simple partial status epilepticus (SESP) (one placebo, one tiagabine) and the sixth patient, randomized to tiagabine, experienced a SEGTC. Each investigator in Trial 775 provided for each episode of SE an estimate of the number of seizures occurring during the episode. used these estimates in their efficacy analyses.

The ITT dataset consisted of all randomized patients (n=154). The primary analysis method was per-protocol based on the set of 2x2 tables, stratified by center, of percentages formed by classifying treatment vs ≥50% seizure reduction. An exact test of the common odds ratio was performed (Metha 1985).

Results for PS are shown in Table 12. Results for other seizure types (CPS, SPS, SGTC) are shown in Tables 13-15. Eleven (11) patients receiving tiagabine (14.3%) and 5 patients receiving placebo (5.6%) experienced a ≥50% reduction in PS from Baseline to the Fixed Dose Period (p=.169). Median percent reductions in PS from Baseline to the Fixed Dose Period for patients receiving tiagabine and placebo were 12.6% and 0.0%, respectively (p=.027)[3]. The trial failed to show a difference on the primary endpoint but did demonstrate significant differences for continuous measures involving PS rate, i.e., absolute and percent reductions. No analyses for CPS were statistically significant.

Statistical interactions between treatment and sex or age were not examined. Race was not examined because all patients were Caucasian.

Trial 775: Abbott re-analysis of raw data

Abbott re-analyzed the data from this trial, making the following changes/additions to the analyses:

- endpoint (**from** responder rate **to** change from Baseline in four-week seizure rate)
- statistical test (**from** exact test of the common odds ratio **to** weighted van Elteren)
- study periods used in analysis (**from** Fixed Dose Period **to** EP)
- estimation of the number of seizures in each SE (**from** investigator estimates **to** the re-estimation procedure used in Trials 603 and 605)

[3] Trial 775 used the endpoint 'seizure rate percentage reduction from Baseline' as the primary means to assess efficacy. This endpoint was analyzed using categorical methods for the binary variable (<50% vs ≥50% reduction) and the van Elteren test for the continuous variable. Absolute change in seizure rate from Baseline was analyzed using the square-root transformation and two-way ANOVA. labelled the van Elteren and square-root transform methods as "secondary" and "alternative" analyses, respectively, in the protocol.

Abbott and analysed the same four seizure types, although there were differences in how particular seizures were categorized, particularly secondarily generalized tonic-clonic seziures. Results for the two sets of analyses are summarized in the table below:

Seizure type	p-value [1]	Abbott p-value [2]
PS	.169	.019
CPS	.37	.014
SPS	.009	.040
SGTC	.40	.008

[1] Primary analysis (exact test of common odds ratio) of primary endpoint (responder rate) as presented in Final Report

[2] Re-analysis of raw data using Baseline-to-EP change in four-week seizure rate as endpoint, weighted van Elteren analysis

parametric analyses of Baseline-to-Fixed Dose Period change in four-week seizure rate and nonparametric analyses of percentage reduction in seizure rate were consistent with Abbott's analyses of PS and SPS types (i.e., $p<.05$). (Tables 12-15) Analyses of CPS and SGTC seizure types did not agree. Differences in results for SGTC may be explained by mis-classification of some seizures (i.e., omitting SGTC, GTC and SEGTC seizures from the SGTC seizure type category) or the use of different study periods. Discrepancies between CPS analyses may have arisen from any or all of the following: (1) the use of different study periods, (2) the reduced size of the Abbott ITT dataset (n=147) due to exclusion of seven patients not experiencing CPS during Baseline, or (3) re-estimation of the number of seizures in episodes of SECP (three patients; nine total episodes).

The sponsor also re-examined the primary endpoint, responder rate, for each seizure type based on EP data instead of Fixed Dose Period data. Abbott results were consistent witl results in that only the analysis of SPS demonstrated statistical significance ($p=.024$).

Trial 481

This trial was a randomized, double-blind placebo-controlled crossover add-on trial conducted at five European centers. The trial compared tiagabine at individualized, investigator-selected daily doses up to 52 mg, to placebo. Final daily doses were allowed to be 2, 3, 4, 5, 6, 8, 10, and 13 mg qid. Study phases included an initial open label phase followed by Screening and Double-Blind Phases. The Screening Phase consisted of Titration and four-week Fixed Dose Periods. The Double Blind Phase consisted of the Run-in Period, First Assessment Period, Crossover

Period, Second Assessment Period and Termination Period (Appendix 2).

During the open label phase, an individualized dose of tiagabine was established and maintained throughout the Double Blind Phase. In this enrichment design, patients who showed a positive response during the open label phase entered the Screening Phase. Protocol-eligible patients entered the Titration Period during which tiagabine was administered in gradually increasing daily doses from 8 mg to a maximum of 52 mg. Dose escalation continued until patients showed either a clear reduction in seizure frequency or developed unacceptable adverse events. Thereafter, the dose of tiagabine was held constant during the Fixed Dose Period.

Patients who experienced ≥25% reduction in **total** seizure frequency during the Fixed Dose Period were randomized in a 1:1 ratio at each center and dose level to one of two treatment sequences, tiagabine/placebo (i.e., tiagabine during the first Assessment Period and placebo during the Second Assessment Period) or placebo/tiagabine (placebo during the first Assessment Period and tiagabine during the Second Assessment Period). Assessment Periods were seven weeks in duration and were preceded by either a three-week Run-In Period (First Assessment Period) or three-week Crossover Period (Second Assessment Period). "Patients who experienced a clear, sustained increase in seizure frequency during the First Assessment Period but who were otherwise suitable to continue the study were to be prematurely crossed over to the Second Assessment Period."

The protocol-specified primary endpoint was the four-week CPS rate during the First and Second Assessment Periods.

Forty-six (46) patients were randomized. Twenty five (25) patients were randomized to the T/P treatment sequence, 21 patients to the P/T treatment sequence. Patient #904 should have been assigned the sequence T/P but was mistakenly assigned, as patient #905, to P/T. However, the patient, ultimately coded as #9005, correctly received the sequence T/P for #904. Patients must have experienced six CPS within the eight weeks preceding the Prestudy Visit in addition to the ≥25% reduction in total seizure frequency to qualify for randomization. Patients were also required to be on stable daily doses of one to three concomitant antiepileptic drugs. Table 16 shows patient demographics by treatment sequence group. Only height showed a significant difference between sequences. Thirty nine (39) patients (85%) completed the trial. Table 17 lists reasons for premature discontinuation.

"Cases of SE were excluded from all seizure rate calculations [calculations made using data from the Fixed Dose Period to determine eligibility for randomization] due to the difficulty in assigning a specific seizure count to them." Three patients experienced a total of 14 episodes of SE (10 absence status (SEAB), 4 SEGTC) during the trial. All episodes occurred during the Fixed Dose Period or before, not during Assessment Periods.

The ITT dataset consisted of all randomized patients who provided data for both Assessment Periods (n=42; 23 T/P, 19 P/T). One patient, randomized to P/T, crossed over early from the

First Assessment Period to the second Assessment Period due to lack of efficacy. The primary analysis method was per-protocol the van Elteren generalization to the multicenter case of Koch's nonparametric method for analyzing two-period crossover designs (Koch, 1972).

Results for CPS are shown in Table 18. Results for other seizure types (PS, SPS, SGTC) are shown in Tables 19-21. The median treatment difference (tiagabine minus placebo) in four-week CPS rate across treatment sequences was -1.8 in favor of tiagabine and nearly statistically significant (weighted van Elteren p=0.054). There was a significant center-by-treatment interaction (p=.002) due primarily to the results (favoring placebo) at the second largest center (Table 18). The sponsor performed analyses which excluded this center, an "epilepsy colony" for very refractory patients, and obtained statistically significant results regardless of the analysis method.

The median achieved dose level was 32 mg/day (n=46).

Trial 565

This trial was a randomized, double-blind placebo-controlled crossover add-on trial conducted at five European centers. The trial compared tiagabine at an individualized, investigator-selected daily doses up to 64 mg, to placebo. The overall design and study phases were intended to mimic those of Trial 481 except that the dosages of tiagabine were allowed to be 3, 4, 5, 6, 8, 10, 13, and 16 mg qid.

The protocol-specified primary endpoint was the weekly PS rate during the First and Second Assessment Periods.

Forty-four (44) patients were randomized in a 1:1 ratio at each center and dose level to T/P or P/T treatment sequences. One center had five clinics; randomization was carried out separately within each clinic. Twenty six (26) patients were randomized to the T/P treatment sequence, 18 patients to the P/T treatment sequence. Patients must have experienced six PS within the eight weeks preceding the Prestudy Visit in addition to the ≥25% reduction in total seizure frequency to qualify for randomization. Patients were also required to be on stable daily doses of one to three concomitant antiepileptic drugs. Table 22 shows patient demographics by treatment sequence group. There were no significant differences in Baseline variables between sequences. Thirty three (33) patients (75%) completed the trial. Table 23 lists reasons for premature discontinuation.

Four patients experienced a total of 23 episodes of SE (18 SECP, five SESP). All episodes occurred during the Fixed Dose Period or before, not during Assessment Periods.

The ITT dataset consisted of all randomized patients who provided data for both Assessment Periods (n=36; 24 T/P, 12 P/T). Three patients, randomized to P/T, crossed over early from the First Assessment Period to the Second Asessment Period due to lack of efficacy. The primary

analysis method was identical to that used in Trial 481.

Results for PS are shown in Table 24. Results for other seizure types (CPS, SPS, SGTC) are shown in Tables 25-27. The sponsor reported a median treatment difference (tiagabine minus placebo) in weekly PS rate across treatment sequences equal to -0.6 in favor of tiagabine ($p=0.002$ weighted van Elteren). This reduction is equivalent to a change in four-week PS rate of -2.4.

The median achieved dose level was 52 mg/day (n=44).

Sponsor's Analysis of Required Demographic Subgroups

Tests of subgroup-by-treatment interaction using combined data from Trials 603 and 605 (except the tiagabine 16 mg dose group in 603) showed that the efficacy of tiagabine (measured by ≥50 reduction in CPS rate) was not affected by age, race or sex ($p \geq .32$).

FDA Analyses

Tables 28-31 summarize the sponsor's efficacy results. Figures 1-24 (Trial 603 Fig. 1-8, Trial 605 Fig. 9-16, Trial 775 Fig. 17-18, Trial 481 Fig. 19-22, Trial 565 Fig. 23-24) show **empirical distribution functions** for various treatment comparisons during treatment (change in four-week seizure rate from Baseline) or Baseline (four-week seizure rate). Some graphs show PS results, others CPS. Trials 775 and 565 used PS rate as the primary endpoint; graphs for these two trials show PS results only. (Addtional notes for all Figures: (1) Figures are drawn to different scales; (2) Some data (i.e., data in the tails of the distributions) are not shown due to limits imposed by the desired scale.).

This reviewer conducted additional analyses of the efficacy data from the five trials. The additional analyses, described briefly below, are explained in greater detail later with the results.

Parallel group trials: Additional statistical analyses

- Analyses exploring differences between sponsor's weighted and unweighted van Elteren analyses
- Sensitivity analyses of SE episodes

Crossover trials: Additional statistical analyses

- Tests of carryover effect in crossover trials
- Analyses of patients with missing data
- Analyses of phenytoin concentration data (Trial 481 only)

Parallel group trials

Weighted vs unweighted analyses: The sponsor's primary analysis method was the van Elteren

analysis. The van Elteren is a linear combination of Wilcoxon rank-sum statistics over centers. It is generally understood to be a weighted approach, as recomended by Lehman (1975), in which center results are weighted in rough proportion to sample size. An unweighted approach to the van Elteren analysis, in which centers contribute equally to the overall test statistic regardless of sample size, is recommended by van Eeden and Hemelrijk (1980). One commonly used set of weights (i.e., coefficients in the linear combination) is, for each Wilcoxon, the inverse of the variance. The sponsor first "centered" and averaged the Wilcoxon statistics at each center, then used weight $3(n1_i \cdot n2_i) / (n1_i+n2_i+1)$. This weight is the inverse of the variance of the centered Wilcoxon for center i with treatment groups of size $n1_i$ and $n2_i$. The weighted analysis increases the precision (i.e., reduces the variance) of the test statistic over strata when sample sizes vary from center to center. The weights also serve to emphasize the contribution of larger centers to the overall test statistic.

For all analyses of CPS and PS in parallel group trials, the sponsor's p-values for the weighted van Elteren were, without exception, smaller than those for the unweighted van Elteren. Weighted and unweighted p-values were moderately different in Trial 605 and dramatically different in Trial 775. For the latter trial, p-values were .014 (weighted) vs .30 (unweighted) for CPS and .019 vs .40 for PS. Weighted analyses of CPS and PS produced smaller p-values due to increased precision and the increased contribution of larger centers which had greater treatment differences. Note in Figure 25 the positive relationship between center sample size and magnitude of treatment difference for PS. To assess the effect of smaller centers on the unweighted results, this reviewer removed the three smallest centers (n=3,4,4) and repeated the sponsor's analyses. The 11 patients removed from analyses were different from the remaining 143 patients in that they had higher Baseline four-week PS rates (median 24.5 vs 11.0). The re-analyses produced p-values of .013 (weighted van Elteren) and .064 (unweighted van Elteren). Thus, the analyses reduced the disparity between weighted and unweighted approaches. For CPS, weighted results were essentially unchanged, but the unweighted p-value was reduced from .30 to .10.

Similar sensitivity analyses were also conducted for pairwise treatment comparisons in Trial 605 for CPS and PS with no change in the sponsor's results.

Status epilepticus: The sponsor applied a post-hoc method to estimate the number of seizures in each episode of SE [4]. Each SE event was assigned a seizure count equal to n+1, where n was the maximum of daily number of seizures of that type during the Baseline or EP. Abbott applied the estimation method in Trials 603, 605 and in their re-analysis of efficacy data from Trial 775. (In Trial 775, allowed each investigator to provide for each episode of SE an estimate of the number of seizures.) There were no SE events reported during Assessment Periods of the

[4] The raw seizure data consisted of patients' daily seizure counts for each seizure type. The sponsor listed each SE episode as consisting of one or an unknown number of seizures. The four-week seizure rates submitted by the sponsor incorporated episodes of SE and their estimated number of seizures using the estimation procedure. This assurance is provided by the sponsor in Attachment 1 of the electronic submission. This reviewer verified that the estimation procedure was correctly carried out in a random selection of four patients with SE.

crossover trials.

A sensitivity analysis was performed to assess the degree of dependence of the analyses on the method for estimating episodes of SE. Dr. McCormick felt that the sponsor's estimation procedure in many cases severely underestimated the "true" number of seizures representative of such an event. 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 no episodes of SE during the trial or SE episodes during the Termination Phase only (i.e., after completion of the EP) were assigned their observed seizure rates.

The table below shows the numbers of patients falling into the first three categories above. SE information was obtained from the raw data. Supporting information was provided by Dr. McCormick:

Patients with Status Epilepticus (SE) episodes [a]

Trial	SE during Baseline only	SE during EP only	SE during Baseline and EP
603	1--tiagabine 32 mg (SECP) 1--tiagabine 56 mg (SEGTC)	1--tiagabine 56 mg (SECP)	1--tiagabine 56 mg (SECP)
605	none	2--placebo (SECP) 1--tiagabine 16 mg bid (SECP)	1--tiagabine 16 mg bid (SEGTC)
775	none	1--tiagabine (SECP) 1--placebo (SECP)	1--tiagabine (SESP) 1--placebo (SECP)

[a] data shown as: number of patients--treatment group (seizure type involving status)

Sensitivity analyses of PS included each type of SE listed in the table (SECP, SEGTC, SESP). Analyses of CPS included only the SECP seizure type.

This reviewer performed the sensitivity analyses using the sponsor's weighted and unweighted van Elteren on the Baseline-to-EP change in four-week seizure rate for the following treatment group comparisons:

-- Trial 603: tiagabine (32+56) mg vs placebo
-- Trial 605: tiagabine 16 mg bid vs placebo
tiagabine 8 mg qid vs placebo
-- Trial 775: tiagabine 10 mg tid vs placebo

Results of the sensitivity analyses were:

Trial: trmt comparison	Van Elteren p-value		Comparison of p-values from sensitivity analysis with sponsor's p-values
	weighted	unweighted	
603: (32+65) mg vs P	CPS .004 PS .0007	CPS .011 PS .001	Very small differences; sponsor's p-values remain statistically significant
605: 8 mg qid vs P	CPS .018 PS .057	CPS .104 PS .173	Unchanged or very small differences; sponsor's CPS weighted van Elteren p-value remains statistically significant
605: 16 mg bid vs P	CPS .035 PS .104	CPS .184 PS .172	CPS sensitivity p-values lower, but no non-significant p-values becoming significant using Dunnett's criteria (α level cutoff=.027 for 2 trmt groups vs placebo)
775	CPS .0498 PS .0465	CPS .50 PS .60	All sensitivity p-values larger; CPS and PS weighted van Elteren results still statistically significant though very close to .05 level

Differences in results between the sensitivity analysis and the sponsor's analysis were generally small. This is not surprising since only four patients in each trial experienced episodes of SE. However, it should be noted that the van Elteren is a stratified approach; rankings are performed **within** each center then combined **across** centers to form the overall test statistic. A patient with SE is ranked within center only, not across all patients in the trial. Presumably a non-stratified analysis would yield different p-values than those obtained here.

Crossover trials

Analysis of carryover effect: This reviewer conducted tests of carryover effect for Trials 481 and 565 (Fleiss 1986). Grizzle (1965) suggested performing these tests at the .10 level of significance. The p-values for the parametric tests were:

Significance tests for carryover effect in crossover trials

Trial	Seizure type	
	CPS	PS
481	.87	.55
565	.73	.61

Results of nonparametric tests were similar.

Analysis of missing data: Four patients in Trial 481 and eight patients in Trial 565 were randomized but did not contribute to the ITT analyses due to missing data in one or more Assessment Periods. Listed below are randomized patients who provided seizure frequency data in exactly one of the Assessment Periods. One 481 patient and two 565 patients (not listed) had missing data in both Assessment periods:

Trial	Patient	Assessment Period with missing data	Treatment
481	5015	2	tiagabine
	7004	2	tiagabine
	7010	2	placebo
565	4015	1 (PS only)	placebo
	4016	2	tiagabine
	4023	2	tiagabine
	4024	1	placebo
	4025	2	placebo
	7012	2	placebo

This reviewer incorporated these patients into the analyses 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 median was then imputed for each patient with missing data. P-values for Trial 481 were .031 and .027 for CPS and PS, respectively. P-values for Trial 565 were .019 and .041 for CPS and PS, respectively. Worst case analyses were also performed by imputing '0' for missing placebo seizure rates and imputing an arbitrarily large number for missing tiagabine seizure rates. Results were not significant for either trial ($p>.25$).

Phenytoin concentrations: Generally, there was no statistical evidence of drug interactions between tiagabine and any comedications in add-on trials. However, in Trial 481, the sponsor reported increased phenytoin (PHT) concentrations during tiagabine treatment periods compared to placebo treatment periods (18% increase) using concentration data from Week 3 of each treatment period ($p=0.049$). Eleven patients received PHT as concomitant medication; only six patients contributed to the sponsor's analyses. (Concentration data were excluded from analysis if (1) sampling times and dosing times were more than two hours apart and (2) PHT doses were different between periods.) Week 7 data indicated only a 1% increase in PHT concentrations during tiagabine treatment periods ($p=.94$). Although patients had higher PHT concentrations during Week 3 of tiagabine treatment periods compared to Week 3 of placebo periods, there was no apparent benefit in seizure control. Median seizure rate **reductions** (placebo rate minus tiagabine rate) was 1.71 for patients receiving PHT ($n=11$) and 1.84 for patients not receiving PHT ($n=31$). Seven of 11 PHT patients (64%) had seziure rate reductions greater than zero (i.e., smaller seizure rates during tiagabine treatment periods comparted to placebo periods) compared to 24 of 31 patients (77%) not receiving PHT.

Summary

Trial 603 compared three daily doses of tiagabine (16, 32, 56 mg all administered as qid doses) to placebo in a parallel groups design. The trial was positive on the primary outcome measure (Baseline-to-EP change in four-week CPS rate) for the primary treatment comparison (tiagabine (32+56) mg treatment groups vs placebo) regardless of the analysis approach. Results for PS were also statistically significant. Sensitivity analyses of SE did not alter the results of the primary comparison for CPS or PS. The 56 mg dose was effective for PS ($p\leq .001$ all analyses) but not for CPS. None of the p-values was significant ($p\geq .028$) after Dunnett's correction for multiple comparisons with a control. (For two treated groups vs control, the required significance level for Dunnett's is $\alpha=.027$; for three groups vs control, $\alpha=.019$) The 32 mg dose was superior to placebo only for PS and only for the primary analysis method (weighted van Elteren, $p=.018$). The 16 mg daily dose was not effective.

Trial 605 compared two 32-mg regimens of tiagabine (8 mg qid, 16 mg bid) to placebo in a

parallel groups design. The tiagabine 8 mg qid vs placebo comparison was statistically significant (after Dunnett's correction) on the primary outcome measure (CPS rate) using the primary analysis methodology (weighted van Elteren, p=.018). Sensitivity analysis of SE did not significantly alter the p-value. This result was hardly robust, however, as all other statistical analyses yielded non-significant p-values. No results for PS were statistically significant. For the tiagabine 16 mg bid vs placebo comparison, only the weighted parametric analysis yielded significant results (CPS and PS).

Trial 775 compared tiagabine 10 mg tid to placebo in a parallel groups design. The sponsor failed on the primary outcome measure (PS response p=.17). Some secondary variables (e.g, percent reduction as continuous variable) were statistically significant. Abbott re-analyses of the raw data using the primary endpoint in Trials 603/605 provided statistically significant results for PS (p=.019) and CPS (p=.014). P-values using the weighted van Elteren just cited were far smaller than the unweighted results (CPS p=.29 and PS p=.40). This troubling disparity in weighted and unweighted approaches was due to a combination of increased precision in the weighted analysis and poorer results in the smaller centers. Removing the three smallest centers (11 patients with high Baseline seizure rates) left the weighted p-values largely unchanged but reduced the unweighted van Elteren p-values to .064 for PS and .10 for PS. The weighted p-values remained (barely) statistically significant after sensitivity analyses of SE (PS .0465 and CPS .0498).

Some patients received additional antiepileptic medications (e.g., lorazepam, diazapam) during treatment periods. The numbers of such patients were roughly balanced between treatment groups and should not affect the statistical results.

Trials 481 and 565 were small (n=46,44) crossover trials comparing tiagabine at individualized doses to placebo. Median achieved tiagabine doses were 32 and 52 mg, respectively. Results on the primary endpoint were generally statistically significant for both trials; only the weighted van Elteren p-value for CPS in Trial 481 was borderline (p=.054). Tests for carryover effect were negative. Trial 565 was meant to have a balanced design but ended up with a 2:1 (T/P : P/T) ratio for ITT analyses. An unusual design feature in both trials was allowing 'suitable' patients, those with a clear, sustained increase in seizure frequency, to be prematurely crossed over from the First assessment Period to the Second Assessment Period. There were four such patients (three 481, one 565; all P/T). It is not known what effect this might have had on trial results. Imputations of seizure rates for dropouts had some worsening effect on trial results, the magnitude depending on the method used for imputation.

Conclusions

The sponsor has submitted efficacy data for five controlled clinical trials of tiagabine, three with a parallel group design and two with a crossover design. The primary evidence for tiagabine's effectiveness comes from the parallel group trials; the crossover trials provide some additional

evidence of tiagabine's effectiveness as add-on therapy but should be considered as supportive only due to their small sample sizes (ITT populations n=42, 36).

Trial 603 presented convincing statistical evidence of the effectiveness of the combined tiagabine 32 and 56 mg dosages (given as qid doses) for both PS and CPS. The 32 and 56 mg doses were also effective **individually** for PS, and nearly so for CPS, after adjustment for multiple comparisons. Tiagabine 16 mg was not effective.

Trial 605 provided statistical evidence of the effectiveness of tiagabine 32 mg for CPS when given as four 8 mg doses, but not when given as two 16 mg doses. Neither dosing regimen was effective for PS. Trials 603 and 605 presented slightly different experiences for the two seizure types: Trial 603's results were superior for PS whereas Trial 605 had better results for CPS.

Trial 775 provided some statistical evidence in support of the efficacy of tiagabine 30 mg (given as 10 mg tid) for PS and CPS, although the statistical results were clearly not robust.

Effect sizes across parallel group trials were uniformly small. Median reductions from Baseline in four-week CPS rate were 1.7 for all patients receiving tiagabine (including ineffective doses) and 0.3 for placebo patients. Median Baseline-to-EP reductions in seizure frequency (PS or CPS) per four weeks for daily doses of at least 30 mg were, after subtracting placebo effects, between one and three seizures. The exact amount of the reduction depended on seizure type and tiagabine dosage. It could be argued that these small seizure reductions were due to inclusion of **all post-randomization (i.e., EP) data**, which included titration period data when the full effect of the drug was not yet established. However, median seziure rate reductions using Fixed Dose Period data were only slightly greater than the reductions observed using EP data. Additional reductions typically amounted to less than one seizure per four weeks.

Overall, there is adequate statistical evidence that the observed differences in response between tiagabine and placebo can reasonably be attributed to the antiepileptic effects of tiagabine.

J. Todd Sahlroot

J. Todd Sahlroot, Ph.D.
Mathematical Statistician

concur: Dr. Chi
9/6/96

cc: Arch NDA 20-646
HFD-120/Dr. Leber
HFD-120/Dr. Katz
HFD-120/Dr. McCormick
HFD-120/Mr. Purvis

HFD-120/Ms. Ware
HFD-710/Dr. Chi
HFD-710/Dr. Sahlroot
HFD-710/chron: T. Sahlroot/x45728/DB1/WordPerfect/7-20-96

This review consists of 19 pages of text, 32 tables and 25 graphs

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

References

Metha CR, Patel NR, Gray R. On computing an exact confidence interval for the common odds ratio in several 2x2 contingency tables. *Biometrics* 40;819-25, 1985.

Van Elteren PH. On the combination of independent two sample tests of Wilcoxon. *Bull. Inst. Intern. Statist.* 37: 351-361, 1960

Koch GG. The use of nonparametric methods in the statistical analysis of the two-period change-over design. *Biometrics* 28: 577-584, 1972

Fleiss JL. The design and analysis of clinical experiments. John Wiley & Sons, 271, 1986

Lehman EL. Nonparametrics: Statistical methods based on ranks. Holden-Day, 1975

Van Eeden C and Hemelrijk J. A test for the equal probabilities against a class of specified alternative hypotheses including trend. *Proc Ned Akad & Wet* 58, 1980 and *Indagationes Mathematical* 17:191-198, 301-308

Grizzle JE. The two-period change-over design and its use in clinical trials. *Biometrics* 21: 473, 1965

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Table 0

BEST POSSIBLE COPY

TABLE OF STUDIES

Controlled Studies as Add-On Therapy for Epilepsy

Abbott Study Number/ Title/ Abbott Report Number	Investigator Name/ Location	Publications	Design, Blinding, Randomization	Start Date/Stop Date	Treatment/ Dose and Regimen/ Formulation [1]	Number Treated [2]	Age Range (Mean)	Gender (%) M/F Race (%) C/B/O [3]	Duration of Treatment	Report Location	CRF
Study M91-603/ TIA-106: Safety and Efficacy of Three Dose Levels of Tiagabine HCl Versus Placebo as Adjunctive Treatment for Complex Partial Seizures R&D/93/447	Multicenter Study - See Study Summary (21 sites)	Epilepsia 1994;35 (suppl 8):116 Epilepsia 1993;34 (suppl 2):182 Epilepsia 1994;35 (suppl 8):54 Ann Neurol 1993; 34(2):272 Epilepsia 1993;34 (suppl 6):103-4 Epilepsia 1993;34 (suppl 2):157	double-blind placebo-controlled parallel-group randomized	01/1992 07/1993	Tiagabine 4 mg QID Tiagabine 8 mg QID Tiagabine 14 mg QID Placebo QID Tablets	61 88 57 91	12-77 (34)	M (58%) F (42 %) C (88%) B (7%) O (5%)	20 weeks	66	Item Vol. 24-34
Study M91-605/ TIA-109: Safety and Efficacy of BID and QID Dosing with Tiagabine HCl Versus Placebo as Adjunctive Treatment for Partial Seizures R&D/94/197	Multicenter Study - See Study Summary (26 sites)	Neurology 1995;45 (4 suppl 4):A202 Epilepsia 1993;34 (suppl 6):36	double-blind placebo-controlled parallel-group randomized	07/1992 08/1993	Tiagabine 16 mg BID Tiagabine 8 mg QID Placebo QID Tablets	106 105 107	12-71 (34)	M (56%) F (44%) C (86%) B (7 %) O (6%)	16 weeks	90	Item Vol. 99-107

1. Refer to Table of Investigational Formulations, Section 2.4 in the NDA.
2. Number of patients/subjects who received at least one dose of the study drug.
3. C = Caucasian, B = Black, O = Other.
4. Interim report based on patient visit cut-off of 04/30/95.
5. Interim report based on patient visit cut-off of 01/31/95.
6 Indicates volume of study cross-reference.

Table 6, cont. BEST POSSIBLE COPY

TABLE OF STUDIES

Controlled Studies as Add-On Therapy for Epilepsy (Continued)

Abbott/ Study Number/ Title/ Abbott Report Number	Investigator Name/ Location	Publications	Design, Blinding, Randomization	Start Date/Stop Date	Treatment/ Dose and Regimen/ Formulation [1]	Number Treated[2]	Age Range (Mean)	Gender (%) M/F Race (%) C/B/O[3]	Duration of Treatment	Report Location	CRF
Study M90-481/ TIA-101: Safety and Efficacy of Tiagabine as Adjunctive Treatment for Complex Partial Seizures R&D/92/250	Multicenter Study - See Study Summary (5 sites)	Epilepsia 1991;32 (suppl 3):20 Epilepsia 1992;33 (suppl 3):119 Epilepsy Res 1995;21(1):37-42 Seizure 1994;3(1) :29-35	open-label period followed by double-blind placebo-controlled two-period crossover randomized	10/1990 06/1992	Tiagabine 2 mg-13 mg QID Placebo QID Tablets	94	19-71 (37)	M (65%) F (35%) C (100%)	35 weeks	124	Item Vol. 17-23
Study M92-775/ TIA-107: Randomized, Double-Blind, Placebo-Controlled Parallel-Group Study of the Safety and Efficacy of Tiagabine Administered TID as Adjunctive Treatment for Partial Seizures R&D/95/653	Multicenter Study - See Study Summary (11 sites)	Epilepsia 1994;35 (suppl 7):61 Epilepsia 1994;35 (suppl 7):74 Neurology 1994;44 (4 suppl 2):A321	double-blind placebo-controlled parallel-group randomized	06/1992 09/1993	Tiagabine 10 mg TID Placebo TID Tablets	77 77	17-71 (37)	M (57%) F (43%) C (100 %)	22 weeks	112	Item Vol. 184-189
Study M91-565/ TIA-103: Phase II Study of Tiagabine: Efficacy and Safety in Adjunctive Treatment of Partial Seizures R&D/94/963	Multicenter Study - See Study Summary (5 sites)	Epilepsia 1993;34 (suppl 2):182 Seizure 1992;1 (supp A): 7/14	double-blind placebo-controlled two-period crossover randomized	11/1991 03/1993	Tiagabine 3 mg - 16 mg QID Tablets	88	18-56 (35)	M (73%) F (27%) C (100%)	16 weeks	132	Item Vol. 172-178

1. Refer to Table of Investigational Formulations, Section 2.4 in the NDA.
2. Number of patients/subjects who received at least one dose of the study drug.
3. C = Caucasian, B = Black, O = Other.
4. Interim report based on patient visit cut-off of 04/30/95.
5. Interim report based on patient visit cut-off of 01/31/95.
6. Indicates volume of study cross-reference.

Table 1 BEST POSSIBLE COPY

Trial 603: Patient Demographics.

Summary of Patient Demographics						
		Tiagabine				
	Placebo	16 mg	32 mg	56 mg	Overall	P-Values*
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	6.0	7.0	7.0	7.0	7.0	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	0.140
min-max	1.8-58.6	3.4-42.8	1.4-65.8	5.2-54.5	1.4-65.8	
Race						0.663
Caucasian	79 (87%)	55 (90%)	79 (90%)	48 (84%)	261 (88%)	
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.						

BEST POSSIBLE COPY

Table 2

Trial 603: Premature Discontinuations

Patients who Prematurely Discontinued From Adverse Events				
Patient	Period of Onset	Total Days on Therapy	Study Drug Tapered	Adverse Event Description (COSTART Terms)
Placebo: 7/91 (8%)				
10508	Fixed-Dose	81	no	facial edema
10612	Titration	44	no	somnolence
10729	Fixed-Dose	91	yes	nausea and vomiting
11805	Fixed-Dose	79	yes	fecal incontinence, urinary incontinence
12104*	Discontinuation	133	N/A	chest pain, dizziness, palpitation, supraventricular tachycardia, sweating
10511	Fixed-Dose	55	no	salpingitis
11014*	Discontinuation	122	N/A	death
Tiagabine 16 mg 4/61 (7%)				
10916	Titration	27	yes	diplopia
11013	Titration	15	no	depression
11208	Titration	16	no	abdominal pain
11401*	Fixed-Dose	119	yes	deep thrombophlebitis
Tiagabine 32 mg 13/88 (15%)				
10404	Titration	76	yes	ataxia, depression, dizziness
10721*	Discontinuation	115	no	hyponatremia
10906	Titration	50	no	confusion, dizziness, somnolence
11111	Fixed-Dose	130	yes	anorexia, nervousness
11211	Titration	56	yes	dizziness
11220	Titration	73	yes	confusion
11302	Titration	67	yes	amblyopia, ataxia, dizziness, somnolence
11412	Titration	19	no	somnolence
11511	Titration	56	yes	asthenia, dizziness, speech disorder
12110	Titration	8	no	ulcerative colitis
12213	Titration	14	no	somnolence
12011	Baseline**	1	no	urinary tract infection, upper respiratory tract infection, fever, otitis media, vaginitis
11127	Fixed-Dose	131	yes	ataxia, dizziness
Tiagabine 56 mg 9/57 (16%)				
10202	Titration	55	yes	asthenia, paresthesia, tremor
10603	Titration	24	no	confusion, dizziness, nervousness
10903	Titration	56	no	dizziness, thinking abnormal (difficulty concentrating)

* Prematurely discontinued during Discontinuation Phase.
** The adverse event was ongoing since Baseline and was not treatment-emergent.

BEST POSSIBLE COPY

Table 2, cont.

Patients who Prematurely Discontinued From Adverse Events				
Patient	Period of Onset	Total Days on Therapy	Study Drug Tapered	Adverse Event Description (COSTART Terms)
Tiagabine 56 mg 9/57 (16%) (Continued)				
10915	Titration	15	no	ataxia, dizziness, speech disorder, tremor, twitching
11512	Fixed-Dose	68	yes	hostility
11906	Titration	56	yes	amnesia, dizziness, somnolence, speech disorder, thinking abnormal (slowness of thought, confused, loss of memory)
11213	Titration	16	no	nervousness
12103	Fixed-Dose	51	no	infection
11122	Titration	22	yes	somnolence, ataxia
* Prematurely discontinued during Discontinuation Phase. ** The adverse event was ongoing since Baseline and was not treatment-emergent. no = Study drug abruptly discontinued.				

Reasons for Premature Discontinuation Other than Adverse Events					
		Tiagabine			Total
Description	Placebo N = 91	16 mg N = 61	32 mg N = 88	56 mg N = 57	297
Lack of Efficacy	11413, 10717*, 11117, 10509, 11306@*, 10918	11110*@, 10613*	11123*	10710@, 10814@*, 10607*@, 10718@, 11411	14 (5%)
Personal			10711*@, 11007*		2 (1%)
Lost to follow-up				11807@	1 (0.3%)
Noncompliance				11309*@	1 (0.3%)
Other			10919@, 11811*@	11609*@	3 (1%)
Total	6 (7%)	2 (3%)	5 (6%)	8 (14%)	21 (7%)
* Study drug discontinued without entering Discontinuation Period. @ Study drug discontinued during Titration Period.					

Table 3A BEST POSSIBLE COPY

Trial 603: Statistical results for CPS

COMPARISON OF CHANGE IN FOUR-WEEK SEIZURE RATES
PLACEBO VERSUS TIAGABINE, 32 AND 56 MG GROUPS COMBINED

INTENT-TO-TREAT DATASET

SEIZURE TYPE = COMPLEX PARTIAL *

	PLACEBO GROUP (N= 91)			TIAGABINE 32 AND 56 MG GROUPS COMBINED (N= 143)		
VARIABLE	BASELINE PERIOD	EXPERIMENT PERIOD	CHANGE	BASELINE PERIOD	EXPERIMENT PERIOD	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)
MINIMUM	2.8	0.5	-21.6	2.1	0.0	-106.6
25%	5.2	4.4	-2.4	5.9	3.0	-5.1
MEDIAN	7.4	7.8	-0.6	9.2	6.9	-2.6
75%	16.9	16.1	1.7	18.8	16.1	0.5
MAXIMUM	109.0	127.3	82.8	400.9	546.9	145.9

	TEST OF TREATMENT EFFECT	
	WEIGHTED COMPARISON	UNWEIGHTED COMPARISON
ANALYSIS METHOD	P-VALUE$	P-VALUE$
NONPARAMETRIC ANALYSIS	0.007T	0.018T
PARAMETRIC ANALYSIS	0.043T	0.019T

* SEIZURE COUNTS FOR EACH TYPE INCLUDE THAT SEIZURE TYPE OCCURRING ALONE OR IN COMBINATION WITH OTHER SEIZURE TYPES (E.G., A SIMPLE PARTIAL SEIZURE EVOLVING TO A COMPLEX PARTIAL SEIZURE IS COUNTED UNDER BOTH SIMPLE PARTIAL AND COMPLEX PARTIAL).
$ FLAG INDICATES STATISTICALLY SIGNIFICANT TREATMENT DIFFERENCE: P=FAVORING PLACEBO, T=FAVORING TIAGABINE.

ADDITIONAL P-VALUE FROM UNWEIGHTED PARAMETRIC ANALYSIS:
INVESTIGATOR*TREATMENT INTERACTION = 0.164

Table 3B BEST POSSIBLE CO

Trial 603: Statistical results for PS

COMPARISON OF CHANGE IN FOUR-WEEK SEIZURE RATES
PLACEBO VERSUS TIAGABINE, 32 AND 56 MG GROUPS COMBINED

INTENT-TO-TREAT DATASET

SEIZURE TYPE = COMBINED PARTIAL *

	PLACEBO GROUP (N= 91)			TIAGABINE 32 AND 56 MG GROUPS COMBINED (N= 143)		
VARIABLE	BASELINE PERIOD	EXPERIMENT PERIOD	CHANGE	BASELINE PERIOD	EXPERIMENT PERIOD	CHANGE
MEAN	21.4	22.7	1.3	30.7	26.9	-3.8
(SD)	(31.04)	(38.51)	(14.44)	(54.12)	(56.86)	(30.08)
MINIMUM	2.9	1.5	-21.6	2.2	0.0	-166.9
25%	6.1	6.6	-2.7	6.9	4.6	-7.2
MEDIAN	10.9	11.9	-0.2	12.0	8.9	-2.9
75%	23.9	20.8	3.0	29.0	27.8	0.7
MAXIMUM	226.3	265.3	82.8	400.9	546.9	145.9

	TEST OF TREATMENT EFFECT	
	WEIGHTED COMPARISON	UNWEIGHTED COMPARISON
ANALYSIS METHOD	P-VALUE$	P-VALUE$
NONPARAMETRIC ANALYSIS	<0.001T	0.001T
PARAMETRIC ANALYSIS	0.015T	0.004T

* SEIZURE COUNTS FOR EACH TYPE INCLUDE THAT SEIZURE TYPE OCCURRING ALONE OR IN COMBINATION WITH OTHER SEIZURE TYPES (E.G., A SIMPLE PARTIAL SEIZURE EVOLVING TO A COMPLEX PARTIAL SEIZURE IS COUNTED UNDER BOTH SIMPLE PARTIAL AND COMPLEX PARTIAL).
$ FLAG INDICATES STATISTICALLY SIGNIFICANT TREATMENT DIFFERENCE: P=FAVORING PLACEBO, T=FAVORING TIAGABINE.

ADDITIONAL P-VALUE FROM UNWEIGHTED PARAMETRIC ANALYSIS:
INVESTIGATOR*TREATMENT INTERACTION = 0.276

BEST POSSIBLE

Table 4

Trial 603: Pairwise comparisons for CPS.

Median 4-Week Complex Partial Seizure Rates and Changes (ITT)					
Dose Group	N	Baseline Period	Experiment Period	Change	P-Value
Placebo	90	7.4	7.6	-0.7	---
Tiagabine 16 mg	61	8.5	7.6	-0.8	0.436
Tiagabine 32 mg	86	9.6	7.0	-2.2	0.030*
Tiagabine 56 mg	55	9.1	5.8	-2.8	0.028*
* Statistically significant when compared to placebo.					

Table 5

BEST POSSIBLE COPY

Trial 603: All Statistical results

Comparisons of Change in Four-Week Seizure Rates (Intent-to-Treat)									
Seizure Type	Analysis Method	32 & 56 mg vs. PBO	Dose Response	16 mg vs. PBO	32 mg vs. PBO	56 mg vs. PBO	32 mg vs. 16 mg	56 mg vs. 16 mg	56 mg vs. 32 mg
Complex Partial	Nonparametric		T**						
	Weighted	T**		NS	T*	T*	NS	NS	NS
	Unweighted	T*		NS	T+	T*	NS	T+	NS
	Parametric		T*						
	Weighted	T*		NS	NS	T*	NS	NS	NS
	Unweighted	T*		NS	NS	T*	NS	T+	NS
Simple Partial	Nonparametric	T**	T***	T***	T+	T**	NS	NS	NS
	Parametric	T+	T*	T+	NS	T*	NS	NS	T+
Secondarily Generalized Tonic-Clonic	Nonparametric	T*	T+	T*	T+	T+	NS	NS	NS
	Parametric	T*	T+	T**	NS	T*	NS	NS	NS
Combined Partial	Nonparametric		T***						
	Weighted	T***		NS	T*	T***	NS	T*	NS
	Unweighted	T***		NS	T*	T***	NS	T*	NS
	Parametric		T**						
	Weighted	T*		NS	NS	T***	NS	T+	T+
	Unweighted	T**		NS	T+	T***	NS	T*	T+

NS - Not statistically significant.
T - Statistically significant in favor of higher dose of Tiagabine.

+ Statistically significant at 0.10 level
* Statistically significant at 0.05 level
** Statistically significant at 0.01 level
*** Statistically significant at 0.001 level

Table 6

BEST POSSIBLE COPY

Trial 605: Patient demographics

PATIENT DEMOGRAPHICS
ALL RANDOMIZED PATIENTS

	TIAGABINE PLACEBO (N = 107)	TIAGABINE 16 MG BID (N = 106)	8 MG QID (N = 105)	OVERALL (N = 318)	P-VALUE @
SEX					
FEMALE	53 (50%)	41 (39%)	45 (43%)	139 (44%)	0.277
MALE	54 (50%)	65 (61%)	60 (57%)	179 (56%)	
RACE					
AFRICAN-AMERICAN	8 (7%)	10 (9%)	5 (5%)	23 (7%)	0.760
CAUCASIAN	92 (86%)	89 (84%)	94 (90%)	275 (86%)	
OTHER #	7 (7%)	7 (7%)	6 (6%)	20 (6%)	
AGE (YEARS)					
N	107	106	105	318	
MEAN (SD)	35.3(12.61)	33.4(13.38)	32.6(11.36)	33.8(12.49)	0.278
MEDIAN	34.0	32.0	32.0	33.0	
MIN-MAX	13.0- 71.0	12.0- 67.0	12.0- 66.0	12.0- 71.0	
WEIGHT (LB)					
N	107	106	105	318	
MEAN (SD)	156.1(37.55)	167.3(48.79)	165.8(43.96)	163.1(43.80)	0.129
MEDIAN	150.0	156.5	160.5	155.7	
MIN-MAX	90.8-260.0	80.5-357.0	73.6-293.0	73.6-357.0	
HEIGHT (IN)					
N	106	102	104	312	
MEAN (SD)	66.0(4.74)	66.7(3.93)	66.6(4.38)	66.5(4.36)	0.481
MEDIAN	65.8	66.5	66.0	66.0	
MIN-MAX	52.0- 78.5	57.0- 79.0	53.0- 77.0	52.0- 79.0	
YEARS WITH EPILEPSY					
N	107	106	105	318	
MEAN (SD)	24.3(13.00)	21.6(12.68)	22.4(10.82)	22.8(12.23)	0.202
MEDIAN	24.0	17.9	22.0	21.9	
MIN-MAX	2.2- 62.4	2.7- 53.9	0.9- 45.2	0.9- 62.4	
NUMBER OF AEDS EVER TAKEN					
N	107	106	105	318	
MEAN (SD)	6.5(3.18)	6.0(2.43)	6.9(2.96)	6.4(2.89)	0.063+
MEDIAN	6.0	6.0	6.0	6.0	
MIN-MAX	2.0- 20.0	1.0- 14.0	2.0- 20.0	1.0- 20.0	

@ FOR SEX AND RACE, FROM FISHER'S EXACT TEST; FOR YEARS WITH EPILEPSY, FROM KRUSKAL-WALLIS TEST;
FOR OTHER VARIABLES, FROM ONE-WAY ANOVA.
OTHER INCLUDES HISPANIC, ASIAN, ETC.
***, **, *, + INDICATE STATISTICAL SIGNIFICANCE AT THE 0.001, 0.01, 0.05, AND 0.10 LEVEL, TWO-TAILED, RESPECTIVELY.

31MAY95 11:39 <T605DMI2 SAS T55GCP>

Table 7 BEST POSSIBLE

Trial 605: Premature discontinuations

PATIENT DISPOSITION
SUMMARIZED BY TREATMENT GROUP

ALL RANDOMIZED PATIENTS

PATIENT CATEGORY:	PLACEBO (N=107) n	(%)	TIAGABINE 16 MG BID (N=106) n	(%)	TIAGABINE 8 MG QID (N=105) n	(%)	TOTAL (N=318) n	(%)
COMPLETED STUDY	97	(90.7)	90	(84.9)	84	(80.0)	271	(85.2)
PREMATURELY DISCONTINUED TITRATION PERIOD	6	(5.6)	12	(11.3)	11	(10.5)	29	(9.1)
REASON:								
ADVERSE EVENT	5	(4.7)	10	(9.4)	6	(5.7)	21	(6.6)
NONCOMPLIANCE	0	(0.0)	0	(0.0)	2	(1.9)	2	(0.6)
PERSONAL	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.3)
LACK OF EFFICACY	0	(0.0)	1	(0.9)	1	(1.0)	2	(0.6)
DID NOT MEET BL PHASE SEIZURE CRITERIA	1	(0.9)	0	(0.0)	2	(1.9)	3	(0.9)
FIXED-DOSE PERIOD	4	(3.7)	3	(2.8)	8	(7.6)	15	(4.7)
REASON:								
ADVERSE EVENT	2	(1.9)	3	(2.8)	2	(1.9)	7	(2.2)
INTERCURRENT MEDICAL EVENTS	0	(0.0)	0	(0.0)	2	(1.9)	2	(0.6)
PERSONAL	0	(0.0)	0	(0.0)	1	(1.0)	1	(0.3)
LACK OF EFFICACY	1	(0.9)	0	(0.0)	0	(0.0)	1	(0.3)
DID NOT MEET BL PHASE SEIZURE CRITERIA	1	(0.9)	0	(0.0)	2	(1.9)	3	(0.9)
OTHER	0	(0.0)	0	(0.0)	1	(1.0)	1	(0.3)
PREMATURELY DISCONTINUED FROM STUDY DURING TERMINATION PERIOD	0	(0.0)	1	(0.9)	2	(1.9)	3	(0.9)
REASON:								
ADVERSE EVENT	0	(0.0)	1	(0.9)	2	(1.9)	3	(0.9)

Table 8A BEST POSSIBLE

Trial 605: Statistical results for CPS

COMPARISON OF CHANGE IN FOUR-WEEK SEIZURE RATES
ALL PAIRWISE COMPARISONS OF TREATMENTS

INTENT-TO-TREAT DATASET ∂

SEIZURE TYPE = COMPLEX PARTIAL ¤

	PLACEBO (N = 185)			TIAGABINE 16 MG BID (N = 186)			TIAGABINE 8 MG QID (N = 183)		
VARIABLE	BASELINE PERIOD	EXPERIMENT PERIOD	CHANGE	BASELINE PERIOD	EXPERIMENT PERIOD	CHANGE	BASELINE PERIOD	EXPERIMENT PERIOD	CHANGE
MEAN (SD)	33.9 (164.57)	23.3 (78.89)	-10.6 (88.99)	30.1 (159.58)	38.8 (272.86)	8.7 (113.54)	24.4 (64.70)	44.0 (220.56)	19.6 (167.90)
MINIMUM	1.9	0.0	-878.4	2.1	0.0	-52.6	1.8	0.0	-25.4
25%	4.6	4.5	-2.4	4.8	3.1	-5.2	4.9	3.3	-3.9
MEDIAN	8.0	8.1	-0.2	8.4	6.1	-1.6	7.9	5.6	-1.2
75%	15.5	15.7	2.5	14.5	15.2	1.1	12.8	12.3	0.9
MAXIMUM	1665.8	787.4	40.5	1646.8	2887.7	1160.9	513.2	1991.9	1618.4

---------- P-VALUES FROM PAIRWISE COMPARISONS OF SEIZURE RATE CHANGE ß ----------

	WEIGHTED			UNWEIGHTED		
ANALYSIS METHOD	TIAGABINE 16 MG BID vs. PLACEBO	TIAGABINE 8 MG QID vs. PLACEBO	TIAGABINE 8 MG QID vs. TIAGABINE 16 MG BID	TIAGABINE 16 MG BID vs. PLACEBO	TIAGABINE 8 MG QID vs. PLACEBO	TIAGABINE 8 MG QID vs. TIAGABINE 16 MG BID
NONPARAMETRIC	0.055	0.018(QID)	0.671	0.255	0.104	0.458
PARAMETRIC	0.010(BID)	0.052	0.495	0.076	0.221	0.600

∂ THE DATA FROM INVESTIGATOR DEAN WAS EXCLUDED FROM THESE DESCRIPTIVE STATISTICS AND STATISTICAL ANALYSES.
¤ SEIZURE COUNTS FOR EACH TYPE INCLUDE THAT SEIZURE TYPE OCCURRING ALONE OR IN COMBINATION WITH OTHER SEIZURE TYPES (E.G., A SIMPLE PARTIAL SEIZURE EVOLVING TO A COMPLEX PARTIAL SEIZURE IS COUNTED UNDER BOTH SIMPLE PARTIAL AND COMPLEX PARTIAL).
ß FLAG INDICATES STATISTICALLY SIGNIFICANT TREATMENT DIFFERENCE:
PBO = FAVORING PLACEBO
BID = FAVORING TIAGABINE, 16 MG BID
QID = FAVORING TIAGABINE, 8 MG QID

ADDITIONAL P-VALUE FROM UNWEIGHTED PARAMETRIC ANALYSIS:
INVESTIGATOR BY TREATMENT INTERACTION = 0.129

Table 8B **BEST POSSIBLE**

Trial 605: Statistical results for PS

COMPARISON OF CHANGE IN FOUR-WEEK SEIZURE RATES
ALL PAIRWISE COMPARISONS OF TREATMENTS

INTENT-TO-TREAT DATASET a

SEIZURE TYPE = COMBINED PARTIAL *

	PLACEBO (N = 105)			TIAGABINE 16 MG BID (N = 106)			TIAGABINE 8 MG QID (N = 103)		
VARIABLE	BASELINE PERIOD	EXPERIMENT PERIOD	CHANGE	BASELINE PERIOD	EXPERIMENT PERIOD	CHANGE	BASELINE PERIOD	EXPERIMENT PERIOD	CHANGE
MEAN (SD)	44.8 (208.24)	29.7 (88.22)	-14.3 (126.87)	36.4 (161.11)	42.5 (271.94)	6.1 (115.94)	29.5 (69.41)	47.8 (220.53)	18.3 (168.25)
MINIMUM	1.9	0.0	-1263.9	2.4	0.0	-225.6	1.0	0.0	-76.0
25%	6.3	6.0	-2.8	6.7	3.7	-6.0	5.3	3.7	-4.6
MEDIAN	10.3	11.3	-0.3	10.5	8.2	-1.6	9.6	6.8	-1.2
75%	19.6	21.3	2.6	19.2	20.7	1.7	21.1	18.7	1.1
MAXIMUM	2118.4	854.5	96.6	1646.8	2807.7	1160.9	513.2	1991.9	1618.4

	P-VALUES FROM PAIRWISE COMPARISONS OF SEIZURE RATE CHANGE @					
	WEIGHTED			UNWEIGHTED		
ANALYSIS METHOD	TIAGABINE 16 MG BID vs. PLACEBO	TIAGABINE 8 MG QID vs. PLACEBO	TIAGABINE 8 MG QID vs. TIAGABINE 16 MG BID	TIAGABINE 16 MG BID vs. PLACEBO	TIAGABINE 8 MG QID vs. PLACEBO	TIAGABINE 8 MG QID vs. TIAGABINE 16 MG BID
NONPARAMETRIC	0.097	0.056	0.950	0.194	0.168	0.695
PARAMETRIC	0.013(BID)	0.131	0.315	0.052	0.392	0.287

THE DATA FROM INVESTIGATOR DEAN WAS EXCLUDED FROM THESE DESCRIPTIVE STATISTICS AND STATISTICAL ANALYSES.
SEIZURE COUNTS FOR EACH TYPE INCLUDE THAT SEIZURE TYPE OCCURRING ALONE OR IN COMBINATION WITH OTHER SEIZURE TYPES (E.G., A SIMPLE PARTIAL SEIZURE EVOLVING TO A COMPLEX PARTIAL SEIZURE IS COUNTED UNDER BOTH SIMPLE PARTIAL AND COMPLEX PARTIAL)
FLAG INDICATES STATISTICALLY SIGNIFICANT TREATMENT DIFFERENCE:
PBO = FAVORING PLACEBO
BID = FAVORING TIAGABINE, 16 MG BID
QID = FAVORING TIAGABINE, 8 MG QID

ADDITIONAL P-VALUE FROM UNWEIGHTED PARAMETRIC ANALYSIS:
INVESTIGATOR BY TREATMENT INTERACTION = 0.108

Table 9

BEST POSSIBLE COPY

Trial 605: All statistical results

Comparisons of Change in Four-Week Seizure Rates (Intent-to-Treat)				
Seizure Type	**Analysis Method**	**16 mg BID vs. PBO**	**8 mg QID vs. PBO**	**16 mg BID vs. 8 mg QID**
Complex Partial	**Nonparametric**			
	Weighted	NS	Q*	NS
	Unweighted	NS	NS	NS
	Parametric			
	Weighted	B**	NS	NS
	Unweighted	NS	NS	NS
Simple Partial	**Nonparametric**			
	Unweighted	NS	Q**	NS
	Parametric			
	Unweighted	NS	NS	NS
Secondarily Generalized Tonic-Clonic	**Nonparametric**			
	Unweighted	NS	NS	NS
	Parametric			
	Unweighted	NS	NS	NS
Combined Partial	**Nonparametric**			
	Weighted	NS	NS	NS
	Unweighted	NS	NS	NS
	Parametric			
	Weighted	B*	NS	NS
	Unweighted	NS	NS	NS

PBO Placebo
NS Not statistically significant
B Statistically significant in favor of tiagabine 16 mg BID
Q Statistically significant in favor of tiagabine 8 mg QID
*,** Statistically significant at the 0.05 and 0.01 levels, respectively

BEST POSSIBLE COPY

Table 10

Trial 775: Patient demographics

Baseline Comparison of Treatment Groups: Demographics
All randomized patients

	Placebo (N= 77)		Ziaphlam (N= 77)		Total (N=154)		P-value@
Sex							
Male	47	(61.04)	43	(55.84)	90	(58.44)	
Female	30	(38.96)	34	(44.16)	64	(41.56)	0.624
Race							
Caucasian	77	(100.0)	77	(100.0)	154	(100.0)	
Black	0	(0.00)	0	(0.00)	0	(0.00)	
Oriental	0	(0.00)	0	(0.00)	0	(0.00)	
Other	0	(0.00)	0	(0.00)	0	(0.00)	
Age (years)	(N= 77)		(N= 77)		(N=154)		
Mean (SD)	36.0	(13.13)	36.4	(10.44)	36.2	(11.83)	0.866
Min - max	17.9 -	71.3	18.7 -	59.7	17.9 -	71.3	
Weight (kg)	(N= 77)		(N= 77)		(N=154)		
Mean (SD)	76.5	(16.58)	72.7	(14.43)	74.6	(15.58)	0.107
Min - max	52.0 -	123.0	48.0 -	106.5	48.0 -	123.0	
Height (cm)	(N= 77)		(N= 77)		(N=154)		
Mean (SD)	170.4	(10.82)	169.0	(9.27)	169.7	(10.06)	0.410
Min - max	144.0 -	193.0	150.0 -	186.0	144.0 -	193.0	
Yrs epilepsy$	(N= 77)		(N= 77)		(N=154)		
Mean (SD)	23.0	(10.04)	24.9	(12.26)	23.9	(11.21)	0.289
Min - max	1.0 -	49.0	2.0 -	52.0	1.0 -	52.0	
No. of AEDs@	(N= 77)		(N= 77)		(N=154)		
Mean (SD)	6.2	(2.28)	6.2	(2.60)	6.2	(2.43)	0.876
Min - max	2.0 -	15.0	1.0 -	13.0	1.0 -	15.0	

@ For sex and race, from Fisher's exact test, for No. of AED's from Kruskal-Wallis test, otherwise from two-sample T-test.
$ From the seizure history form.
$ From the AE medication history form.

Table 11

BEST POSSIBLE COPY

Trial 775: Premature discontinuations

Overall Patient Disposition.

Patient category	N
Enrolled in study	277
Prematurely terminated during baseline period due to:	
Adverse event	0
Intercurrent medical event	3
Lack of efficacy	0
Personal reasons	1
Noncompliance	0
Lost to follow-up	0
Other	0
Total	12
Completed baseline period but not randomized due to:	
Failed baseline seizure criteria	4
Failed inclusion/exclusion criteria	5
Required change in AED dose	1
Adverse event	0
Other	1
Total	11

	Placebo	Zinpidine	Total
Randomized	77	77	154
Prematurely terminated during double-blind phase due to:			
Adverse event	2 (2.60)	17 (22.08)	19 (12.34)
Intercurrent medical event	0 (0.00)	0 (0.00)	0 (0.00)
Lack of efficacy	1 (1.30)	2 (2.60)	3 (1.95)
Personal reasons	1 (1.30)	0 (0.00)	1 (0.65)
Noncompliance	0 (0.00)	1 (1.30)	1 (0.65)
Lost to follow-up	1 (1.30)	0 (0.00)	1 (0.65)
Other	3 (3.90)	1 (1.30)	4 (2.60)
Total	8 (10.39)	21 (27.27)	29 (18.83)
Completed study‡	69	56	125
Intention to Treat	77	77	154
Evaluable	71	59	130
Enrolled in extension study	64	55	119

● Defined as those randomized patients who did not prematurely terminate the study or prematurely enter termination period prior to visit 10.

‡ Three placebo patients (11004, 18014 and 18019), whose reason for termination was recorded as 'other', terminated in fact due to lack of efficacy.
The three patients (19011, 19015 and 19023) whose reason for termination was recorded as 'intercurrent medical events', terminated in fact due an administrative reason, change of contraceptive (19011), an adverse event, intermenstrual bleeding (19015), and an adverse event, anaemia (19023), respectively. The table shows the recorded reason.
In addition, two zinpidine patients terminated due to adverse events: 13020, whose reason for termination was recorded as "non-compliance", terminated in fact due to somnolence, and 18003 whose reason for termination was recorded as "other", terminated in fact due to accidental injury. In the table these appear under "adverse event".

Table 12
Trial 775
Results for all partial seizures.

All Partial Seizure Response Rate (≥50% Reduction in 4-Weekly Seizure Rate During Fixed-Dose Period)			
Dataset	Placebo (P)	Tiagabine (T)	Test that Common Odds Ratio is Unity (p-value)
Intent-to-treat (n=154; P:77, T:77))	6.5%	14.3%	0.169
Evaluable (n=130; P:71, T:59)	7.0%	17.0%	0.095
Completers (n=125; P:69, T:56)	7.3%	17.9%	0.151

Median 4-Weekly Partial Seizure Rate for the Intent-to-treat Population		
Period	Placebo (n=77)	Tiagabine (n=77)
Baseline	10.5	12.2
Fixed-dose	11.0	10.1
Percentage reduction	0.0	12.6 (p=.027)

Reduction (From Baseline) in Mean (± SD) Square-Root Transformed Partial Seizure Rate During Fixed-Dose Period							
Dataset	Placebo (P)			Tiagabine (T)			p-value
	Baseline	Fixed-Dose	Reduction	Baseline	Fixed-Dose	Reduction	
Intent-to-treat (n=154; P:77, T:77)	3.69 (1.90)	3.77 (2.14)	-0.08 (1.09)	4.21 (2.19)	3.80 (2.31)	0.42 (1.21)	0.008
Evaluable (n=130; P:71, T:59)	3.62 (1.88)	3.72 (2.14)	-0.09 (1.14)	4.17 (2.14)	3.67 (2.04)	0.50 (1.12)	0.005
Completers (n=125; P:69, T:56)	3.63 (1.88)	3.61 (2.06)	0.03 (0.78)	4.25 (2.17)	3.72 (2.08)	0.53 (1.14)	0.006

BEST POSSIBLE COPY

Table 13
Trial 775
Results for complex partial seizures

Complex Partial Seizure Response Rate (≥50% Reduction in 4-Weekly Seizure Rates During the Fixed-Dose Period)			
Dataset	Placebo (P)	Tiagabine (T)	Test that Common Odds Ratio is Unity (p-value)
Intent-to-treat (n=148; P:75, T:73)	14.7%	20.6%	0.371
Evaluable (n=125; P:69, T:56)	15.9%	25.0%	0.243
Completers (n=120; P:67, T:53)	16.4%	24.5%	0.456

Table 7F. Comparison of median 4-weekly seizure rate reductions. Complex partial seizures. Intent-to-treat dataset.

Treatment Group	N	Baseline Period	Fixed-dose Period	Percent Reduction
Placebo	75	7.70	7.25	0.00
Tiagabine	73	6.89	6.39	8.82
Total	148	7.38	6.64	0.63

(p=.230)

The table shows the median 4-weekly seizure rates during baseline and fixed-dose periods, and the median seizure rate reduction from the baseline to the fixed dose periods, for each treatment group.

Reduction (From Baseline) in Mean (± SD) Square-Root Transformed Complex Partial Seizure Rate During Fixed-Dose Period							
Dataset	Placebo (P)			Tiagabine (T)			p-value
	Baseline	Fixed-Dose	Reduction	Baseline	Fixed-Dose	Reduction	
Intent-to-treat (n=148; P:75, T:73)	3.36 (1.88)	3.29 (2.16)	0.08 (0.81)	3.23 (1.94)	2.85 (1.90)	0.37 (1.21)	0.084
Evaluable (n=125; P:69, T:56)	3.29 (1.84)	3.21 (2.14)	0.08 (0.84)	3.32 (2.09)	2.91 (2.03)	0.41 (1.22)	0.112
Completers (n=120; P:67, T:53)	3.32 (1.84)	3.21 (2.16)	0.11 (0.84)	3.38 (2.13)	2.96 (2.07)	0.42 (1.25)	0.155

BEST POSSIBLE COPY

Table 14
Trial 775
- Results for simple partial seizures

Simple Partial Seizure Response Rate (≥50% Reduction in 4-Weekly Seizure Rate During Fixed-Dose Period)			
Dataset	Placebo (P)	Tiagabine (T)	Test that Common Odds Ratio is Unity (p-value)
Intent-to-treat (n=103; P:50,T:53)	6.0%	20.8%	0.009**
Evaluable (n=87; P:47,T:40)	6.4%	25.0%	0.007**
Completers (n=84; P:45,T:39)	6.7%	23.1%	0.024*

* significant at the 5% level
** significant at the 1% level

Median 4-Weekly Simple Partial Seizure Rate for the Intent-to-treat Population		
Period	Placebo (n=50)	Tiagabine (n=53)
Baseline	11.1	10.9
Fixed-dose	11.1	7.8
Percentage reduction	0.0	12.6 (p = .008)

Reduction (From Baseline) in Mean (± SD) Square-Root Transformed Simple Partial Seizure Rate During Fixed-Dose Period							
Dataset	Placebo (P)			Tiagabine (T)			p-value
	Baseline	Fixed-Dose	Reduction	Baseline	Fixed-Dose	Reduction	
Intent-to-treat (n=103; P:50,T:53)	3.58 (1.95)	3.78 (1.95)	-0.20 (1.29)	3.98 (2.59)	3.55 (2.69)	0.43 (1.46)	0.014*
Evaluable patients (n=87; P:47,T:40)	3.55 (1.97)	3.75 (1.98)	-0.21 (1.33)	3.90 (2.54)	3.32 (2.31)	0.58 (1.51)	0.011*
Completers (n=84; P:45,T:39)	3.56 (1.98)	3.59 (1.83)	-0.03 (0.88)	3.98 (2.51)	3.40 (2.28)	0.58 (1.53)	0.026*

* significant at the 5% level

BEST POSSIBLE COPY

Table 15
Trial 775
Results for SGTC seizures

SGTC Seizure Response Rate (≥50% Reduction in 4-Weekly Seizure Rate During Fixed-Dose Period)			
Dataset	**Placebo (P)**	**Tiagabine (T)**	**Test that Common Odds Ratio is Unity (p-value)**
Intent-to-treat (n=73; P:35,T:38)	25.7%	31.6%	0.399
Evaluable patients (n=63; P:34, T:29)	26.5%	37.9%	0.227
Completers (n=60; P:33, T:27)	27.3%	40.7%	0.200

Median 4-Weekly SGTC Seizure Rate for the Intent-to-treat Population		
Period	**Placebo (n=35)**	**Tiagabine (n=38)**
Baseline	0.7	1.4
Fixed-dose	1.0	1.0
Percentage reduction	0.0	21.8 (p=.26)

Reduction (From Baseline) in Mean (± SD) Square-Root Transformed SGTC Seizure Rate During Fixed-Dose Period							
Dataset	**Placebo (P)**			**Tiagabine (T)**			**p-value**
	Baseline	**Fixed-Dose**	**Reduction**	**Baseline**	**Fixed-Dose**	**Reduction**	
Intent-to-treat (n=73; P:35, T:38)	1.30 (1.77)	1.33 (1.91)	-0.03 (0.58)	1.43 (1.22)	1.24 (1.24)	0.19 (0.77)	0.289
Evaluable patients (n=63; P:34,T:29)	1.28 (1.80)	1.31 (1.94)	-0.03 (0.59)	1.44 (1.28)	1.21 (1.34)	0.23 (0.75)	0.304
Completers (n=60; P:33, T:27)	1.32 (1.81)	1.31 (1.97)	0.01 (0.56)	1.46 (1.32)	1.20 (1.38)	0.26 (0.76)	0.368

BEST POSSIBLE COPY

Table 16

BEST POSSIBLE COPY

Trial 481: Patient demographics

PATIENT PRESTUDY CHARACTERISTICS

RANDOMIZED PATIENT DATASET

VARIABLE#	TGB-PCB (N=25)	PCB-TGB (N=21)	TOTAL (N=46)	P-VALUE$
AGE (YEARS)				
N	25	21	46	0.721
MEAN (SD)	35.4(10.4)	34.3(9.81)	34.9(10.0)	
MEDIAN	33.0	35.0	34.5	
MIN-MAX	21-61	21-53	21-61	
SEX				
FEMALE	9 (36%)	3 (14%)	12 (26%)	0.176
MALE	16 (64%)	18 (86%)	34 (74%)	
RACE				
CAUCASIAN	25 (100%)	21 (100%)	46 (100%)	N/A
WEIGHT (KG)				
N	25	21	46	0.918
MEAN (SD)	74.7(13.7)	74.3(12.3)	74.5(13.0)	
MEDIAN	74.0	73.5	73.8	
MIN-MAX	51.1-106.2	52.5-97.5	51.1-106.2	
HEIGHT (CM)				
N	25	21	46	0.016*
MEAN (SD)	168.9(8.43)	174.9(7.80)	171.6(8.61)	
MEDIAN	171.0	175.0	172.0	
MIN-MAX	148-185	157-190	148-190	
YEARS WITH EPILEPSY				
N	25	21	46	0.182
MEAN (SD)	24.9(10.5)	20.5(10.7)	22.9(10.7)	
MEDIAN	21.2	20.6	21.0	
MIN-MAX	8.4-56.8	1.9-45.8	1.9-56.8	

AS ASSESSED AT PRESTUDY VISIT OF SCREENING PHASE.
$ FROM ONE-WAY ANALYSIS OF VARIANCE FOR AGE, WEIGHT, HEIGHT, AND NUMBER OF AEDS EVER TAKEN; FROM WILCOXON RANK SUM TEST FOR YEARS WITH EPILEPSY. FROM FISHER'S EXACT TEST FOR SEX. N/A MEANS NOT APPLICABLE.
+, *, **, *** INDICATE STATISTICAL SIGNIFICANCE AT 0.10, 0.05, 0.01, AND 0.001 LEVELS, TWO-TAILED, RESPECTIVELY.

Table 17

BEST POSSIBLE COPY

Trial 481: Premature discontinuations

PATIENT DISPOSITION

RANDOMIZED PATIENT DATASET

PATIENT CATEGORY	NUMBER (%) OF PATIENTS RANDOMIZED TGB-PCB		PCB-TGB		TOTAL	
COMPLETED THE STUDY	23	(92.0%)	16	(76.1%)	39	(84.7%)
PREMATURELY CROSSED OVER FROM ASSESSMENT PERIOD 1 TO ASSESSMENT PERIOD 2						
REASON: LACK OF EFFICACY - PATIENT 7011	0	(0.0%)	1	(4.7%)	1	(2.1%)
PREMATURELY DISCONTINUED STUDY WITHOUT ENTERING TERMINATION PERIOD:						
FOLLOWING CROSSOVER PRIOR TO ASSESSMENT PERIOD 2						
REASON: ADVERSE EVENT - PATIENT 7010	1	(4.0%)	0	(0.0%)	1	(2.1%)
DURING ASSESSMENT PERIOD 2						
REASON: ADVERSE EVENT - PATIENT 6006	0	(0.0%)	1	(4.7%)	1	(2.1%)
PREMATURELY ENTERED TERMINATION PERIOD:						
PRIOR TO ASSESSMENT PERIOD 1						
REASON: LACK OF EFFICACY - PATIENT 6025	1	(4.0%)	0	(0.0%)	1	(2.1%)
DURING ASSESSMENT PERIOD 1						
REASON: ADVERSE EVENT - PATIENT 5015	0	(0.0%)	1	(4.7%)	1	(2.1%)
FOLLOWING CROSSOVER PRIOR TO ASSESSMENT PERIOD 2						
REASON: ADVERSE EVENT - PATIENT 7004	0	(0.0%)	1	(4.7%)	1	(2.1%)
DURING ASSESSMENT PERIOD 2						
REASON: ADVERSE EVENT - PATIENT 4005	0	(0.0%)	1	(4.7%)	1	(2.1%)
RANDOMIZED PATIENTS	25		21		46	

Table 18

Trial 481: Statistical results for CPS

FOUR-WEEK COMPLEX PARTIAL SEIZURE RATES
INVESTIGATOR BY TREATMENT SUMMARY AND TREATMENT COMPARISONS

INTENT-TO-TREAT DATASET

INVESTIGATOR	# OF PATS	TIAGABINE MEAN (SD)	TIAGABINE 25%	TIAGABINE MEDIAN	TIAGABINE 75%	PLACEBO MEAN (SD)	PLACEBO 25%	PLACEBO MEDIAN	PLACEBO 75%	TIAGABINE MINUS PLACEBO DIFFERENCE MEAN (SD)	DIFFERENCE 25%	DIFFERENCE MEDIAN	DIFFERENCE 75%
CHADWICK	6	12.8 (17.37)	4.7	5.7	6.9	16.7 (20.80)	7.4	10.3	10.9	-4.7 (4.13)	-9.1	-5.6	-2.8
DAM	6	5.0 (8.05)	0.6	2.3	5.7	12.8 (19.69)	2.4	5.4	8.7	-7.8 (11.66)	-5.0	-5.4	-1.8
DUNCAN	12	15.6 (19.68)	4.9	6.6	23.7	13.2 (14.37)	3.4	10.3	17.7	2.4 (6.44)	-1.1	0.9	5.1
MORROW	4	19.4 (26.12)	5.1	8.9	33.7	37.1 (50.39)	8.0	16.6	66.3	-17.7 (24.36)	-32.6	-7.7	-2.9
RICHENS	14	14.2 (22.12)	3.4	6.0	12.8	15.3 (24.65)	4.6	9.0	12.6	-1.1 (5.77)	-2.9	-1.7	0.3
OVERALL	42	13.5 (19.28)	5.4	6.3	12.8	16.6 (24.02)	4.0	9.1	13.7	-3.1 (10.88)	-4.0	-1.8	0.3

ANALYSIS METHOD	TEST OF TREATMENT EFFECTS& UNWEIGHTED COMPARISON P-VALUE	WEIGHTED COMPARISON P-VALUE
NONPARAMETRIC ANALYSIS ∂	0.008## (FAVORING TIAGABINE)	0.054+ (FAVORING TIAGABINE)
PARAMETRIC ANALYSIS ∮	<0.001###(FAVORING TIAGABINE)	0.002## (FAVORING TIAGABINE)

∂ NONPARAMETRIC ANALYSIS BASED ON METHOD PROPOSED BY KOCH FOR TWO-PERIOD CROSSOVER STUDIES AND APPLICATION OF IT TO MULTICENTER STUDIES USING THE VAN ELTEREN METHOD.
∮ PARAMETRIC ANALYSIS OF SQUARE-ROOT TRANSFORMED DATA BASED ON CROSSOVER ANALYSIS OF VARIANCE MODEL INCORPORATING INVESTIGATOR AND INVESTIGATOR INTERACTION EFFECTS.
ADDITIONAL P-VALUES FOR UNWEIGHTED COMPARISONS:

SEQUENCE GROUP EFFECT:	0.702
INV*SEQUENCE GROUP INTERACTION:	0.558
INV*TREATMENT INTERACTION:	0.002##
PERIOD EFFECT:	0.869
INV*PERIOD INTERACTION:	0.558

###, ##, #, + INDICATE STATISTICAL SIGNIFICANCE AT THE 0.001, 0.01, 0.05 AND 0.10 LEVEL, TWO-TAILED, RESPECTIVELY.
& TESTS OF EFFECTS WHEN DATA FOR INVESTIGATOR DUNCAN ARE EXCLUDED: P-VALUE FOR NON-PARAMETRIC WEIGHTED TREATMENT COMPARISON WAS 0.002 (FAVORING TIAGABINE); P-VALUES FOR ALL OTHER TREATMENT COMPARISONS WERE <=0.002 (FAVORING TIAGABINE); INVESTIGATOR BY TREATMENT INTERACTION WAS SIGNIFICANT AT THE 0.05 LEVEL. P-VALUES FOR ALL OTHER EFFECTS WERE NOT SIGNIFICANT.

Table 19 BEST POSSIBLE COPY

Trial 481: Statistical results for PS

FOUR-WEEK PARTIAL SEIZURE RATES
INVESTIGATOR BY TREATMENT SUMMARY AND TREATMENT COMPARISONS

INTENT-TO-TREAT DATASET

INVESTIGATOR	# OF PATS	TIAGABINE MEAN (SD)	TIAGABINE 25%	TIAGABINE MEDIAN	TIAGABINE 75%	PLACEBO MEAN (SD)	PLACEBO 25%	PLACEBO MEDIAN	PLACEBO 75%	TIAGABINE MINUS PLACEBO DIFFERENCE MEAN (SD)	DIFFERENCE 25%	DIFFERENCE MEDIAN	DIFFERENCE 75%
CHADWICK	6	12.0 (17.37)	4.7	5.7	6.9	16.7 (20.08)	7.4	10.3	10.9	-4.7 (4.13)	-9.1	-3.6	-2.8
DAM	6	6.2 (9.78)	1.1	2.9	4.3	16.7 (24.30)	2.9	6.9	16.8	-10.5 (14.67)	-11.7	-4.2	-1.9
DUNCAN	12	28.7 (41.52)	4.9	6.6	25.1	22.1 (36.87)	3.4	10.3	19.7	6.6 (26.40)	-3.1	-0.6	4.3
MORROW	4	19.4 (26.12)	5.1	8.9	33.7	37.1 (50.39)	8.8	16.6	66.3	-17.7 (24.36)	-32.6	-7.7	-2.9
RICHENS	14	14.3 (22.88)	3.4	6.0	12.8	15.7 (24.58)	4.6	10.8	14.9	-1.4 (6.05)	-3.4	-1.7	0.3
OVERALL	42	17.4 (36.50)	3.4	6.3	12.8	19.8 (30.84)	4.0	10.3	16.8	-2.4 (16.11)	-5.1	-1.8	-0.6

ANALYSIS METHOD	TEST OF TREATMENT EFFECT UNWEIGHTED COMPARISON P-VALUE	TEST OF TREATMENT EFFECT WEIGHTED COMPARISON P-VALUE
NONPARAMETRIC ANALYSIS @	0.004## (FAVORING TIAGABINE)	0.018# (FAVORING TIAGABINE)
PARAMETRIC ANALYSIS $	<0.001### (FAVORING TIAGABINE)	0.004## (FAVORING TIAGABINE)

@ NONPARAMETRIC ANALYSIS BASED ON METHOD PROPOSED BY KOCH FOR TWO-PERIOD CROSSOVER STUDIES AND APPLICATION OF IT TO MULTICENTER STUDIES USING THE VAN ELTEREN METHOD.

$ PARAMETRIC ANALYSIS OF SQUARE-ROOT TRANSFORMED DATA BASED ON CROSSOVER ANALYSIS OF VARIANCE MODEL INCORPORATING INVESTIGATOR AND INVESTIGATOR INTERACTION EFFECTS.
ADDITIONAL P-VALUES FOR UNWEIGHTED COMPARISONS:

SEQUENCE GROUP EFFECT:	0.598
INV*SEQUENCE GROUP INTERACTION:	0.741
INV*TREATMENT INTERACTION:	0.005##
PERIOD EFFECT:	0.924
INV*PERIOD INTERACTION:	0.148

###, ##, #, + INDICATE STATISTICAL SIGNIFICANCE AT THE 0.001, 0.01, 0.05 AND 0.10 LEVEL, TWO-TAILED, RESPECTIVELY.

Table 20 BEST POSSIBLE COPY

Trial 481: Statistical results for SPS

FOUR-WEEK SIMPLE PARTIAL SEIZURE RATES
INVESTIGATOR BY TREATMENT SUMMARY AND TREATMENT COMPARISONS

INTENT-TO-TREAT DATASET
OF PATIENTS WITH A SIMPLE PARTIAL SEIZURE DURING THE STUDY

INVESTIGATOR	# OF PATS	TIAGABINE MEAN (SD)	TIAGABINE 25%	TIAGABINE MEDIAN	TIAGABINE 75%	PLACEBO MEAN (SD)	PLACEBO 25%	PLACEBO MEDIAN	PLACEBO 75%	TIAGABINE MINUS PLACEBO DIFFERENCE MEAN (SD)	DIFFERENCE 25%	DIFFERENCE MEDIAN	DIFFERENCE 75%
DAH	6	6.2 (9.78)	1.1	2.9	4.3	16.3 (24.58)	2.9	6.9	16.0	-10.2 (14.95)	-11.7	-4.0	-1.7
DUNCAN	4	64.0 (105.4)	3.4	16.0	124.6	44.5 (59.25)	10.9	21.7	78.1	19.5 (47.79)	-9.7	4.6	48.7
MORROW	1	0.6 (0.00)	0.6	0.6	0.6	12.6 (0.00)	12.6	12.6	12.6	-4.0 (0.00)	-4.0	-4.0	-4.0
RICHENS	2	0.6 (0.81)	0.0	0.6	1.1	3.0 (4.21)	0.0	3.0	6.0	-2.4 (5.02)	-6.0	-2.4	1.1
OVERALL	13	23.3 (60.17)	1.1	3.4	8.6	22.6 (37.19)	2.9	9.6	19.4	0.6 (29.10)	-6.2	-1.9	0.6

ANALYSIS METHOD	-TEST OF TREATMENT DIFFERENCE- P-VALUE	
NONPARAMETRIC ANALYSIS @	0.199	(FAVORING TIAGABINE)
PARAMETRIC ANAYSIS $	0.276	(FAVORING TIAGABINE)

@ NONPARAMETRIC ANALYSIS BASED ON THE METHOD PROPOSED BY KOCH FOR TWO-PERIOD CROSSOVER STUDIES.
$ PARAMETRIC ANALYSIS OF SQUARE-ROOT TRANSFORMED DATA BASED ON CROSSOVER ANALYSIS OF VARIANCE MODEL IGNORING INVESTIGATOR AND INVESTIGATOR INTERACTION EFFECTS.
ADDITIONAL P-VALUES:
SEQUENCE GROUP EFFECT: 0.398
PERIOD EFFECT: 0.941
###, ##, #, + INDICATE STATISTICAL SIGNIFICANCE AT THE 0.001, 0.01, 0.05 AND 0.10 LEVEL, TWO-TAILED, RESPECTIVELY.

Table 21

Trial 481: Statistical results for SGTC sz.

FOUR-WEEK TONIC CLONIC SEIZURE RATES
INVESTIGATOR BY TREATMENT SUMMARY AND TREATMENT COMPARISONS

INTENT-TO-TREAT DATASET
OF PATIENTS WITH A TONIC CLONIC SEIZURE DURING THE STUDY

INVESTIGATOR	# OF PATS	TIAGABINE MEAN (SD)	TIAGABINE 25%	TIAGABINE MEDIAN	TIAGABINE 75%	PLACEBO MEAN (SD)	PLACEBO 25%	PLACEBO MEDIAN	PLACEBO 75%	TIAGABINE MINUS PLACEBO DIFFERENCE MEAN (SD)	DIFFERENCE 25%	DIFFERENCE MEDIAN	DIFFERENCE 75%
CHADWICK	5	4.7 (4.36)	1.5	4.7	6.4	9.7 (12.38)	2.3	5.7	9.7	-5.0 (8.46)	-3.3	-2.3	-1.0
DAH	2	0.0 (0.00)	0.0	0.0	0.0	0.6 (0.81)	0.0	0.6	1.1	-0.6 (0.81)	-1.1	-0.6	0.0
DUNCAN	9	1.6 (2.04)	0.0	1.1	2.3	3.1 (3.21)	1.1	2.3	4.0	-1.5 (3.67)	-2.8	-1.1	0.0
MORROW	3	15.6 (23.12)	1.1	3.4	42.3	37.9 (54.49)	1.7	11.4	100.6	-22.3 (31.48)	-58.3	-8.0	-0.6
RICHENS	8	1.9 (3.00)	0.0	0.3	2.9	2.7 (3.17)	0.0	1.7	4.9	-0.9 (1.96)	-1.4	0.0	0.3
OVERALL	27	3.7 (8.25)	0.0	1.1	3.4	7.9 (19.56)	0.0	2.3	5.7	-4.2 (11.70)	-3.3	-1.0	0.0

ANALYSIS METHOD	-TEST OF TREATMENT DIFFERENCE- P-VALUE	
NONPARAMETRIC ANALYSIS @	0.009##	(FAVORING TIAGABINE)
PARAMETRIC ANAYSIS $	0.009##	(FAVORING TIAGABINE)

@ NONPARAMETRIC ANALYSIS BASED ON THE METHOD PROPOSED BY KOCH FOR TWO-PERIOD CROSSOVER STUDIES.
$ PARAMETRIC ANALYSIS OF SQUARE-ROOT TRANSFORMED DATA BASED ON CROSSOVER ANALYSIS OF VARIANCE MODEL IGNORING INVESTIGATOR AND INVESTIGATOR INTERACTION EFFECTS.
ADDITIONAL P-VALUES:
SEQUENCE GROUP EFFECT: 0.125
PERIOD EFFECT: 0.512
###, ##, #, + INDICATE STATISTICAL SIGNIFICANCE AT THE 0.001, 0.01, 0.05 AND 0.10 LEVEL, TWO-TAILED, RESPECTIVELY.

Table 22

Trial 565: Patient demographics

PATIENT PRESTUDY CHARACTERISTICS

RANDOMIZED PATIENT DATASET

VARIABLE@	TGB-PCB (N=26)	PCB-TGB (N=18)	TOTAL (N=44)	P-VALUE$
AGE (YEARS)				
N	26	18	44	0.562
MEAN (SD)	35.0 (9.4)	33.3 (9.1)	34.3 (9.2)	
MEDIAN	33.5	30.5	31.5	
MIN-MAX	20- 56	20- 51	20- 56	
SEX				
FEMALE	8 (31%)	2 (11%)	10 (23%)	0.161
MALE	18 (69%)	16 (89%)	34 (77%)	
RACE				
CAUCASIAN	26 (100%)	18 (100%)	44 (100%)	N/A
WEIGHT (KG)				
N	26	17	43	0.783
MEAN (SD)	78.7 (15.2)	79.9 (12.6)	79.2 (14.1)	
MEDIAN	76.0	79.0	77.0	
MIN-MAX	55.0-122.3	61.0-110.0	55.0-122.3	
HEIGHT (CM)				
N	26	17	43	0.898
MEAN (SD)	174.4 (11.1)	174.8 (7.9)	174.6 (9.8)	
MEDIAN	178.0	174.5	177.0	
MIN-MAX	151-194	161-188	151-194	
YEARS WITH EPILEPSY				
N	26	18	44	0.821
MEAN (SD)	23.9 (12.8)	23.9 (11.4)	23.9 (12.1)	
MEDIAN	23.2	24.6	23.6	
MIN-MAX	3.2- 52.4	4.4- 49.4	3.2- 52.4	

@ AS ASSESSED AT PRESTUDY VISIT OF SCREENING PHASE.
$ FROM ONE-WAY ANALYSIS OF VARIANCE FOR AGE, WEIGHT, HEIGHT, AND NUMBER OF AEDS EVER TAKEN; FROM WILCOXON RANK SUM TEST FOR YEARS WITH EPILEPSY; FROM FISHER'S EXACT TEST FOR SEX. N/A MEANS NOT APPLICABLE.
+, *, **, *** INDICATE STATISTICAL SIGNIFICANCE AT 0.10, 0.05, 0.01, AND 0.001 LEVELS, TWO-TAILED, RESPECTIVELY.

WEIGHT AND HEIGHT WERE NOT RECORDED FOR PATIENTS 4023 AND 5030 RESPECTIVELY.

Table 23

Trial 565: Premature discontinuations

PATIENT DISPOSITION

RANDOMISED PATIENT DATASET

PATIENT CATEGORY		- NUMBER (%) OF PATIENTS RANDOMISED - TGB-PCB	PCB-TGB	TOTAL
COMPLETED THE STUDY		22 (84.6)	11 (61.1)	33 (75.0)
PREMATURELY CROSSED OVER:				
PRIOR TO ASSESSMENT PERIOD 1				
REASON: LACK OF EFFICACY	- PATIENT 4015 4024	0 (0.0)	2 (11.1)	2 (4.5)
FROM ASSESSMENT PERIOD 1 TO ASSESSMENT PERIOD 2				
REASON: LACK OF EFFICACY	- PATIENT 4020	0 (0.0)	1 (5.6)	1 (2.3)
PREMATURELY DISCONTINUED STUDY WITHOUT ENTERING TERMINATION PERIOD:				
PRIOR TO ASSESSMENT PERIOD 1				
REASON: OTHER	- PATIENT 5022	0 (0.0)	1 (5.6)	1 (2.3)
DURING ASSESSMENT PERIOD 1				
REASON: ADVERSE EVENT	- PATIENT 4025	1 (3.8)	0 (0.0)	1 (2.3)
OTHER	- PATIENT 4023 7012	1 (3.8)	1 (5.6)	2 (4.5)
DURING ASSESSMENT PERIOD 2				
REASON: ADVERSE EVENT	- PATIENT 4019	1 (3.8)	0 (0.0)	1 (2.3)
PREMATURELY ENTERED TERMINATION PERIOD:				
PRIOR TO ASSESSMENT PERIOD 1				
REASON: OTHER	- PATIENT 9013	0 (0.0)	1 (5.6)	1 (2.3)
FOLLOWING CROSSOVER				
PRIOR TO ASSESSMENT PERIOD 2				
REASON: ADVERSE EVENT	- PATIENT 4016	0 (0.0)	1 (5.6)	1 (2.3)
DURING ASSESSMENT PERIOD 2				
REASON: LACK OF EFFICACY	- PATIENT 9002	1 (3.8)	0 (0.0)	1 (2.3)
OTHER	- PATIENT 4024	0 (0.0)	1 (5.6)	1 (2.3)
RANDOMISED PATIENTS		26	18	44

NOTE: PATIENT 4024 APPEARS TWICE IN THE ABOVE TABLE.

Table 24

Trial 565: Statistical results for PS

WEEKLY PARTIAL SEIZURE RATES
INVESTIGATOR BY TREATMENT SUMMARY AND TREATMENT COMPARISONS

INTENT-TO-TREAT DATASET

INVESTIGATOR	# OF PATS	TIAGABINE MEAN (SD)	TIAGABINE 25%	TIAGABINE MEDIAN	TIAGABINE 75%	PLACEBO MEAN (SD)	PLACEBO 25%	PLACEBO MEDIAN	PLACEBO 75%	TIAGABINE MINUS PLACEBO DIFFERENCE MEAN (SD)	DIFFERENCE 25%	DIFFERENCE MEDIAN	DIFFERENCE 75%
PEDERSEN	2	0.5 (0.06)	0.4	0.5	0.5	1.6 (1.01)	0.9	1.6	2.3	-1.1 (0.95)	-1.8	-1.1	-0.4
CRAWFORD	9	1.3 (1.21)	0.7	0.9	2.0	2.9 (2.67)	1.1	2.3	4.3	-1.6 (2.92)	-2.1	-0.4	0.0
BROWN	8	1.9 (1.06)	1.4	2.0	2.5	3.3 (3.25)	1.6	2.3	3.5	-1.4 (3.31)	-1.6	-0.6	0.1
MEINARDI	12	2.7 (2.56)	0.8	2.3	4.0	3.9 (2.80)	1.7	3.3	5.9	-1.2 (1.82)	-1.8	-0.7	-0.1
RENTMEESTER	5	5.3 (8.26)	1.0	2.1	2.6	5.9 (8.53)	2.0	2.1	3.3	-0.6 (0.55)	-1.1	-0.7	-0.4
OVERALL	36	2.4 (3.49)	0.7	1.5	3.0	3.7 (3.97)	1.4	2.3	4.2	-1.2 (2.31)	-1.6	-0.6	-0.1

ANALYSIS METHOD	TEST OF TREATMENT EFFECTS: UNWEIGHTED COMPARISON P-VALUE		WEIGHTED COMPARISON P-VALUE	
NONPARAMETRIC ANALYSIS @	0.005**	(FAVOURING TIAGABINE)	0.002**	(FAVOURING TIAGABINE)
PARAMETRIC ANALYSIS $	0.030*	(FAVOURING TIAGABINE)	0.020*	(FAVOURING TIAGABINE)

@ NONPARAMETRIC ANALYSIS BASED ON METHOD PROPOSED BY KOCH FOR TWO-PERIOD CROSSOVER STUDIES AND APPLICATION OF IT TO MULTICENTER STUDIES USING THE VAN ELTEREN METHOD.

$ PARAMETRIC ANALYSIS OF SQUARE-ROOT TRANSFORMED DATA BASED ON CROSSOVER ANALYSIS OF VARIANCE MODEL INCORPORATING INVESTIGATOR AND INVESTIGATOR INTERACTION EFFECTS.

ADDITIONAL P-VALUES FOR UNWEIGHTED COMPARISONS:

SEQUENCE GROUP EFFECT:	0.695
INV*SEQENCE GROUP INTERACTION:	0.673
INV*TREATMENT INTERACTION:	0.971
PERIOD EFFECT:	0.336
INV*PERIOD INTERACTION:	0.844

***, **, *, + INDICATE STATISTICAL SIGNIFICANCE AT THE 0.001, 0.01, 0.05 AND 0.10 LEVEL, TWOTAILED, RESPECTIVELY

Table 25

BEST POSSIBLE

Trial 565: Statistical results for CPS

WEEKLY COMPLEX PARTIAL SEIZURE RATES
INVESTIGATOR BY TREATMENT SUMMARY AND TREATMENT COMPARISONS

INTENT-TO-TREAT DATASET
PATIENTS WITH A COMPLEX PARTIAL SEIZURE DURING THE STUDY

INVESTIGATOR	# OF PATS	TIAGABINE MEAN (SD)	TIAGABINE 25%	TIAGABINE MEDIAN	TIAGABINE 75%	PLACEBO MEAN (SD)	PLACEBO 25%	PLACEBO MEDIAN	PLACEBO 75%	TIAGABINE MINUS PLACEBO DIFFERENCE MEAN (SD)	DIFFERENCE 25%	DIFFERENCE MEDIAN	DIFFERENCE 75%
PEDERSEN	2	0.5 (0.06)	0.4	0.5	0.5	1.6 (1.01)	0.9	1.6	2.3	-1.1 (0.95)	-1.8	-1.1	-0.4
CRAWFORD	5	0.8 (0.63)	0.6	0.7	1.0	1.4 (0.65)	1.0	1.1	1.7	-0.6 (0.48)	-0.7	-0.4	-0.4
BROWN	7	1.6 (1.06)	0.7	1.3	2.9	3.0 (3.63)	0.9	1.9	3.3	-1.4 (3.51)	-1.5	-0.6	0.5
HEINARDI	10	1.9 (2.85)	0.4	0.8	1.4	3.3 (3.16)	1.1	2.3	5.7	-1.4 (1.71)	-2.0	-1.1	-0.1
RENTHEESTER	4	1.6 (0.89)	0.9	1.6	2.4	2.1 (0.88)	1.6	2.1	2.7	-0.5 (0.56)	-0.9	-0.6	-0.1
OVERALL	28	1.5 (1.83)	0.5	0.9	1.9	2.6 (2.66)	1.0	1.9	2.9	-1.1 (1.99)	-1.4	-0.7	-0.3

ANALYSIS METHOD	TEST OF TREATMENT EFFECTS& UNWEIGHTED COMPARISON P-VALUE	WEIGHTED COMPARISON P-VALUE
NONPARAMETRIC ANALYSIS @	0.004** (FAVOURING TIAGABINE)	<0.001*** (FAVOURING TIAGABINE)
PARAMETRIC ANALYSIS $	0.009** (FAVOURING TIAGABINE)	0.003** (FAVOURING TIAGABINE)

@ NONPARAMETRIC ANALYSIS BASED ON METHOD PROPOSED BY KOCH FOR TWO-PERIOD CROSSOVER STUDIES AND APPLICATION OF IT TO MULTICENTER STUDIES USING THE VAN ELTEREN METHOD.

$ PARAMETRIC ANALYSIS OF SQUARE-ROOT TRANSFORMED DATA BASED ON CROSSOVER ANALYSIS OF VARIANCE MODEL INCORPORATING INVESTIGATOR AND INVESTIGATOR INTERACTION EFFECTS.

ADDITIONAL P-VALUES FOR UNWEIGHTED COMPARISONS:

SEQUENCE GROUP EFFECT:	0.768
INV*SEQENCE GROUP INTERACTION:	0.714
INV*TREATMENT INTERACTION:	0.946
PERIOD EFFECT:	0.212
INV*PERIOD INTERACTION:	0.334

***, **, *, + INDICATE STATISTICAL SIGNIFICANCE AT THE 0.001, 0.01, 0.05 AND 0.10 LEVEL, TWOTAILED, RESPECTIVELY

Table 26.

Trial 565: Statistical results for SPS

WEEKLY SIMPLE PARTIAL SEIZURE RATES
INVESTIGATOR BY TREATMENT SUMMARY AND TREATMENT COMPARISONS

INTENT-TO-TREAT DATASET
PATIENTS WITH A SIMPLE PARTIAL SEIZURE DURING THE STUDY

INVESTIGATOR	# OF PATS	TIAGABINE MEAN (SD)	TIAGABINE 25%	TIAGABINE MEDIAN	TIAGABINE 75%	PLACEBO MEAN (SD)	PLACEBO 25%	PLACEBO MEDIAN	PLACEBO 75%	TIAGABINE MINUS PLACEBO DIFFERENCE MEAN (SD)	DIFFERENCE 25%	DIFFERENCE MEDIAN	DIFFERENCE 75%
PEDERSEN	1	0.0		0.0		0.9		0.9		-0.9		-0.9	
CRAWFORD	7	1.2 (1.21)	0.0	0.9	2.0	2.9 (2.87)	0.5	2.3	4.3	-1.7 (3.33)	-3.2	-0.4	0.3
BROWN	5	1.7 (1.30)	1.3	1.6	2.1	1.9 (1.30)	1.3	1.4	2.2	-0.2 (0.96)	-0.6	-0.4	0.7
HEINARDI	7	2.2 (1.72)	0.4	3.1	3.9	3.2 (2.48)	0.3	3.3	6.1	-1.0 (2.46)	-3.0	-0.1	0.6
RENTHEESTER	1	20.0		20.0		21.1		21.1		-1.1		-1.1	
OVERALL	21	2.5 (4.25)	0.4	1.3	3.1	3.5 (4.62)	0.9	2.3	4.0	-1.0 (2.38)	-1.1	-0.4	0.3

ANALYSIS METHOD	-TEST OF TREATMENT DIFFERENCE- P-VALUE	
NONPARAMETRIC ANALYSIS @	0.339	(FAVOURING TIAGABINE)
PARAMETRIC ANALYSIS $	0.254	(FAVOURING TIAGABINE)

@ NONPARAMETRIC ANALYSIS BASED ON METHOD PROPOSED BY KOCH FOR TWO-PERIOD CROSSOVER STUDIES
$ PARAMETRIC ANALYSIS OF SQUARE-ROOT TRANSFORMED DATA BASED ON CROSSOVER ANALYSIS OF VARIANCE MODEL IGNORING INVESTIGATOR AND INVESTIGATOR INTERACTION EFFECTS.
ADDITIONAL P-VALUES:
SEQUENCE GROUP EFFECT: 0.737
PERIOD EFFECT: 0.857
***, **, *, + INDICATE STATISTICAL SIGNIFICANCE AT THE 0.001, 0.01, 0.05 AND 0.10 LEVEL, TWOTAILED, RESPECTIVELY

Table 27

Trial 656: Statistical results for SGTC se

WEEKLY TONIC CLONIC SEIZURE RATES
INVESTIGATOR BY TREATMENT SUMMARY AND TREATMENT COMPARISONS

INTENT-TO-TREAT DATASET
PATIENTS WITH A TONIC CLONIC SEIZURE DURING THE STUDY

INVESTIGATOR	# OF PATS	TIAGABINE MEAN (SD)	TIAGABINE 25%	TIAGABINE MEDIAN	TIAGABINE 75%	PLACEBO MEAN (SD)	PLACEBO 25%	PLACEBO MEDIAN	PLACEBO 75%	TIAGABINE MINUS PLACEBO DIFFERENCE MEAN (SD)	DIFFERENCE 25%	DIFFERENCE MEDIAN	DIFFERENCE 75%
CRAWFORD	8	1.0 (0.88)	0.3	0.8	1.9	1.3 (1.41)	0.2	0.8	2.2	-0.3 (0.95)	-0.8	-0.4	0.2
BROWN	7	0.5 (0.64)	0.1	0.3	0.7	1.5 (1.81)	0.4	0.9	1.4	-1.0 (1.82)	-1.1	-0.3	-0.1
RENTHEESTER	3	0.4 (0.43)	0.0	0.4	0.9	0.8 (0.42)	0.6	0.6	1.3	-0.4 (0.22)	-0.6	-0.4	-0.1
OVERALL	18	0.7 (0.75)	0.1	0.6	0.9	1.3 (1.43)	0.4	0.8	1.4	-0.6 (1.29)	-0.7	-0.4	-0.1

ANALYSIS METHOD	-TEST OF TREATMENT DIFFERENCE- P-VALUE	
NONPARAMETRIC ANALYSIS @	0.030*	(FAVOURING TIAGABINE)
PARAMETRIC ANALYSIS $	0.028*	(FAVOURING TIAGABINE)

@ NONPARAMETRIC ANALYSIS BASED ON METHOD PROPOSED BY KOCH FOR TWO-PERIOD CROSSOVER STUDIES
$ PARAMETRIC ANALYSIS OF SQUARE-ROOT TRANSFORMED DATA BASED ON CROSSOVER ANALYSIS OF VARIANCE MODEL IGNORING INVESTIGATOR AND INVESTIGATOR INTERACTION EFFECTS.
ADDITIONAL P-VALUES:
SEQUENCE GROUP EFFECT: 0.974
PERIOD EFFECT: 0.513
***, **, *, + INDICATE STATISTICAL SIGNIFICANCE AT THE 0.001, 0.01, 0.05 AND 0.10 LEVEL, TWOTAILED, RESPECTIVELY

BEST POSSIBLE

Table 28

Parallel group trials
Median change from Baseline to Experiment Period in four-week CPS rate[a]

Target daily dose	0 mg	16 mg	30 mg	32 mg		56 mg
Trial/regimen	(placebo)	(qid)	(tid)	16 mg bid	8 mg qid	(qid)
603	-0.7 (n=90)	-0.8 (n=61) p=.44 (p=.46)			-2.2 (n=86) p=.030 (p=.089)	-2.8 (n=55) p=.028 (p=.050)
605	-0.2 (n=105)			-1.6 (n=106) p=.055 (p=.26)	-1.2 (n=103) p=.018 (p=.104)	
775	0.1 (n=75)		-1.3 (n=72) p=.014 (p=.30)			

[a] change from Baseline to EP was measured by EP rate minus Baseline rate.

N.B. p-values represent pairwise comparisons with placebo using the weighted van Eltern test. P-values in parentheses represent pairwise comparisons with placebo using the unweighted van Eltern test.

BEST POSSIBLE

Table 29

Crossover trials
Median difference between tiagabine and placebo in four-week CPS rate[a]

Median daily dose[b]	32 mg[c]	52 mg
Trial/regimen	qid	qid
481	-1.8 (n=42) p=.054 (p=.008)	
565		-2.8 (n=36) p<.001 (p=.004)

[a] difference between tiagabine and placebo was measured by tiagabine rate minus placebo rate.
[b] Patients received individualized doses of the test drug.
[c] The median dose for Trial 481 as reported in Final Report for Trial 565, NDA vol 068 page 038.
N.B. p-values obtained from weighted van Eltern test. Unweighted van Elteren p-values in parentheses.

POSSIBLE COPY

Table 30

Parallel group trials
Median change from Baseline to Experiment Period in four-week PS rate[a]

Target daily dose	0 mg	16 mg	30 mg	32 mg		56 mg
Trial/regimen	(placebo)	(qid)	(tid)	16 mg bid	8 mg qid	(qid)
603	-0.3 (n=90)	-1.2 (n=61) p=.24 p=.49			-2.7 (n=86) p=.018 (p=.036)	-3.3 (n=55) p<.001 (p<.001)
605	-0.3 (n=105)			-1.6 (n=106) p=.097 (p=.19)	-1.2 (n=103) p=.056 (p=.17)	
775	0.5 (n=77)		-1.1 (n=77) p=.019 (p=.40)			

[a] change from Baseline to EP was measured by EP rate minus Baseline rate.

N.B. p-values represent pairwise comparisons with placebo using the weighted van Eltern test. P-values in parentheses represent pairwise comparisons with placebo using the unweighted van Eltern test.

Table 31

Crossover trials
Median difference between tiagabine and placebo in four-week PS rate [a]

Median daily dose [b]	32 mg [c]	52 mg
Trial/regimen	qid	qid
481	-1.8 (n=42) p=.018 (p=.004)	
565		-2.4 (n=36) p=.002 (p=.005)

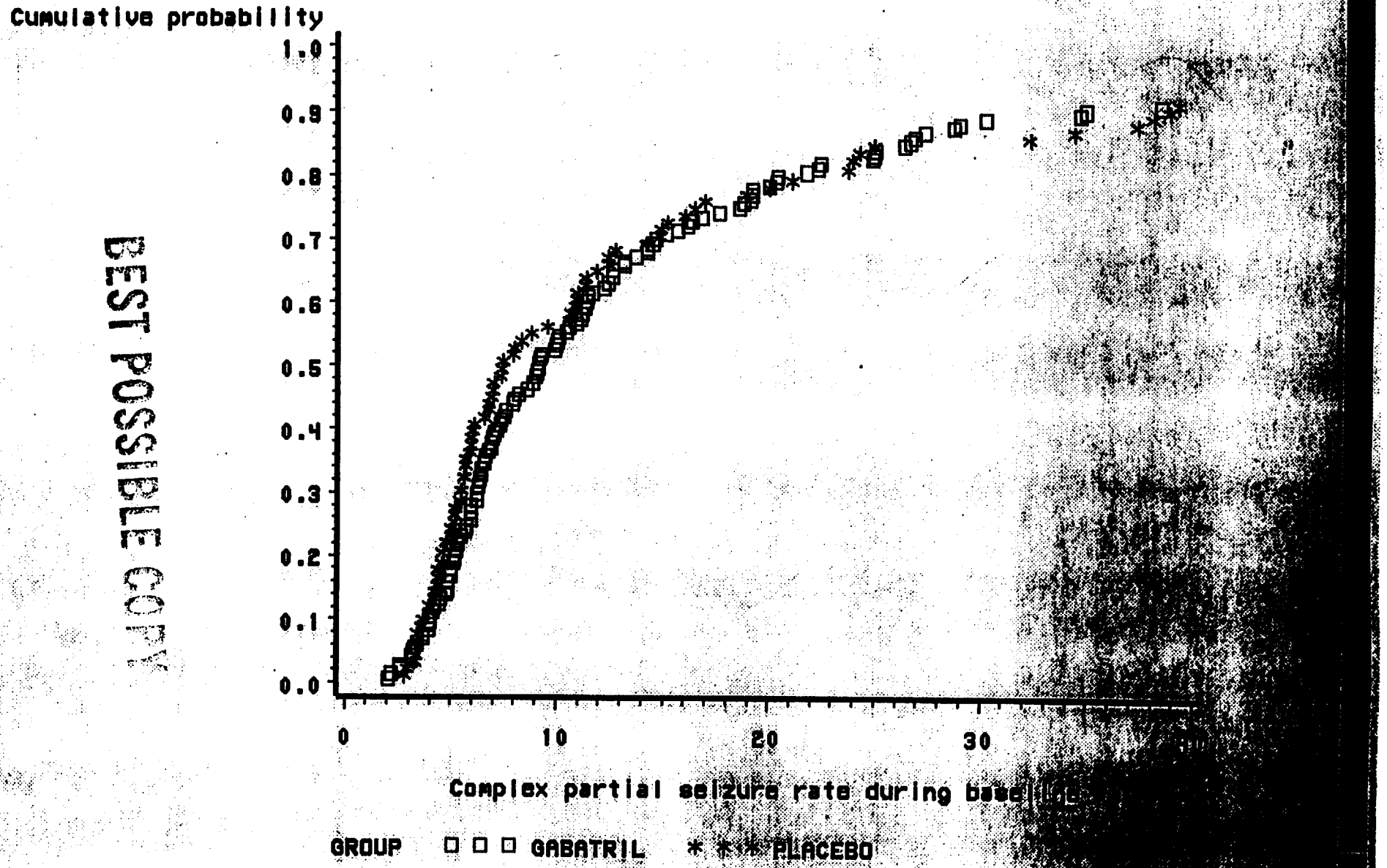
[a] difference between tiagabine and placebo was measured by tiagabine rate minus placebo rate.
[b] Patients received individualized doses of the test drug.
[c] The median dose for Trial 481 as reported in Final Report for Trial 565, NDA vol 068 page 038.

N.B. p-values obtained from weighted van Eltern test. Unweighted van Elteren p-values in parentheses.

Fig. 1

Trial 603

Gabatril (32mg + 56mg) vs placebo comparison

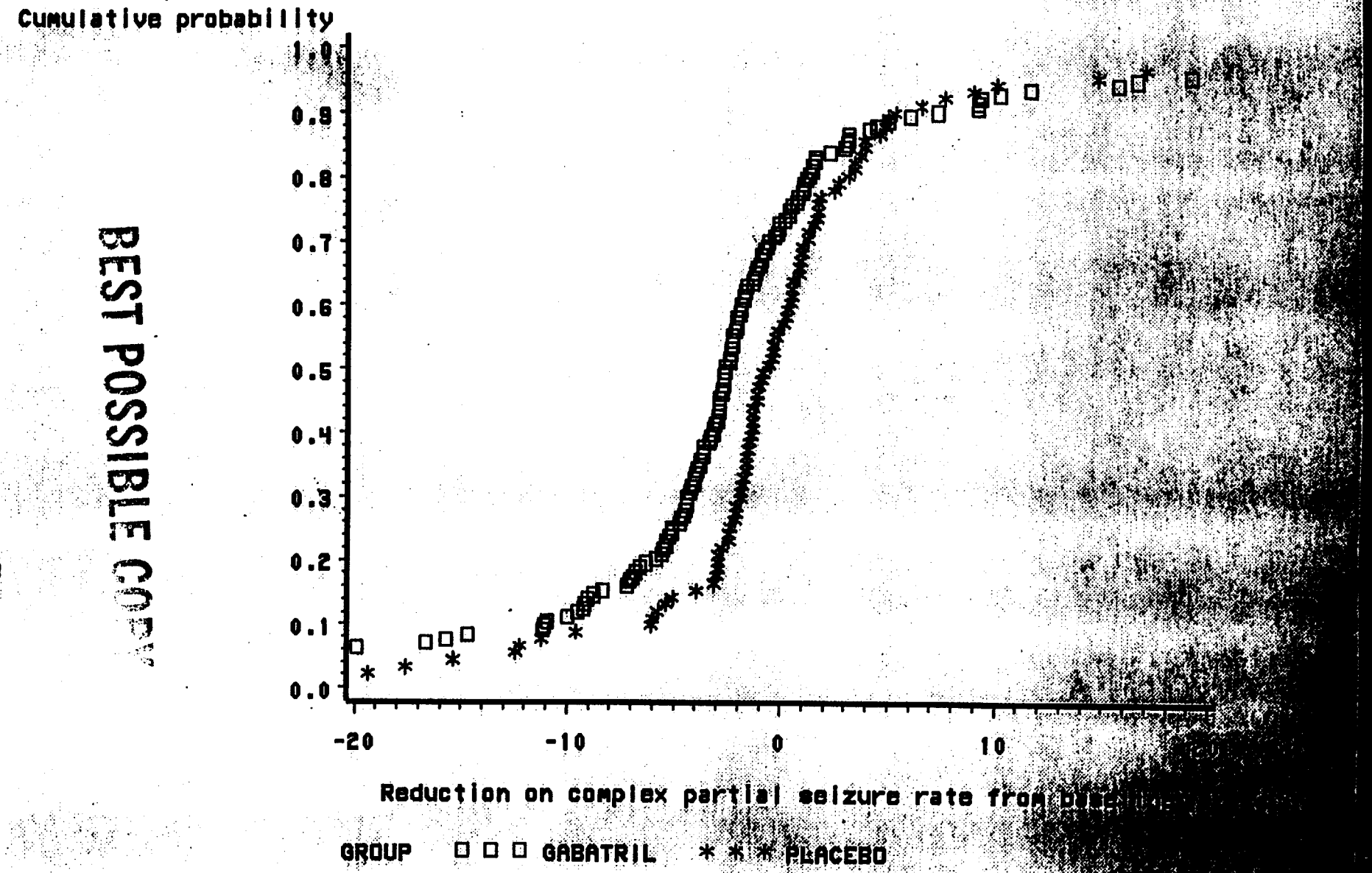


BEST POSSIBLE COPY

Fig. 2

Trial 603

Gabatril (32mg + 56mg) vs placebo comparison



BEST POSSIBLE COPY

Fig. 3

Trial 603

tiagabine (32mg + 56mg) vs placebo

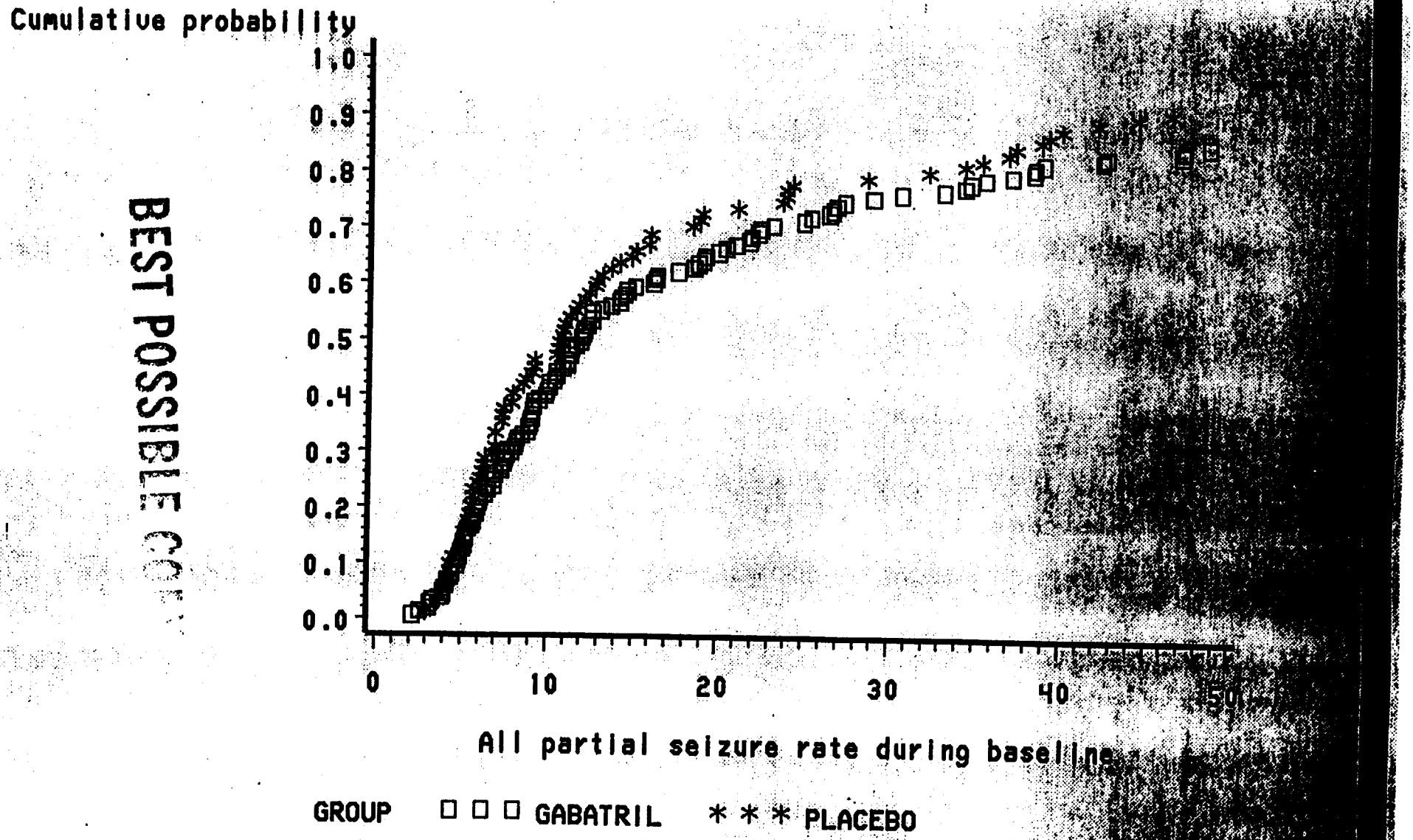
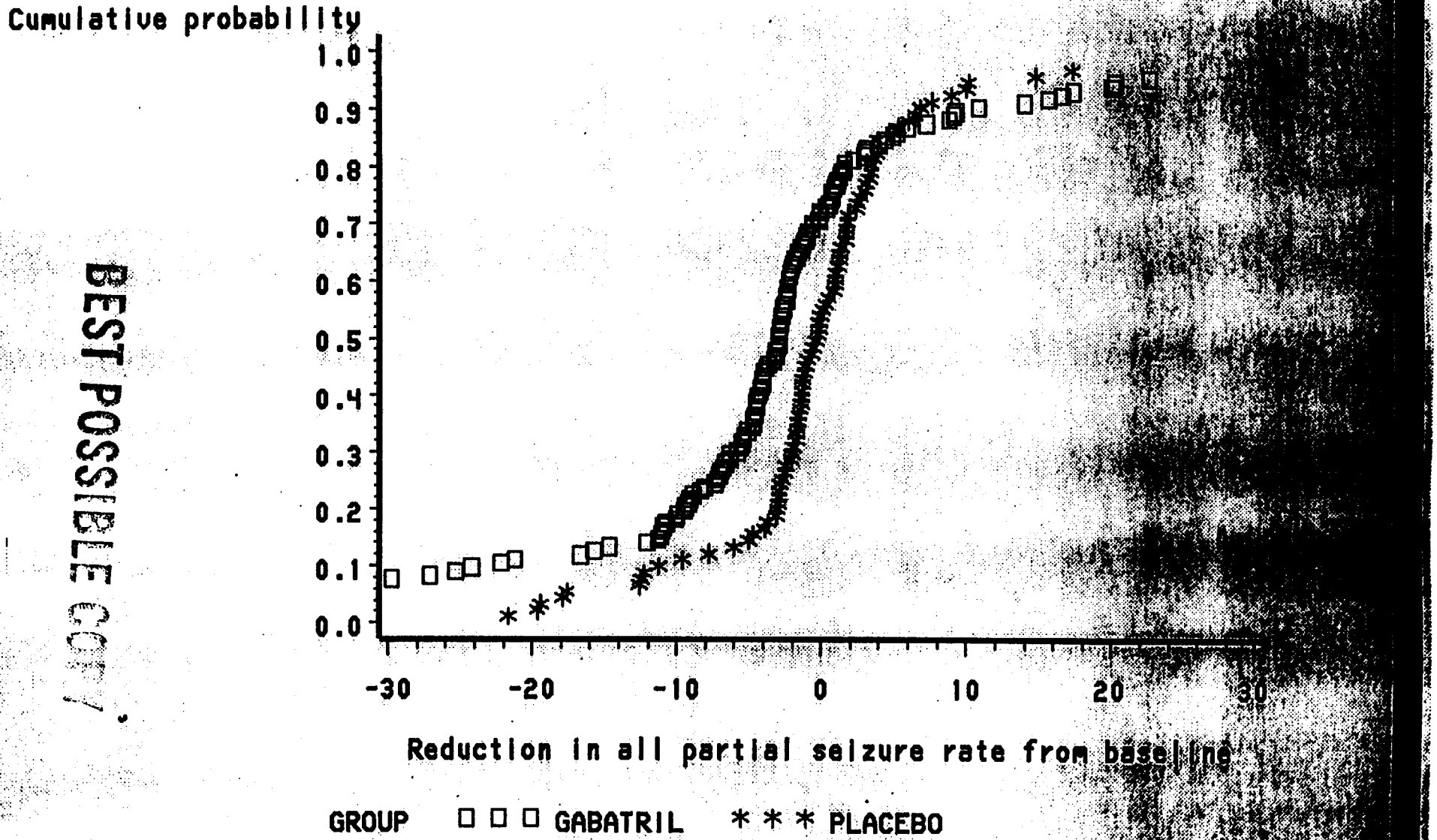


Fig. 4

Trial 603

tiagabine (32mg + 56mg) vs placebo comparison



BEST POSSIBLE COPY

Fig. 5

Trial 603

tiagabine all doses vs placebo

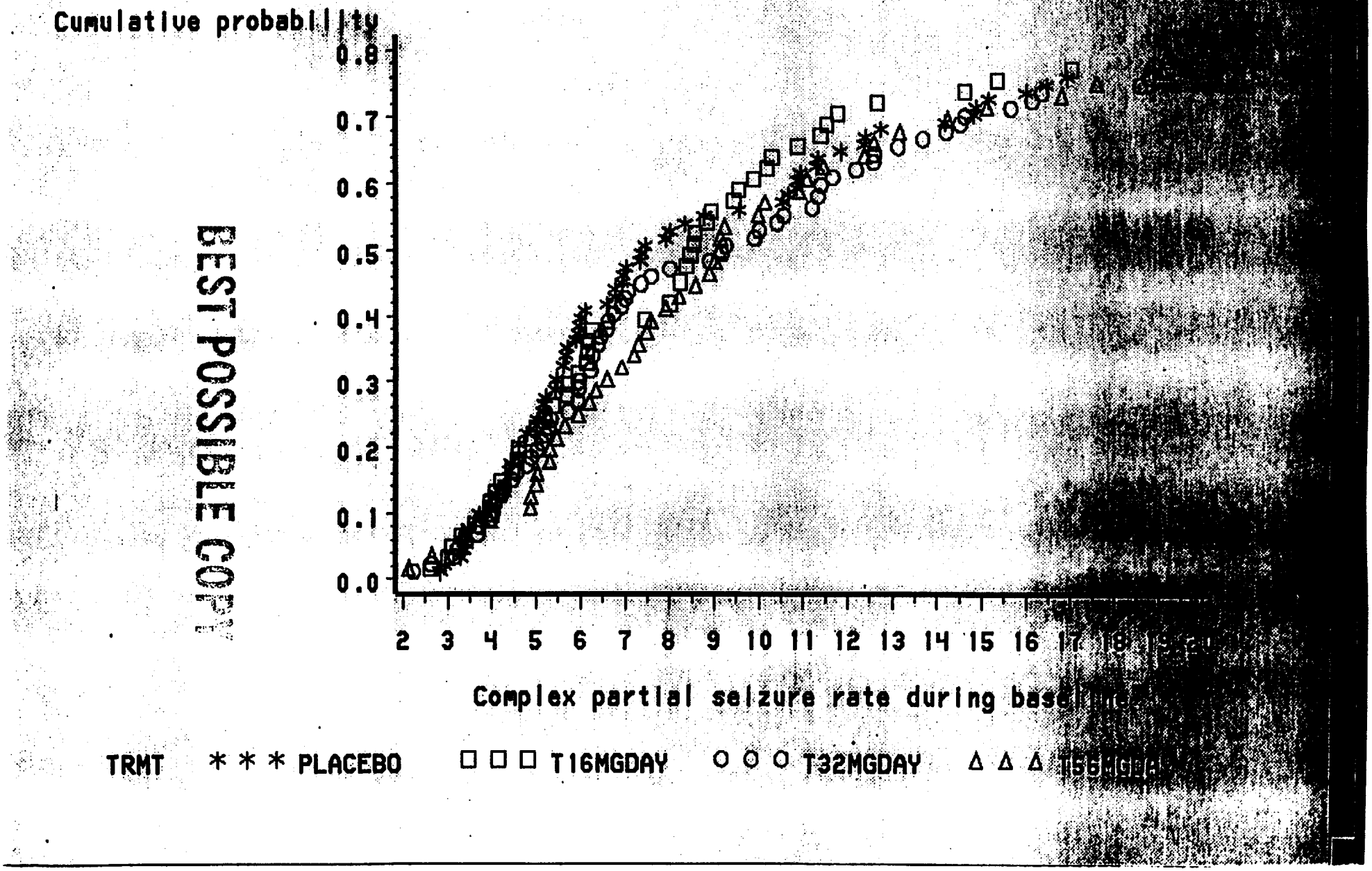


Fig. 6.

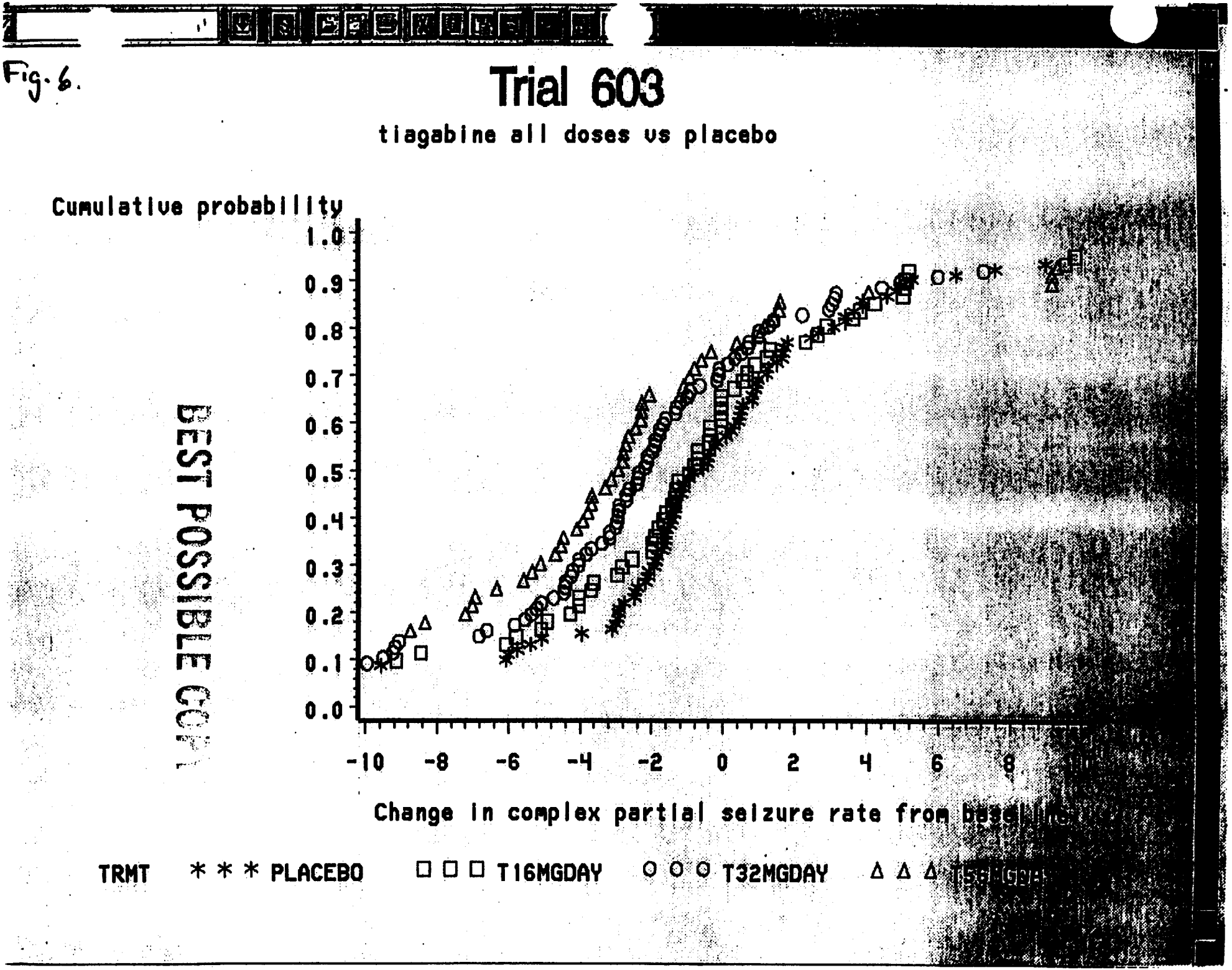

Trial 603
tiagabine all doses vs placebo
Cumulative probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
BEST POSSIBLE COPY
-10
-8
-6
-4
-2
0
2
4
6
8
Change in complex partial seizure rate from baseline
TRMT
* * * PLACEBO
□ □ □ T16MGDAY
O O O T32MGDAY
Δ Δ Δ T56MGDAY

Fig. 7

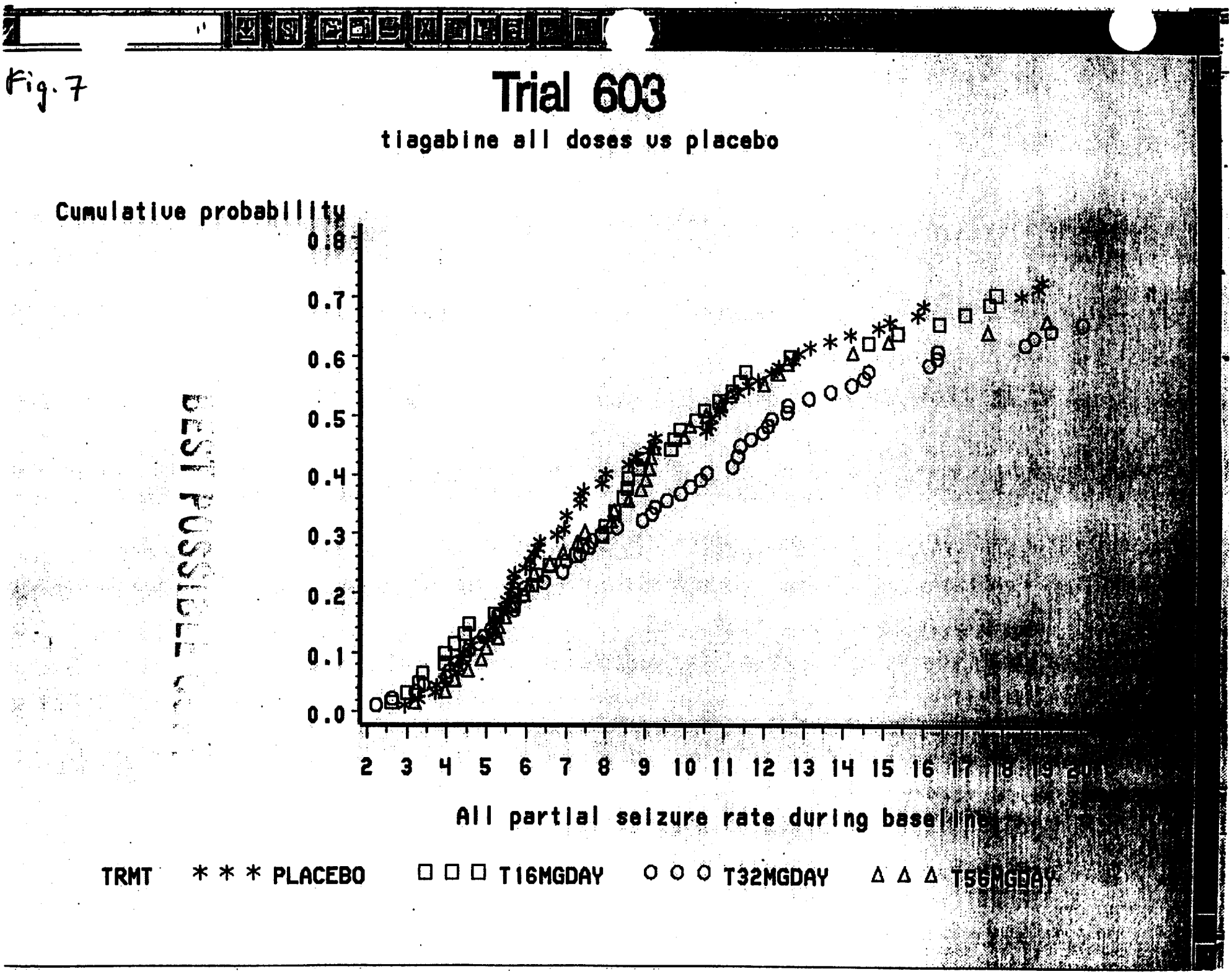

Trial 603
tiagabine all doses vs placebo
Cumulative probability
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
All partial seizure rate during baseline
TRMT * * * PLACEBO □ □ □ T16MGDAY O O O T32MGDAY Δ Δ Δ T56MGDAY

Fig. 8

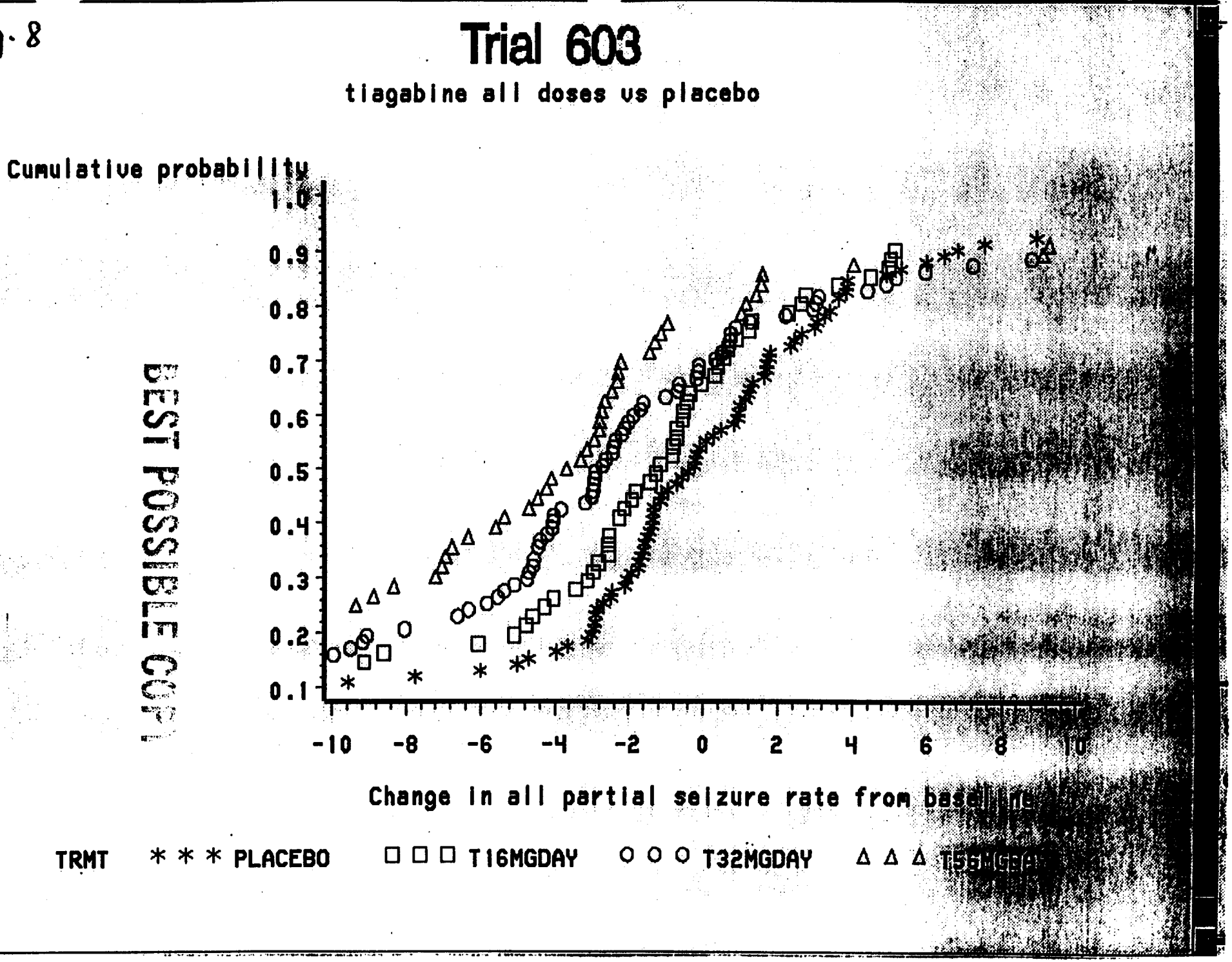
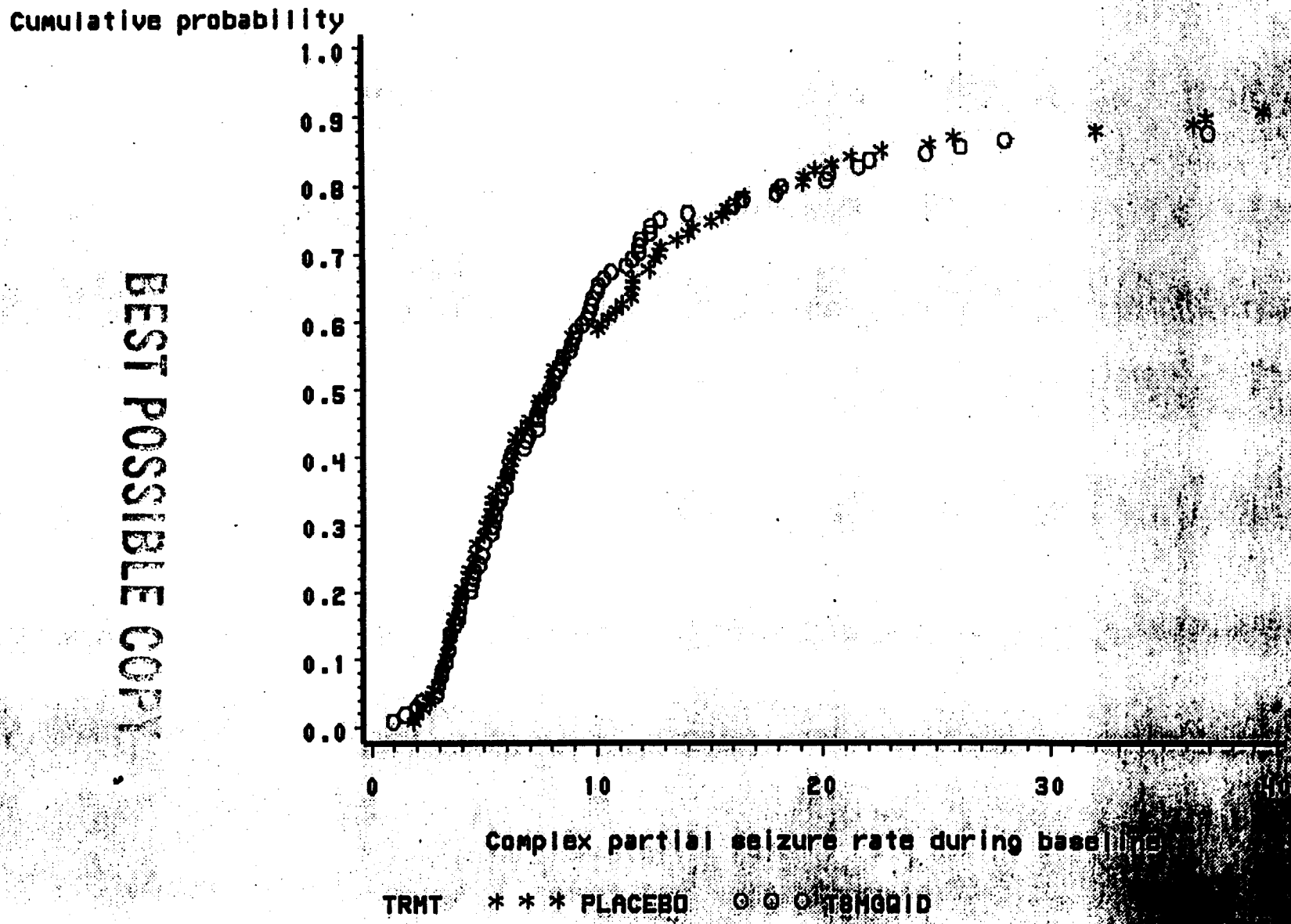

Trial 603
tiagabine all doses vs placebo
Cumulative probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
BEST POSSIBLE COPY
-10
-8
-6
-4
-2
0
2
4
6
8
10
Change in all partial seizure rate from baseline
TRMT
* * * PLACEBO
□ □ □ T16MGDAY
O O O T32MGDAY
Δ Δ Δ T56MGDAY

Fig. 9

Trial 605

Gabatril 8mg qid vs placebo comparison

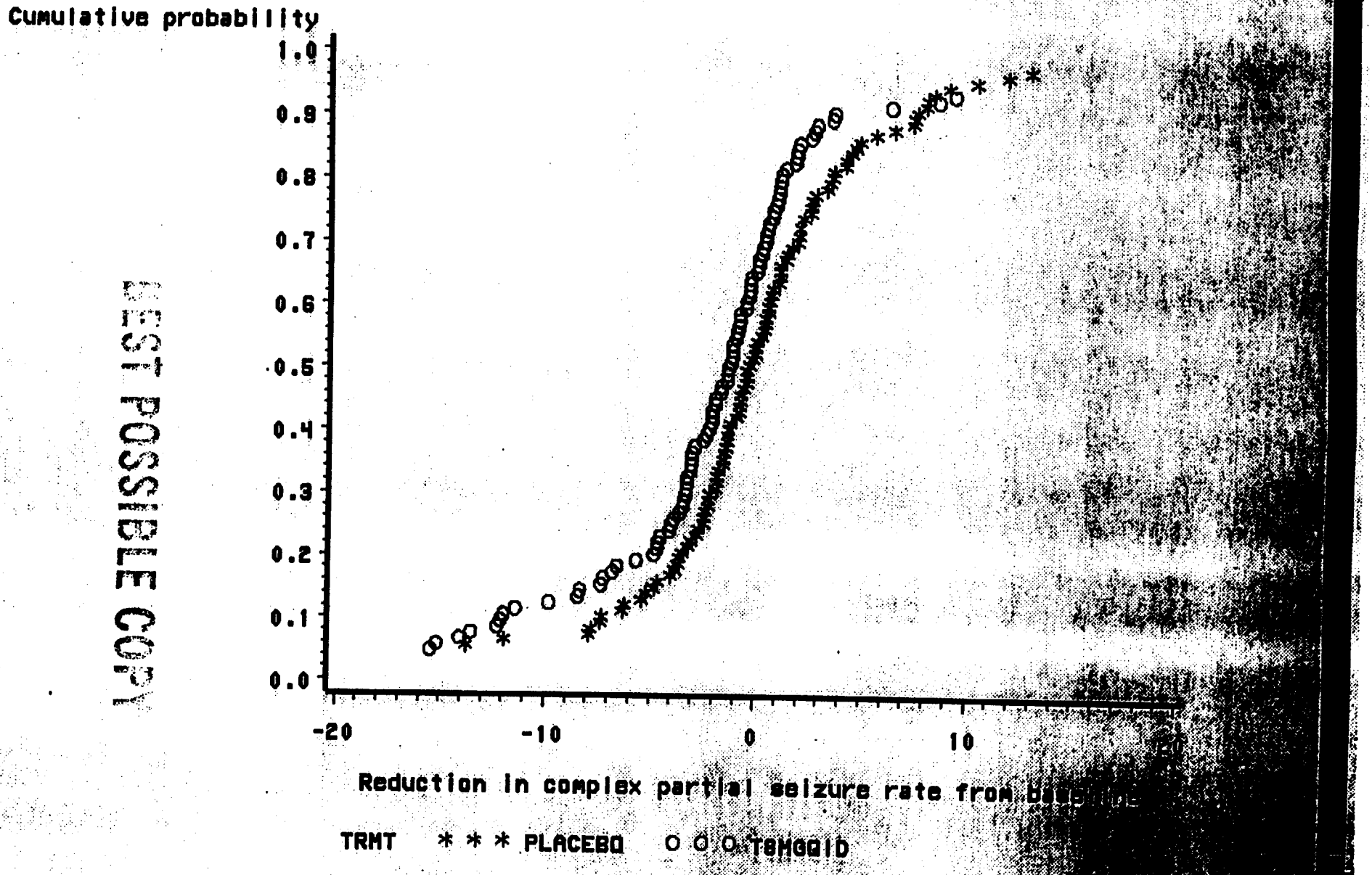


BEST POSSIBLE COPY

Fig. 10

Trial 605

Gabatril 8mg qid vs placebo comparison

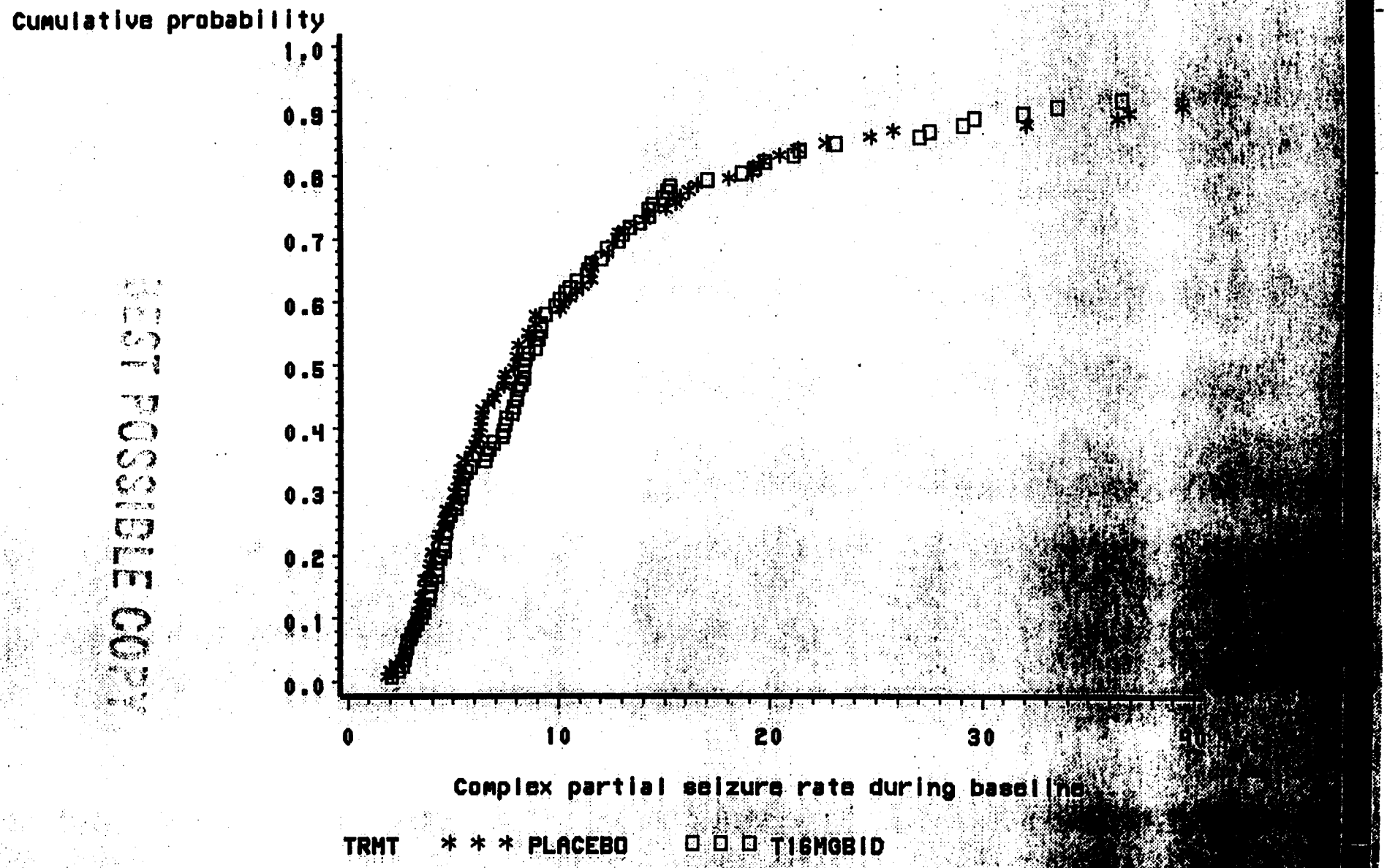


BEST POSSIBLE COPY

Fig. 11

Trial 605

Gabatril 16mg bid vs placebo comparison



DO NOT COPY

Fig. 12

Trial 605

Gabatril 16mg bid vs placebo comparison

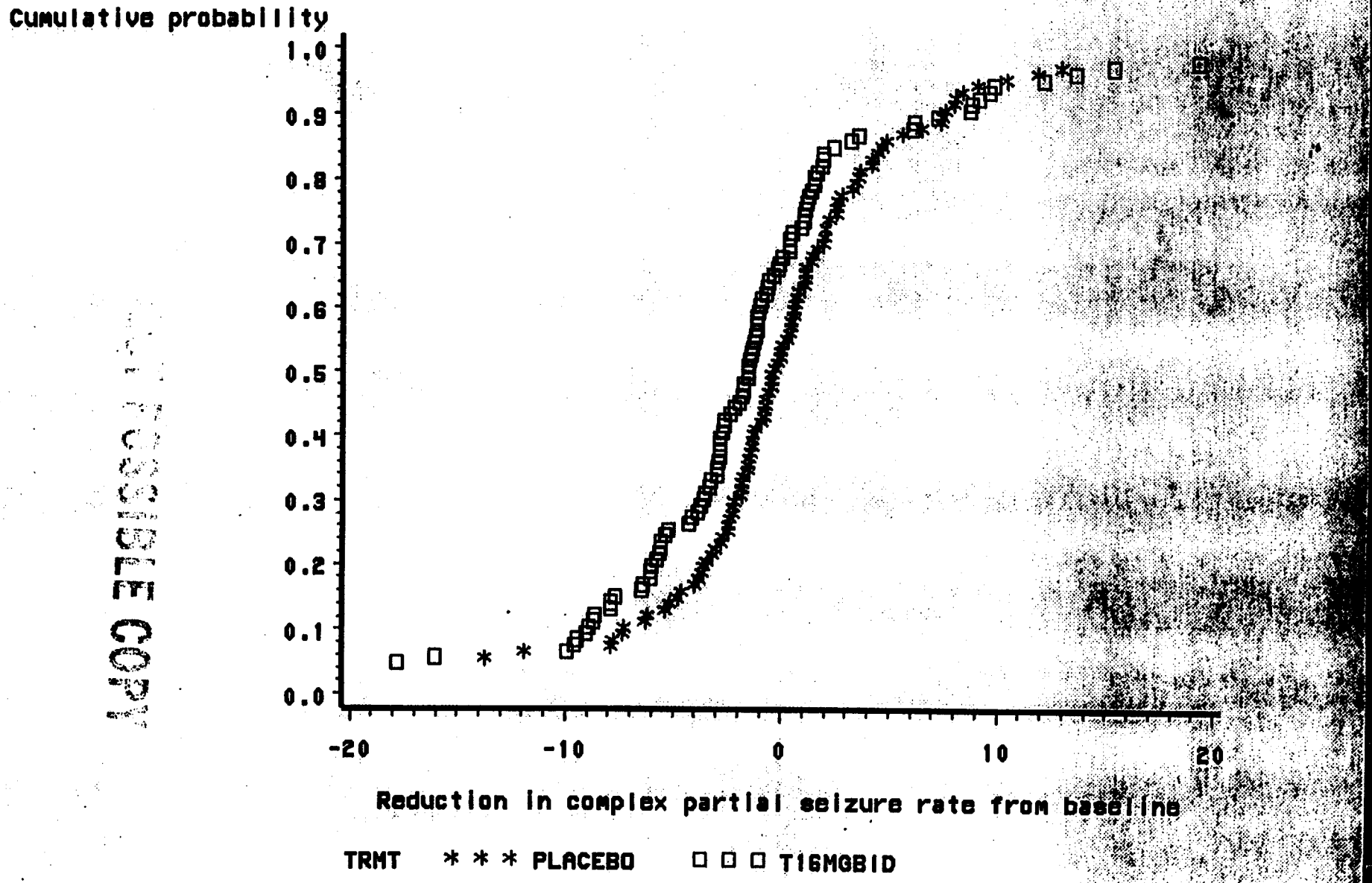


Fig-13

Trial 605

tiagabine 8mg qid vs placebo

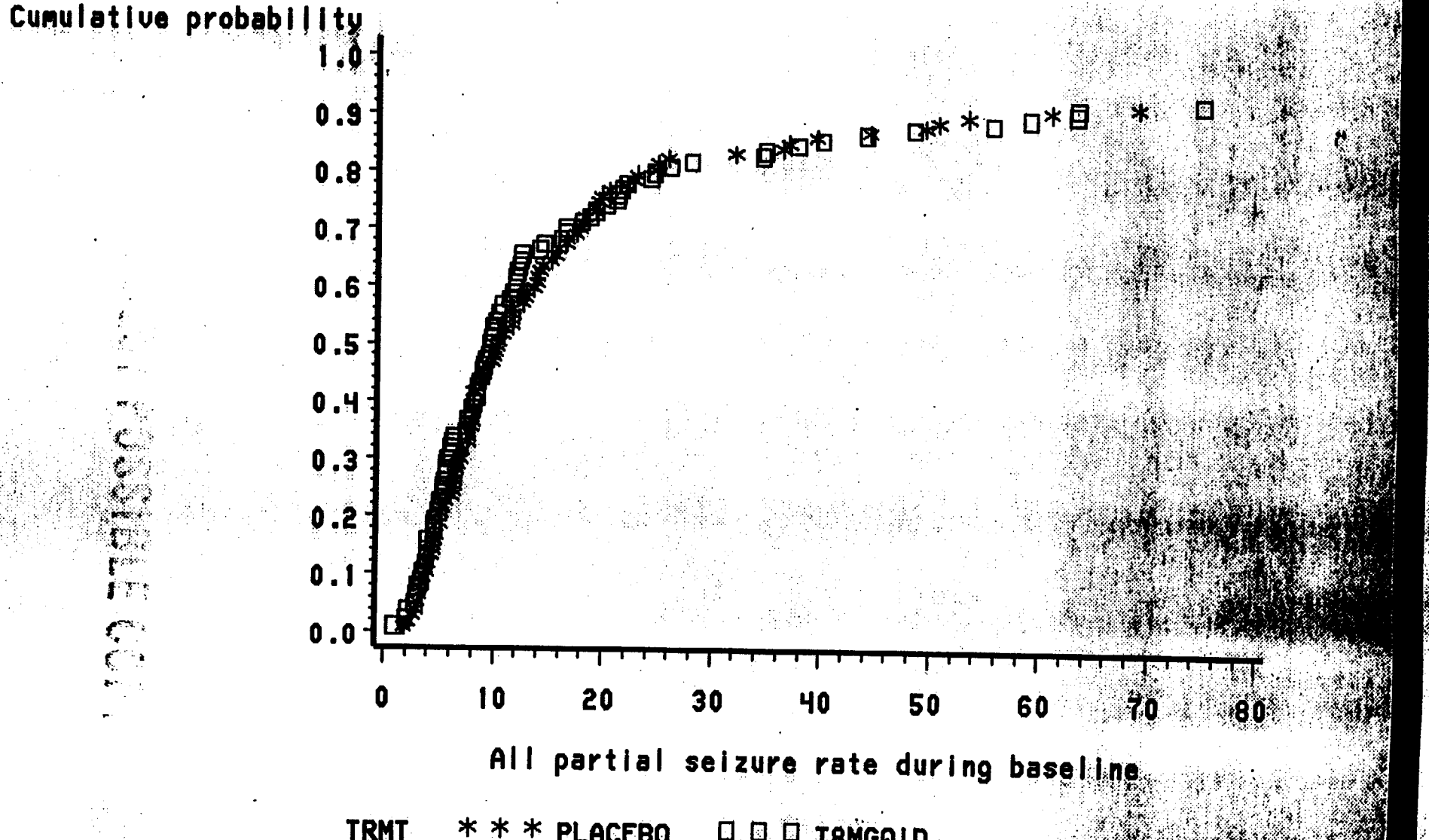
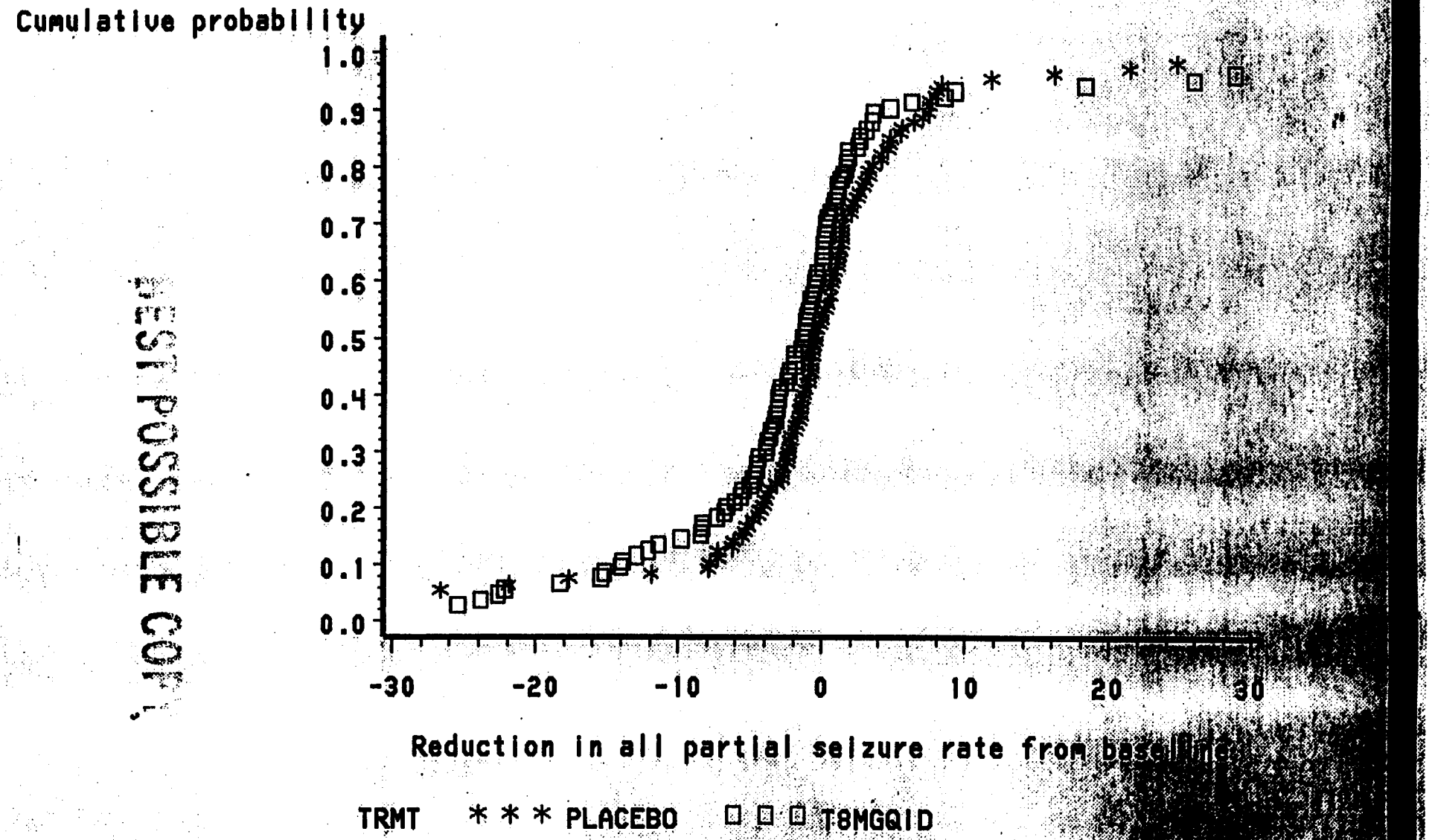


Fig. 14

Trial 605

tiagabine 8mg qid vs placebo



BEST POSSIBLE COPY

Fig. 15

Trial 605

tiagabine 16mg bid vs placebo

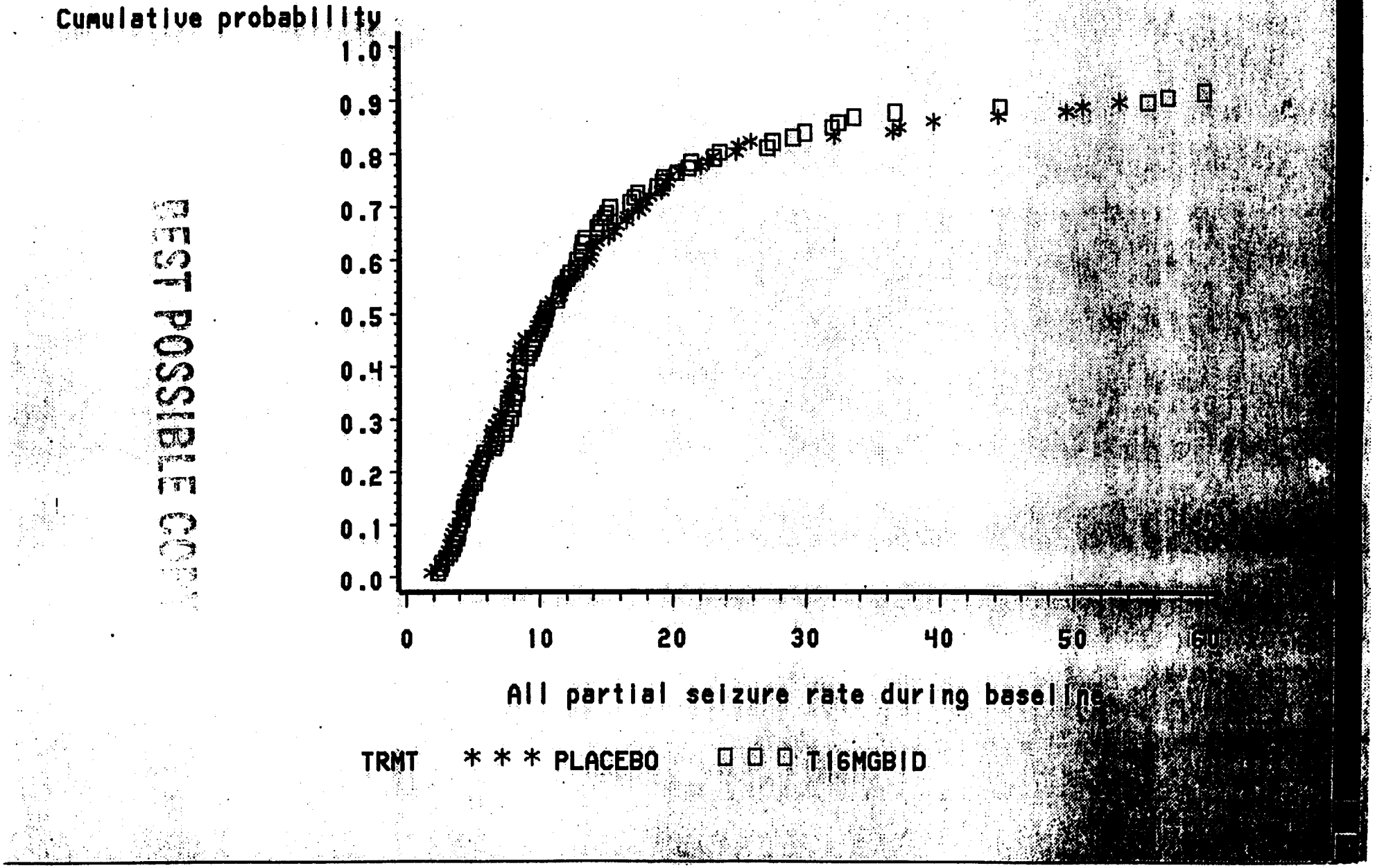
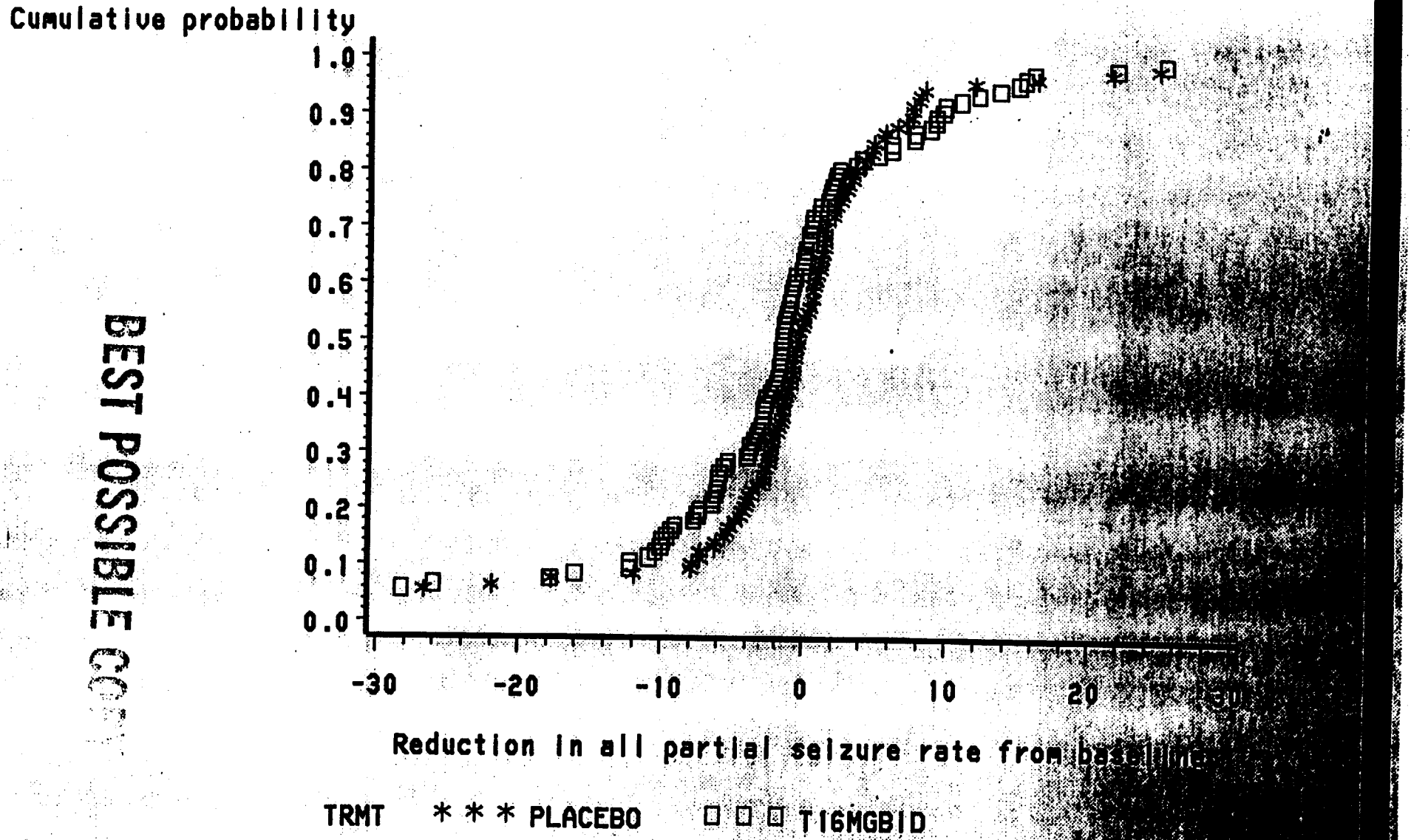


Fig. 16.

Trial 605

tiagabine 16mg bid vs placebo

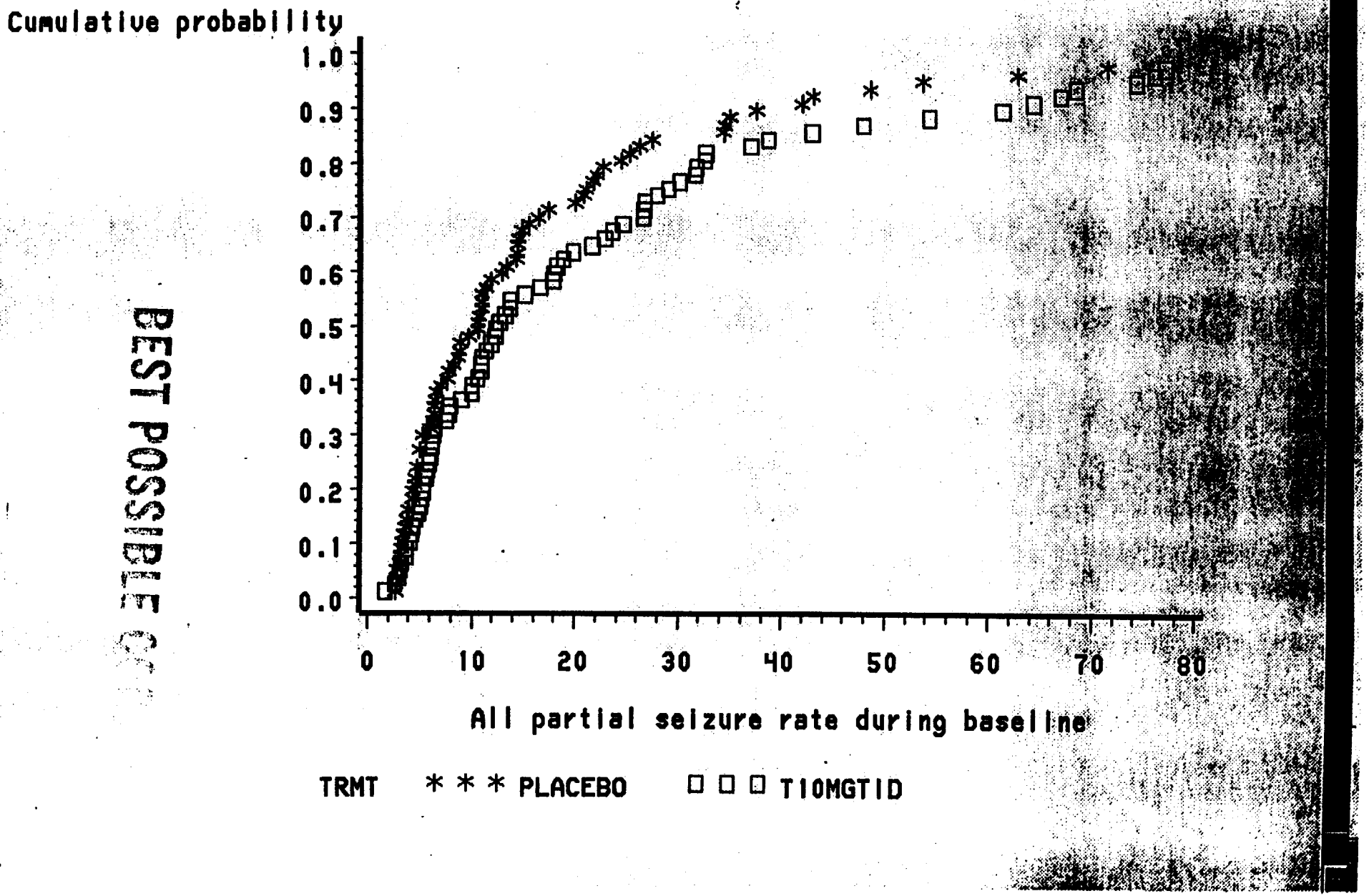


BEST POSSIBLE CO

Fig. 17

Trial 775

tiagabine 10mg tid vs placebo

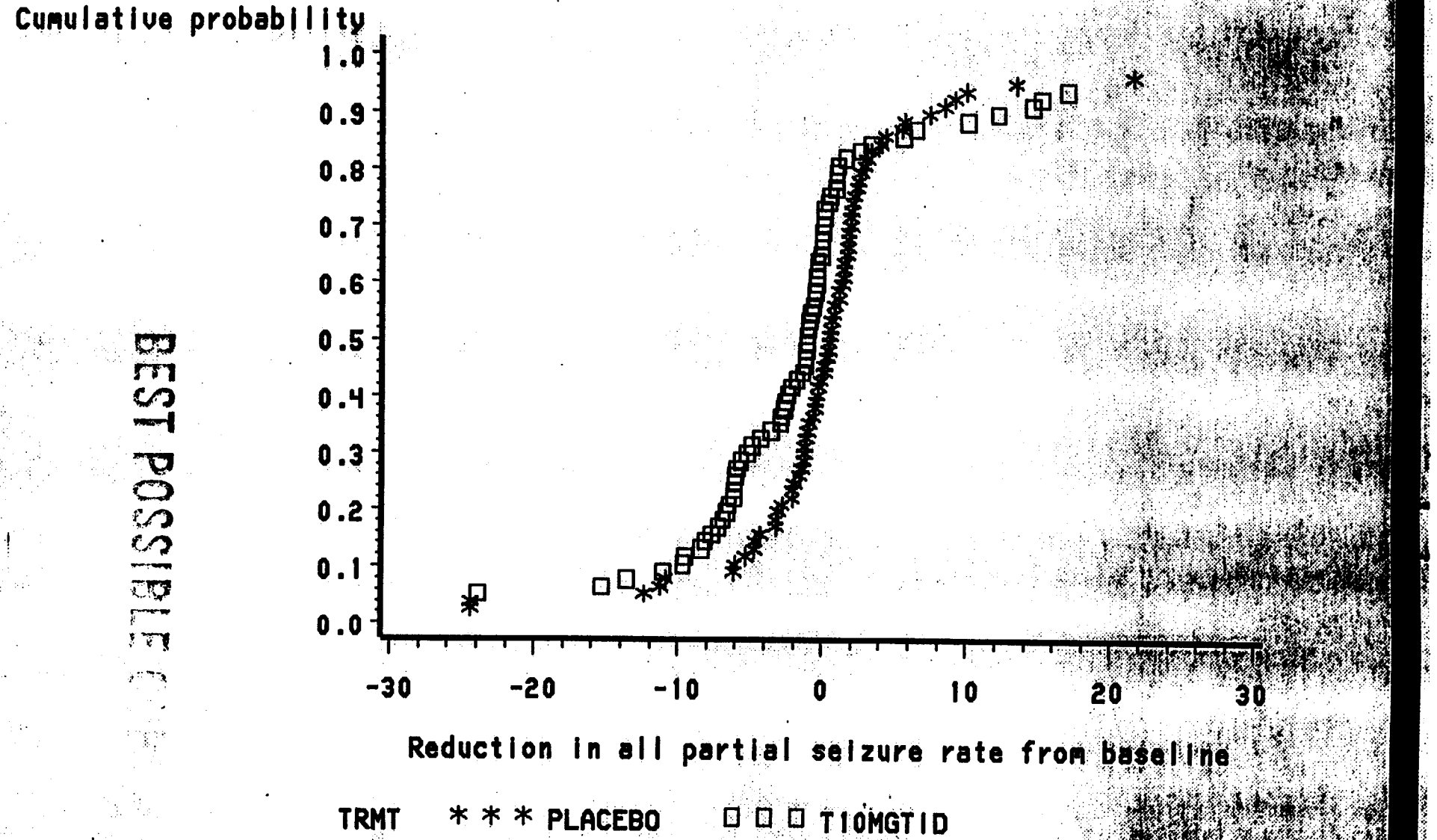


BEST POSSIBLE COPY

Fig. 18

Trial 775

tiagabine 10mg tid vs placebo



BEST POSSIBLE

Fig. 19

Trial 481: First Assessment Period

tiagabine vs placebo

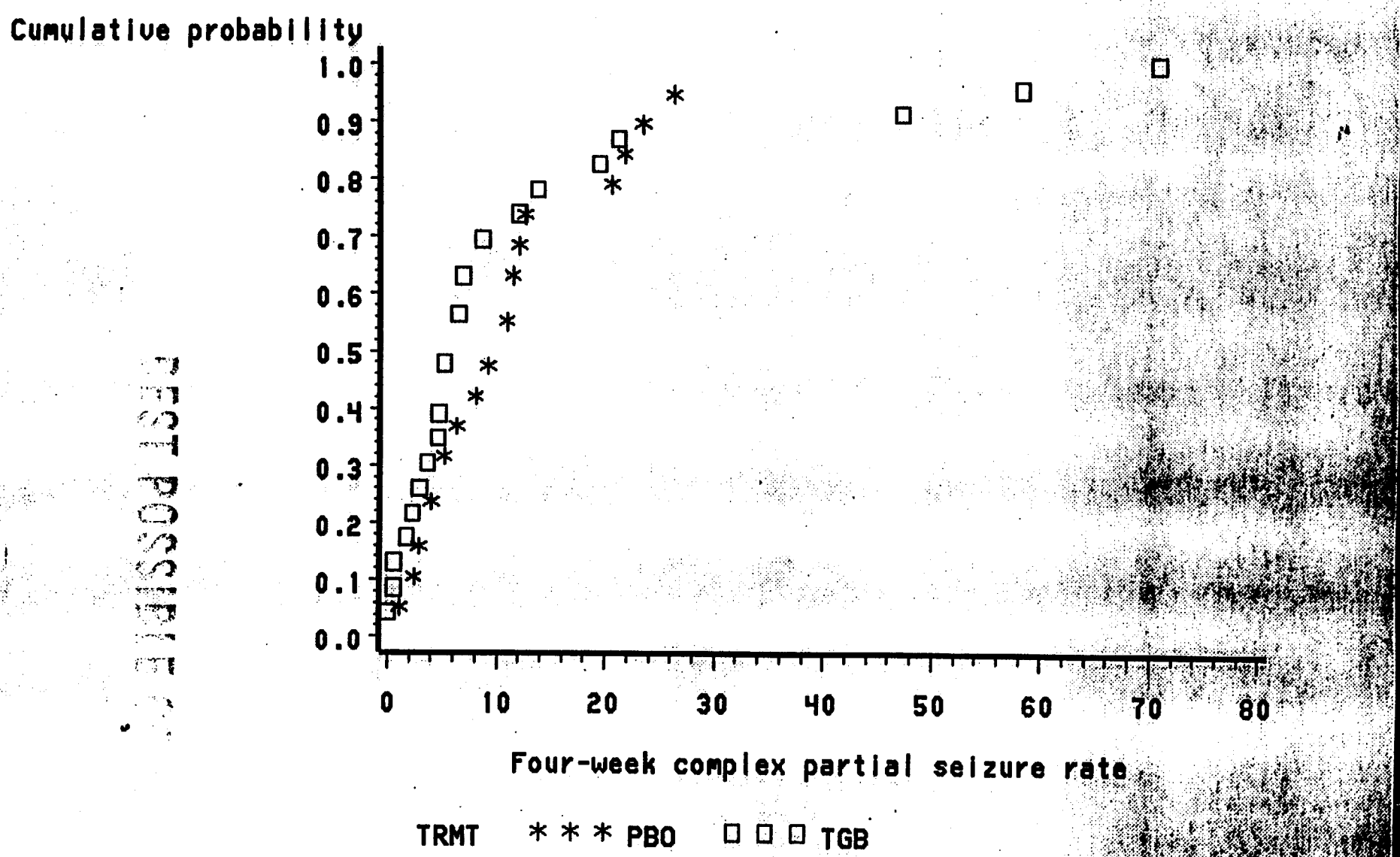


Fig. 20

Trial 481: Second Assessment Period

tiagabine vs placebo

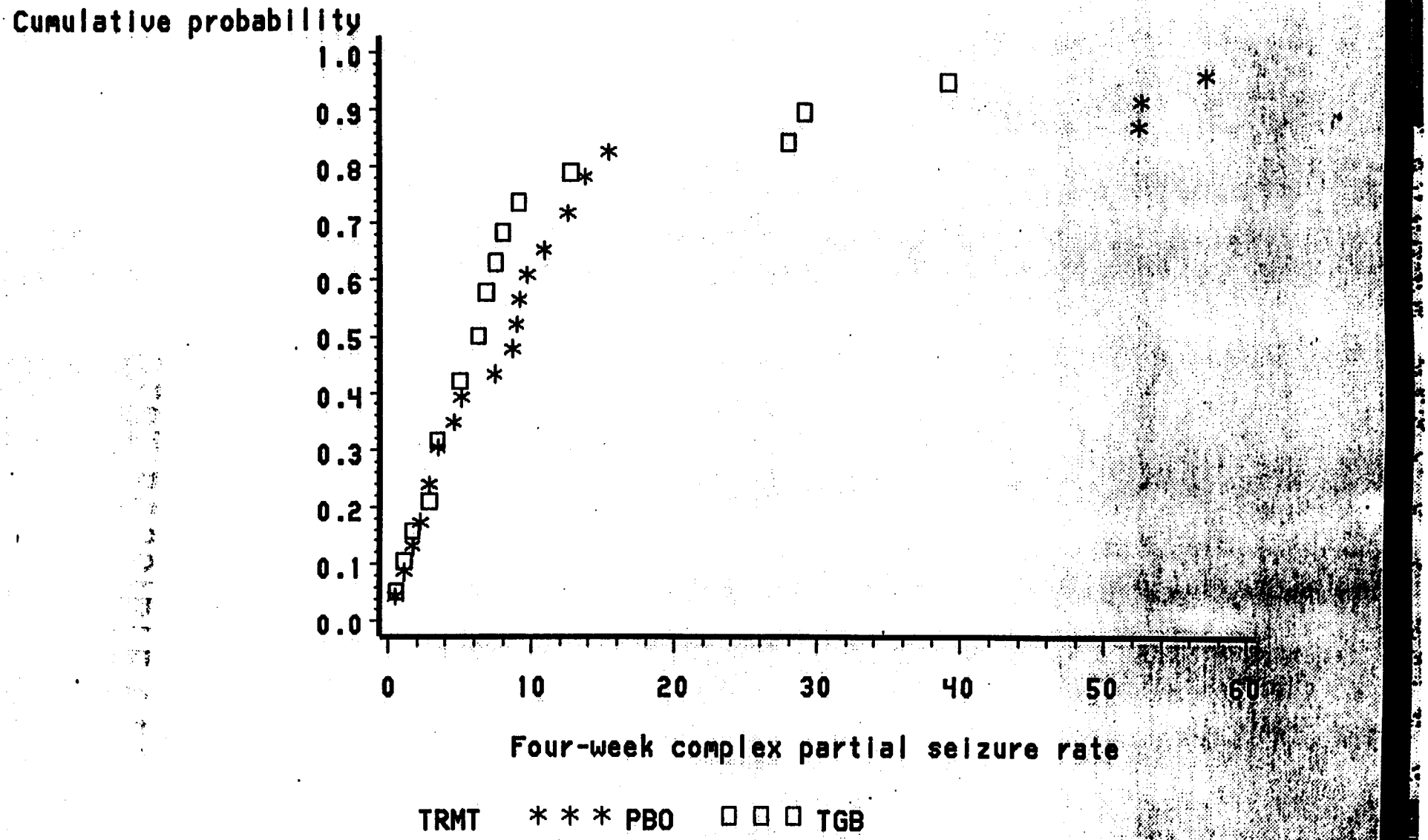


Fig. 21

Trial 481: First Assessment Period

tiagabine vs placebo

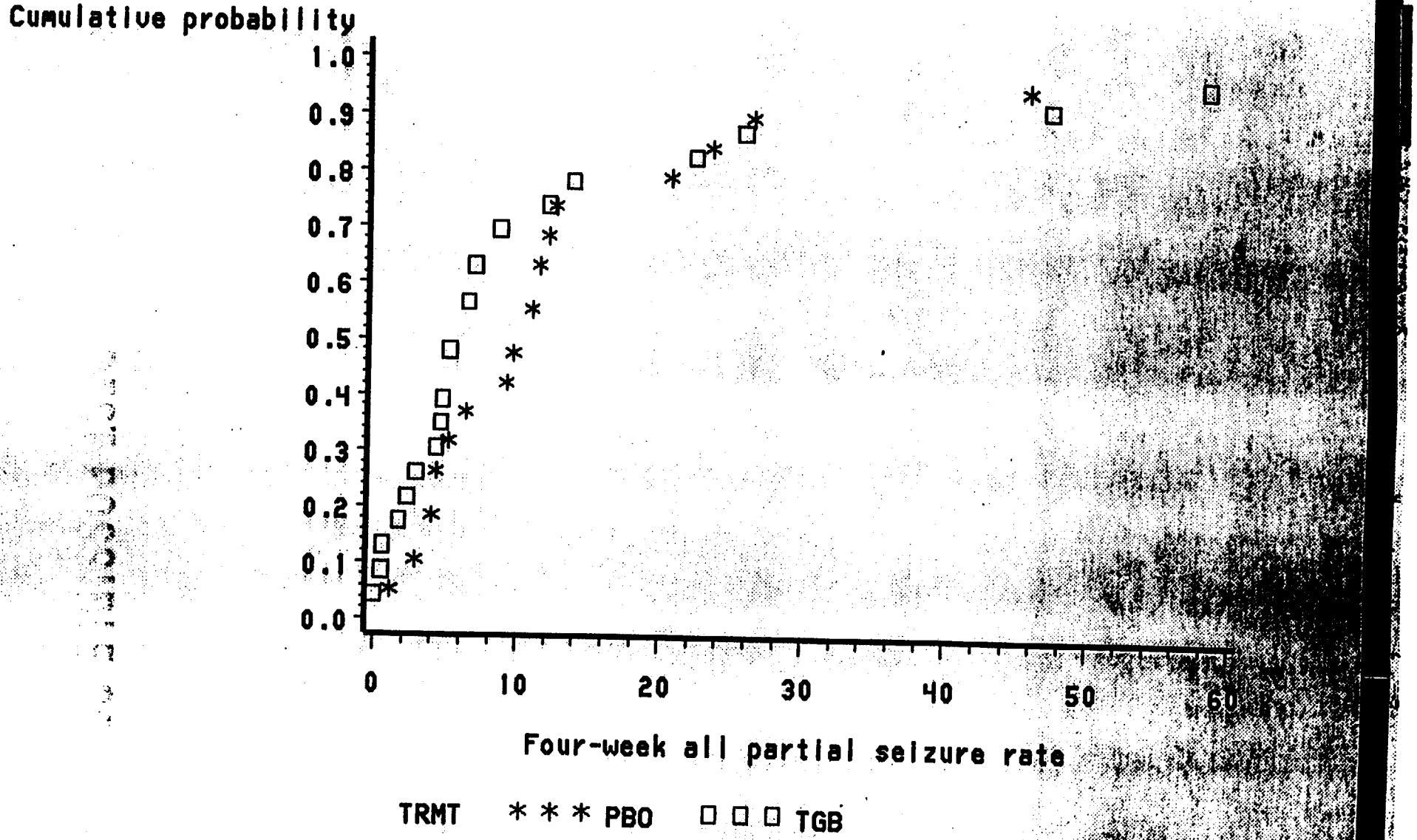


Fig. 22

Trial 481: Second Assessment Period

tiagabine vs placebo

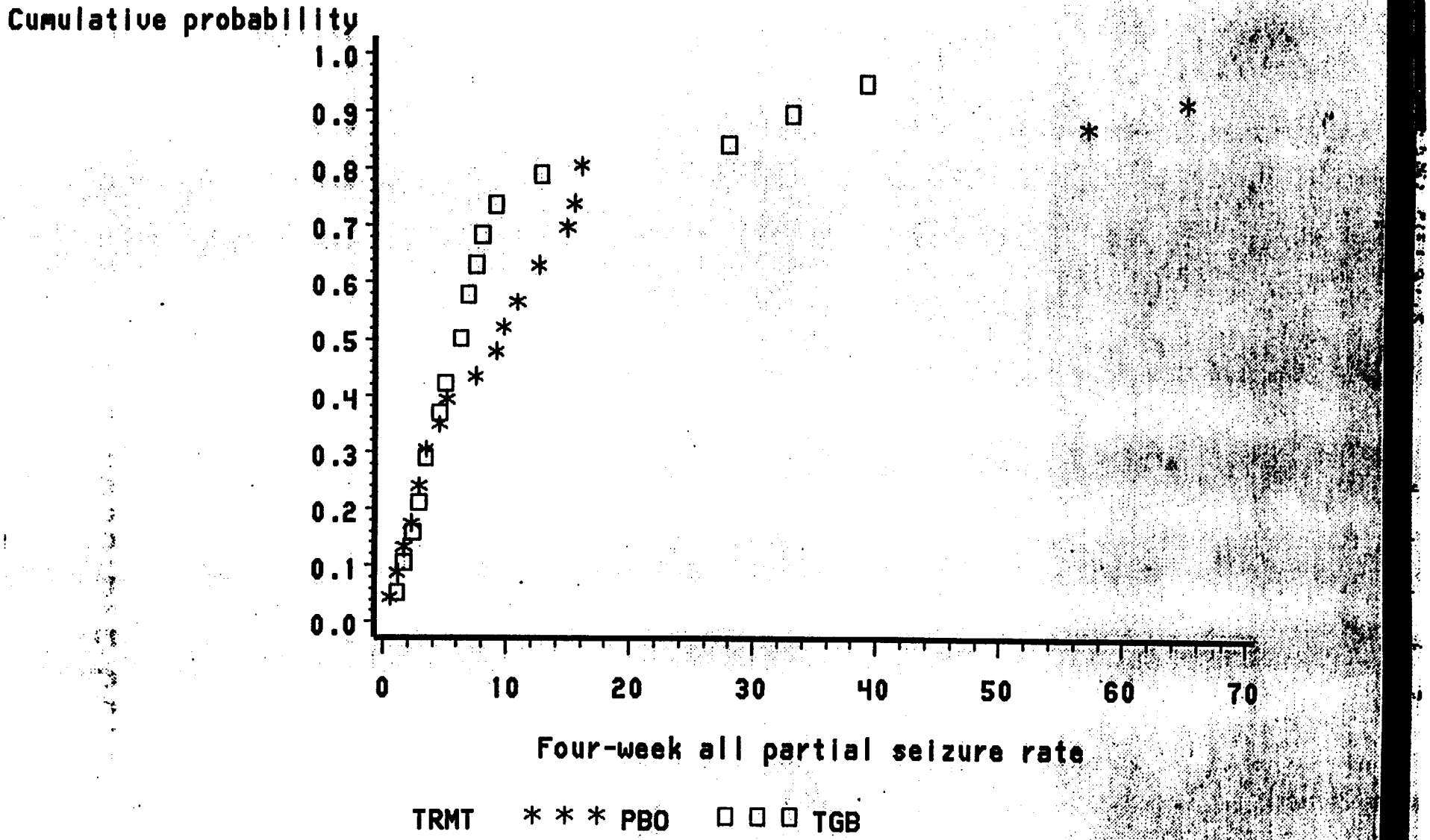


Fig. 23

Trial 565: First Assessment Period

tiagabine vs placebo

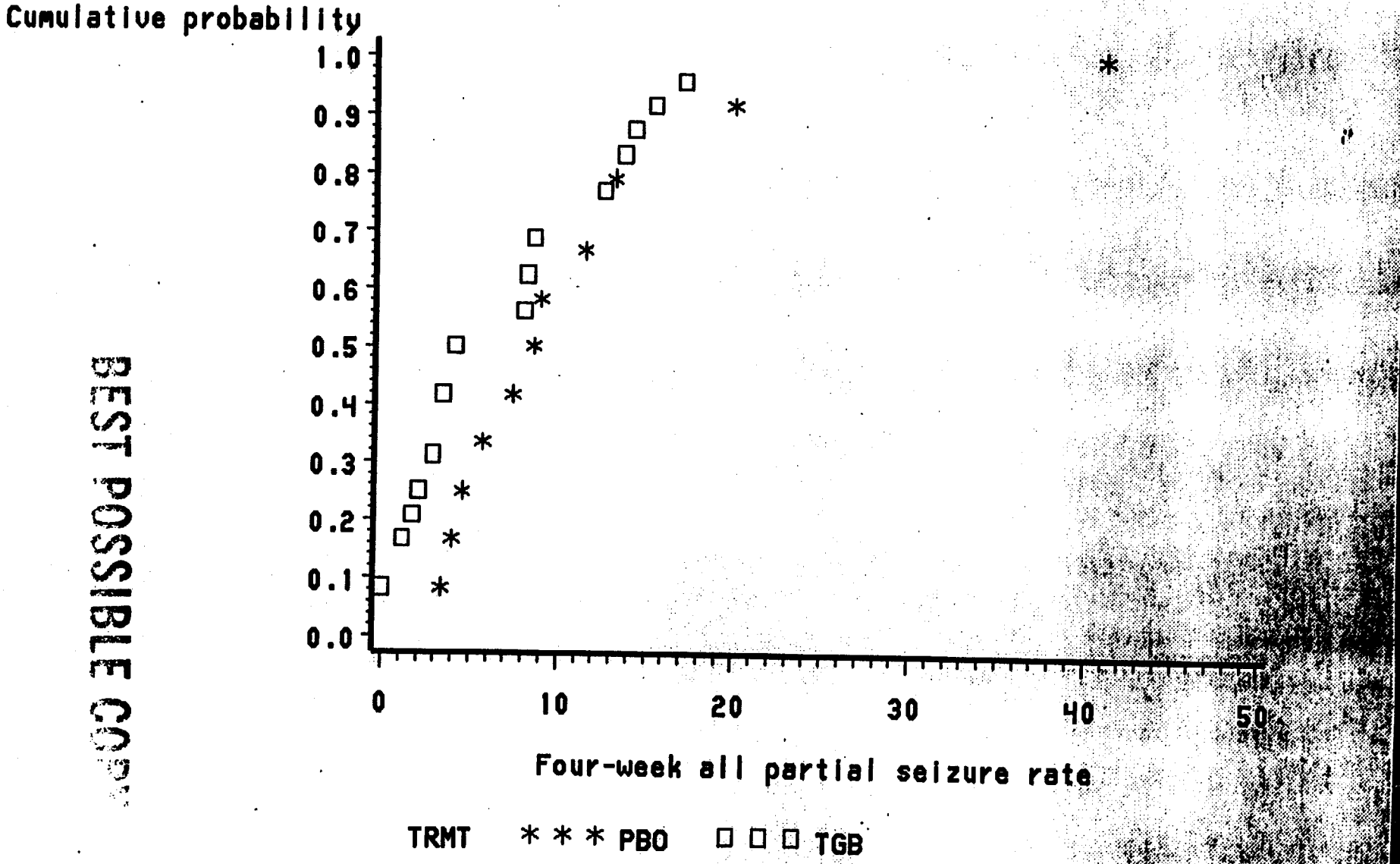
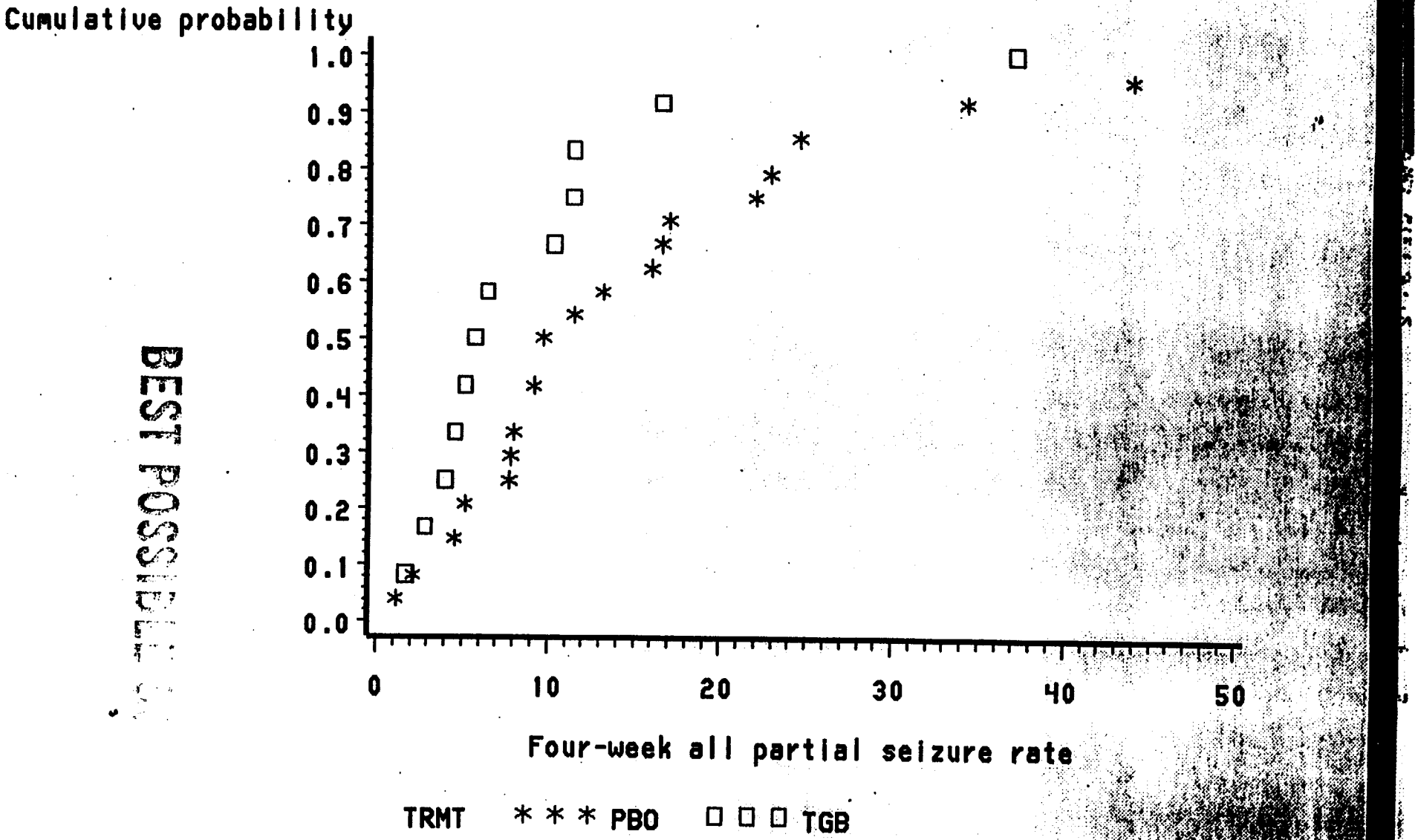


Fig. 24.

Trial 565: Second Assessment Period

tiagabine vs placebo



BEST POSSIBLE

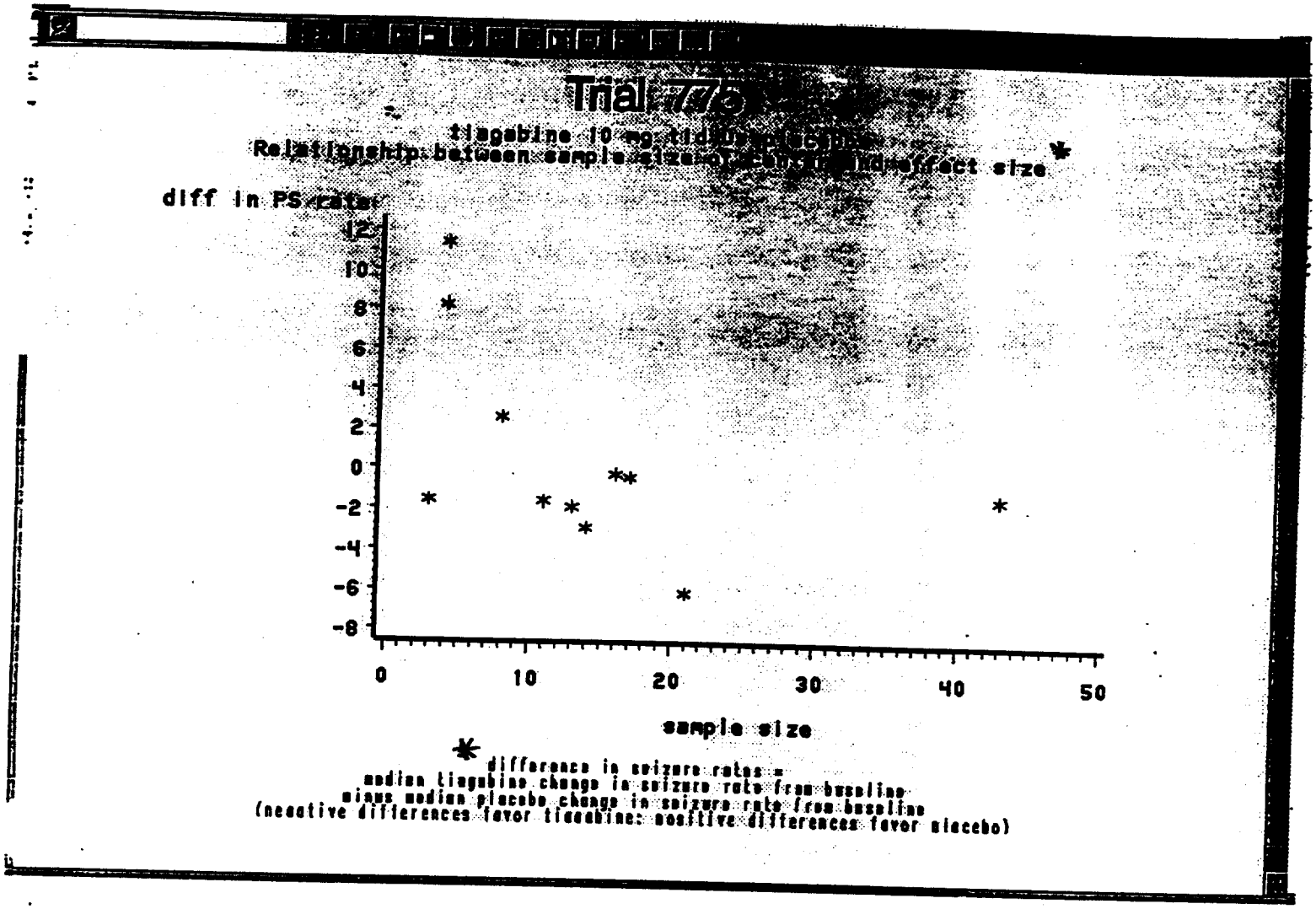


Figure 25

BEST POSSIBLE COPY

Appendix I

List of Seizure Codes

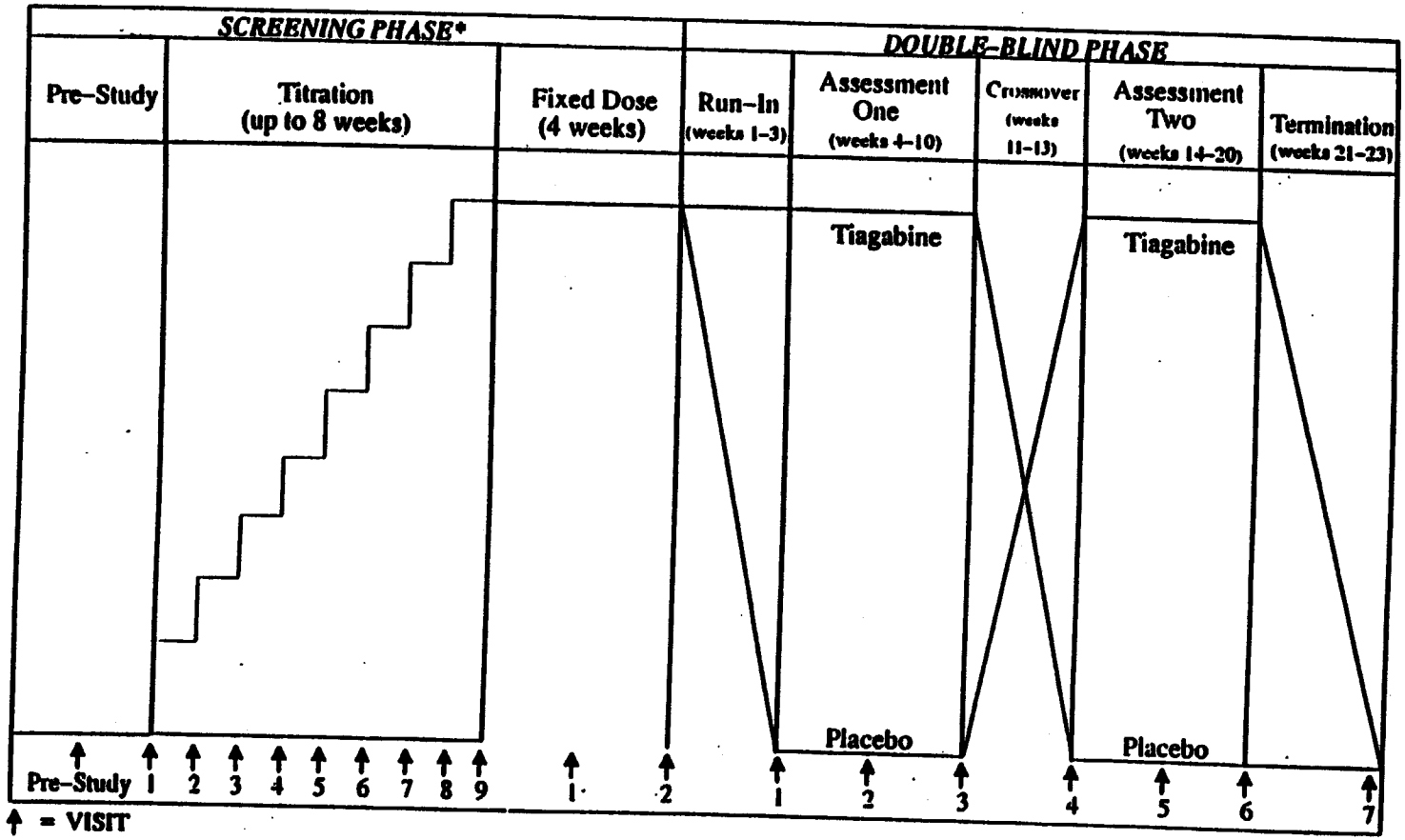
Specific Seizure Type		Seizure Types for Analysis@ (X if included in analysis)			
Code	Description	CPS	SPS	SGTCS	PS
AA	ATYPICAL ABSENCE				
AB	ABSENCE				
AT	ATONIC				
CP	COMPLEX PARTIAL				
CPAB	COMPLEX PARTIAL EVOLVING TO ABSENCE	X			X
CPAT	COMPLEX PARTIAL EVOLVING TO ATONIC	X			X
CPCTC	COMPLEX PARTIAL EVOLVING TO CLONIC-TONIC-CLONIC	X			X
CPGTC	COMPLEX PARTIAL EVOLVING TO GENERALIZED TONIC-CLONIC	X		X	X
CPM	COMPLEX PARTIAL EVOLVING TO MYOCLONIC	X		X	X
CPT	COMPLEX PARTIAL EVOLVING TO TONIC	X			X
CPTC	COMPLEX PARTIAL EVOLVING TO GENERALIZED TONIC-CLONIC	X			X
GTC	GENERALIZED TONIC-CLONIC	X		X	X
M	MYOCLONIC			X	X
NSE	NON-SPECIFIC EVENT				
OTHS	OTHER SEIZURES				
PGTC	PARTIAL GENERALIZED TONIC-CLONIC				
SCGC	SIMPLE PART.EVOLVING TO COMPLEX PARTL.EVOLV. TO GENERALIZED T-C			X	X
SCGTC	SIMPLE PARTIAL EVOLVING TO COMPLEX PARTL EVOLVING TO GENERALZD TONIC-CLONIC	X	X	X	X
SCT	SIMPLE PARTIAL EVOLVING TO COMPLEX PARTIAL EVOLVING TO TONIC	X	X	X	X
SEAB	STATUS EPILEPTICUS, ABSENCE	X	X		X
SECP	STATUS EPILEPTICUS, COMPLEX PARTIAL				
SEGTC	STATUS EPILEPTICUS, GENERALIZED TONIC-CLONIC	X			X
SESP	STATUS EPILEPTICUS, SIMPLE PARTIAL (EPILEPSIA PARTIALIS CONTINUA)			X	X
SGTC	SECONDARILY GENERALIZED TONIC-CLONIC		X		X
SM	SIMPLE PARTIAL EVOLVING TO MYOCLONIC			X	X
SP	SIMPLE PARTIAL		X		X
SPCP	SIMPLE PARTIAL EVOLVING TO COMPLEX PARTIAL		X		X
SPCTC	SIMPLE PARTIAL EVOLVING TO CLONIC-TONIC-CLONIC	X	X		X
SPGTC	SIMPLE PARTIAL EVOLVING TO GENERALIZED TONIC-CLONIC		X	X	X
SPTC	SIMPLE PARTIAL EVOLVING TO GENERALIZED TONIC-CLONIC		X	X	X
ST	SIMPLE PARTIAL EVOLVING TO TONIC		X	X	X
	TONIC		X		X

CPS = Complex Partial Seizures
SPS = Simple Partial Seizures
SGTC = Secondarily Generalized Tonic Clonic Seizures
PS = Combined Partial Seizures

BEST POSSIBLE COPY

Appendix 2

Study design for Trials 481 and 565



* NOTE: The Termination Period of 2 weeks length which ended the Screening Phase for patients who prematurely discontinued or who failed to meet the criteria for randomization is not shown.

Abbott-70569
Study M90-481
R&D/92/250 - Clinical/Statistical

BEST POSSIBLE COPY