

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number **20-789**

STATISTICAL REVIEW(S)

RECEIVED FEB 20 1998
Statistical Review and Evaluation**NDA: 20-789****FEB 18 1998****Drug: zonisamide****Indication: Partial seizures with and without secondary generalization****Sponsor: Athena Neurosciences****Medical reviewer: James Sherry, M.D. (HFD-120)****Background**

The sponsor has submitted results for three placebo-controlled add-on trials in support of zonisamide's effectiveness in partial seizures with and without secondary generalization. Trials 912-US and 912-EUR compared flexible doses of zonisamide to placebo in parallel groups. Trial 922 compared zonisamide to placebo in an imbalanced parallel group design with fixed incremental doses. Table 0 lists the trials and pertinent design characteristics.

Trial 922

Figure 1 shows the design schematic for Trial 922, a 20-center trial. The objective was to compare three doses (100, 200 and 400mg) of zonisamide over 20 weeks. Due to the unusual pattern of titrations, direct comparisons of each dose with placebo were possible only up to Week 12.

After a 4-week placebo baseline period for stabilization of background antiepileptic drugs (AEDs) and establishment of baseline seizure frequency, subjects were randomized to one of three titration schemes. Subjects were required at randomization to have at least four partial seizures/month and no seizure-free interval exceeding 30 days during the preceding three months. Subjects were to be receiving one or two concomitant AEDs.

Group A subjects received placebo for 12 weeks then were titrated up to and maintained at zonisamide 400mg until Week 20. Group B1 subjects received zonisamide 100mg during Weeks 1-5, 200mg during Week 6, 300mg during Week 7 and 400mg during Weeks 8-20. Subjects in Group B2 received zonisamide 100mg during Week 1, 200mg during Weeks 2-6, 300mg during Week 7 and 400mg during Weeks 8-20.

Subjects recorded their seizures in personal diaries. Seizures were ultimately classified as simple partial (SP), simple partial with or without secondary generalization (SPG), complex partial (CP), complex partial with or without secondary generalization (CPG), flurry or other. A seizure flurry was defined as ≥ 10 seizures which occurred so closely together the the subject could not

distinguish the end of one seizure and the beginning of the next. It appears each flurry was counted as 10 seizures.

Per protocol, the primary efficacy parameter was the median percentage change from baseline in 28-day partial seizure frequency¹. The secondary efficacy parameter was the proportion of subjects with a 50% reduction in partial seizure frequency (response rate). A partial seizure included any of the subtypes SP, SPG, CP and CPG. The sponsor also evaluated these parameters for complex partial seizures (CP+CPG) and all seizures. The protocol did not specify a statistical analysis method for the primary or secondary variables.

To evaluate the efficacy of each of the three doses, the protocol specified three comparisons of zonisamide with placebo. Each comparison entailed a different time domain:

- **To evaluate 100mg:** Compare groups B1 and A during Weeks 1-5, the Dose introduction period.
- **To evaluate 200mg:** Compare groups B2 and A during Weeks 2-6, also referred to as the Dose introduction period.
- **To evaluate 400mg:** Compare the combined groups B1 and B2² vs A during Weeks 8-12, the Primary analysis period.

At the pre-NDA meeting, the sponsor proposed longitudinal mixed-effects models with a number of contrasts to account for all the planned comparisons of zonisamide doses with placebo. The Medical Division suggested the sponsor concentrate on the A vs B comparison during Weeks 8-12. At a follow-up meeting between the sponsor and Drs. Hoberman and Sahlroot (HFD-710) to discuss statistical analyses of the efficacy variables, several analysis populations were discussed and agreed upon³:

- **Population 1 (Primary).** Week 8-12 data deleting subjects who dropped prior to Week 8. No data were imputed for subjects dropping before Week 8. For subjects completing Week 7, seizure rates were calculated based on the actual number of days in the trial from Week 8 to the last day or the end of Week 12, whichever occurred first.
- **Population 2 (Data sensitivity).** Week 8-12 data with “worst-case” values imputed for

¹ Percentage change was calculated as: $100 \cdot (\text{Double-blind seizure frequency} - \text{baseline seizure frequency}) / \text{baseline seizure frequency}$. Negative percentage changes were associated with reductions in seizure frequency from baseline, positive percentage changes with increases in seizure frequency. By construction, this endpoint is bounded below by -100 and has no upper bound.

² The combined B1 and B2 treatment groups will be designated as Group B.

³ The labels of the different analysis populations, e.g., Primary, Data sensitivity, etc., were assigned by the sponsor.

subjects who dropped during Weeks 1-7. The imputation method was not specified at the meeting with HFD-710 but was described in the sponsor's 1/20/98 submission. According to the sponsor, the group maximum percentage *increase* was imputed for subjects in the group withdrawing before Week 8.

■ **Population 4 (Intent to treat).** Week 1-12 data. Includes all subjects who contributed any post-randomization data. Seizure rates were calculated based on the actual number of days starting at Week 1 up to the maximum of 12 weeks.

The sponsor also analyzed a fourth population, **Population 3 (Efficacy evaluable)**, consisting of Week 8-12 data from subjects with at least 2 weeks exposure to test drug who met all inclusion criteria. Major protocol violators were excluded.

The sponsor conducted additional analyses of 400mg data by conducting within-subject (Group A only) comparisons of Week 17-20 and 8-12 seizure rates. For analyses of the primary variable during Weeks 1-6 and 17-20 and for secondary variables, only subjects who received at least one dose of test drug and had some seizure data during the relevant period were examined.

Several analysis approaches were discussed at the sponsor/HFD-710 meeting, including the mixed model which the sponsor ultimately did not pursue. All analyses of the primary variable were performed by 2-way ANOVA (factors for treatment and center with interaction term) on ranks. Response rates were analyzed by CMH controlling for center. Investigators and subjects also performed Global Assessments at 12 weeks relative to the start of double-blind using four status categories: marked improvement, slight improvement, no change or worse. The improvement categories were combined and compared with the combined 'no change/worse' category using CMH. The analysis used 12-week completers only.

Sponsor's Results

Two hundred three (203) subjects were randomized in a 3:2:2 ratio: 85 subjects to Group A, 60 to Group B1 and 58 to Group B2. Groups were comparable at baseline with respect to age, race and median seizure frequency but not sex (Table 1). Group A had 59% female subjects vs 38% in Group B1 and 45% in Group B2 ($p=.015$). Fifty-seven (57) subjects withdrew before completing 20 weeks, 24 in Group A and 33 from Group B. One hundred sixty-six (166, 82%) subjects completed 12 weeks. Table 2 shows subject disposition and the time-pattern of dropouts.

During Weeks 8-12 (Table 3, Population 1), subjects in Group B ($n=98$) received zonisamide 400mg and experienced a 40.5% reduction in partial seizures compared to 9.0% for placebo-treated subjects (Group A, $n=72$) ($p=.009$). The results for Populations 2 and 3 also achieved nominal statistical significance.

During Weeks 1-12 (Population 4, not shown in Table 3), subjects in Group B ($n=113$) experienced a 22.9% reduction in partial seizures compared to 4.0% for placebo-treated subjects

(Group A, n=84). Although the percent reductions were smaller compared to Week 8-12 data due to the inclusion of data from titration periods, the difference between groups was still statistically significant ($p=.027$).

Table 4 shows results for the Weeks 1-5 and Weeks 1-6 comparisons between low doses of zonisamide and placebo. The statistical analyses of partial seizures utilized $\geq 94\%$ of randomized subjects. Median percentage reductions from baseline in partial seizures during the first 5 weeks were 8.3% for placebo (Group A) and 24.7% for subjects receiving zonisamide 100mg (Group B1) ($p=.038$). The corresponding median percent reductions for zonisamide Group B2 (100mg during Week 1 and 200mg during Weeks 2-6) and placebo were 20.4% and 4.0%, respectively ($p=.003$).

Forty-two percent (42%, 41/98) of Group B subjects were treatment responders vs 22% (16/72) of placebo-treated subjects (Population 1, $p=.014$).

None of the analyses of complex partial seizures yielded nominally significant results, although three of the four Populations (all except Efficacy evaluable) yielded significant trends (Table 3, $.08 \leq p \leq .09$). Response rates were also not different between groups (zonisamide 40% vs placebo 27%, $p=.18$)

The results for the analyses of all seizures were virtually indistinguishable from the results for partial seizures due to the occurrence of only a small fraction of seizures that were not partial onset.

Subjects and investigators in their Global Assessments rated a higher percentage of zonisamide-treated subjects as improved ("marked or some improvement") compared to subjects receiving placebo. The differences were not statistically significant.

Reviewer's Analysis

The analysis of Population 1 is not an ITT analysis due to the exclusion of a nontrivial number ($n=32$) and percentage (16%) of randomized subjects. Note that the Population 1 analysis is essentially an analysis of 12-week completers. The Population 1 and 12-week completer datasets differ only in four subjects not included in the completer dataset because they dropped during Weeks 8-12.

Although the Population 2 analysis is closer to the mark as an ITT analysis ($n=202$), it is flawed as well. The imputation procedure not only was not specified in advance but is not really a conservative procedure.⁴ This reviewer obtained $p=.048$ using the sponsor's methodology – the

⁴ For imputation, the sponsor calculated separate group (A, B1 or B2) maximum percentage increases. The group maximum was applied to all subjects in the group with missing

sponsor obtained .009 -- despite duplicating all the sponsor's summary measures (mean, median, etc.). Statistical significance was lost ($p=.07$) when this reviewer imputed the observed placebo maximum for all subjects with missing data irrespective of treatment assignment.

The Population 4 analysis, admittedly conservative due to the inclusion of seizure data collected during titration, is a rigorous ITT approach which obviates the need for data imputation. While the analysis does not address the efficacy of a specific dose of zonisamide, it does address 'proof of principle' concerning zonisamide's antiseizure activity. This reviewer calculated $p=.025$ for this analysis.

The Sponsor's Figure 2 shows dropout cohorts for selected weeks. The sponsor provided efficacy results only for weeks associated with clinic visits (weeks 5, 6, 7 and 12). Each set of bars except the last two shows responses for subjects who dropped on or before that week who are not captured by a previous cohort. For example, "Week 5" on the horizontal axis includes subjects who dropped on or before Week 5. "Week 6" captures subjects who dropped during Week 6 only. The last two sets of bars show medians for Populations 1 and 4, respectively. Most dropouts occurred before Week 6. Dropouts appeared to experience similar seizure frequency changes as completers, particularly in the zonisamide group.

The Figure shows an erroneous result, namely the wrong median for Week 12 -- ZNS/A (sic). The correct value is -52%. Dropout Figures for the 912 Trials submitted by the sponsor clearly contained multiple errors and so were omitted from this review.

Trial 912-US

This 4-center trial compared zonisamide to placebo in subjects with complex partial seizures (CP). The trial consisted of two phases, baseline and double-blind. Eligible subjects had to have a history of at least 4 CP/month and no more than 8 primary or secondary-generalized tonic, clonic or tonic-clonic (TC) seizures/month. Allowable background AEDs were one or two of the following: PHT, CBZ, PB and PRM. Baseline duration was 8-12 weeks depending on seizure frequency. Subjects experiencing 15 seizures the first 4 weeks of baseline or 30 seizures at 8 weeks were randomized after 8 weeks; otherwise, baseline was extended another 4 weeks. Subjects recorded the description and duration of seizures in diaries.

Treatment duration was 12 weeks. Initially the dose of zonisamide was set at 7mg/kg/day to achieve a daily dose in the 400-600mg range. Due to adverse experiences in the earliest set of randomized subjects, the sponsor amended the protocol so that subjects were titrated more

data. The observed maximums were 572, 128 and 600, respectively. This procedure is inherently flawed from the start due to the imbalance in sample sizes. Consider that the expected maximum of a sample is an increasing function of (increasing) sample size. One would expect a priori that the placebo maximum, based on $n=85$, would exceed the zonisamide maximums based on *smaller* sample sizes of 60 and 57.

slowly: 100mg during Week 1, 200mg during Week 2, and 400mg during Weeks 3-4. The investigator could adjust the dose after Week 4 to improve seizure control or reduce adverse events. A "nonblinded observer" recommended dose adjustments to maintain the zonisamide plasma concentration within the 20-30µg/ml range. Random dosage adjustments were made for placebo subjects to maintain the blind.

Seizures were classified (different from the coding system in 922) as simple partial (SP), complex partial moderate (CPM), complex partial severe (CPS), generalized TC awake (G1), generalized TC asleep (G2), flurry and other. In the Report, the sponsor stated *in the discussion of the inclusion criteria* that it did not distinguish between generalized TC seizures that appeared to be primary or were secondarily generalized (see Reviewer's Analysis).

Per protocol, the primary efficacy parameter was the "type, frequency and duration of seizures". The protocol was silent on the matter of statistical methods. Although the possibility of an interim analysis was mentioned, one was never carried out.

The declared primary efficacy parameter in the submission was the percentage change from Weeks 5-12 to baseline for partial seizure (SP+CP) and complex partial seizure (CPM+CPS) frequencies. Secondary efficacy parameters were the response rate and Global Assessments. The sponsor also examined the primary and secondary parameters for all seizures. All analysis methods were consistent with those employed in 922.

The same four analysis Populations were specified except that the labels for Populations 3 and 4 were switched. (The ITT Population was now Population 3 and the Evaluable Population was now Population 4.) Populations 1, 2 and 4 used Week 5-12 (maintenance) data whereas Population 3 used all post-randomization data. The imputation procedure in Population 2 was the the one employed in 922.

Sponsor's results

One hundred fifty two (152) subjects were randomized. Table 5 shows subject characteristics at baseline. Groups were comparable at baseline with respect to age, race and pre-study seizure frequency but not sex. Seventy-four percent (74%) of zonisamide subjects were male vs 58% in the placebo group ($p<.05$).

Twenty-three (23, 15%) subjects (16 zonisamide, 7 placebo) withdrew prematurely. Table 6 shows patient disposition and the time-pattern of dropouts.

In Population 1, the median percent reduction in partial seizure frequency for zonisamide-treated subjects ($n=69$) was 29.5% compared to a 1.8% increase for subjects receiving placebo ($n=72$) (Table 7, $p=.0004$). Median percentage changes in the three other populations were roughly similar to these. Statistical results were significant as well. P-values for the Data Sensitivity and ITT Populations, both of which used all randomized subjects, were .034 and .0003,

respectively.

Partial seizure response rates were 26% (18/69) for zonisamide and 17% (12/72) for placebo (Population 1, $p=.18$).

Analyses of CP (Table 8) demonstrated statistically significant reductions in favor of zonisamide for all four Populations. CP response rates were marginally statistically different between treatment groups (Population 1, $p=.057$). The response rate in the zonisamide arm (19/69, 28%) was double that in the placebo group (10/70, 14%).

Sixty-eight percent (68%) of zonisamide-treated subjects rated themselves as improved vs 12% of subjects receiving placebo ($p<.001$). Investigator ratings were 64% and 11%, respectively ($p<.001$).

Reviewer's analysis

This reviewer obtained $p=.01$ for Population 2 using the sponsor's stated imputation scheme. The result remained statistically significant ($p=.037$) when this reviewer imputed the observed placebo maximum for all subjects with missing data irrespective of treatment assignment. Statistical significance was not lost with this method because, although the placebo maximum exceeded the zonisamide maximum, the zonisamide group had only nine subjects requiring imputation at the placebo (less favorable) value.

This reviewer consulted the Medical Reviewer concerning the following issue. In the Report, the sponsor stated *in the discussion of the inclusion criteria* that it did not distinguish between generalized TC seizures that appeared to be primary or were secondarily generalized. It was unclear from the sponsor's statement whether the stated lack of distinction between primary and secondarily generalized TC seizures applied only to documentation of seizure history or actually carried over into the collection and analysis of the data from the trial. In other words, it *could* have happened that some partial seizures with secondary generalization observed during the trial were inadvertently classified as generalized seizures (G1 or G2) and therefore were not included in the analysis of partial onset seizures. As it turns out, the combined number of (G1 + G2) seizures was <0.1% relative to the number of partial seizures (SP+CPM+CPS). All analyses of partial seizures would give nearly identical results regardless of the particular choice for classification of G1 and G2 seizures.

Trial 912-EUR

This 10-center trial used the same basic design as 912-US, again comparing zonisamide to placebo in subjects with complex partial seizures. Analysis Populations 1-4 were similarly defined as was the primary outcome variable.

At the pre-NDA meeting, the sponsor stated that, because audit findings indicated the data did

not conform to GCPs, the trial was not considered adequate and well-controlled. The audit cited lack of informed consent for some subjects and protocol deviations such as lack of a prospective baseline for others. Dr. Leber, HFD-120 Director, responded that the trial should nonetheless be included in the NDA and the FDA would render a decision regarding its adequacy as an adequate, well-controlled trial.

All efficacy analyses were performed twice, first using data from all 10 centers and a second time excluding data from site 31. Some data from this center could not be confirmed from source documents.

Sponsor's results

One hundred forty four (144) subjects, all Caucasian, were randomized to zonisamide or placebo. Table 9 shows subject characteristics at baseline. Groups were comparable at baseline with respect to age, sex and pre-study seizure frequency.

Ninety percent (90%) of subjects completed the trial. Table 10 shows subject disposition and the time-pattern of dropouts.

In Population 1, the median percent reduction in partial seizure frequency for zonisamide-treated subjects (n=69) was 20.0% compared to a 0.3% increase in the placebo arm (n=70) (Table 11, p=.21). Results for Populations 2 (Data sensitivity) and 3 (ITT) were also not statistically significant (p>.11). Only the Evaluable Population (Population 4) achieved statistical significance (p=.041).

Response rates were significantly different between groups (favoring zonisamide) for partial seizures (Population 1, p=.047). Rates were 17/69 (25%) in the zonisamide group and 8/70 (11%) for placebo. None of the other populations reached statistical significance.

Analyses of CP demonstrated statistically significant reductions in favor of zonisamide for Population 4 only (Table 12). CP response rates were not different between groups (p=.14).

The statistical results for all seizures mimicked the results for partial seizures.

Sixty-eight percent (59%) of zonisamide-treated subjects rated themselves as improved vs 30% of subjects receiving placebo (p<.002). Investigator ratings were 59% and 20%, respectively (p<.001).

Results were not modified in any significant way when the questionable center was removed from statistical analyses.

Reviewer's analysis

recreated an electronic database from the CRFs because the original database could not be located. As part of this process, extended the baseline to periods longer than specified in the protocol and the report (maximum 12 weeks). The sponsor did not provide a rationale for this maneuver. Sixty percent (60%) of zonisamide and 81% of placebo subjects had changes made to their baseline durations ranging from several days to several weeks. Baseline durations were variable, ranging from 6 to 173 days with a median of 12 weeks. Twenty-seven subjects (n=27, 18%) had baselines of 15 weeks or longer, a 25% increase over the protocol-specified maximum.⁵ This reviewer did not attempt any reanalyses of the primary endpoint calculated with baselines truncated at 12 weeks.

In addition to changes in baseline seizure frequencies, changes were also made to double-blind seizure frequencies: According to the sponsor, "The overall impact of these changes would be to reduce the seizure frequency during baseline with resultant impact upon the percentage change from baseline calculations and responder efficacy parameters." This is true only if baseline seizure frequencies during the extensions were lower than frequencies during the first 8-12 weeks. It is unclear what the uncertainties associated with the database had on the final statistical results.

Sponsor's Table:

Number and percent of subjects with changes to number of days in period or seizure counts in period

Treatment group	Baseline period weeks -8 to -12		Double-blind period weeks 5 to 12	
	Changed number of days n (%)	Changed seizure counts n (%)	Changed number of days n (%)	Changed seizure counts n (%)
zonisamide (n=73)	44 (60)	25 (34)	17 (23)	21 (29)
placebo (n=70)	57 (81)	29 (41)	13 (19)	21 (30)

A key question is why this trial failed to achieve statistical significance on the primary endpoint when a similarly-designed trial with the same approximate sample size did. Note that the trial, despite having a smaller overall sample size than 912-US, had 15 zonisamide subjects (>20% of zonisamide group) who experienced >50% increases in seizure frequency compared to only four such subjects in 912-US. (Placebo subjects performed comparably in the two trials.) Four 912-EUR subjects receiving zonisamide experienced 100% increases. No zonisamide subject in 912-

⁵ Baseline durations in 912-US were less variable. The median duration was 12 weeks and the range 34 to 167 days. By comparison, only nine percent (9%) of subjects had durations of at least 15 weeks.

US had a doubling of seizure frequency. Because the presence of extreme observations has no effect on the response rate, this may explain why the response rate endpoint was statistically significant in the presence of so many zonisamide subjects with >50% increases in seizure frequency.

The only statistically significant effect in the model was the center effect ($p=.01$). (This is different from the treatment-by-center interaction term which was not significant.) The most likely explanation is that placebo and zonisamide subjects at center 35, the largest ($n=30$, 21%) in the trial, performed poorly relative to other centers. Five of the 15 (33%) zonisamide subjects with >50% increases were located at this center.

Sponsor's analyses of required subgroups (sex, age and race)

Differences in sex distribution between treatment groups in Trials 922 and 912-US were statistically significant. ANOVA on partial seizures adjusting for gender (including the interaction term with treatment) was performed for the two trials separately. In both analyses the treatment effect remained statistically significant ($p<.01$). The interaction terms were not significant. Treatment group differences were also consistent across gender in 912-EUR.

For age categories (<40, 40-65, >65), the sponsor performed statistical analyses for 922 only (NS). The 912 Trials were examined in a descriptive fashion. Subgroups results were consistent across trials and age categories; zonisamide subjects had greater reductions in partial seizure frequency than placebo subjects.

For the relevant trials (922 and 912-US) and within each race category (caucasian, black, asian, other), zonisamide subjects had greater reductions in partial seizure frequency than placebo subjects.

Summary

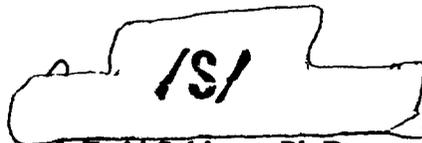
Trial 922 demonstrated a statistically significant treatment effect in partial seizures in favor of zonisamide based on the results of three of four analysis Populations. Regarding the effectiveness of individual doses, both 100 and 200mg were nominally more effective than placebo over short durations not exceeding six weeks. The strength of arguments in favor of the effectiveness of 400mg depends on the weights given the Population 1, 2 and 4 results, particularly the nonsignificant result in Population 2.

None of the analyses of complex partial seizures in 922 yielded statistically significant results.

Trial 912-US was a positive trial for both partial onset and complex partial seizures. 912-EUR failed on the primary endpoint but managed a positive result on a secondary endpoint, the partial seizure response rate. Because zonisamide subjects in both trials received a range of dosages from <200 to ≥ 600 mg/day, it is impossible to disentangle the effect of specific doses.

Trials 922 and 912-US had significantly higher percentages of males receiving zonisamide compared to placebo. In either case, statistical adjustment for the imbalances at baseline did not change the significance of the treatment effects.

The sponsor did not submit any statistical analyses addressing the issue of secondary generalization.

 /S/

J. Todd Sahlroot, Ph.D.
Mathematical Statistician

concur: Dr. Chi

 /S/
2/18/98

cc: NDA 20-789
HFD-120
HFD-120/Drs. Leber, Katz, Sherry
HFD-344/Dr. Barton
HFD-120/Mr. Purvis, Ms. Ware
HFD-710/Drs. Chi, Sahlroot
HFD-710

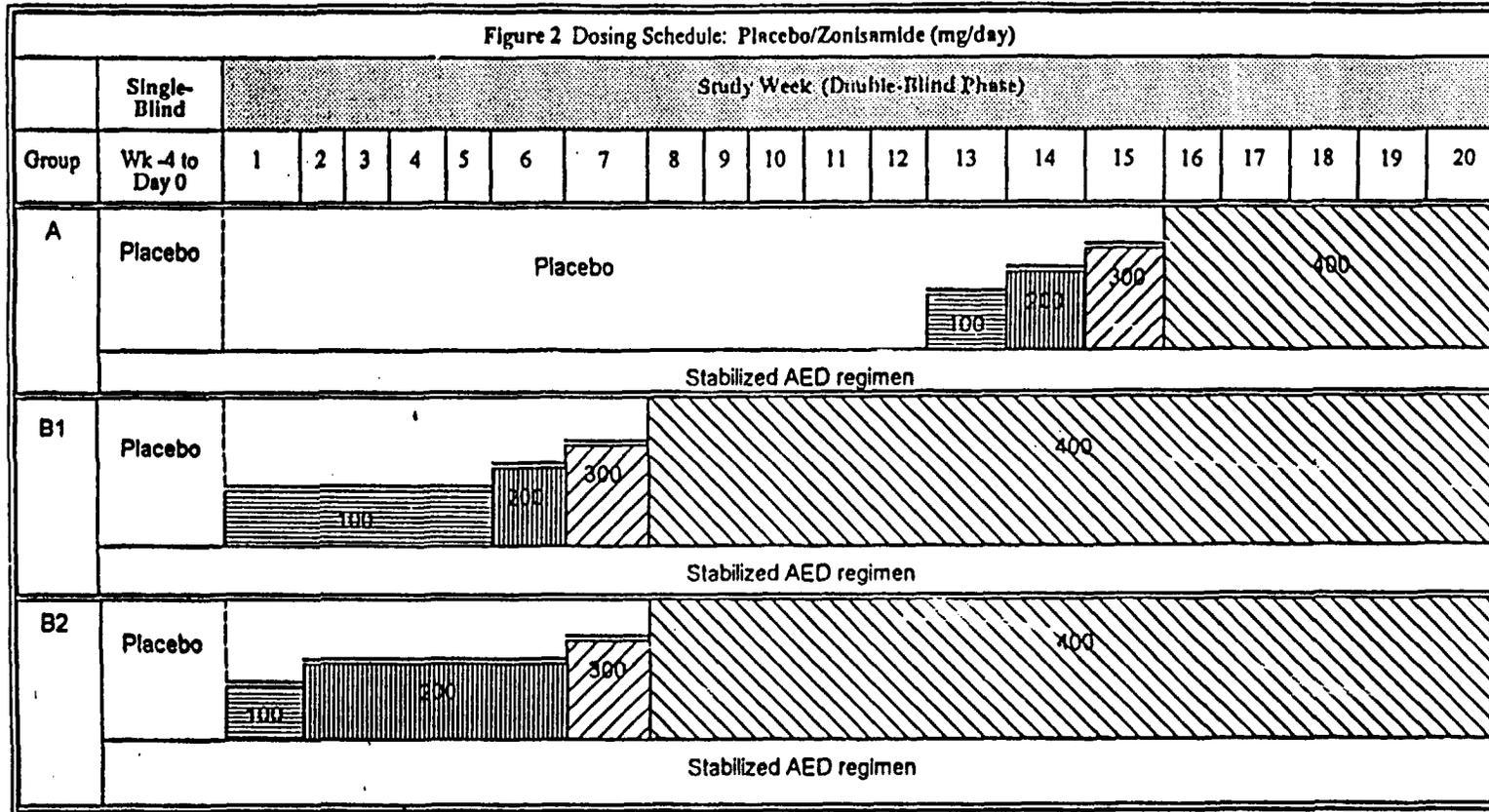
APPEARS THIS WAY
ON ORIGINAL

Table 0

Table 8g-1 All Studies Pertinent to Efficacy									
Report No./ Protocol No./ Investigators/ Publications	Status/ Start Date/ Location	Study Design	Study Description	Number Entered	Age Range (Mean)	M/F	Duration	Dosage (mg/day)	NDA Data Location Full Report/ Data Listings/ CRFs
CONTROLLED STUDIES									
DAINU-922/ 810-922/ 810-922/ Multicenter *	Completed 3/24/94 US	Double-blind, Placebo-controlled, US, Dainippon/IRG	ZNS 100-mg capsule/ 694Z02 Placebo/ 694P01	203	13-68 (34.5)	104/99	DB: 20 weeks Open : Up to 24 mos	DB: 100-400 Open: Titrated	S8-V59-P5/ S8-V64-P5; S11- V416-P3/ S12-V427-P2
720-02266-96/ 912-12, -13, -15 and -21/ 912-US/ Multicenter *	Completed 8/24/83 US	Double-blind, Placebo-controlled, US, W-L ^a	ZNS: 100-mg capsule/ CL 005014 CL 119053 CL 088054 CL 200114 CL 201114 Placebo/ CL 171083 CL 021022	78 74	17-64 (35.6) 17-67 (35.8)	58/20 43/31	12 weeks	22 41 15 100-300 400-600 > 600	S8-V79-P4/ S8-V82-P1a; S11- V416-P26; S11- V417-P3/ S12-V435-P89
720-02275-96/ 912-27, -28, -29, - 30, -31, -32, -33, - 35, -36 and -48/ 912-Eur/ Multicenter *	Completed 6/27/84 Europe	Double-blind, Placebo-controlled, European, W-L	ZNS: 100-mg capsule/ xRx6077, xRx6078, xRx6099, xRx6101, xRx6132, xRx6150, xRx6236, xRx6295 Placebo/ xRx6079, xRx6096, xRx6125, xRx6176	73 71	18-60 (36.2) 19-60 (33.4)	Z: 41/30 P: 40/28	12 weeks	13 54 6 100-300 400-600 > 600	S8-V100-P1a/ S8-V103-P415; S11-V416-P79/ S12-V438-P2

BEST POSSIBLE COPY

Figure 1



BEST POSSIBLE COPY

Table 1

Table 3 Patient Demographic and Baseline Seizure Characteristics

Demographic Characteristic	Group A	Zonisamide	
	Placebo/ZNS N=85	Group B1 N=60	Group B2 N=58
Sex N (%)^a			
Male	35 (41%)	37 (62%)	32 (55%)
Female	50 (59%)	23 (38%)	26 (45%)
Race N (%)			
Caucasian	72 (85%)	50 (83%)	51 (88%)
Black	9 (11%)	7 (12%)	4 (7%)
Asian	1 (1%)	1 (2%)	0 (0%)
Other	3 (4%)	2 (3%)	3 (5%)
Age (yr)			
Mean ±SD	34.2 ± 11.4	35.8 ± 11.4	33.6 ± 11.2
Range	(14-67)	(13-66)	(15-68)
Distribution			
12-40	62 (72.9%)	39 (65.0%)	43 (74.1%)
>40-65	21 (24.7%)	20 (33.3%)	14 (24.1%)
>65	2 (2.4%)	1 (1.7%)	1 (1.7%)
Mean Age at Seizure Onset (yr)			
Mean ±SD	12.2 ± 12.2	12.0 ± 10.7	12.9 ± 11.7
Range	(0-54)	(0-45)	(0-39)
Weight (kg)			
Mean ±SD	75.0 ± 18.4	81.7 ± 20.3	75.6 ± 18.7
Range	(45-140)	(44-133)	(44-128)
Baseline Seizure Frequency			
All Partial			
Mean	40.9	23.4	48.0
Median	13.0	11.2	13.0
Range			
Complex Partial			
Mean	29.8	11.5	29.2
Median	7.0	6.2	8.0
Range			
All Seizure Types			
Mean	40.9	23.4	48.3
Median	13.0	11.2	14.0
Range			
Primary Seizure Classification (N%)			
Complex Partial	65 (77%)	46 (77%)	46 (79%)
All partial	81 (95%)	57 (95%)	57 (98%)
Other	4 (5%)	3 (5%)	1 (2%)

^a The difference in sex distribution was significant between Group A and combined zonisamide groups (B1+B2); p=0.0152

BEST POSSIBLE COPY

Table 2

Table 4 Summary of Patient Disposition

Reason	Group A				Groups B1+B2	
	PLB (Weeks 1-12) N=85		ZNS (Weeks 13-20) N=72		ZNS (Weeks 1-20) N=118	
	N	%	N	%	N	%
Completed	72	84.7	61	84.7	85	72.0
<u>Discontinued</u>	<u>13</u>	<u>15.3</u>	<u>11</u>	<u>15.2</u>	<u>33</u>	<u>28.0</u>
Adverse Event	7	8.2	5	6.9	14	11.9
Lack of Efficacy	1	1.2	4	5.6	5	4.2
Lack of Compliance	0	0.0	1	1.4	5	4.2
Lost to Follow-Up	0	0.0	1	1.4	2	1.7
Personal Reasons	1	1.2	0	0.0	2	1.7
Other	4	4.7	0	0.0	5	4.2

Reference: Appendices C.5, D.10.1, D.10.2, D.11

The individual and cumulative totals of patients withdrawn at each study week are presented in Table 5.

Table 5 Patient Withdrawals by Study Week

End of Week	Group A (N=85)			Zonisamide Groups B1+B2 (N=118)		
	Withdrawn during Wk	Cumulative	%	Withdrawn during Wk	Cumulative	%
1	<u>(PLB)</u> 1	1	1.2	7	7	2.5
5	7	8	9.4	8	15	7.6
6	2	10	11.8	0	15	8.5
7	2	12	14.1	1	16	8.5
12	1	13	15.3	7	23	13.6
16	<u>(ZNS)</u> 4	17	20.0	3	26	15.3
20	7	24	28.2	7	33	19.5

References: Appendices C.5, D.10.1, D.10.2, D.11

Table 3

Table 10 Median Percentage Change From Baseline in Seizure Frequency Weeks 8-12

Analysis Population	Seizure Type	Treatment				p-Value
		Placebo (Group A)		Zonisamide (Group B1+B2)		
		N	Median % Change	N	Median % Change	
Population 1 ^a (Primary)	All Partial	72	-9.0	98	-40.5	0.0091
	Complex Partial	66	-11.7	87	-37.8	0.0883
	All Seizures	72	-9.0	98	-40.5	0.0109
Population 2 ^b (Data Sensitivity)	All Partial	85	-2.6	117	-29.0	0.0094
	Complex Partial	81	2.3	104	-21.4	0.0797
	All Seizures	85	-2.6	117	-29.0	0.0112
Population 3 ^c (Efficacy Evaluable)	All Partial	70	-9.7	94	-40.5	0.0273
	Complex Partial	64	-13.4	83	-37.8	0.3030
	All Seizures	70	-9.7	94	-40.5	0.0331

APPEARS THIS WAY
ON ORIGINAL

- ^a Intent-to-treat analysis using data from Weeks 8 through 12 of the double-blind phase, with no imputation of data for patients withdrawing prior to Week 8;
- ^b Same as intent-to-treat population but with imputation of "worst-case" values for patients withdrawing before Week 8;
- ^c Efficacy-evaluable population: ITT patients having at least four partial seizures during the single-blind phase, and at least (through Week 9) two weeks' exposure to zonisamide 400 mg/day; Group A withdrawals had to have continued in study through Week 9 or longer; patients withdrawn for a protocol violation were excluded.

APPEARS THIS WAY
ON ORIGINAL

Table 4

APPEARS THIS WAY
ON ORIGINAL

**Table 11 Median Percentage Change From Baseline in Seizure Frequency -
Dose Introduction Period**

Seizure Type	Treatment									
	Placebo Group A				Zonisamide					
	Weeks 1-5		Weeks 1-6		Group B1 (100 mg/day) ^a			Group B2 (200 mg/day) ^b		
	N	Median % Change	N	Median % Change	N	Median % Change	p-Value	N	Median % Change	p-Value
All Partial	80	-8.3	82	-4.0	56	-24.7	0.0376	55	-20.4	0.0031
Complex Partial	73	-8.6	75	-9.5	49	-33.3	0.0095	49	-17.2	0.2961
All Seizures	80	-8.3	82	-4.0	56	-24.7	0.0375	55	-20.4	0.0029

^a Efficacy assessed during Weeks 1-5

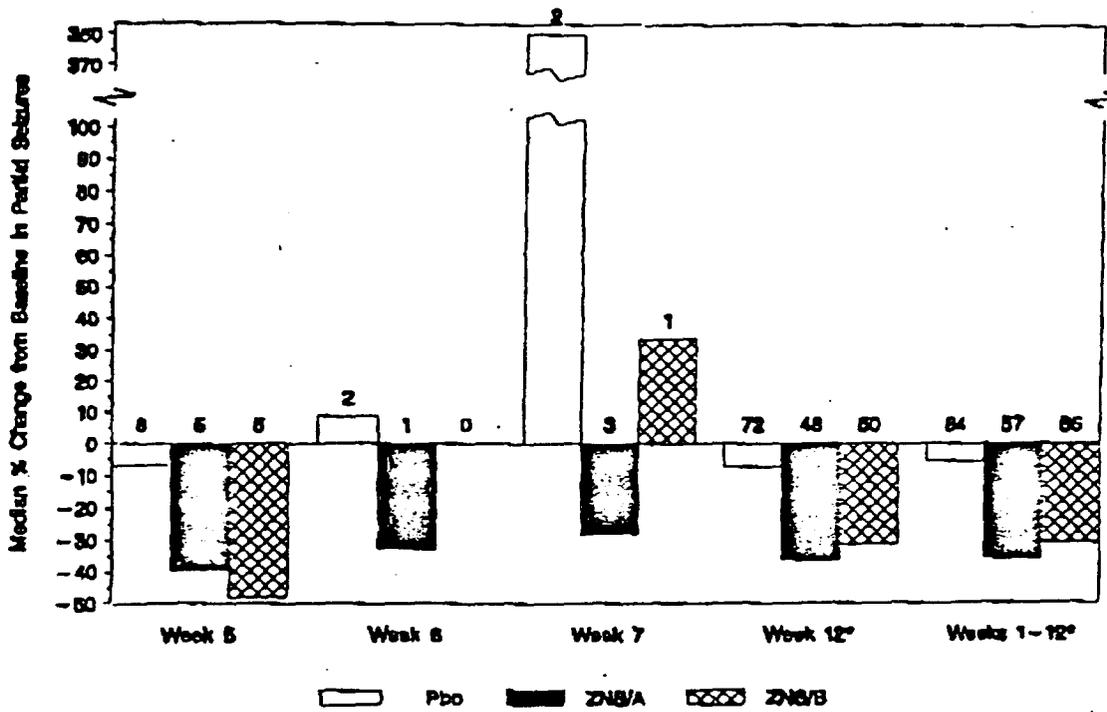
^b Efficacy assessed during Weeks 1-6

APPEARS THIS WAY
ON ORIGINAL

Figure 2

APPEARS THIS WAY
ON ORIGINAL

Dropout Cohorts for 810-922



* Includes patients who completed the study.

BEST POSSIBLE COPY

APPEARS THIS WAY
ON ORIGINAL

Table 5

Table 5 Patient Demographic and Prestudy Seizure Characteristics
(Protocol 912-US)

Demography Characteristic	Zonisamide (N = 78)	Placebo (N = 74)
Gender^a N (%)		
Male	58 (74.4)	43 (58.1)
Female	20 (25.6)	31 (41.9)
Race N (%)		
Caucasian	68 (87.2)	64 (86.5)
Black	4 (5.1)	5 (6.8)
Other ^b	6 (7.7)	5 (6.8)
Age (yr)		
<40	57 (73.1)	49 (66.2)
≥40- <65	21 (26.9)	23 (31.1)
≥65	0 (0.0)	2 (2.7)
Mean±SD	35.6±12.1	36.4±11.3
Range	17.9-64.1	17.8-67.5
Weight (kg)		
Mean±SD	74.8±15.7	72.8±16.1
Range	44.2-114.1	40.9-120.0
Height (cm)		
Mean±SD	173.0±9.7	171.0±11.9
Range	147.0-195.6	140.0-195.6
Prestudy Monthly Seizure Activity (4 months before baseline)		
All Partial (Complex + Simple)		
Mean	21.7	18.3
Median	7.5	11.1
Range		
Complex Partial		
Mean	19.5	12.4
Median	7.0	7.8
Range		
Other Types (Including Generalized)		
Mean	0.3	2.2
Median	0.0	0.0
Range		

^a Statistical difference between treatment groups (p<0.05).

^b Other included Hispanic.

BEST POSSIBLE COPY

Table 6

**Table 7 Summary of Patient Disposition
(Protocol 912-US)**

Reason	Zonisamide (N = 78)		Placebo (N=74)		All Patients (N = 152)	
	N	%	N	%	N	%
Study completed	62	79.5	67	90.5	129	84.9
Study discontinued	16	20.5	7	9.5	23	15.1
Lack of efficacy	0	0.0	4	5.4	4	2.6
Adverse event	12	15.4	1	1.4	13	8.6
Death	0	0.0	1	1.4	1	0.7
Other ^a	4	5.1	1	1.4	5	3.3

^a Other included personal reasons, study discontinued by sponsor, or reason unknown.

**Table 8 Cumulative Withdrawal During Double-Blind Phase
(Protocol 912-US)**

End of Week	Zonisamide (N = 78)		Placebo (N = 74)	
	N	%	N	%
1	2	2.6	1	1.4
2	4	5.1	1	1.4
4	9	11.5	2	2.7
6	10 ^a	12.8	3	4.1
8	11	14.1	4	5.4
10	13	16.7	7	9.5
12	14	17.9	7	9.5
>12	16 ^a	20.5	-	-

^a Two patients received zonisamide beyond the 12-week treatment period.

BEST POSSIBLE COPY

Table 7

APPEARS THIS WAY
ON ORIGINAL

**Table 13 Reduction From Baseline in the Frequency of All Partial Seizures
(Protocol 912-US)**

Population	Zonisamide		Placebo	
	N	Median % Change	N	Median % Change
1 ^b	69	-29.5 ^a	72	1.8
2 ^c	78	-22.9 ^a	74	4.6
3 ^d	78	-25.4 ^a	74	2.2
4 ^e	66	-30.1 ^a	71	3.0

- ^a Significantly greater reduction than placebo ($p \leq 0.05$).
- ^b Intent-to-treat using data from last 8 weeks of the double-blind phase; patients not completing the 4-week dose introduction phase are excluded (Population 1).
- ^c Same as intent-to-treat population but includes patients who dropped during dose introduction phase (includes imputation for patients not completing dose introduction).
- ^d Intent-to-treat using all post-randomization data with no imputation.
- ^e Efficacy evaluable population.

Table 8

APPEARS THIS WAY
ON ORIGINAL

**Table 14 Reduction From Baseline in the Frequency of Complex Partial Seizures
(Protocol 912-US)**

Population	Zonisamide		Placebo	
	N	Median % Change	N	Median % Change
1 ^b	69	-29.6 ^a	70	-1.2
2 ^c	78	-19.2 ^a	72	+1.1
3 ^d	78	-25.2 ^a	72	-1.9
4 ^e	64	-31.1 ^a	68	+1.1

- ^a Significantly greater reduction than placebo ($p \leq 0.05$).
- ^b Intent-to-treat using data from last 8 weeks of the double-blind phase; patients not completing the 4-week dose introduction phase are excluded (Population 1).
- ^c Same as intent-to-treat population but includes patients who dropped during dose introduction phase (includes imputation for patient not completing the dose introduction phase).
- ^d Intent-to-treat using all post-randomization data with no imputation.
- ^e Efficacy evaluable population.

BEST POSSIBLE COPY

Table 9

APPEARS THIS WAY
ON ORIGINAL

Table 4 Demographic and Baseline Seizure Characteristics

Demography Characteristic	Zonisamide (N = 73)	Placebo (N = 71)
Gender N (%)		
Male	43 (58.9)	42 (59.2)
Female	30 (41.1)	29 (40.8)
Race N (%)		
Caucasian	73 (100.0)	71 (100.0)
Age (yr)		
<40 yrs	52 (71.2)	48 (67.6)
≥40 yrs, <65 yrs	21 (28.8)	23 (32.4)
≥65 yrs	0 (0.0)	0 (0.0)
Mean±SD	35.4±10.9	33.9±11.8
Range	17.4 - 60.9	18.5 - 60.2
Weight (kg)		
Mean±SD	66.7±10.9	65.7±10.3
Range	45.0 - 103.0	43.0-96.0
Height (cm)		
Mean±SD	168.4±8.4	168.1±9.9
Range	147.0 - 187.0	125.0 - 190.0
Prestudy Monthly Seizure Activity (4 months before baseline)		
All Partial (Complex + Simple Partial)		
Mean	29.7	24.0
Median	11.3	11.0
Range		
Complex Partial		
Mean	28.5	20.5
Median	10.0	10.0
Range		
Other (Including Generalized)		
Mean	0.5	0.4
Median	0	0
Range		

BEST POSSIBLE COPY

Table 10

Table 6 Summary of Patient Disposition

Reason	Zonisamide (N = 73)		Placebo (N = 71)		All (N = 144)	
	N	%	N	%	N	%
Study completed	61	83.6	68	95.8	129	89.6
Study discontinued	12	16.4	3	4.2	15	10.4
Lack of efficacy	4	5.5	0	0	4	2.8
Adverse event	5	6.8	1	1.4	6	4.2
Other ^a	3	4.1	2	2.8	5	3.5

^a Other included personal reasons, study discontinued by sponsor, seizure

APPEARS THIS WAY
ON ORIGINAL

Table 7 Cumulative Withdrawal During Double-Blind Phase

End of Week	Zonisamide (N = 73)		Placebo (N = 71)	
	N	%	N	%
1	1	1.4	0	0.0
2	1	1.4	1	1.4
4	3	4.1	1	1.4
6	3	4.1	2	2.8
8	4	5.5	2	2.8
10	4	5.5	2	2.8
12	7	9.6	2	2.8
>12	12 ^a	16.4 ^a	3	4.2

^a Five patients received zonisamide and one patient received placebo beyond the 12-week treatment period.

BEST POSSIBLE COPY

Table 11

Table 13 Reduction From Baseline in the Frequency of All Partial Seizures

Population	Zonisamide		Placebo		p-value
	N	Median % Change	N	Median % Change	
1 ^b	69	-20.0	70	0.3	0.210
2 ^c	72	-17.5	71	4.5	0.234
3 ^d	72	-24.8	71	2.9	0.117
4 ^e	65	-20.5 ^a	67	4.5	0.041

- ^a Significantly greater reduction than placebo ($p \leq 0.05$)
- ^b Intent-to-treat using data from last 8 weeks of the double-blind phase; patients not completing the 4-week dose introduction phase are excluded (Population 1).
- ^c Same as intent-to-treat population but includes patients who dropped during dose introduction phase (includes imputation for patients not completing the dose introduction phase).
- ^d Intent-to-treat using all post-randomization data with no imputation.
- ^e Efficacy evaluable population.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Table 12

Table 14 Reduction From Baseline in the Frequency of Complex Partial Seizures

Population	Zonisamide		Placebo		p-value
	N	Median % Change	N	Median % Change	
1 ^b	69	-20.0	70	3.9	0.161
2 ^c	72	-17.5	71	11.7	0.192
3 ^d	72	-24.8	71	2.9	0.110
4 ^e	65	-20.5 ^a	66	3.9	0.027

- ^a Significantly greater reduction than placebo ($p \leq 0.05$).
- ^b Intent-to-treat using data from last 8 weeks of the double-blind phase; patients not completing the 4-week dose introduction phase are excluded (Population 1).
- ^c Same as intent-to-treat population but includes patients who dropped during dose introduction phase (includes imputation for patients not completing the dose introduction phase).
- ^d Intent-to-treat using all post-randomization data with no imputation.
- ^e Efficacy evaluable population.

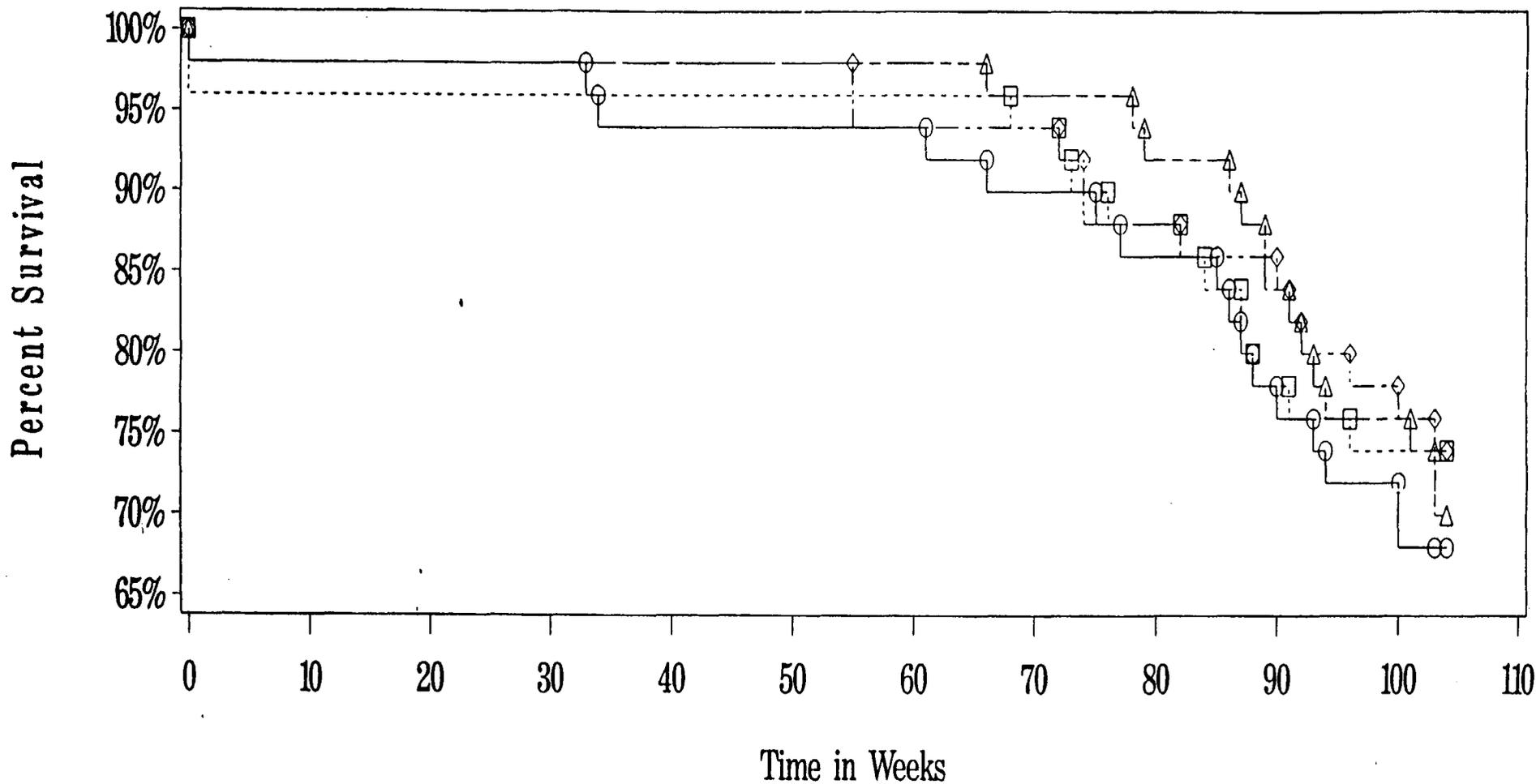
APPEARS THIS WAY
ON ORIGINAL

Kaplan-Meier Survival Function

Species: Rat

Sex: Female

BEST POSSIBLE COPY



MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 13, 1998

FROM: Glenna G. Fitzgerald, Ph.D.
Pharmacology Team Leader
Division of Neuropharmacological Drug Products

TO: NDA 20-789
Zonisamide
100 mg. Capsules
Sponsor: Dainippon Pharmaceutical USA

SUBJECT: Overview of Pharmacology and Toxicology

The pharmacology and toxicology studies submitted to this NDA for zonisamide, indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy, have been summarized in the excellent review by J. Edward Fisher, Ph.D. and are adequate to support its approval. Recommended labeling is attached to this memo. There are no outstanding issues.

The mechanism by which zonisamide exerts its anticonvulsant activity is unknown. It is active in several animal models which are routinely used to screen for promising antiepileptic agents, suggesting a relatively broad spectrum of activity. Like carbamazepine and phenytoin, it is effective in rodents against maximal electric shock but not against pentylenetetrazol-induced seizures. Like valproate (and unlike CBZ or PHT) it suppressed spiking activity induced by cortical freezing in cats and tungstic acid gel application in rats. It also inhibits carbonic anhydrase activity, but is much weaker than topiramate. No receptor binding studies were submitted to the NDA.

Zonisamide is extensively metabolized in all species. In rats, monkeys and humans it undergoes acetylation to form N-acetyl zonisamide; in rats, dogs, monkeys and humans it undergoes reduction to form the ring-opened metabolite, 2-sulfamoylacetyl phenol, which is then glucuronidated. It appears that the monkey is a better model for humans than the dog; however, the toxicology studies were conducted in the dog except for a

teratogenicity study in monkeys.

In routine toxicology studies there was an unusual finding in the livers of dogs treated for one year at 30 mg/kg/day, not seen at 10 mg/kg/day. Dark brown discoloration was noted macroscopically in 5/5 high dose (75 mg/kg/day) females, 3/5 high dose males and 1/5 middle dose (30 mg/kg/day) males. Some, but not all, of the affected dogs had mild hepatocyte hypertrophy and vacuolization or bile duct hyperplasia; there was a correlation with elevated AP and/or ALT and GGT levels. EM examination of livers from the high dose males revealed concentric lamellae of paired smooth membranes within the cytoplasm of the hepatocytes, which were devoid of ribosomes and occasionally seen to be continuous with smooth ER. The no-effect dose is slightly less than the clinical dose on a surface area basis and the toxic effect dose is approximately 2.5 times the clinical dose. It is not known if there is a relationship between the discoloration and the occurrence of the lamellar bodies. The sponsor reported that concentric lamellar bodies have been reported with high doses of enzyme-inducing drugs. However, zonisamide does not induce either its own metabolism or the metabolism of other drugs. These findings were not observed in a two month dog study, although there were increases in liver weights. Since this is a rather unusual finding we have added an Animal Toxicology section to labeling to report it, although the significance is not known. The only other findings in the toxicology studies worthy of note, because of findings in clinical trials, were the relatively modest renal effects reported for the one year rat study. These consisted of effects on urine volume, increases in BUN and bilirubin, and calculus formation, possibly resulting from carbonic anhydrase inhibition, and were primarily observed at doses which were 5 times the human therapeutic dose on a surface area basis (BUN elevations also occurred at much lower doses).

Zonisamide was negative in a genotoxicity battery, with the exception that it produced an increase in forward mutations in the V79 Chinese hamster lung cell assay, only in the absence of metabolic activation. There was no dose response in that assay (conducted by the previous sponsor of this drug), which used an unusually narrow range of concentrations (5 doses from 1000 to 1400 µg/ml), but there was a highly significant ($p = 0.0008$) increase in mutations measured at the low and the high concentrations. It should be noted that the solvent control produced a much lower mutation frequency in the -S9 portion of the assay than it did in the +S9 portion. However, the two doses noted were high relative to the +S9 control as well. We have therefore reported that study as being positive in the absence of S9 in recommended labeling, although the sponsor did not and the results are admittedly strange. Although it is normally not possible to "eliminate" a positive result in a genetic toxicology assay, it conceivably may be possible to examine whether or not this was an invalid assay if the sponsor does not agree that the assay was positive. Factors to be considered would be the range of historical control values from the same lab and for the same time period (1984) and any information from the study that indicates there were problems with the

conduct of the assay which would render it invalid. Before making any such commitment we would necessarily consult a genetic toxicology expert. It would then also be necessary to repeat the assay, preferably using a wider concentration range, and to obtain clearly negative results. In any event, positive results in that assay do not impact the approvability of zonisamide.

Lifetime (2 year) dietary carcinogenicity studies were conducted in mice and rats at doses up to 80 mg/kg/day and there were no statistically significant increases in tumors (oral communication from Dr. T. Sahlroot, statistical review incomplete). However, on a surface area basis, the maximum doses used were only equal to the human dose (in mice) or twice the human dose (in rats). The studies were taken to the CAC-EC and that report is attached to this memo.

The major issue for zonisamide concerns its reproductive and developmental toxicity. There was teratogenicity (high in incidence and serious in nature, including external, visceral and skeletal malformations) and/or embryoletality or spontaneous abortion demonstrated in all species tested, including mice, rats, dogs and monkeys, when the drug was administered during organogenesis. Given the high incidences of defects across species and the fact that exposures (C_{max} of parent) were similar to or lower than therapeutic levels in humans receiving a 400 mg dose¹, the potential risk to the human fetus must be considered to be high. Therefore the findings should be prominently displayed in labeling. Surprisingly, there were no limb reduction defects, typical of carbonic anhydrase inhibitors (acetazolamide, topiramate), observed. This probably reflects the fact that zonisamide is a weak carbonic anhydrase inhibitor. In monkeys there were no malformations noted, but there was a high incidence of abortions, 50% at the high dose which produced plasma levels below human therapeutic levels. As Dr. Fisher notes in his review, intrauterine death is "somewhat more prevalent than malformations in monkeys (and probably humans) at embryotoxic doses, but it is also possible that malformations were masked by embryoletality."

For a complete summary of the malformations, variations and embryoletal effects of zonisamide the reader is referred to pages 44 through 46 in the summary and evaluation section of Dr. Fisher's review. Of particular note and concern are the cardiovascular defects which occurred in rats and dogs. In rats there was a dose-related increase in ventricular septal defects at half of the human therapeutic dose and higher on a surface area basis. In dogs, ventricular septal defects were observed at C_{max} values equivalent to approximately half of the C_{max} in humans receiving 400 mg/day. At exposures equal to clinical exposures based on C_{max} there was a 50% incidence of cardiovascular defects which included cardiomegaly, various aortic

¹ C_{max} at steady state approximately 40 μ g/ml; oral communication Dr. J. Sherry

anomalies, valvular defects, transposition of the great vessels. There were, in addition to the cardiovascular effects, other effects in both rat and dog including effects on the thymus (both species), impaired fertility and perinatal death (rat), skeletal malformations and fetal growth retardation (dog). Dr. Fisher points out in his review that dogs are not commonly used in teratology studies and information about spontaneous malformations is sparse. In spite of that, the effects seen in this study, which are dose-related, are clearly related to zonisamide administration. He also points out that dogs metabolize zonisamide differently than other species (they produce only one of the two major human metabolites), but data are inadequate to make a valid comparison of metabolism between dogs and humans. Until proven otherwise it must be assumed that the findings in dogs predict a significant risk to the human fetus.

Conclusions and Recommendations:

This NDA is approvable for pharmacology and toxicology with the attached recommended labeling. I also recommend that, because of the strong signal for teratogenicity and embryo lethality at maternal plasma levels which are equal to or lower than therapeutic levels in humans, a statement be placed in **WARNINGS** and also in **Information for Patients** indicating that the use of this drug during pregnancy represents a significant risk to the fetus. The first three sentences in the **Pregnancy** section of recommended labeling, or a version thereof, are suggested. The decision to implement this suggestion is deferred to the clinical team.

APPEARS THIS WAY
ON ORIGINAL


Glenna G. Fitzgerald, Ph.D.
Pharmacology Team Leader

Attachments: 2

NDA 20789

cc:

Division File, HFD-120

Leber/Katz/Sherry/Ware/Fitzgerald/Fisher

APPEARS THIS WAY
ON ORIGINAL

M:\DOS\WPFILES\NDA20789.WPD

4 pages
REDACTED

DRAFT
LABELING

RECEIVED MAR 9 1998

Statistical Review and Evaluation
Review of Carcinogenicity Data
ADDENDUM

MAR 9 1998

NDA#: 20-789

APPLICANT:

NAME OF DRUG: Zonisamide Capsules

DOCUMENTS REVIEWED: Volumes 22, 25, and 02/04/98 Amendment
Containing Diskette.

PHARMACOLOGY REVIEWER: E. Fisher, Ph.D.

I. Background

All original diskettes submitted by the sponsor contained only rat data. The sponsor submitted the mouse data on diskette on 02/05/98. This reviewer created the tumor and tissue files from the hard copy submission. The following review contains the analysis of these data.

II. The Mouse Study

II.1 Sponsor's Findings

In this study 50 B6C3F1 mice per sex were assigned to four treatment groups receiving the drug at 0, 20, 40, and 80 mg/kg/day as dietary admixture. The animals were treated for 104 weeks after which all surviving animals were sacrificed.

By the end of the study mortality had reached only 10-20 % among the males and 22-28 % among the females. Also, no dose-relationship in the mortality experience of either sex was found. The sponsor found no evidence that the drug induced neoplastic changes in the animals.

II.2 Reviewer's Findings

This reviewer confirmed the percent surviving till terminal sacrifice and also that there were no statistically significant linear trends in mortality with dose for

either sex (Tables 1-4, Figures 1-2). All animals dying after week 104 were treated as sacrificed, which led to minor numeric differences in this reviewer's and the sponsor's tabulations.

When analyzing increasing tumor incidence rates the level of significance needs to be adjusted for multiplicity of testing. This is done for rare and common tumors separately: for tumors occurring in less than one percent of the control animals, α -values of ≤ 0.025 would be considered statistically significant, and for common tumors, α -values of ≤ 0.005 would be considered statistically significant. None of the tumor findings for either the male or female mice reached these criteria (Tables 5-6).

As there were no statistically significant tumor trends among either female or male mice, the validity of the two study arms needs to be evaluated. For this, two questions need to be answered (Haseman, Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies, Environmental Health Perspectives, Vol 58, pp 385-392, 1984):

- (i) Were enough animals exposed for a sufficient length of time to allow for late developing tumors?
- (ii) Were the dose levels high enough to pose a reasonable tumor challenge in the animals?

The following are some rules of thumb as suggested by experts in the field: Haseman (Issues in Carcinogenicity Testing: Dose Selection, Fundamental and Applied Toxicology, Vol 5, pp 66-78, 1985) had found that on the average, approximately 50 % of the animals in the high dose group survived the two-year study. In a personal communication with Dr. Karl Lin of HFD-715, he suggested that 50 % survival of the usual 50 initial animals in the high dose group between weeks 80-90 would be considered as a sufficient number and adequate exposure. Chu, Cueto, and Ward (Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays, Journal of Toxicology and Environmental Health, Vol 8, pp 251-280, 1981) proposed that "To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50 % survival at one year". From these sources, it appears that the proportions of survival at weeks 52, 80-90, and at two years are of interest in determining the adequacy of exposure and number of animals at risk.

In determining the adequacy of the chosen dose levels, it is generally accepted that the high dose should be close to the MTD. Chu, Cueto, and Ward (1981) suggest:

- (i) "A dose is considered adequate if there is a detectable weight loss of up to 10 % in a dosed group relative to the controls."
- (ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."
- (iii) "In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls."

In another paper, Bart, Chu, and Tarone (Statistical Issues in Interpretation of Chronic Bioassay Tests for Carcinogenicity, Journal of the National Cancer Institute 62, 957-974, 1979), stated that the mean body weight curves over the entire study period should be taken into consideration with the survival curves, when adequacy of dose levels is to be examined. In particular, "Usually, the comparison should be limited to the early weeks of a study when no or little mortality has yet occurred in any of the groups. Here a depression of the mean weight in the treated groups is an indication that the treatment has been tested on levels at or approaching the MTD."

Following these points, it is clear that there were sufficient numbers of animals at the end of the study. As mortality was unusually low, it raises the question whether two years was a sufficient length of time for this particular strain of mice. However, for a standard carcinogenicity bioassay this study provided a sufficient length of exposure. In evaluating whether the high dose was close to the MTD, the mortality experience does not confirm the appropriateness of the high dose, as it was low and not associated with treatment. The average body weights of the male controls and high dose group were identical at the beginning of the study. By week 26 the control animals had gained over 20 % more than the high dose animals. By the end of the first year the further gain of the controls was 27 % higher than the gain of the high dose animals, indicating that the high dose may have been beyond the MTD. The female controls and high dose animals also had the same average bodyweight at the beginning of the study. Again, as there was little mortality throughout the study it is reasonable to compare average body weight gains. By the end of 26 weeks the control animals had gained 11 % more than the high dose animals. The further average increase till the end of the first year was identical for the two groups. Based on the female bodyweight gains one could conclude that the high dose was close to the MTD.

III. Summary

In the mouse study there was very low mortality and no drug effect on survival for either sex. As there were no statistically significant tumor trends in either sex, the validity of the study was evaluated. The excellent survival till terminal sacrifice at week 105 showed that there were sufficient numbers of animals at risk for a sufficient length of time to manifest any late developing tumors. In assessing whether the high dose was close to the MTD, the mortality experience gave no indication in this direction. The average bodyweight gain of the male controls was over 20 percent higher than the high dose animals indicating that the high dose probably exceeded the MTD. For the females one could conclude that the high dose was close to the MTD, as the controls gained up to 11 % more than the high dose animals during the first year. It is suggested that the evaluation of trends in clinical signs or severe histopathological toxic effects by the pharmacologist is used to definitively decide whether the male arm was also a valid study.

/s/

Roswitha E. Kelly
Mathematical Statistician

Concur:

/s/

Todd Sahlroot, Ph. D.
Team Leader

8/3/98

APPEARS THIS WAY
ON ORIGINAL

/s/

George Chi, Ph.D.
Director, DB I

8/9/98

cc:Archival NDA 20-789, Zonisamide Capsules, IBRD Rostrum

CARCINOGENICITY

- HFD-120/Division File
- HFD-120/Dr. Fisher
- HFD-120/Dr. Fitzgerald
- HFD-120/Ms. Ware, CSO
- HFD-344/Dr. Barton
- HFD-710/Chron.
- HFD-710/Dr. Chi
- HFD-710/Dr. Sahlroot
- HFD-710/Ms. Kelly
- HFD-700/Dr. Fairweather

APPEARS THIS WAY
ON ORIGINAL

This review consists of 4 pages of text, 6 tables, and 2 figures.
RKELLY/02/20/98/wp-zonis2.rev

Table 1: Number of Animals
Species: Mouse
Sex: Male

13:10 Friday, February 6, 1998

Time Interval	Treatment Group				Total Count
	CTRL	LOW	MED	HIGH	
	Count	Count	Count	Count	
0-52	.		.		2
53-78	3		3		9
79-91	2		3		7
92-104	.		4		9
105-106	45		40		173
Total	50		50		200

APPEARS THIS WAY
ON ORIGINAL

Table 2: Dose-Mortality Trend Tests

13:10 Friday, February 6, 199

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Mouse

Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.66	0.4173
	Depart from Trend	2.09	0.3515
	Homogeneity	2.75	0.4320
Kruskal-Wallis	Dose-Mortality Trend	0.67	0.4136
	Depart from Trend	1.96	0.3746
	Homogeneity	2.63	0.4519

**APPEARS THIS WAY
ON ORIGINAL**

Table 3: Number of Animals
Species: Mouse
Sex: Female

13:10 Friday, February 6, 1998

Time Interval	Treatment Group				Total
	CTRL	LOW	MED	HIGH	
	Count	Count	Count	Count	
0-52	2		.		9
53-78	2		1		5
79-91	4		4		15
92-104	5		7		21
105-106	37		38		150
Total	50		50		200

APPEARS THIS WAY
ON ORIGINAL

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Mouse
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.46	0.4957
	Depart from Trend	0.29	0.8664
	Homogeneity	0.75	0.8612
Kruskal-Wallis	Dose-Mortality Trend	0.56	0.4530
	Depart from Trend	0.45	0.8004
	Homogeneity	1.01	0.7992

APPEARS THIS WAY
ON ORIGINAL

Table 5: Test for Positive Dose-Response (Tumor) Linear Trend

Species: Mouse

13:10 Friday, February 6, 199.

Sex: Male

Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
AD	ADRENALS	218	B-CORTICAL ADENOMA	0.9381	0.9233	0.9239
EP	EPIDIDYMIDES	373	M-LEIOMYOSARCOMA	0.7389	0.6850	0.6910
HG	HARDERIAN GL.(S)	262	B-CYSTADENOMA	0.7979	0.7745	0.7758
HG	HARDERIAN GL.(S)	56	M-CYSTADENOMCARCINOMA	0.4444	0.2965	0.3035
HL	HEM. LYMPH.RETIC.	26	M-MALIGNANT LYMPHOMA, HIS	0.4798	0.4246	0.4312
HL	HEM. LYMPH.RETIC.	134	M-MALIGNANT LYMPHOMA, LYM	0.4369	0.3701	0.3737
HL	HEM. LYMPH.RETIC.	75	M-MALIGNANT LYMPHOMA, MIX	0.9054	0.8810	0.8822
JE	JEJUNUM	349	M-ADENOCARCINOMA	0.2486	0.0625	0.0646
TEL	LEFT TESTIS	302	B-LEYDIG CELL TUMOR	0.2838	0.2352	0.2382
LI	LIVER	205	B-HEMANGIOMA	1.0000	0.8757	0.8791
LI	LIVER	87	B-HEPATOCELLULAR ADENOMA	0.6687	0.6456	0.6470
LI	LIVER	69	M-HEMANGIOSARCOMA	0.1111	0.0163	0.0171
LI	LIVER	50	M-HEPATOCELLULAR CARCINOM	0.8383	0.8184	0.8195
LU	LUNG	231	B-ALVEOGENIC ADENOMA	0.9336	0.9199	0.9204
LU	LUNG	76	M-ALVEOGENIC CARCINOMA	0.5886	0.5374	0.5407
MS	MESENTERIC L.N.	330	B-HEMANGIOMA	0.1763	0.1107	0.1129
MS	MESENTERIC L.N.	136	M-MAL. FIBROUS HISTIOCYTO	0.7143	0.5000	0.5066
PI	PITUITARY	51	B-ADENOMA	0.5472	0.5103	0.5154
RE	RECTUM	299	M-LIPOSARCOMA	0.7399	0.6850	0.6910
TER	RIGHT TESTIS	271	B-LEYDIG CELL TUMOR	1.0000	0.8757	0.8791
SP	SPLEEN	115	B-HEMANGIOMA	0.2486	0.0625	0.0646
SQ	SUBCUTANEOUS TIS	52	M-SARCOMA	0.4444	0.2965	0.3035
TH	THYMUS	173	M-THYMIC LYMPHOMA	1.0000	0.8438	0.8491
TY	THYROID	270	B-ADENOMA, FOLLICULAR CEL	0.9335	0.8769	0.8793
TY	THYROID	258	M-CARCINOMA, FOLLICULAR CE	1.0000	0.9491	0.9503

APPEARS THIS WAY
ON ORIGINAL

Table 6: Test for Positive Dose-Response (Tumor) Linear Trend

Species: Mouse

13:10 Friday, February 6, 1998

Sex: Female

Sorted by: Organ Name

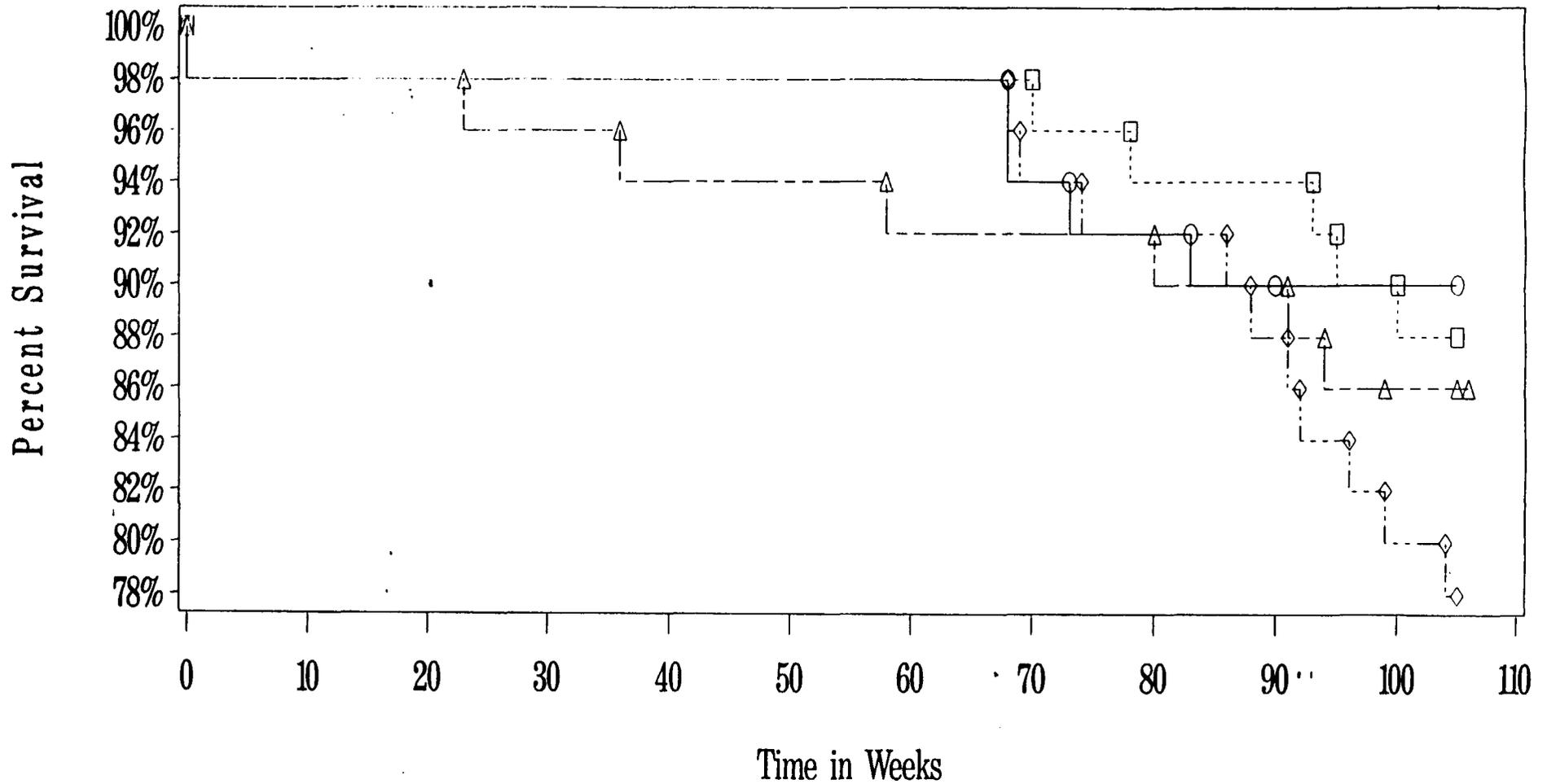
Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
AD	ADRENALS	218	B-CORTICAL ADENOMA	0.5166	0.4195	0.4242
AD	ADRENALS	335	B-PHEOCHROMOCYTOMA	0.6390	0.6076	0.6122
AD	ADRENALS	86	M-CORTICAL CARCINOMA	1.0000	0.8827	0.8859
AD	ADRENALS	162	M-GANGLIONEUROMA, UNILATE	1.0000	0.8252	0.8295
CO	COLON	321	B-LEIOMYOMA	0.7533	0.7012	0.7069
ER	EAR(S)	345	B-PAPILLOMA	1.0000	0.8827	0.8859
HG	HARDERIAN GL.(S)	262	B-CYSTADENOMA	0.8174	0.7883	0.7901
HG	HARDERIAN GL.(S)	56	M-CYSTADENOMCARCINOMA	0.2600	0.0688	0.0710
HL	HEM. LYMPH.RETIC.	89	M-GRANULOCYTIC LEUKEMIA	0.2062	0.1280	0.1305
HL	HEM. LYMPH.RETIC.	26	M-MALIGNANT LYMPHOMA, HIS	0.2381	0.0635	0.0656
HL	HEM. LYMPH.RETIC.	134	M-MALIGNANT LYMPHOMA, LYM	0.3627	0.3380	0.3394
HL	HEM. LYMPH.RETIC.	75	M-MALIGNANT LYMPHOMA, MIX	0.4425	0.4177	0.4191
HL	HEM. LYMPH.RETIC.	303	M-RETICULUM CELL SARCOMA	0.7102	0.6603	0.6632
HL	HEM. LYMPH.RETIC.	286	M-RETICULUM CELL SARCOMA,	1.0000	0.8964	0.8994
OVL	LEFT OVARY	68	B-TERATOMA	1.0000	0.8252	0.8295
LI	LIVER	205	B-HEMANGIOMA	0.5111	0.4780	0.4834
LI	LIVER	87	B-HEPATOCELLULAR ADENOMA	0.2206	0.1668	0.1687
	LIVER	50	M-HEPATOCELLULAR CARCINOM	0.7494	0.7021	0.7055
	LUNG	231	B-ALVEOGENIC ADENOMA	0.8525	0.8268	0.8284
LU	LUNG	76	M-ALVEOGENIC CARCINOMA	0.7840	0.7437	0.7467
MG	MAMMARY GLAND	323	B-ADENOMA	0.7533	0.7012	0.7069
MG	MAMMARY GLAND	113	M-ADENOCARCINOMA	0.8036	0.7662	0.7687
MS	MESENTERIC L.N.	330	B-HEMANGIOMA	0.7533	0.7012	0.7069
PI	PITUITARY	51	B-ADENOMA	0.6395	0.6124	0.6139
OVR	RIGHT OVARY	292	B-LUTEOMA	1.0000	0.8847	0.8879
OVR	RIGHT OVARY	362	B-MIXED TUMOR (TUBULAR AD	0.2600	0.0688	0.0710
SK	SKIN	122	B-ADENOMA, SEBACEOUS	0.6126	0.5598	0.5640
SK	SKIN	280	B-BASAL CELL TUMOR	1.0000	0.8847	0.8879
SP	SPLEEN	115	B-HEMANGIOMA	0.7333	0.7014	0.7070
SQ	SUBCUTANEOUS TIS	363	M-ADENOCARCINOMA	0.2600	0.0688	0.0710
TY	THYROID	270	B-ADENOMA, FOLLICULAR CEL	0.2600	0.0688	0.0710
UT	UTERUS	223	B-ENDOMETRIAL STROMAL POL	0.9556	0.9321	0.9330
UT	UTERUS	124	M-ENOMETRIAL SARCOMA	0.2218	0.1552	0.1577
VA	VAGINA	316	M-LEIOMYOSARCOMA	1.0000	0.8964	0.8994
VC	VERTEBRAL COLUMN	332	M-SARCOMA, ANAPLASTIC	0.7533	0.7012	0.7069

APPEARS THIS WAY
ON ORIGINAL

Figure 1: Kaplan–Meier Survival Function

Species: Mouse
Sex: Male

BEST POSSIBLE COPY

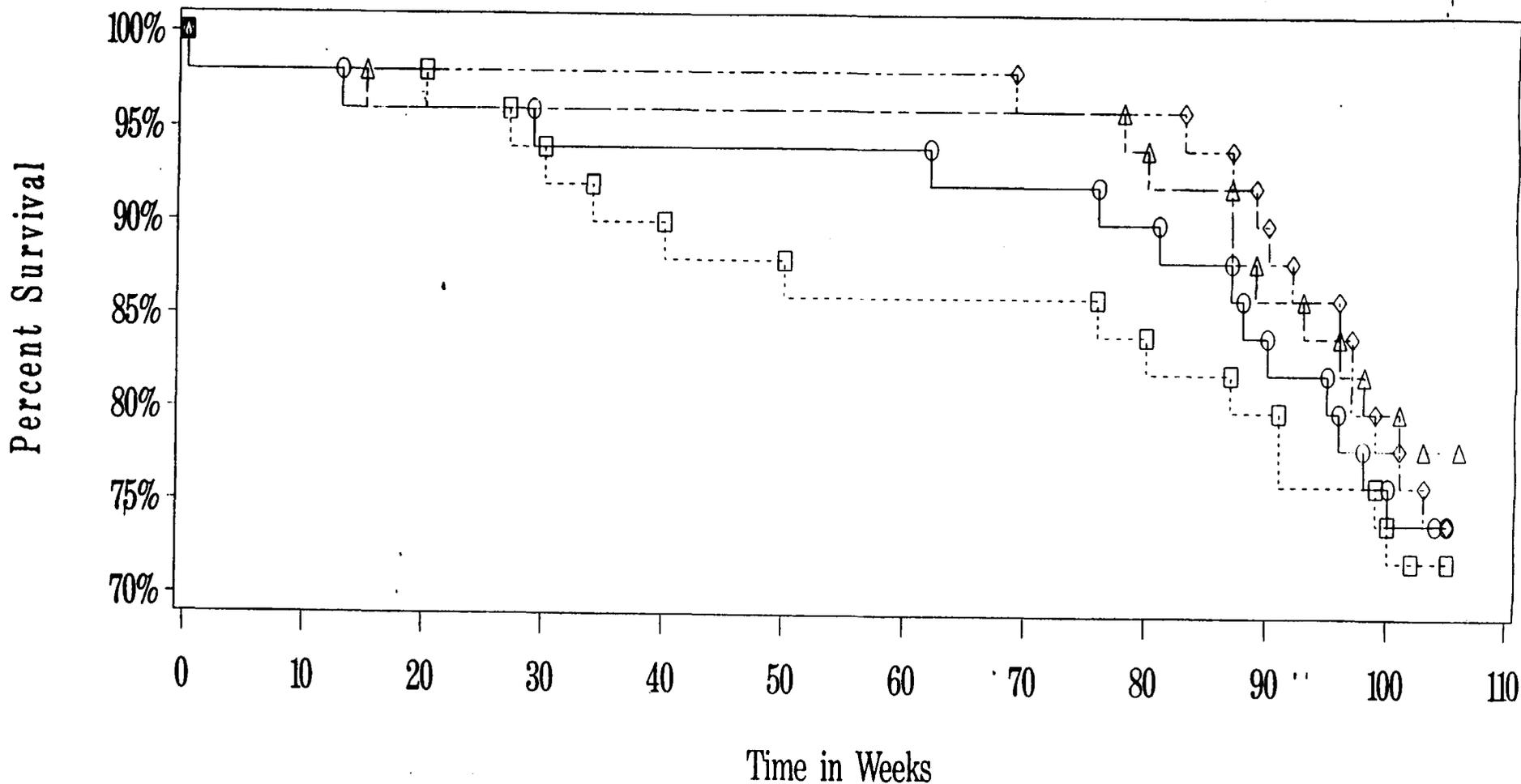


○-○-○ CTRL □-□-□ LOW ◇-◇-◇ MED △-△-△ HIGH

Figure 4: Kaplan—Meier Survival Function

Species: Mouse
Sex: Female

BEST POSSIBLE COPY



○ ○ ○ ○ CTRL □ □ □ □ LOW △ △ △ △ MED ◇ ◇ ◇ ◇ HIGH

Statistical Review and Evaluation
Review of Carcinogenicity Data

NDA#:

20-789

FEB 18 1998

APPLICANT:

NAME OF DRUG:

Zonisamide Capsules

DOCUMENTS REVIEWED: Volumes 22 and 26, Undated.

PHARMACOLOGY REVIEWER: E. Fisher, Ph.D.

I. Background

Dr. Fisher (HFD-120) requested from the Division of Biometrics I a statistical review of the rat and mouse studies data as well as an evaluation of the sponsor's report.

II. The Rat Study

II.1 Sponsor's Findings

In this study 200 male and female Wistar rats were given the drug as dietary admixture in concentrations of 0, 20, 40, and 80 mg/kg/day for two years.

The drug did not affect the survival of either sex negatively. Mortality before terminal sacrifice did not exceed 32 % (controls) among the females and 48 % (controls) among the males. The sponsor investigated possible drug effect on tumor incidence by testing for trend and by comparing tumor risks of each drug group against the controls. The sponsor observed no statistically significant increase in tumor incidences among the female or the male rats.

II.2 Reviewer's Findings

This reviewer's analyses showed some numeric differences from the sponsor's results. In the mortality tables (Tables 1-2) these differences arose from the fact

that some animals were classified as dying a natural death during the week of Terminal Sacrifice. This reviewer treated all animals dying in week 104 as sacrificed. The numeric differences in p-values associated with testing for trend in mortality are likely to be due to these minor differences in classification as well as the use of somewhat different statistical methods (Tables 3-4). However, it is apparent that the drug had no negative effect on mortality among either sex (Figures 1-2).

When analyzing increasing tumor incidence rates the level of significance needs to be adjusted for multiplicity of testing. This is done for rare and common tumors separately: for tumors occurring in less than one percent of the control animals -values of ≤ 0.025 would be considered statistically significant, and for common tumors -values of ≤ 0.005 would be considered statistically significant. None of the tumor findings for either the male or female rats reached these criteria (Tables 5-6).

As there were no statistically significant tumor trends among either female or male rats, the validity of the two study arms need to be evaluated. For this, two questions need to be answered (Haseman, Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies, Environmental Health Perspectives, Vol 58, pp 385-392, 1984):

- (i) Were enough animals exposed for a sufficient length of time to allow for late developing tumors?
- (ii) Were the dose levels high enough to pose a reasonable tumor challenge in the animals?

The following are some rules of thumb as suggested by experts in the field: Haseman (Issues in Carcinogenicity Testing: Dose Selection, Fundamental and Applied Toxicology, Vol 5, pp 66-78, 1985) had found that on the average, approximately 50 % of the animals in the high dose group survived the two-year study. In a personal communication with Dr. Karl Lin of HFD-715, he suggested that 50 % survival of the usual 50 initial animals in the high dose group between weeks 80-90 would be considered as a sufficient number and adequate exposure. Chu, Cueto, and Ward (Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays, Journal of Toxicology and Environmental Health, Vol 8, pp 251-280, 1981) proposed that "To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50 % survival at one year". From these sources, it appears that the proportions of survival at weeks 52, 80-90, and at two years are of interest in determining the adequacy of exposure and number of animals at risk.

In determining the adequacy of the chosen dose levels, it is generally accepted that the high dose should be close to the MTD. Chu, Cueto, and Ward (1981) suggest:

- (i) "A dose is considered adequate if there is a detectable weight loss of up to 10 % in a dosed group relative to the controls."
- (ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."
- (iii) "In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls."

In another paper, Bart, Chu, and Tarone (Statistical Issues in Interpretation of Chronic Bioassay Tests for Carcinogenicity, Journal of the National Cancer Institute 62, 957-974, 1979), stated that the mean body weight curves over the entire study period should be taken into consideration with the survival curves, when adequacy of dose levels is to be examined. In particular, "Usually, the comparison should be limited to the early weeks of a study when no or little mortality has yet occurred in any of the groups. Here a depression of the mean weight in the treated groups is an indication that the treatment has been tested on levels at or approaching the MTD."

As noted above, the numerically highest mortality occurred in the control groups, 32 % for the females and 48 % for the males after 103 weeks of treatment. It is apparent that there were sufficient numbers of animals exposed for a sufficient length of time to manifest late developing tumors.

In Table 5 of the submission the sponsor lists average body weight data by week. The high dose males experienced statistically significant lower average body weight than the controls starting with week one. By week 30 the average body weights for the high dose males were up to 10 percent less than the controls and remained at about 12 percent less through the remainder of the study. It needs to be pointed out that the high dose animals started out with an average body weight of 2 percent less than the controls. As the sponsor did not provide the data for body weight gains, the effect of this early differential cannot be assessed precisely. It appears, however, that the high dose was close to the MTD. As there was no increase in mortality with dose, the evaluation of any increase in clinical signs or severe histopathological toxic effects by the pharmacologist may answer this question definitively.

A similar picture was seen among the female rats. At the beginning of the study the high dose animals were on the average about 2 percent lighter than the controls and became statistically significantly so starting with week one. At 30 weeks this differential had grown to about 10 percent and continued to increase to about 16 percent. When considering only the early part of the study this criterion supports the high dose being close to the MTD. As with the male rats, the drug had not affected mortality and it is left to the expertise of the pharmacologist to evaluate trends in clinical signs or severe histopathological toxic effects to clearly establish whether the high dose was close to the MTD.

III. The Mouse Study *Note: To be included as an addendum. JTS.*

III.1 Sponsor's Findings

III.2 Reviewer's Findings

IV. Summary

In the rat study it was found that the drug did not have any negative effect on the survival of either sex. Also, neither sex showed a statistically significant increased linear trend in any tumor incidence rates with dose. Investigating the validity of each study arms it was found that there were sufficient numbers of high dose animals surviving a sufficient length of time to manifest late developing tumors. When compared to controls both high dose sexes had decreased average weights throughout the study reaching about 12 percent (males) and 16 percent (females) by the end. As in both sexes the high dose animals started out about 2 percent lighter than the controls, the body weight gain data would have given a more definitive answer, but they were not available. However, based on average body weight data it appears that the high dose was close to the MTD.

Concur:

TS/
 Roswitha E. Kelly
 Mathematical Statistician

TS/ 2/5/98
 Todd Sahlroot, Ph. D.
 Team Leader

TS/ 2/18/98
 George Chi, Ph.D.
 Director, DB I