

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

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This review consists of 5 pages of text, 6 tables, and 2 figures.  
RKELLY/02/04/98/wp-zonis.rev

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Species: Rat  
Sex: Male

Time Interval	Treatment Group				Total
	CTRL	LOW	MED	HIGH	
	Count	Count	Count	Count	
0-52	2		1		9
53-78	4		2		14
79-91	8		7		21
92-103	9		9		38
104-104	26		31		117
Total	49		50		199

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Species: Rat

Sex: Female

Time Interval	Treatment Group				Total
	CTRL	LOW	MED	HIGH	
	Count	Count	Count	Count	
0-52	2		.		2
53-78	4		4		15
79-91	5		4		21
92-103	5		4		15
104-104	34		38		147
Total	50		50		200

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**Table 3: Dose-Mortality Trend Tests**

16:20 Thursday, January 29, 1998

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: Rat  
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.13	0.7159
	Depart from Trend	0.97	0.6162
	Homogeneity	1.10	0.7769
Kruskal-Wallis	Dose-Mortality Trend	0.01	0.9155
	Depart from Trend	1.42	0.4904
	Homogeneity	1.44	0.6971

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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: Rat

Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.40	0.5257
	Depart from Trend	0.73	0.6950
	Homogeneity	1.13	0.7697
Kruskal-Wallis	Dose-Mortality Trend	0.57	0.4513
	Depart from Trend	0.60	0.7409
	Homogeneity	1.17	0.7609

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

Species: Rat

16:20 Thursday, January 29, 1998

Sex: Male

Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
ADR	ADRENAL	M1	BENIGN ADENOMA OF ADRENAL	0.5062	0.4670	0.4694
ADR	ADRENAL	M3	BENIGN PHEOCHROMOCYTOMA O	0.9934	0.9894	0.9895
ADR	ADRENAL	M2	MALIGNANT PHEOCHROMOCYTOM	0.7400	0.6964	0.6996
BON	BONE	M4	MALIGNANT OSTEOSARCOMA OF	0.0789	0.0248	0.0254
BRA	BRAIN	M6	BENIGN GRANULAR CELL TUMO	0.5499	0.4984	0.5021
BRA	BRAIN	M5	MALIGNANT GLIOMA OF BRAIN	0.1473	0.1049	0.1065
CAE	CAECUM	M8	BENIGN POLYP OF CAECUM	0.4286	0.2680	0.2746
CAE	CAECUM	M7	MALIGNANT ADENOCARCINOMA	0.0405	0.0161	0.0165
GEN	GENERAL	M9	MALIGNANT LEUKEMIA OF GEN	0.5715	0.5330	0.5388
GEN	GENERAL	M10	MALIGNANT LYMPHOMA OF GEN	0.9404	0.9255	0.9263
JEJ	JEJUNUM	M11	MALIGNANT ADENOCARCINOMA	0.5172	0.4275	0.4323
JEJ	JEJUNUM	M12	MALIGNANT LEIOMYOSARCOMA	0.5214	0.4488	0.4556
KID	KIDNEY	M13	BENIGN ADENOMA OF KIDNEY	1.0000	0.8925	0.8956
LIV	LIVER	M15	BENIGN HEMANGIOMA OF LIVE	0.5214	0.4488	0.4556
LIV	LIVER	M17	BENIGN LIVER CELL ADENOMA	0.0549	0.0376	0.0382
LIV	LIVER	M14	MALIGNANT CHOLANGIOCARCIN	0.5214	0.4488	0.4556
LIV	LIVER	M16	MALIGNANT HISTIOCYTIC SAR	1.0000	0.8928	0.8955
	LIVER	M18	MALIGNANT LIVER CELL CARC	0.7521	0.7098	0.7129
	LYMPH NODE	M19	BENIGN ANGIOMA OF LYMPH N	0.5172	0.4275	0.4323
LYM	LYMPH NODE	M20	BENIGN HEMANGIOMA OF LYMP	0.3014	0.2526	0.2549
LYM	LYMPH NODE	M21	MALIGNANT UNDIFFERENTIATE	1.0000	0.8925	0.8956
MGL	MAMMARY GLAND	M23	BENIGN FIBROADENOMA OF MA	0.9331	0.9018	0.9030
MES	MESENTERY	M22	MALIGNANT CARCINOMA OF ME	0.2564	0.0672	0.0694
MUS	MUSCLE	M24	MALIGNANT RHABDOMYOSARCOM	1.0000	0.8928	0.8955
NER	NERVE	M25	MALIGNANT SARCOMA OF NERV	0.7778	0.7108	0.7166
PAN	PANCREAS	M26	BENIGN ACINAR CELL ADENOM	0.9900	0.9615	0.9623
PAN	PANCREAS	M27	BENIGN ISLET CELL ADENOMA	0.4156	0.3614	0.3648
PAR	PARATHYROID	M28	BENIGN ADENOMA OF PARATHY	0.8207	0.7821	0.7849
PIT	PITUITARY	M29	BENIGN ADENOMA OF PITUITA	0.0972	0.0881	0.0883
SKN	SKIN	M30	BENIGN FIBROMA OF SKIN	1.0000	0.8925	0.8956
SKN	SKIN	M31	BENIGN PAPILLOMA OF SKIN	0.4211	0.3703	0.3773
SKN	SKIN	M32	MALIGNANT SQUAMOUS CELL C	0.3765	0.3176	0.3209
SUB	SKIN/SUBCUTANEOUS	M36	BENIGN FIBROMA OF SKIN/SU	0.9619	0.9426	0.9432
SUB	SKIN/SUBCUTANEOUS	M38	BENIGN HEMANGIOMA OF SKIN	1.0000	0.8925	0.8956
SUB	SKIN/SUBCUTANEOUS	M39	BENIGN HEMANGIOPERICYTOMA	1.0000	0.8925	0.8956
SUB	SKIN/SUBCUTANEOUS	M42	BENIGN LIPOMA OF SKIN/SUB	0.6260	0.5690	0.5727
SUB	SKIN/SUBCUTANEOUS	M37	MALIGNANT FIBROSARCOMA OF	0.5172	0.4275	0.4323
SUB	SKIN/SUBCUTANEOUS	M40	MALIGNANT HEMANGIOSARCOMA	0.8106	0.7535	0.7574
SUB	SKIN/SUBCUTANEOUS	M41	MALIGNANT HISTIOCYTIC SAR	0.7619	0.6132	0.6172
SUB	SKIN/SUBCUTANEOUS	M43	MALIGNANT SARCOMA OF SKIN	0.6707	0.6124	0.6157
	SPLEEN	M33	BENIGN HEMANGIOMA OF SPLE	0.8911	0.8693	0.8718
	SPLEEN	M34	MALIGNANT HEMANGIOSARCOMA	0.7632	0.6587	0.6654
SPL	SPLEEN	M35	MALIGNANT SARCOMA OF SPLE	0.4286	0.2680	0.2746
TES	TESTIS	M45	BENIGN INTERSTITIAL CELL	0.1159	0.1002	0.1010
TES	TESTIS	M44	MALIGNANT HEMANGIOSARCOMA	0.4286	0.1410	0.1443
THM	THYMUS	M46	BENIGN THYMOMA OF THYMUS	0.5344	0.4771	0.4812

Test for Positive Dose-Response (Tumor) Linear Trend

Species: Rat

16:20 Thursday, January 29, 1998

Sex: Male

Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
THY	THYROID	M47	BENIGN C-CELL ADENOMA OF	0.7064	0.6781	0.6800
THY	THYROID	M48	BENIGN FOLLICULAR ADENOMA	0.8629	0.8392	0.8404
THY	THYROID	M49	MALIGNANT FOLLICULAR CARC	0.7754	0.7087	0.7132

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

Species: Rat

16:20 Thursday, January 29, 1998

Sex: Female

Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
ABC	ABDOMINAL CAVITY	F1	BENIGN LEIOMYOMA OF ABDOM	1.0000	0.8883	0.8915
ADR	ADRENAL	F3	BENIGN ADENOMA OF ADRENAL	0.4684	0.4338	0.4360
ADR	ADRENAL	F4	BENIGN GANGLIONEUROMA OF	0.6667	0.7140	0.7191
ADR	ADRENAL	F6	BENIGN PHEOCHROMOCYTOMA O	0.7124	0.6646	0.6676
ADR	ADRENAL	F2	MALIGNANT ADENOCARCINOMA	1.0000	0.8883	0.8915
ADR	ADRENAL	F5	MALIGNANT LYMPHOMA OF ADR	0.7619	0.7015	0.7071
BRA	BRAIN	F8	BENIGN GRANULAR CELL TUMO	0.1931	0.1189	0.1213
BRA	BRAIN	F7	MALIGNANT GLIOMA OF BRAIN	0.3241	0.2433	0.2471
CER	CERVIX	F9	MALIGNANT ADENOCARCINOMA	0.4715	0.4038	0.4077
CER	CERVIX	F10	MALIGNANT SARCOMA OF CERV	0.9459	0.9214	0.9226
CER	CERVIX	F11	MALIGNANT SQUAMOUS CELL C	0.7619	0.7015	0.7071
GEN	GENERAL	F12	MALIGNANT LYMPHOMA OF GEN	0.7619	0.7015	0.7071
KID	KIDNEY	F13	BENIGN ADENOMA OF KIDNEY	0.2517	0.0649	0.0671
LIV	LIVER	F15	BENIGN LIVER CELL ADENOMA	0.7659	0.7352	0.7372
LIV	LIVER	F14	MALIGNANT CHOLANGIOPHOSPH	0.2517	0.0649	0.0671
LIV	LIVER	F16	MALIGNANT LIVER CELL CARC	0.5755	0.5377	0.5429
LUN	LUNG	F17	MALIGNANT LEUKEMIA OF LUN	1.0000	0.8883	0.8915
	LYMPH NODE	F18	BENIGN HEMANGIOMA OF LYMP	0.6996	0.6517	0.6549
	MAMMARY GLAND	F20	BENIGN ADENOMA OF MAMMARY	0.6780	0.6406	0.6429
MGL	MAMMARY GLAND	F21	BENIGN CYSTADENOMA OF MAM	0.6000	0.4839	0.4900
MGL	MAMMARY GLAND	F22	BENIGN FIBROADENOMA OF MA	0.3932	0.3735	0.3755
MGL	MAMMARY GLAND	F19	MALIGNANT ADENOCARCINOMA	0.7697	0.7378	0.7397
MUS	MUSCLE	F23	MALIGNANT HEMANGIOSARCOMA	0.2517	0.0649	0.0671
OVA	OVARY	F25	BENIGN GRANULOSA CELL TUM	0.5102	0.4409	0.4477
OVA	OVARY	F27	BENIGN GRANULOSA-THECA CE	1.0000	0.8678	0.8720
OVA	OVARY	F24	MALIGNANT ADENOCARCINOMA	1.0000	0.8883	0.8915
OVA	OVARY	F26	MALIGNANT GRANULOSA-THECA	1.0000	0.8883	0.8915
OVA	OVARY	F28	MALIGNANT UNDIFFERENTIATE	0.7619	0.7015	0.7071
PAN	PANCREAS	F30	BENIGN ISLET CELL ADENOMA	0.8824	0.8590	0.8603
PAN	PANCREAS	F29	MALIGNANT ACINAR CELL CAR	0.6667	0.7140	0.7191
PAR	PARATHYROID	F31	BENIGN ADENOMA OF PARATHY	0.5696	0.5212	0.5244
PIT	PITUITARY	F32	BENIGN ADENOMA OF PITUITA	0.7215	0.7031	0.7034
SKN	SKIN	F33	BENIGN PAPILOMA OF SKIN	0.7687	0.7035	0.7094
SKN	SKIN	F34	MALIGNANT UNDIFFERENTIATE	0.7333	0.6251	0.6326
SUB	SKIN/SUBCUTANEOUS	F37	BENIGN FIBROMA OF SKIN/SU	0.4050	0.3341	0.3378
SUB	SKIN/SUBCUTANEOUS	F39	BENIGN LIPOMA OF SKIN/SUB	0.4371	0.3819	0.3853
SUB	SKIN/SUBCUTANEOUS	F38	MALIGNANT FIBROSARCOMA OF	0.4000	0.3162	0.3234
SUB	SKIN/SUBCUTANEOUS	F40	MALIGNANT SARCOMA OF SKIN	1.0000	0.8678	0.8720
SPL	SPLEEN	F35	BENIGN HEMANGIOMA OF SPLE	0.7687	0.7035	0.7094
SPL	SPLEEN	F36	MALIGNANT LEUKEMIA OF SPL	1.0000	0.8883	0.8915
	THYMUS	F41	BENIGN THYMOMA OF THYMUS	1.0000	0.8883	0.8915
	THYROID	F42	BENIGN C-CELL ADENOMA OF	0.0399	0.0322	0.0325
THY	THYROID	F43	BENIGN FOLLICULAR ADENOMA	0.8933	0.8599	0.8619
THY	THYROID	F44	MALIGNANT FOLLICULAR CARC	0.3377	0.2840	0.2868
UTE	UTERUS	F45	MALIGNANT ADENOCARCINOMA	0.1448	0.1237	0.1246
UTE	UTERUS	F46	MALIGNANT SARCOMA OF UTER	1.0000	0.8814	0.8846

Test for Positive Dose-Response (Tumor) Linear Trend

Species: Rat

16:20 Thursday, January 29, 1998

Sex: Female

Sorted by: Organ Name

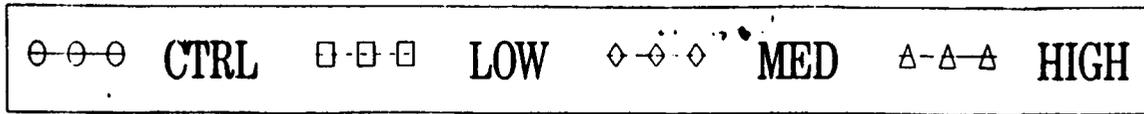
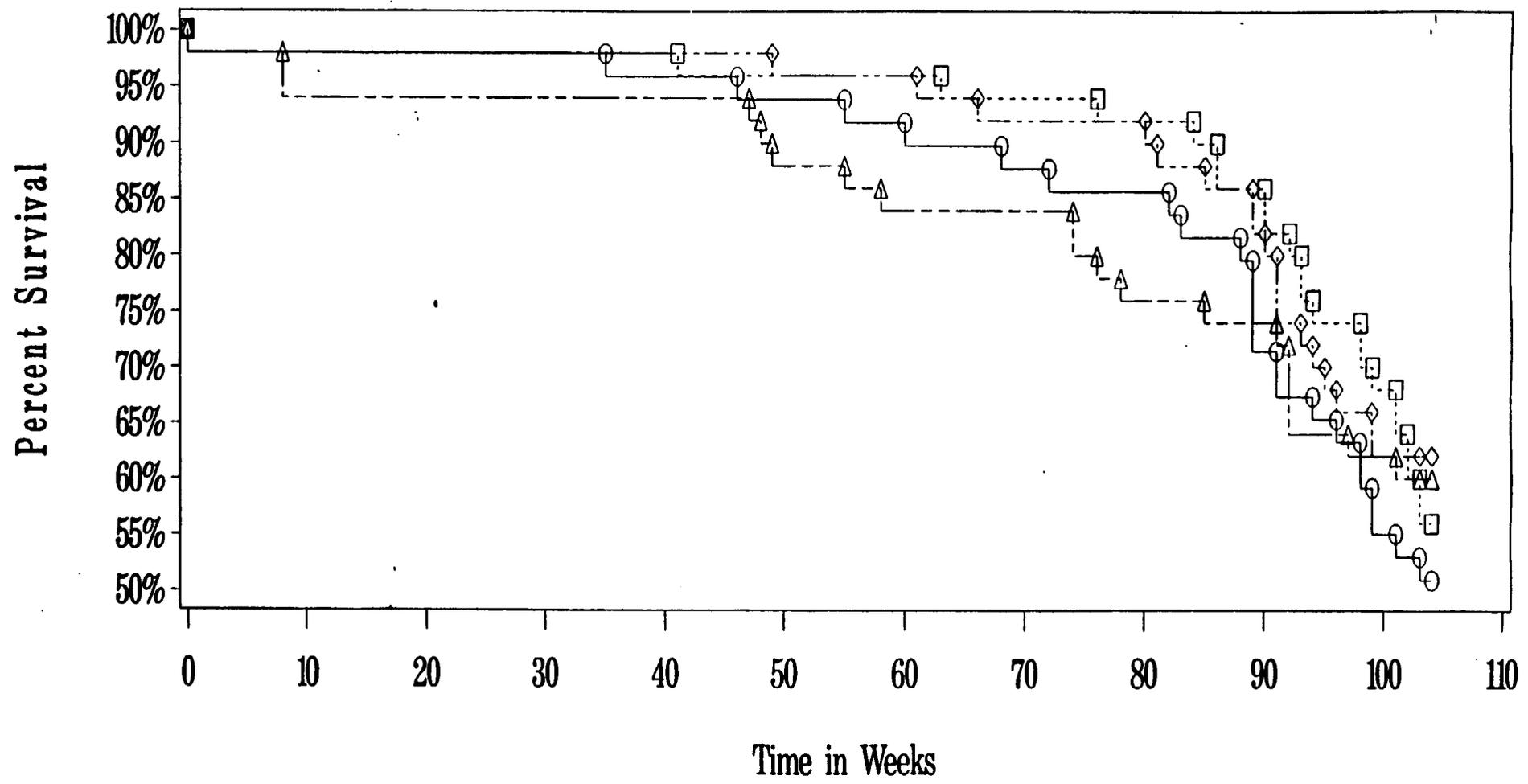
Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
UTE	UTERUS	F47	MALIGNANT SQUAMOUS CELL C	0.7687	0.7035	0.7094
VAG	VAGINA	F48	MALIGNANT SARCOMA OF VAGI	0.6325	0.5775	0.5811
VAG	VAGINA	F49	MALIGNANT SQUAMOUS CELL C	0.5102	0.4409	0.4477

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# Kaplan-Meier Survival Function

Species: Rat

Sex: Male



**Statistical Review and Evaluation  
Stability Review of Zonisamide Capsules**

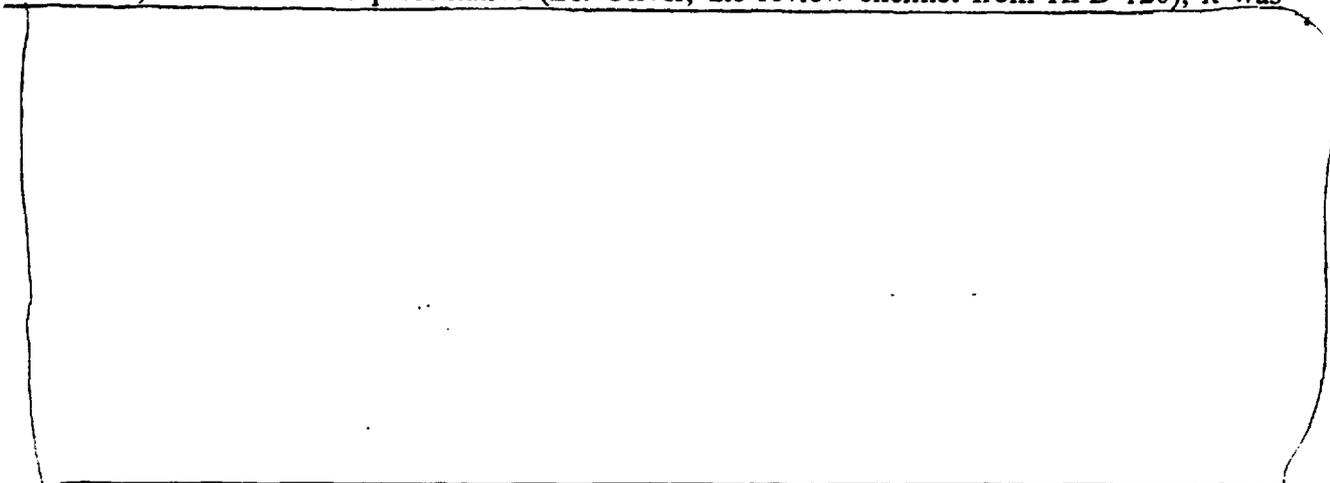
MAY 7 1999

**DATE:****NDA #:** 20-789**DATE CDER RECEIVED:** February 26, 1999**APPLICANT:** Elan Pharmaceuticals**NAME OF DRUG:** Zonegran®, Zonisamide Capsules (100 mg Capsules)**DOCUMENTS REVIEWED:** Vol. 1 (Vol. 1 of 1)**INDICATION:**

Dr. Tom Oliver, Review Chemist from the Division of Neuropharmacological Drug Products (HFD-120) requested the review of the stability of Zonegran (NDA 20-789).

**I. INTRODUCTION**

In a telephone conversation, on February 4, 1999, between the representative of Elan (Luis Johnson) and the FDA representative (Dr. Oliver, the review chemist from HFD-120), it was

**II. DESCRIPTION OF DATA**

As discussed in the previous section, the stability data of Zonegran 100 mg capsules comprises the stability (potency) test results of 9 batches with three different packaging. For the stability

determination these 9 batches were stored at the same storage condition of 25°C/60% RH for 36 months. The 3 packaging varieties are as follows:

Batch	Package
31, 41 and 51	100 CC [redacted] Bottle
39, 49 and 59	950 CC [redacted] Bottle
37, 47 and 57	[redacted] Blister

Further:

- The Batches 31, 37 and 39 are sub-lots of the Batch 694Z03
- The Batches 41, 47 and 49 are sub-lots of the Batch 694Z04
- The Batches 51, 57 and 59 are sub-lots of the Batch 694Z05.

We will refer to sub-lots as “batches” in our discussion as well.

The observed stability (Potency) results are summarized in the following table.

**Table 1**  
Potency Data of the 9 Batches of Zonegran Capsules

Month	Batch 31	Batch 41	Batch 51	Batch 37	Batch 47	Batch 57	Batch 39	Batch 49	Batch 59
0									
0									
0									
3									
3									
6									
6									
9									
9									
12									
12									
18									
18									
24									
24									
36									
36									

As can be seen for each batch three stability determinations was made at origin and two determinations at time points 3, 6, 9, 12, 18, 24.

For the life shelf of Zonegran capsules, the sponsor is claiming the expiry period of 36 month, for all three type of packaging.

### III. STATISTICAL ANALYSIS

For a detail description of statistical analysis for determination of the stability (shelf life) of a drug product the readers may consult Appendix A. However, in summary, for each batch a straight regression line is fitted to stability data (Potency vs. Time) along with its 95% simultaneous confidence bands. Next, the shelf life (**Expiry Period**) is determined as the earliest of the two times at which either the lower 95% band intersects the lower specification limit or the upper 95% confidence band intersects the upper specification limit.

Prior to the regression line fitting, the poolability of the data across the batches will be examined via the conduct of series of tests of hypothesis for the following set of the null and alternative hypotheses at  $\alpha = 0.25$ .

C: *Ho: sep. intercept com. slope, Ha: sep. intercept sep. slope*  
 B: *Ho: com. intercept com. slope, Ha: sep. intercept com. slope*  
 A: *Ho: com. intercept com. slope, Ha: sep. intercept sep. slope.*

Then, depending upon the results of the tests conducted on the set of null and alternative hypotheses A, B and C a decision will be made as to what sort of model should be fitted to the data of all batches. The decision rules are summarized in the following table.

**Table 2**  
Table of Decision Rules

Test Results	Pr(C) < 0.25	Pr(C) ≥ 0.25
Pr(B) < 0.25	<p><b>Model 3</b>  <b>Data Cannot be Pooled</b>  <i>Fit lines with Separate Intercepts and Separate Slopes to Each Batch</i></p>	<p><b>Model 2</b>  <b>Data Cannot be Pooled</b>  <i>Fit lines with Separates Intercept but Common Slope to Each Batch (Parallel Lines)</i></p>
Pr(B) ≥ 0.25	<p><b>Model 3</b>  <b>Data Cannot be Pooled</b>  <i>Fit lines with Separates Intercept and Separate Slopes to Each Batch</i></p>	<p><b>Model 1</b>  <b>Data Should be Pooled</b>  <i>Fit a Single Line to the Pooled Data of All Batches</i></p>

**Comment:** *With our procedure, if the earliest time that either lower 95% CI intersects the lower specification limit or upper 95% CI intersect the upper specification limit is beyond 84 month, then the expiry dating period will be estimated as 84 month.*

### III. SPONSOR'S ANALYSIS AND RESULTS

As was mentioned earlier in the Introduction Section, with respect to the expiry period estimation, the sponsor submitted two sets of analyses. In the first set, the data of three Batches 31, 41 and 51 (100 cc [ ] bottles) along with the data of three Batches 39, 49 and 59 (950 cc bottles) were analyzed simultaneously. In the second set, the data three Batches 37, 47 and 57

Blisters) along with the data of the six batches in the first set were analyzed simultaneously. The sponsor only considered the lower specification limit of 90% potency (%LS) as the limit at which below that the potency is not acceptable. Therefore, only one-sided 95% simultaneous lower confidence interval was computed and the expiry was determined to be the timepoint (in month) at which the lower one-sided 95% CI intersects with the 90% specification limit. The results are presented in the following table.

**Table 3**  
Sponsor's Stability Results of the Estimates of Expiry Period  
Based on One-Sided Lower 95% Confidence Interval

Batches	Analysis of Nine Batches Simultaneously		Analysis of Six Batches Simultaneously	
	Fitted Equation	Expiry Period (Month)	Fitted Equation	Expiry Period (Month)
Batch 31		42		84
Batch 41		84		84
Batch 51		84		84
Batch 39		36		84
Batch 49		84		84
Batch 59		76		84
Batch 37		46		
Batch 47		84		
Batch 57		84		
		Minimum = 36		Minimum = 84

For the cases that the estimate of the expiry dating period is greater than 84 months, the estimated expiry period is reported as 84 months. The results in Table 3 shows that the minimum expiry period is 36 month, for Batch 30 in the set of 9 batches.

**Comment:** There are two issues needed to be addressed:

1. *The FDA Guidelines for the stability review has specified that, for the expiry period estimation, two-sided 95% confidence intervals should be considered. Then, as discussed earlier, the expiry period is estimated as the earliest of the two times at which either the lower 95% band intersects the lower specification limit or the upper 95% confidence band intersects the upper specification limit. However, ICH Guidelines indicates that, for the expiry period estimation, one-sided 95% confidence interval is admissible. For instance, if the elevation, but not the decline, of the potency is acceptable, then construction of lower one-sided confidence interval is admissible. In that case, the estimate for the expiry period is the timepoint at which the one-sided lower 95% confidence interval intersects with the lower specification limit. This reviewer leaves this issue for the review chemist to deal with. In his analysis the choice of two-sided is considered, specifically because the results show some of the fitted lines are sloped upward. The readers may consult Appendices B, C and D.*

2. As was mentioned earlier, the sponsor has conducted two sets of analyses with of the 6 batches are common in the two analyses. The issue is that, as can be seen from Table 3, for the 6 batches that are in both sets of analysis the estimates of expiry period are different from one set to another. The question is that, to resolve the problem of discrepancy the results of which of the two sets should be accepted. A conservative approach is that for each batch select the smaller expiry period of the two columns.

#### IV. SREVIEWER'S ANALYSIS AND RESULTS

The results of this reviewer's analyses in detail are presented in Appendices B, C, D, and E. This reviewer performed the analyses for both the two-sided as well as one-sided 95% confidence intervals, with the specification limits of 90% (lower) and 110% (upper). However, the main analysis is the two-side one and should be the base of the expiry period estimation, particularly, because some of the regression lines are sloped upward (see the Figures in the Appendices B, C and D). Four sets of analyses were performed: Set 1 consists of analysis on the data of Batches 31, 41, and 51, with 100 cc [redacted] packaging, simultaneously; Set 2 consists of analysis on the data of Batches 39, 49, and 59, with 950 cc [redacted] packaging, simultaneously; Set 3 consists of analysis on the data of Batches 37, 47, and 57, with [redacted] Blister packaging, simultaneously; and the analysis on the data of all 9 batches simultaneously.

For all four sets, the results of poolability tests (see Section III and Appendix A) show that the data are not poolable. Therefore, separate regression line should be fitted to the data of each batch. As a conclusion, the estimates of the expiry period for the batches in Set 4 are exactly the same as those estimates in Sets 1, 2 and 3. The readers my consults the results in Appendices B, C, D and E for the comparisons. The results are summarized in the following Table.

**Table 4**  
Fitted regression Lines and the Estimated Expiry Period  
Using Two-Sided and One-Sided 95% Confidence Intervals of Mean Predicted Values

Batch	Fitted Line	Estimated Expiry Period With 2-Sided 95% CI (Month)	Estimated Expiry Period With 1-Sided 95% CI (Month)
Batch 31		46	49
Batch 41		123 (84)†	143 (84)†
Batch 51		80	144 (84)†
Batch 39		38	41
Batch 49		73	144 (84)†
Batch 59		105 (84)†	143 (84)†
Batch 37		61	64
Batch 47		83	144 (84)†
Batch 57		84	144 (84)†
		<b>Minimum Time = 38</b>	<b>Minimum Time = 41</b>

†: The expiry period will be reported as 84 months if the estimate of expiry time is greater than 84 month

Table 4 shows that for the estimation with two-sided 95% confidence interval, the minimum estimated expiry dating period is 38 months. For the estimation with one-sided 95% confidence

interval, the minimum estimated expiry dating period is 41 months, which is different from the sponsor's results presented in Table 3.

## V. CONCLUSION

The sponsor's results are based on the one-side lower limit of 95% confidence interval, whereas this reviewer's results are based on a more conservative analysis, using two-sided 95% confidence interval analysis. At any rate, this reviewer's results supports the sponsor's claim of 36 months shelf life stability (expiry period). Further, the potency of Zonegran capsules will stay within the boundary of 90% to 110% for a period of: minimum of 46 months for the 100 cc [redacted] bottle packaging (Batch 31); minimum of 36 months for the 950 cc [redacted] bottle packaging (Batch 39); and at least 61 months for the [redacted] Blister packaging (Batch 37).

As the last comment, the estimated expiry period of Batches 31, 37 and 39 which are the sub-lots of Batch 694Z03 are shorter than the sub-lot batches in the Batches 694Z04 and 694Z05, correspondingly.

This review consists of 6 pages

[redacted] /S/

Kooros Mahjoob, Ph.D.  
Mathematical Statistician

APPEARS THIS WAY  
ON ORIGINAL

Concur:

[redacted] /S/

Dr. Jin

Dr. Chi

[redacted] /S/

CC:

IND 20-789/Stability Submission  
HFD-120  
HFD-120/Dr. Guzewska  
HFD-120/Dr. Oliver  
HFD-120/Ms. Ware  
HFD-710/Dr. Chi  
HFD-710/Dr. Jin  
HFD-710/Dr. Mahjoob

APPEARS THIS WAY  
ON ORIGINAL

K. Mahjoob: 4-5301: Biometrics 1/Team 1:km/Date of 1st draft 04/02/99.

Statistical Reviewer: Kooros Mahjoob/DB1 (HFD-710)/Ext. 4-5301

Warc  
COMPLETED DEC 21 1999

## Statistical Review and Evaluation

DEC 17 1999

NDA 20-780

Document reviewed: Response to Approvable Letter

Date of submission: December 29, 1998

Drug: Zonisamide

Indication: Partial seizures with and without secondary generalization

Sponsor: Athena Neurosciences

Medical Reviewers: Dr. Greg Burkhart and Dr. Leonard Capcala

### Purpose of this review

This review is intended to supplement the original statistical review of this NDA by Dr. J. Todd Sahlroot dated February 18, 1998. This was prompted by a change in the data sets from two trials since that review. Trials 921-US and 912-EUR had inaccurate assignments of Day 1 of therapy.

This review is only concerned with the efficacy variables from trials 912-US and 912-EUR that are affected by this change in the data. The tables from Dr. Sahlroot's review which are affected by the modification of the data are reproduced in Tables 2,3,6, and 7 of this review with the statistics recalculated from the revised data set. Analysis of safety data, baseline characteristics, and dropouts are not included in this review (see the original review).

## REVIEW AND EVALUATION OF CLINICAL MATERIALS

NDA	20,789
SPONSOR	Elan Pharmaceuticals (formerly Athena Neuroscience)
DRUG	Zonisamide (Zonegran)
INDICATION	Epilepsy
MATERIAL SUBMITTED	Response to approvable letter
CORRESPONDENCE DATE	12/29/98
RECEIPT DATE	12/30/98
DATE REVIEWED	5/19/99

### Introduction

An approvable letter, dated 19 March 1998, was sent to the sponsor for its NDA to support the new molecular entity zonisamide (ZNS) as an adjunctive agent to treat partial seizure disorders, with and without secondary generalization. The company forwarded its response on 29 December 1998. Zonisamide has been available in Japan since 1989, and Korea since 1992 (no data were provided from the Korean experience with the drug); a detailed administrative history can be found in earlier reviews of the NDA by Drs. James Sherry (efficacy) and Greg Burkhart (safety).

With respect to the NDA, the cutoff date for reporting deaths at the time of FDA submission was 31 October 1996, with the cutoff date for serious AEs 4 months earlier and the cutoff date for the project database 9 months earlier (reference: Greg Burkhart's safety review). The Four-Month Safety Update, submitted on 19 July 1997, included information through 28 February 1997 and reports of deaths and other serious AEs through 31 March 1997. The current database cutoff date for the present submission is 30 April 1998; however, the response also includes all reports of deaths from 1 April 1997-15 October 1998.

I want to thank Dr. Michael Sevka, the original safety reviewer, for assistance with the current review. Certain sections were written jointly with reviewers from the respective divisions: dose response (efficacy) with Dr. Kun Jin (Biostatistics); Pharm/Tox with Dr. Edward Fisher (Pharmacology); and Biopharmaceutics with Dr. Iftekar Mahmood (Biopharm).

NOTE: my review first discusses drug exposure, since the sponsor has now re-assessed the entire NDA and provides completely new numbers. The sections that follow conform to the order of topics as presented in the approvable letter.

### Exposure

US and Europe: The original NDA database had 1572 unique patients, having – by the sponsor's estimate – 1000 patient-years of exposure. This number includes both the primary and the supplementary databases. The original NDA database had 981 patients. The updated primary database has 993 patients, for a total of 1167.6 patient-years, *through* the Four-Month Safety Update; in other words, this number includes 12 patients who had not completed the clinical trials by the NDA cutoff date and so were not included in the original NDA primary database. (This point has been clarified by a 5/19/99 fax from Louise Johnson and Octavia Norris.)

The database update was done by STATPROBE – the new CRO hired by Elan to review both the safety and efficacy data – which “corrected the number of patients exposed to zonisamide at the time of the NDA, and corrected a programming error that caused double-counting of certain dosing records in the NDA tables” [v 6, p 3]. Elan reassessed the available data from the Japanese experience.

Japanese database: Approval cohort: 1008 patients, 717.8 patient-years. The postmarketing safety experience derives from 3 sources, described by Greg Burkhart in his NDA safety review:

Source	Duration	Patients	Safety Reports
general survey	4/89-5/95	4028 (3604.4 patient-years)	3906
prospective survey	9/89-12/94	1793	1522
spontaneous reports	3/89-1/98	Unknown*	202

\* "In the absence of data, we have tried to estimate the ranges of unique patients. . . . We believe that the minimum feasible number of patients exposed to zonisamide in Japan would be 257K, since 257K received a full year of zonisamide therapy in 1997 alone [IMS data]. The maximum feasible number of patients exposed to zonisamide is estimated to be 1M, since this represents the average number of patients who received a full year of treatment" (v 3, pp 10-11). See the attached IMS data, showing [redacted] scripts over [redacted] years, yielding approximately [redacted] patient-years. The denominator used to calculate incidence is 257K.

All frequencies and incidences presented in this review have been quoted from the sponsor's submission.

Data quality: Narrative summaries for both Japanese and American/European adverse events are generally very limited in clinical detail (serious hematological, serious hepatic, and neuropsychiatric disorders, as well as renal function, and serious rash, as requested in the approvable letter).

For the Japanese data, baseline laboratory values are seldom available. Actual case report forms were submitted for 3 deaths and 1 discontinuation in the US and European trials; there were no case report forms for the entire Japanese database.

## Labeling

### 1. INDICATIONS AND USAGE

**AGENCY REQUEST:** Provide evidence to support the labeling claim for secondarily generalized seizures, in addition to partial seizures in adults with epilepsy, as claimed in the sponsor's version of the ZNS label.

This was not done. Because of the absence of data ("only one of the pivotal studies collected the appropriate data" [v 5, p 89]), the sponsor has dropped this indication.

### 2. WARNINGS

(a) General Statement: The sponsor has included the general statement on sulfonamides.

(b) Serious Rash: The NDA (US/European) database for all rash was reviewed and re-evaluated by both STATPROBE and its independent consultant, Charles Ellis MD (Dermatology, U. Michigan).

For the purposes of its review, the sponsor defined serious rash as "a rash that led to either discontinuation of treatment or hospitalization, or was diagnosed as Stevens-Johnson" (v 2, p 3).  
NOTE: AEs in the placebo population were not discussed by the sponsor.

Additionally, the sponsor did not (1) discuss dose response or time to rash occurrence, or (2) provide full, clear descriptions, including follow-up, for each case of serious rash. These were requested in the approvable letter.

**US/Europe database:**

Of 66 cases identified as serious rash in the original NDA, 61 were reviewed by Ellis and 5 by Elan. One patient, classified as on drug in Ellis's review, was subsequently found to have been on placebo and therefore excluded by the sponsor from the re-analysis. However, 6 treats whom the sponsor claims had dropped out for reasons other than rash *but still had serious rash accompanying the AE cited as responsible for the discontinuation*, were not considered by the sponsor among discontinuations due to rash (1 of the patients was on placebo and not included in Table 3). Table 3 below is confusing but seems to distinguish among (1) serious rashes leading to hospitalization, (2) nonserious rashes which led to hospitalization (but presumably reclassified as nonserious in the *posthoc* analysis by the sponsor and/or Ellis), (3) discontinuation due to rash, and (4) Stevens-Johnson.

**Table 3: Serious Rash Events and Discontinuations**

Event	Placebo- Controlled Studies	Open-Label Studies	Total
Serious Rash Leading to Hospitalization	1	0	1
Non-Serious Rash, but Serious Adverse Event due to Hospitalization	1	1	2
Discontinuations due to rash	5	9	14
<b>TOTAL</b>	<b>7</b>	<b>10</b>	<b>17</b>

The reclassification of all rash in the new review identified serious rashes occurring in 0.3% (3/993) patients, for an incidence of 2.6 events per 1000 person-years; if discontinuations are added (n=17), the incidence becomes 14.6 events per 1000 patient-years:

**Table 4: Updated Summary of Review of US and European Data**

Type of Event	Total Number of Events	Placebo- Controlled Studies	Open-Label Studies
Stevens-Johnson Syndrome, Erythema multiforme or Erythroderma	0	0	0
Angioedema	0	0	0
Hospitalizations	3	2	1
Discontinuations due to rash, no hospitalizations	14	5	9
Non-Serious Events	48	13	3
<b>Total</b>	<b>65</b>	<b>20</b>	<b>45</b>
Events Related to Zonisamide	29	9	20
Events not Related to Zonisamide	36	11	25

There appear to be two problems with the reclassification. First, rash cannot be dismissed with certainty as a major contributing factor driving the discontinuation. Second, at least one

patient (#921/5652/1483), who was excluded from the list of serious rash, was reported to have had soft palate lesions along with rashes over her chest and upper extremities and a skin biopsy consistent with "dermal hypersensitivity reaction," and so may actually have had Stevens-Johnson; the rash reportedly persisted for 6 months after ZNS discontinuation.

*Japanese database:*

**APPROVAL COHORT** The sponsor reports the frequency of serious rash as occurring in 0.1% (1/1008) patients, for an incidence of 1.4 events per 1000 patient-years; but when discontinuations are included, the frequency becomes 2% (20/1008), and incidence 27.9 events per 1000 patient-years. It is difficult to understand how, in Table 5 below, an *exfoliative* rash could be classified as only discontinued and not also as serious; this difference is not explained by the sponsor.

Diagnosis	Frequency	
	serious	discontinued
Total	1	19
Drug eruption		12
Pruritic rash		5
Erythematous rash	1	1
Exfoliation		1

**POSTMARKETING**

General survey: there were 2 serious rashes (exanthem in an 18-year-old female and severe erythema multiforme in an 11-year-old female) and 3 nonserious leading to discontinuation (1 muco-cutaneo-ocular syndrome, 1 exanthem, 1 urticaria). The frequency was 0.05% (2/3906) patients, and incidence 0.6 events per 1000 patient-years; when discontinuations are added, the incidence becomes 1.4 events per 1000 patient-years (no frequency was provided by the sponsor).

Prospective survey: There were no patients with serious rash or rash events leading to discontinuation.

Spontaneous reports: There were 4 deaths, 3 from Stevens-Johnson and 1 from TEN; patient ages ranged from 37-69, and AEs leading to death started after 9-47 days:

Diagnosis	Frequency	
	serious	discontinued
Total	69	13
Stevens Johnson syndrome	41	2
Drug eruption	7	3
Toxic epidermal necrolysis	5	1
Lyell syndrome	4	
Muco-cutaneo-ocular syndrome	3	1
Erythema exudativum multiforme	3	
Exanthema	4	1
Erythematous rash	1	1
Hypersensitivity	1	
Erythroderma		2
Pruritic rash		1

It is difficult to understand how the sponsor, in Table 10 below, distinguished between serious and discontinued Stevens-Johnson and TEN when all the narratives supplied by the sponsor indicate that ZNS was stopped.

Since the Response, three additional cases of Stevens-Johnson have come to attention (Japanese spontaneous postmarketing reports):

(1) Stevens-Johnson: rash accompanied by fever, elevated LFTs, jaundice, anemia, exfoliation and edema ("AED hypersensitivity syndrome," which has a 20% mortality in the presence of toxic hepatitis), leading to *death*;

(2) Stevens-Johnson: 67-year-old male who developed generalized erythroderma, with plantar and palmar hyperkeratosis; the patient recovered (published as Araki K, et al, "A Case of Erythroderma Due to Zonisamide," *Skin Research* 39 [1997]:260-3).

(3) 18-year-old female (Mfr #ZONI-0319990078) who, 1 month after beginning ZNS therapy, developed whole body rash and corneal lesions, associated with hepatic dysfunction and jaundice, as well as coagulopathy requiring infusions of FFP. Zonisamide was discontinued, and the patient was treated with steroids, clemastine and other antiallergenics, and antibiotics. PMH was remarkable for a "drug eruption" with CBZ (ZNS was started 9 months after CBZ was discontinued) and "agranulocytosis" on PHT (ZNS was started 6 months after CBZ was discontinued). The investigator definitively attributed the Stevens-Johnson to ZNS; however, the sponsor ascribed the disorder to ZNS and phenobarbital, which the sponsor claims the patient was on in the attached summary (without providing dates of treatment), though there is no record of concomitant phenobarbital in the MedWatch report. Follow-up is unknown.

### (c) Serious Hematologic

Elan searched the database for cases of either WBC  $<2000 \text{ mm}^3$  or ANC  $< 500 \text{ mm}^3$ , but defined agranulocytosis as the combination of the two criteria.

With respect to aplastic anemia, the sponsor writes: "As bone marrow biopsies/aspirations were not systematically performed nor collected, the case definition from the International Aplastic Anemia Study Group based on laboratory criteria cannot be applied." Consequently, the search strategy was based on "(a) AEs recorded that indicate aplastic anemia, pancytopenia, thrombocytopenia, anemia, anisocytosis," "(b) "any patients with clinical laboratory results of platelet count  $<20,000 \text{ mm}^3$ ." It is not clear whether either or both criteria were used to determine cases of aplastic anemia.

#### *US/Europe database:*

Events reviewed by Elan. Of 4 cases identified as leukopenia or agranulocytosis, 1 was classified as possibly, 1 probably, and 2 unrelated to zonisamide (and 1 of the unrelated cases was "probably a transcription error"). SAE occurred in 0.4% (4/993) patients, for an incidence of 3.4 events per 1000 person-years (no frequency was given); when discontinuations are included (n=7), the incidence becomes 6 events per 1000 patient-years (no frequency was given).

According to the sponsor, "There were no reports or laboratory findings indicating aplastic anemia" (v 2, p 119). Following are the lowest counts, all in different patients:

- (a) WBC 2.1 (ANC 420 but no other available hematologic indices; a similar case in another patient with more complete indices: WBC 2.2, ANC 902, Hgb 10.6);
- (b) ANC 231;
- (c) Hgb as low as 9.5 (but no other hematologic indices available); and
- (d) platelets as low as 56K (all values in different patients).

#### *Japanese database:*

From the sponsor's submission, it is not clear that the same definitions for aplastic anemia and agranulocytosis were applied to the Japanese databases.

**APPROVAL COHORT** Elan's review of the database identified 10 patients with "hematological abnormalities": leukopenia (9 reports, lowest WBC 1500 mm<sup>3</sup>), moderate thrombocytopenia (2 reports, but only 1 patient's platelet count was given -- 6.5 x 10<sup>4</sup>), iron-deficiency anemia (1 report but no values given). WBC counts generally dropped after 1 month of treatment, then recovered when zonisamide was withdrawn; patients were usually on other AEDs concurrently, including CBZ and PHT. There were no reports of deaths.

The frequency of serious hematologic AEs was 0.4% (4/909) patients (labs were not available for the entire cohort; see note below), for an incidence of 6.2 events per 1000 patient-years (no frequency given); when discontinuations are added, the frequency becomes 1.1%, and incidence 15.5 events per 1000 patient-years. (NOTE the sponsor's claim: "To account for those patients for whom no laboratory data are available, the decision was made by Athena to adjust the value for estimated person-years of exposure for laboratory parameters by multiplying the median exposure time for the population times 100 patients [approximate difference between 1008 and 909] and subtracting the result from the overall person-years of exposure [718 person-years]. The median exposure time falls between 181-360 days with the midpoint of 2370 days. Therefore 74 person-years [270 x 100 / 365 = 74] were subtracted 718 person years to yield 644 person-years" [v 3, p 99].)

### POSTMARKETING

**General survey:** 4 cases of leukopenia (WBC  $\leq$  2000 mm<sup>3</sup>) were identified, yielding a frequency of 0.1% (4/4028) patients, and incidence of 1 event per 1000 patient-years. The greatest drop in WBC count was from 8500 mm<sup>3</sup> predose to 1100 mm<sup>3</sup> postdose (Hgb and platelet count remained relatively constant). One patient (75-year-old female) had a WBC drop from 5900 to 1800 with an improvement to 3200 over a 4-week period on treatment, but simultaneously saw a drop in platelets from 60,000 to 10,000 and Hgb from 14.1 to 6.7; during this month, her BUN rose from 14 to 73, and creatinine from 0.7 to 1.2.

**Prospective survey:** According to the sponsor, "There were no hematologic events for patients in this cohort which were determined to be serious or which led to discontinuation." However, 1 case was identified of 3-year-old male whose WBC dropped from 9800 mm<sup>3</sup> at baseline to 1000 after 3 months; his platelets rose from 190,000 to 300,000, and Hgb dropped slightly from 13 to 12.

#### Spontaneous reports:

Table 29: Patients with Potentially Serious Hemic/ Lymphatic Events and Discontinuations in Spontaneous Reports Diagnosis

	Frequency	
	serious	discontinued
Total	5	22
Leukopenia	1	5
Neutropenia	1	4
Pancytopenia/Marrow depression		4
Thrombocytopenia		3
Agranulocytosis	1	3
Anemia - hemolytic	1	
Aplasia pure red cell	1	
Anemia - aplastic		2
Lymphadenosis		1

Included in these cases are:

- (a) 8-year-old female, also on CBZ, etotoin, and acetazolamide, who developed hemolytic anemia after 1 month on the drug (a bone marrow biopsy was reportedly unremarkable), requiring RBC transfusions;
- (b) 15-year-old female, with rash, whose WBC fell to 500 cell/mm<sup>3</sup> after 5 weeks and normalized after drug discontinuation;
- (c) 44-year-old male developed fever, exanthem, swollen cervical nodes 8 days after starting ZNS at 400 mg/d (concurrent medication: VPA); WBC dropped to 800/mm<sup>3</sup> (no baseline value), with no neutrophils; ZNS was discontinued and he was treated with "a G-CSF agent and antibiotics . . . with normalization of hematological and renal symptoms over the course of a week";
- (d) one death due to leukopenia and thrombocytopenia: 71-year-old male, with malignant astrocytoma, developed leukopenia and thrombocytopenia 9 days after starting ZNS 300 mg/d; concurrent medications: flomoccef, ticlopidine, famotidine, cimetidine, dexamethasone, diltiazem, nicolandil, and isosorbide dinitrate. No other information was provided in the narrative (v 3, p 109).

### 3. PRECAUTIONS

#### (a) Kidney Stones

*US/Europe database:*

NDA events were independently reviewed by Eric Young MD (Nephrology, U Michigan). Elan calculated the frequency of renal calculi at 1.2% (12/993) patients, with an incidence of 10.7 events per 1000 patient-years.

On average, renal stones occurred 19 months after study start. The crude incidence of symptomatic renal calculi in the general population has been estimated at 0.7-2.1 per 1000 person years (from Young's report). Based on this incidence range, Dr. Young estimated the crude relative risk of symptomatic kidney stones in patients treated with zonisamide – compared to the general population – to be 5-15, and the crude relative risk of symptomatic confirmed kidney stones at 3-10 (v 2, p 192), or 18 stones per 1000 patient-years (v 2, p 217). According to Young, the risk increased with higher doses, ranging from 200-800 mg/d. The analyzed stones for 6 patients were composed of calcium or urate salts; 1 stone, "largely composed of calcium," was found to have a "very tiny portion" of ZNS (v 2, pp 216). "Urinary calcium excretion increased by 38 mg/d for ZNS-treated patients who developed new stones. Also, ZNS is a weak carbonic anhydrase inhibitor, and this class of drugs may be associated with kidney stones" (v 2, p 218).

*Japanese database:*

**APPROVAL COHORT** "No reports of renal stones or of symptoms associated with renal stones."

#### **POSTMARKETING**

**General survey:** No reports.

**Prospective survey:** No reports.

**Spontaneous reports:** There were 2 reports of renal calculi, one associated with renal failure:

- (a) 33-year-old male (on ZNS 100-400 mg/d x 18 months; concurrent medication: VPA) developed urinary tract stone 3 months after ZNS was increased to 400 mg/d and was treated with lithotripsy;

(b) 59-year-old male, on ZNS 200 mg/d x 6.5 years (concurrent medications: PHT, phenobarbital, and caffeine), a ureteral stone and was treated with transcutaneous vesicotomy and lithotripsy.

#### 4. DRUG/LABORATORY TEST INTERACTIONS

##### (a) Renal Function

###### *US/Europe database:*

The sponsor first discusses the results of the Jaffe reaction to test possible interference of ZNS with plasma creatinine levels. A statistically significant increase was seen in creatinine levels at the lowest ZNS concentration (5 ug/mL), compared to controls, but there were no statistically significant differences from control creatinine levels in the 25, 50, or 100 ug/mL samples. (The sponsor cannot explain the reason of interference at a low concentration but not at high concentrations.) The sponsor concludes that "it is not likely that ZNS interferes with the Jaffe reaction for creatinine determination" (v 2, p 238).

However, the controlled clinical trials demonstrated a statistically significant increase in both BUN and creatinine. The NDA events were independently reviewed by Eric Young MD (Nephrology, U Michigan). Renal dysfunction was defined as  $\geq 30\%$  increase in serum creatinine or BUN. The controlled studies were analyzed separately:

**912-US:** Young's initial analysis was revised when STATPROBE was able to provide new patient data; his initial analysis failed to reveal a statistically significant change in BUN or creatinine during the clinical trial. However, the revised analysis showed that "Follow-up (off treatment) creatinine exceeded the baseline creatinine by a mean of 3.44% and median of 0% after zonisamide treatment and by a mean of 8.98% and a median of 0% after placebo treatment. Surprisingly, the difference was significant for ZNS ( $p=0.046$ ) but not placebo ( $p=0.7168$ )." No between-treatment comparison was made.

With regard to BUN in study 912US, the last on-study value exceeded the baseline by a mean of 10.13% and median of 7.69% for ZNS, and mean of 1.52% and median of 0% for placebo. The change from baseline approached significance for ZNS ( $p=0.0773$ ) but was not significant for placebo ( $p=0.7416$ ). Comparison between the two treatments was not significant ( $p=0.1084$ ).

**922:** Follow-up (off treatment) creatinine exceeded the baseline creatinine by a mean of 4.98% and median of 4.17% after ZNS treatment and by a mean of 3.5% and a median of 0% after placebo treatment; the difference was significant for ZNS ( $p=0.0172$ ) but not placebo ( $p=0.0839$ ).

"The results confirm the incidence of renal dysfunction as defined by an increase of the EUN of at least 30% (compared to baseline) during the treatment phase. . . . [T]he incidence of renal dysfunction by this definition was 23.73% for ZNS compared to 12.94% for placebo . . . ( $p=0.055$ )" (v 2, p 309).

"The bulk of the evidence still indicated that the serum creatinine returns to the baseline value after ZNS is stopped. The data from studies 920 and 924 show full recovery. The data from the controlled studies (912-US, 912-Europe, and 922) show a small elevation of the follow-up serum creatinine over baseline levels following both ZNS and placebo treatments with variable significance findings. The magnitude of the elevation is smaller (mean 3-11%) than the expected laboratory variation in the measurement of serum creatinine (approximately 10-20%). Changes of the observed magnitude have no clinical significance. . . .

"In general, the data indicate a small potential change in BUN during ZNS treatment. . . . A significant difference between baseline and last on-study measurement was only seen in the new analysis for study 922. . . .

"In view of the variable changes in creatinine and BUN, it might be reasonable to provide a

mild cautionary warning in the drug package insert. Additional assessment of the influence of ZNS on renal function would also be worthwhile during the conduct of postmarketing studies" (v 2, pp 309-10).

The findings of the independent consultant reinforce the concerns expressed by Dr. Iftekhar Mahmood (OCPB) in his review of the NDA.

*Japanese database:*

**APPROVAL COHORT** The sponsor did not provide a frequency or incidence for renal events. There were three renal events leading to discontinuation:

- (1) 44 y/o female (on concomitant PHT, CBZ, VPA), experienced "severe sleepiness" 1 month after starting ZNS 300 mg/d and "severe retardation of mental activity" at 3 months on 400 mg/d. At 5 months on 500 mg/d, she had "severe incontinence," but renal function tests were reportedly normal. All symptoms resolved after ZNS discontinuation.
- (2) 34 y/o male (on concomitant PHT, VPA, primidone) had elevated LFTs (AST 41, GGT 133) one week after starting ZNS, and "mild fretfulness," double vision, vomiting, "feeling of residual urine," and pollakiuria developed 1 week later at a dose of 200 mg/d. The symptoms resolved after ZNS discontinuation. About 10 days later, he had a fever, WBC 2600, and platelets 65,000. Three days later, WBC was 2800. No further information.
- (3) 14 y/o female (on PHT, CBZ, clonazepam) developed "mild nocturnal enuresis" about 3 weeks after starting ZNS 75 mg/d; the symptoms resolved after ZNS discontinuation.

**POSTMARKETING**

General survey: The sponsor did not provide a frequency or incidence for renal events. There was 1 case of serious acute renal failure: 44 y/o female developed "moderate inertia," "slowing of mental activity," and anorexia ("considered related to dementia") about 1 month after starting ZNS 200 mg/d for epilepsy; the dose was then decreased to 100 mg/d. Several days later, she developed proteinuria, hemoglobinuria, and sever renal failure (no values given). About 2 weeks later, "ZNS was discontinued with remission of renal symptoms. However, hydrocephalus developed as a complication." "The relationship of this event to ZNS is uncertain."

Three renal events, classified as "nonserious" by Elan, led to discontinuation: 44 y/o male who developed "mild pollakiuria" 14 days after starting ZNS 200 mg/d; 68 y/o male (on inderoxazine, lisuride, bifemelane) had "severe renal function disorder" 100 days after starting ZNS 200 mg/d; and 4 y/o female developed "moderate pollakiuria" and urinary and fecal incontinence 112 days on ZNS 200 mg/d. In all 3 cases the symptoms resolved or abated after ZNS discontinuation. No further information is provided.

Finally, four patients are identified with abnormal BUN and/or Cr values, but no further information is given:

Patient ID	Age/ Gender	Abnormal Parameter	Laboratory Data			
2603	75/F	BUN	07/15/89	04/20/90	05/01/90	
			<i>predosing</i>	<i>dose</i>	<i>dosed</i>	
		WBC				
		Platelet	14.0	25.0	73.0	
		RBC	0.7	0.6	1.2	
		HB	5,900	1,800	3,200	
		HCT	60	60	10	
			RBO	4.1	2.8	2.1
			HB	14.1	9.3	6.7
	HCT	43.0	28.0	20.0		

431	66/M	S-Creat		02/05/90	04/02/90		
		BUN	Zonisamide	predosing	dosed		
			S-Creat	1.1	2.2		
			BUN	9.0	45.0		
865	44/F	S-Creat	02/26/90	03/26/90	04/09/90	07/25/90	
		BUN	Zonisamide	pre dosing	dosed	dosed	follow-up
			S-Creat	0.6	3.7	4.6	1.4
			BUN	7.0	49.0	81.0	20.0
2515	72/M	S-Creat		05/28/90	10/11/90		
		BUN	Zonisamide	predosing	dose		
			S-Creat	1.8	1.7		
			BUN	43.0	57.0		

Prospective survey: There were 2 cases of hematuria: 5 y/o male with "mild hematuria" and irritability after 760 days on ZNS 120 mg/d, discontinued ZNS with symptom abatement; and 40 y/o male (with h/o ureterolithiasis) developed abdominal pain and moderate hematuria after 20 days on ZNS 100 mg/d, with negative pyelography, and continued ZNS with resolution of symptoms.

Spontaneous reports: There were 5 serious events, of which 2 were related to calculi (one also with renal failure) and 3 with renal failure:

- (1) 4 y/o male (PMH for nonketotic glycinuria characterized by cerebral palsy, MR, and epilepsy) developed severe renal failure with oliguria and nephrogenic edema after 42 days on ZNS 50 mg/d (concomitant meds: diazepam, PB, Bactrim); ZNS was discontinued (serum concentration: 7.8 ug/ml). According to the narrative, his BUN had risen from 4 to 43, and Cr from 0.3 to 2.6, three months prior to ZNS initiation. Symptoms abated over about 10 days with general treatment, though beta-2-microglobulin remained high.
- (2) 27 y/o male had elevated BUN (16), Cr (2.5), and CPK (1045) after 471 days on ZNS 250-300 mg/d. ZNS was discontinued, but his BUN rose further to 31, and Cr to 7.1. Values normalized over the next 10 days. Concomitant meds: PHT, VPA.
- (3) 9 y/o male, with epilepsy, had cloudy urine after 4 days on ZNS 240 mg/d; macroscopic hematuria was noted the next day. About 10 days later, the urine was strongly positive for phosphate, microscopic hematuria, and hemoglobinuria; the patient had left flank pain. U/S revealed left hydronephrosis without calcification. Symptoms reportedly improved over the next few days, but he had not fully recovered. ZNS was continued; at the time of report, he had been on drug for 58 days. Concomitant meds: PHT, VPA, nitrazepam, acetazolamide.
- (4) 33 y/o male, with epilepsy, was diagnosed with a left urinary tract stone 3 months after ZNS was increased to 400 mg/d (he had been on ZNS for a total of 571 days, 100-400 mg/d), and treated with lithotripsy. About 2 weeks later, he was diagnosed with a left urinary tract stone, with anuria and increased BUN/creatinine, and again treated with lithotripsy. ZNS was not discontinued; concomitant med: VPA.
- (5) 59 y/o male, with epilepsy, was diagnosed with renal calculus after about 6.5 years on ZNS 200 mg/d and was treated with transcutaneous vesicotomy and urethral lithectomy. ZNS was continued; concomitant meds: PHT, PB, caffeine.

There were 4 additional reports classified as nonserious by the sponsor: 51 y/o female (on VPA, PHT, cefazolin, cefamandole, and IV prep for "hepatic insufficiency") discontinued ZNS after developing "severe tubular renal acidosis" on 400 mg/d x 5 days (the sponsor claims a "possible link" to cefamandole); 49 y/o male discontinued ZNS (on nifedipine, nitrazepam, bifemelane, eperisone, diclofenac, rebarnipide, senna, aniracetam, chlorpromazine, promethazine) after developing "moderate renal function disorder" on 200 mg/d x 16 days; 18 y/o female discontinued ZNS because of "mild oliguria" after 63 days on 200 mg/d; 50 y/o female who

discontinued ZNS due to "moderate renal function disorder" after 34 days on 200 mg/d. In all cases, reportedly, the patient recovered or the symptoms abated.

Since the Rēponse, there has been a case of acute interstitial nephritis: 55-year-old male who was resuscitated following cardiopulmonary arrest (after an attempted suicide) and status epilepticus. 8 days later, he developed generalized redness; PHT and cefazolin were discontinued; there was with a rise in BUN to 117 and creatinine to 6.3, necessitating dialysis x 11 days. Three weeks after steroid therapy, creatinine was normal at 0.8 mg/dl.

## 5. ADVERSE EVENTS

The sponsor did not draft three separate subsections (most common ADRs, most common ADRs associated with discontinuations, controlled trial table) for the 3 different controlled trials. See the attached Tables 5-9, described below under "Safety Update."

## 6. ANIMAL TOXICOLOGY

This section was written with Dr. Edward Fisher (Pharm/Tox).

Two Pharm/Tox issues are outstanding. One involves the inclusion of human postmarketing data in the pregnancy label. Ordinarily, only robust human data are included in the pregnancy section of the label. The sponsor has, however, placed sporadic postmarketing reports, most of them retrospective, which would likely not meet current criteria for inclusion. The sponsor also lists only 22 pregnancies, but there are 36 cases in the present submission.

The second involves the possible need for juvenile animal studies to support a pediatric indication. Postmarketing reports from Japan show that children may be uniquely sensitive to the effect of ZNS; please see the sections below dealing with pediatrics and additional postmarketing issues (oligohydrosis). We feel, therefore, that additional preclinical issues should be satisfied prior to granting approval. If the sponsor chooses to include patients younger than 12 years of age, juvenile animals studies will be needed. Since there are no standard protocols in this area, the sponsor should design study(ies) addressing drug effects in animals of an age range analogous to that of the proposed patient population.

## Safety Issues

### 1. Serious Hepatic

The NDA (US/European) and Japanese databases for hepatic events were reviewed and re-evaluated by STATPROBE. For the purposes of its review, the sponsor defined search criteria as any of the following: SGOT or SGPT >3x ULN, if the baseline is normal; SGOT or SGPT >2x baseline, if the baseline is abnormal; or bili >2.5; or such key words as jaundice, dark urine, hyperammonemia, encephalopathy, ascites, asterixis, and right upper quadrant tenderness. But only those cases with LFTs "8-10x ULN were considered clinically relevant" (v 2, p 320), and values  $\geq 10x$  the upper limit of normal were deemed "serious." Note should be made that sponsor did not review hepatic AEs in the placebo population. Furthermore, the sponsor did not (1) discuss dose response or time to hepatic dysfunction, or (2) provide full, clear descriptions, including follow-up, for each case of serious hepatic AE. These were requested in the approvable letter.

#### *US/Europe database:*

According to the sponsor, 42 patients in controlled and uncontrolled trials (but only 38 are tabulated – 22 from controlled-trial, and 16 from open-label, cases) met the search criteria for "potentially serious AEs" (presumably by search criteria), but only 1 open-label case was identified

as exhibiting LFT elevations that were 8-10x ULN: transaminases were elevated (SGOT 575, SGPT 76, normal bili) 25 days after ZNS was discontinued (the patient had previously been on ZNS for 563 days and was taking CBZ and PHT when ZNS was stopped).

There were 31 cases of "confirmed hepatic events... probably related to ZNS" identified by the sponsor in this submission from controlled trials, among them 4 were on placebo, 2 had LFT elevations only at baseline and 1 on the first day of ZNS administration [100 mg], 1 had a liver cyst and no lab abnormalities, and 1 was encephalopathic due to toxic concentrations of other AEDs). With respect to the other 22 controlled-trial cases, all were also on such concomitant AEDs as CBZ, PHT, VPA, and PB/primidone in addition to ZNS (15 were on a combination of two or three of the AEDs), and several had only an isolated LFT elevation (highest value: ALT 152) while other LFT values remained normal. In a few patients, a single bilirubin may have been high (>7), but the rest of the LFT profile was normal. The sponsor classified all of these elevations as nonserious, and similarly, with 16 open-label cases classified as "confirmed hepatic cases" and either "probably related to ZNS" (4 cases) or "unrelated to ZNS" (12 cases). Two of the cases had LFT elevations at baseline only; 1 had elevated LFTs 25 days after ZNS discontinuation; all but one were also on such concomitant AEDs as CBZ, PHT, VPA, and PB/primidone in addition to ZNS (11 were on a combination of two or three of the AEDs); and several had only an isolated LFT elevation while other LFT values were normal.

There were no deaths attributed to hepatic dysfunction.

### *Japanese database:*

**APPROVAL COHORT** The frequency of serious hepatic events was 0.1% (1/1008) patients, for an incidence of 1 event per 718 patient-years; when discontinuations are added, the frequency becomes 0.9% (9/1008), and incidence 0.13 events per 1000 patient-years.

The one case that the sponsor identified as serious "due to the need for hospitalization" involved a 20-year-old female (also on PHT and CBZ) with baseline SGOT 32/SGPT 39 that increased after 3 months on drug to 604 and 1084, respectively; urobilinogen, bilirubin, and protein were noted in urine; she was hospitalized. She was also noted to have severe confusion, anorexia, and malaise. One month after discontinuation, SGOT (23) and SGPT (40) returned to normal, but GGT remained high (152).

There were 10 reports of "nonserious hepatic events leading to discontinuation": 3 cases have no data and, in the other cases, LFT values are less than 2-3 times baseline values (the sponsor has not provided normal ranges); the most significant elevations are in children <3 years (e.g., 3 y/o male, weight 3 kg, also on PHT, CBZ, and VPA, whose AST 41 increased to 79, and ALT 55 to 137, after 3.5 months on ZNS [3 mg/d]). Because of the lack of information, it is difficult to evaluate most of the reports.

### **POSTMARKETING**

**General Survey:** The frequency of serious hepatic events was calculated at 0.13% (5/4028), and the incidence at 1.4 events per 1000 patient-years.

There were 2 discontinuations due to elevated LFTs (both considered serious by the original investigator but nonserious in Elan's review: 1 case had no information; in the second case, baseline AST of 18 rose to 70, and ALT 30 to 215, in a 39 y/o male after 1 week on ZNS [300 mg/d]), and returned to baseline 3 weeks after discontinuation).

Three cases had LFT elevations 8-10x ULN, but no further information than the following was provided:

Table 16: General Survey Patients with Abnormal Hepatic Laboratory Values							
Patient ID	Age/ Gender	Abnormal Parameter	Laboratory Data				
2052	41/M	GPT	09/04/89	09/21/89	10/10/89	10/31/89	
		GOT	<i>Zonisamide pre dosing</i>	<i>dosed</i>	<i>dosed</i>	<i>follow-up</i>	
		GPT	42.0	529.0	127.0	26.0	
		GOT	33.0	1,084.0	50.0	22.0	
		ALP	106.0	146.0	160.0	114.0	
3737	69/M	GPT	07/29/92	08/26/92	09/09/92	10/21/92	
		GOT	<i>Zonisamide pre dosing</i>	<i>dosed</i>	<i>dosed</i>	<i>follow-up</i>	
		ALP	GPT	14.0	236.0	50.0	27.0
		GOT	13.0	107.0	22.0	17.0	
		ALP	225.0	628.0	518.0	402.0	
3779= 93040203	47/F	GPT	12/16/92	02/26/93		03/25/93	
		GOT	<i>Zonisamide pre dosing</i>	<i>dosed</i>		<i>follow-up</i>	
		ALP	GPT	14.0	638.0		31.0
		GOT	20.0	167.0		25.0	
		ALP	64.0	425.0		120.0	

Prospective survey: No events or abnormal labs were reported.

Spontaneous reports: Following were serious hepatic events (my summaries based on limited data provided by the sponsor):

- (1) 45 y/o female, with postoperative convulsions (*presumably* following surgery for meningioma resection), developed generalized rash and itching 1 month after starting ZNS (100 mg/d), at which point "ZNS was discontinued and the patient was maintained on VPA" (the narrative does not make clear whether she had been on both AEDs concurrently or that VPA replaced ZNS). "Several days later," she was diagnosed with "toxicoderma" and treated with steroids with "gradual disappearance of the rash." She was "then" hospitalized for increased seizures; found to have hepatic dysfunction (no lab values are given), anorexia, and jaundice; and treated with glycyrrhizin, liver extract, vit C, glutathione, and steroids. VPA was stopped. She developed fever and abdominal swelling; AST, ALT, and alk phos decreased but bilirubin was elevated (no values). There was no improvement over the next month; abdominal U/S and CT were nonrevelatory. Renal dysfunction supervened, and the patient died of "multiorgan failure."
- (2) 5 y/o female, on ZNS 40 mg/d for about 3 weeks, "found it impossible to eat and slept all the time"; she was hospitalized for "liver function impairment," developed Class V (deep) hepatic coma 4 days later, requiring intubation. About 1 month later, "daily life was almost normal except for awkward finger movements and hyperactive tendon reflex." "This event was considered severe and probably related to ZNS treatment." The narrative gives VPA as concurrent medication, but the table of "Serious Hepatic Events – Spontaneous Reports" states, under the column headed "Concomitant Medications," "not provided in listing from Dainippon."
- (3) 44 y/o female, with seizure disorder, developed thrombocytopenia (no values given), hepatopathy, and rash about 1 month after starting ZNS 200 mg/d. ZNS was discontinued and, following steroids and transfusions of 20 units of platelets, her platelet count "recovery." Bone marrow biopsy 2 weeks later showed "no evidence of hematological disease to account for the thrombocytopenia." Two weeks after this, "glucagon-insulin therapy was begun and total bilirubin increased; cholinesterase and hepaplastin values were decreased." Steroids were re-initiated and liver function improved over the next 3 weeks. Liver biopsy revealed "acute hepatopathy. DLST for ZNS was positive. Her PMH was significant for SAH (date in

relation to ZNS event?). "This event was considered definitely related to ZNS treatment." Concomitant med listed in the table of "Serious Hepatic Events -- Spontaneous Reports" but not the narrative, is acetaminophen/salicylamide/chlorphenylamine.

- (4) 25 y/o male developed jaundice and elevated LFTs (no values given) 3 days after starting ZNS (200 mg/d). ZNS was discontinued and "hepatic therapy initiated," with normalization of LFTs "over about a week." "This event was considered moderate and possibly related to ZNS treatment." PMH was significant for SAH and femoral fracture.
- (5) 20 y/o male (age given as 28 in the table of "Serious Hepatic Events -- Spontaneous Reports" and 20 in the narrative), with h/o AVM, on ZNS 400 mg/d for epilepsy for about 1 year (concomitant meds: CBZ and clonazepam), developed hyperammonemia (no value given), tremor, and delusion. ZNS was discontinued and "was considered recovered approximately 9 months later." Concomitant meds given in the narrative were CBZ and clonazepam, and in the table of "Serious Hepatic Events -- Spontaneous Reports," PHT, PB, CBZ, and clonazepam.
- (6) 44 y/o male with hepatic function disorder, severe leucopenia, and severe thrombocytopenia after 85 days on ZNS 400 mg/d. ZNS was discontinued. Concomitant meds "not provided in listing from Dainippon." "Considered to be serious per treating physician, not serious per Athena evaluation." No other information is given.

NOTE: the sponsor has unilaterally moved both the "Serious Hepatic Events" and "Cognitive/Neuropsychiatric" sections from the WARNINGS to PRECAUTIONS section "due to the low incidence of adverse findings" (v 5, p 89). However, the content of these two sections is generally differentiated by the severity of the AE and the potential for therapeutic intervention, and not to incidence. (see CFR 201.57, paragraphs e and f). Both categories should therefore be returned to WARNINGS. AE incidence is dealt with in the ADVERSE EVENTS section of the label.

## **2. Cognitive Neuropsychiatric**

The NDA (US/European) and Japanese databases for neurocognitive events were reviewed and re-evaluated by STATPROBE. For the purposes of its review, the sponsor based its "operational definition for 'psychosis'" on the DSM-IV diagnostic criteria under the category "Behavioral Abnormalities - Psychosis-Related": schizophrenia, subtypes of schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, psychotic disorder not otherwise specified, and major depression of the bipolar type. NOTE: the sponsor did not review cognitive/neuropsychiatric AEs in the placebo population. Furthermore, the sponsor did not (1) provide full, clear descriptions, including follow-up, for each case of serious cognitive and neuropsychiatric AEs, (2) reclassify NDA reports for psychosis and paranoid reaction, (3) discuss the differential diagnosis of altered mental status vs absence status, or (4) make clear why one particular diagnostic assignment was made in preference to another. All were requested in the approvable letter.

### ***US/Europe database:***

The sponsor's Table 1 (appended) gives dose response and time to event for cognitive/psychiatric events, compared to placebo. The most frequent events, occurring with a frequency >5% (in descending order), are somnolence, fatigue, agitation/irritability, confusion, tiredness, depression, insomnia, difficulty with memory, difficulty concentrating, mental slowing, and speech abnormalities. Most develop within 2-3 weeks of commencing the drug and typically at doses of 300-400 mg/day. Psychosis-related events, identified schizophrenic/schizophreniform behavior, paranoid behavior, psychosis, at a frequency of 2% each.

## *Japanese database:*

**APPROVAL COHORT** It is difficult to comment with precision about the data presented by the sponsor, in light of the unclear descriptions of . "133 patients were identified with nervous system events potentially associated with discontinuation" (v 3, p 119). Two hospitalizations were adjudged to be serious:

- one with severe toxic ataxia: 32 y/o female who developed dizziness and vertigo "several days after she began taking ZNS 200 mg/d. . . ataxia became marked and she was admitted to hospital with acute antiepileptic intoxication"; ZNS was discontinued, the doses of other AEDs reduced [PHT, CBZ, VPA, and primidone], and hepatoprotective treatment administered" (v 3, p 145);
- the other delusional (22 y/o hospitalized after 1 week at ZNS 100 mg/d with mild giddiness, severe unsteady emotion, religious delusion; her symptoms improved 2 months after discontinuation [v 3, p 145]).

One patient discontinued "probably related to PHT toxicity. Although some terms are vague and difficult to interpret, at least 20 reports possibly indicate some degree of cognitive dysfunction, while 11 may indicate some degree of psychotic-like responses" (v 3, p 119). Some examples of reports: moderate stiff expression; slow in speech and thinking; moderate feeling dull, forgetfulness; decrease of thinking ability, feeling of heavy head; moderate insomnia, tremor, feeling of numbness, disorientation, loss of calculating ability, disturbed orientation, failing to put ideas together, lack of volition; moderate muscle relaxation, feeling giddy, double vision, disturbance of consciousness; severe feeling of vagueness with poor volition; moderate slowdown of behavior; moderate sleepiness, decreased volition; mild giddiness, severe unsteady emotion, religious delusion; severe delusions of persecution/relation; moderate auditory hallucination, delusions of persecution, xenopathic experience; moderate smiling alone and talking to oneself; severe sleepiness, feeling of irritation, decreased judgment, idea of suicide; moderate feeling of irritation, violent behavior; moderate desire for death, idea of self-reproach; moderate infant-like behavior, persecution-like thinking; moderate psychiatric symptoms.

## **POSTMARKETING**

**General Survey:** There were 9 reports adjudged to be "serious" by Dainippon, 7 of whom had events "which were psychosis-like in nature, one was severe depression, and . . . one with apparent severe behavioral retardation." The psychosis-like reaction in 7 patients constitute 0.18 patients in the general survey for an incidence of about 2 per 100 patient-years. However, in the calculated incidence, Elan did not include another patient with complaints of hallucinations who should probably have also been listed (v 3, P 182, patient #93040104). The patients with psychotic symptoms ranged in age from 19-43 and were on ZNS 100-400 mg/d; symptoms began anywhere from 8-159 days on drug. Five patients have concomitant medications listed, and 4 of them were on multiple AEDs.

**Prospective survey:** There were 3 reports of discontinuations for neurological events. One patient was identified with "a serious adverse event of psychosis-like symptoms": 13 y/o female, also on PHT, clonazepam, acetazolamide, VPA, and nitrazepam, who developed "severe hallucination auditory" and "psychosis-like symptom" ("she began to fall silent, refused to go to school, and spoke to an imaginary being") after 63 days on ZNS 270 mg/d.

With respect to the other two patients, one had mild seizures increased, disturbed consciousness, ataxia; and the other had mild moroseness, sleepiness.

There was no case of anencephaly.

**Spontaneous reports:** Six reports were identified at serious leading to discontinuation: --33 y/o female, with AVM, on ZNS 100-200 mg/d x 8 months, developed delusions of persecution and reference, took 6 ZNS tablets, and cut her wrist. Four months later, she was diagnosed with borderline personality disorder and treated with antipsychotic agents;

- and 3-4 months after that, she took 10-13 ZNS tablets with suicidal purpose. The next month she had increased LFTs (AST 1280, ALT 1352) and was hospitalized. The LFTs recovered on ZNS, but it was discontinued 6 months later.
- 52 y/o female, on ZNS 300 mg/d (for epilepsy) x 10 days, developed memory difficulties, strange behavior, and hallucinations, treated with Haldol; ZNS concentration was 19 ug/ml. Over the next 3 weeks, she became depressed, and 1 week later developed a truncal exanthem; ZNS concentration was 44 ug/ml. All symptoms improved over the next week.
  - 19 y/o male, with mild MR, experienced irritability and excitement shorting after starting ZNS 50-2200 mg/d for epilepsy, PHT, and clonazepam. He was given Haldol twice over the next 5 months. He committed suicide; He had been on ZNS for 1872 days.
  - 8 y/o mal, with h/o MR and febrile seizures, was hospitalized, after 2 weeks on ZNS 50-100 mg/d, for fever and status epilepticus. There was poor recovery of consciousness; antibiotics and mannitol were given. Asymmetric pupils and poor movement of the left side of his body were noted 3 days later. CT scan showed right hemispheric edema; LFTs were elevated. ZNS and antibiotics were discontinued, he was placed on dialysis and intubated for respiratory arrest. He died 6 days later.
  - 33 y/o female, on ZNS (dose?) for unknown time, took 200 mg ZNS in a suicide attempt; she suffered hypothermia, algodiaphoria, and hypotension. No other information is available.
  - 21 y/o male, on ZNS 200-400 mg/d x 18 months for epilepsy, began to switch jobs, was absent from work, and complained of stress. He was hospitalized 2 months later; ZNS concentration was elevated (66 ug/ml). He was given antipsychotics and discharged 2 weeks later.

Other discontinuations, not considered serious by the sponsor include 4 for "psychosis-like" events (moderate schizophrenoid state transient, moderate hallucination, severe psychiatric symptom NOS, moderate psychotic state), and 1 each for excitement, depressive stupor, severe initiative decreased and lower extremity weakness, moderate consciousness disturbed, moderate choreoathetoid involuntary movements, moderate psychomotor excitability, moderate convulsions, and moderate gait disorder/ sleep disorder/excitement.

NOTE: the sponsor has unilaterally moved both the "Serious Hepatic Events" and "Cognitive/Neuropsychiatric" sections from the WARNINGS to PRECAUTIONS section "due to the low incidence of adverse findings" (v 5, p 89). However, the content of these two sections is generally differentiated by the severity of the AE and the potential for therapeutic intervention, and not to incidence. (see CFR 201.57, paragraphs e and f). Both categories should therefore be returned to WARNINGS. AE incidence is dealt with in the ADVERSE EVENTS section of the label.

## 2. SAFETY FROM THE JAPANESE EXPERIENCE

### (a) **Prospective Survey**

The report submitted by Elan offers no new description of the methods of data collection in addition to that already provided in the NDA. Furthermore, nothing more was sent when I requested further clarification. The nature of the enrollment procedures (which patients were enrolled) is not described at all, and there is very little information on the extent and nature of data capture and follow-up. No listing of dropouts is provided. Serious adverse events have been tabulated and, though narratives for hematologic, hepatic, renal, and skin events are given when appropriate, they are very sketchy.

A Survey schedule is appended. The objectives of the survey were "evaluation of usefulness (therapeutic spectrum) and safety" with monotherapy and "confirmation of usefulness

and safety with long-term use." Although 1200 patients were anticipated, 1522 were actually enrolled, including both adults and children with either partial or generalized epilepsy. Survey methods are described as

- (a) "Form research groups to conduct the survey under the supervision of epileptologists according to geographical area";
- (b) "Register study subjects according to CFRs with the Postmarketing Surveillance Division, perform various prestudy examinations";
- (c) "Administration/observation period: at least 1 year (excluding dropout/discontinuation cases);
- (d) Administration method:
  - (1) previously untreated cases, start on monotherapy and maintain as such
  - (2) begin with adjunctive therapy in case refractory to other AEDs and switch to monotherapy.

Unevaluable cases and those for whom data were unknown or not recorded on the Survey CRF were excluded from the statistical analysis, for which chi square was used, with a significance level at  $p=0.05$ .

A total of 1793 patients were registered: survey case report forms were collected on 1522 during the first year, 885 in the second, 493 in the third, and 113 in the fourth (because the latter were collected before the inclusion closing date, they were excluded from safety and usefulness data, but AEs were "handled according to standard procedures concerning treatment cases). Excluded from the survey were 27 incomplete CFRs, 17 of which were from the second year and 11 from the third; safety was analyzed for 1512 patients (the sponsor does not comment on the ten not included).

There were 584 adults (280 males, 48%; 301 females, 46%; 3 with gender unknown) and 928 children (<16 years; 502 males, 54%; 425 females, 46%, and 1 with unknown gender). 1044 (69%) had partial epilepsy and 458 (30%) with generalized (147 with primary generalized, 91 with Lennox-Gastaut, 30 with West syndrome, 146 with other secondarily generalized, and 44 with unclassified disorders).

Daily dosages and concomitant meds are indicated in the attached tables. AE incidence rates in monotherapy was 21% (89/424), 19% in children (64/334) and 29% in adults (387/1088). With concomitant AEDs, incidences were 30% (179/589) in children and 42% (208/499) in adults. Overall rates were 26% (243/928) in children and 40% (233/583) in adults.

The sponsor's adverse events tables are appended. Appropriate sections above discuss specific body systems (hematologic, hepatic, renal, and skin), giving patient-time exposure information. There appears to be no significant difference in AE incidence with respect to gender. As for age, it was highest in  $\leq 1$  year (9%); "no AEs specific to the elderly were observed." With regard to dose, incidence rates can be found on the appended demographic table. Abnormal lab values, as well as abnormal liver function tests (ALV), are also tabulated.

There was an overall discontinuation rate 22%, as indicated on the appended table. 864/152 (57%) patients continued for longer than 1 year.

In every category, AE incidence by body-system classification was lower than rates in the approval cohort. There were a total of 58 events classified as severe: 27 psychiatric, 11 gastrointestinal, 9 body as a whole, 6 central and peripheral nervous system, 2 skin and appendages, 1 white blood cell and RES, 1 urinary system disorder, and 1 fetal disorder (anencephaly); only two occurrences are singled out in the table of serious events with brief, limited accompanying narratives (see Table 50, v 3). Four nonserious discontinuations are tabulated (see Table 51, v 3). "Unexpected" AEs include: alopecia (1 patient), induced microseizure (1), hypertonia (1), fecal incontinence (1), increased LDH (1), decreased serum inorganic phosphorus (1), developmental disturbance (small stature; 1); tachycardia (1), respiratory distress (1), breath shortness (1), anencephaly (1), muscle weakness (1), eyelid edema

(1), hyperammonemia (2), increased CPK (2; no values given), hematuria (3; generally associated with renal stones), moroseness (3), and hypocalcemia (5; no values given).

### (b) Japanese Approval Cohort

The sponsor provides a very sketchy summary of the Japanese ZNS experience, which was comprised of the following clinical trials:

- one Phase 1 trial enrolling 12 healthy volunteers.
- one Phase 2 trial enrolling 131 epilepsy patients in 24 centers (presumably an open-label since all patients were on ZNS; see Table VII-3).
- two Phase 3 trials, consisting of
  - (a) 8-week double-blind active-control trial with 116 epilepsy patients (59 ZNS, 56 CBZ) in 34 centers: "the frequency of seizures in patients with partial seizures was significantly lower in the CBZ group than in the ZNS group after 4 weeks of treatment, while no significant difference was found between the two groups after 8 weeks. . . . There was no significant difference in the frequency of secondarily generalized tonic-clonic seizures between the two groups" (v 3, p 243) (primary outcome measure?).
  - (b) 8-week multicenter (12) "comparative" trial (blinded?) with 34 epilepsy patients (18 ZNS, 16 VPA) with different seizure types (tonic-clonic, atypical absence, typical absence) 12 centers; "no significant difference" was noted between treatments in "percent decrease in seizure frequency," "outcome of clinical seizures" (i.e., "frequency, degree and duration of seizures"), "evaluation of EEG changes," "evaluation of changes in mental symptoms," and "overall improvement" (none was identified as primary outcome measure).
- one multicenter Phase 3 long-term, open-label trial with 931 epilepsy patients (538 adults, 393 children; "664 had partial seizures, 147 generalized seizures, 119 combined seizures and 1 unclassified seizures"); 270 patients were treated for >1 year. "In overall improvement rating, the improvement rate covering moderately improved and markedly improved combined 41.4% in adults and 27.9% in children. The rate covering slightly improved to markedly improved was 57% and 51%, respectively" (p 252).

The Japanese approval cohort consisted of 1008 patients. Not included in the total were the 12 healthy volunteers in the Phase 1 study and the 131 patients from the Phase 2 trial; the latter were omitted for an "unknown reason," according to Octavia Norris (Elan) -- who seemed unaware of this when I initially pointed it out -- in a 5/19/99 phone conversation.

Information about safety is also very sketchy. There were no deaths. Overall 392 of 1008 patients discontinued. "Of these Athena reviewed the 202 discontinuations which were due to adverse events (190 discontinuations were due to lack of efficacy); among those 202, 1 was for lack of efficacy. Of the 201 remaining patients who discontinued for AE, 12 were judged to have serious events, of which, 6 were urogenital, 4 were hematologic, 2 nervous system, 2 hepatic, and 1 rash. Nervous system AE were the most frequently noted with 131 reports" (v 3, p 119). Aside from the fact that this sentence is self-contradictory, the numbers given for urogenital fail to match other numbers in the respective AE subsections (only 1 serious hepatic events is listed [v 3, p 77]; no urogenital events listed [v 3, p 89]).

### 3. LABORATORY DATA CLARIFICATION

(a) Provide information about 3 patients in controlled trials with significantly elevated creatinine.

Patient 912-28-3 [redacted] received placebo during the double-blind phase of the study. During this time the patient complained of intermittent dizziness from 9/26/84 until 11/84. The patient began zonisamide at 600 mg/day on 12/17/84. The single elevated creatinine level of 2.2 mg/dl occurred on 5/7/86, 1 year and 5 months after beginning study drug. On 7/2/86 the creatinine had returned to normal. The patient had no further adverse events and had normal physical and neurological examinations throughout the study.

Patient 912-28-06 [redacted] had one single elevated creatinine level of 6.2 mg/dl 41 days prior to receiving any study drug. On the day the patient began study drug the creatinine level had returned to normal.

Patient 912-28-26 [redacted] had one single elevated creatinine level of 7.0 mg/dl 2 weeks after starting zonisamide. Two weeks later the creatinine level had returned to normal. The patient had no adverse events and no change in the physical and neurological examinations during this time.

According to the sponsor, each of the three patients had "a single elevated creatinine level without any previous increase and with an abrupt return to normal at the next sampling. All three patients were from the same investigational site and would have used the same laboratory. No patient had any other accompanying abnormalities" (v 5, p 1).

**(b) Provide lab data for patient JPZ 3201, with thrombocytopenia.**

We were unable to locate an adverse event report of thrombocytopenia for patient [redacted] 201. However, this patient had a drop in platelet count from 95,000 at week 4 (baseline) to 68,000 at week 20. Review of the medical history shows that the patient had a history of pancytopenia occurring in 1977. At that time the patient was diagnosed with undifferentiated connective tissue disorder. The physician commented that patient has "history of bone marrow hypoplasia. It is quite possible that med may contribute (to the abnormal laboratory values)". The patient continued in the 922 Ext and 921 Ext studies. Platelet reports from all studies are listed below:

Visit	Date	Dose
Screening (922)	4/26/95	0
Day 1	6/21/95	begin 100 mg/day
Month 1	7/26/95	200 mg/day
Month 2	8/9/95	400 mg/day
Month 3	9/13/95	400 mg/day
Month 4	11/8/95	400 mg/day
Month 6 (922 Ext)	1/31/96	500 mg/day
Month 12	6/19/96	500 mg/day
Month 18	12/18/96	600 mg/day
Month 6 (921 Ext)	12-17/97	700 mg/day

We are assuming that while this patient had a drop in platelet count during the study, the medical history indicates that this may have been the result of a preexisting condition. Note that platelet counts recovered and remained stable with continued therapy at doses ranging from 500 mg/day to 700 mg/day.

**(c) Provide information on the patient with a Hgb 3.9.**

We were unable to locate a patient with a hemoglobin of 3.9 gm/ml in the listings for the three controlled trials. We did however locate patient 912-015-8 with a hemoglobin of 3.7 gm/ml. A review of the case report forms for 1/10/84 revealed hematology results as follows: Hemoglobin 3.7 gm%, Hematocrit 40%, RBC  $4.31 \times 10^6/\text{mm}^3$ , Platelets  $230 \times 10^3/\text{mm}^3$ , RBC  $5.1 \times 10^3/\text{mm}^3$ . No laboratory reports were available. Because the results are within normal limits except for the hemoglobin, we are assuming that this is a transcription error and most likely should have been recorded as 13.9 mg/ml. The hematology results immediately preceding and following this result were within normal limits.

	HGB	HCT	RBC	Platelet	WBC
1/3/84	14.3	40	4.31	238	6.1
11/10/84	3.7	43	4.5	230	5.1
1/31/84	14.3	41	4.34	>238	6.2

#### 4. ADVERSE EVENT CLARIFICATION

(a) *Provide follow-up information about patient 912-201-358, whose last Hgb was 6.9 and not in the case report tabulations.*

In Study 912-201-358 patient 2057 discontinued the study at day 166 due to anemia. This study was conducted from December 1985 through September 1987 in Finland. Case Report forms add no additional information. Follow-up information is not available. The available information was summarized in the ISS and is repeated here.

This 16-year-old, 30.6-kg male was withdrawn after 166 days of zonisamide therapy due to anemia. At the time of withdrawal he was receiving 200 mg/day. His hemoglobin Although the investigator stated that the cause of the anemia was unknown, iron therapy was instituted. The investigator considered this anemia severe. No follow-up details are available. (NOTE: This ISS report states that the patient is female, however, the case report forms and laboratory listings indicate the patient is male.)

There is one serious adverse event of anemia in a patient who subsequently died of breast cancer. This occurred in the Compassionate Use study (912-CU).

Investigator 5503, Patient 20. Death, (breast cancer):

This 61-year-old, 80-kg woman experienced anemia and neoplasm while receiving zonisamide as compassionate use therapy. Breast cancer was first reported after 1,306 days of zonisamide therapy and the patient had a mastectomy. Anemia was reported to have first occurred after 1,758 days of zonisamide therapy and throughout the remainder of the compassionate use study. Examination of her laboratory data over the duration of her participation in the compassionate use study, by the IRB Medical Monitor, failed to show any drug-induced hematologic abnormalities. On October 19, 1995, zonisamide was stopped permanently for the adverse events. She had received 2,912 days of zonisamide therapy. Anemia was rated as mild and neoplasm rated as severe. The investigator considered both adverse events to be unrelated to zonisamide. The patient was reported to have died on October 20, 1995. Death was not attributed to zonisamide. Concomitant medications included carbamazepine 1,000 mg/day.

No additional patients withdrew from studies due to anemia. In the ISS anemia was reported as occurring in 4 of 976 patients. The 4 month safety update added 2 cases for a total of 6 cases in 976 patients, a 0.615% incidence.

(b) *Describe the clinical nature of the GI adverse events.*

The sponsor has compared the relative frequencies of GI AEs, occurring in >1% patients, in the placebo-controlled trials:

## **Trial 912-US**

Patients were randomized into a treatment group or placebo group. The treatment dose was titrated up to 400 mg. Patients recorded the description and duration of seizures in diaries. The primary efficacy variable is the percentage change from weeks 5-12 to baseline for partial seizure and complex partial seizure frequencies. This was analyzed using a general linear model. The response is the ranks of the primary efficacy variable and the covariates are treatment, center, and the interaction term. Secondary efficacy parameters are response rate and Global Assessments. The response rate is the proportion of subjects with a 50% reduction. This was analyzed using CMH controlling for center. The Global Assessments were not affected by the change in the data sets. Although not identified as efficacy parameters, analyses are also done on all seizures.

The summary of the data on percent reduction in frequency of seizures appears in Table 1. The last 3 rows are identical to the sponsor's results in Table 6, p. 28 of the section on Effectiveness in the document under review.

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**Table 1.** Summary of 912-US data on percent reduction for population 1. The p-values are two-sided and were calculated from Type III MS using SAS proc GLM with ranked response and covariates treatment group, center, and the interaction between these covariates.

Endpoint (variable is the % reduction from baseline to endpoint)	Seizure Type	Placebo	Zonisamide	p-value		
		N	Median	N	Median	
weeks 5-8	Partial	72	-2.5	69	31.7	0.0006
	Complex partial	70	-4.6	69	31.3	0.0009
	All	72	-2.4	69	32.2	0.0004
weeks 9-12	Partial	69	6.5	68	33.6	0.0005
	Complex partial	67	9.3	68	32	0.0030
	All	69	2.8	68	30.8	0.0002
weeks 5-12	Partial	72	-3.15	69	29.6	0.0002 <sup>†</sup>
	Complex partial	70	2.75	69	30.2	0.0009 <sup>†</sup>
	All	72	-3.9	69	29.6	0.0001

† primary efficacy analysis

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**Table 2.** Reduction from baseline in the Frequency of All Partial Seizures (Table 13 relabeled Table 7 from Dr. Sahlroot's review). The data in this table agrees with the sponsor's summaries in Tables 6- 9 on pp. 28-29 in the Effectiveness section of the document under review. Note: The sponsor's section for the re-analysis in Table 8 for population 3 is blank. Using the sponsor's data set, this reviewer calculated the summary statistics, but they are identical to the summaries for population 1. In population 3, 9 observations from treatment group and 2 from the placebo group are missing- the 11 patients that are not in population 1.

(Protocol 912-US)

Population	Zonisamide		Placebo	
	N	Median % Change	N	Median % Change
1 <sup>b</sup>	69	-29.6 <sup>a</sup>	72	3.9
2 <sup>c</sup>	78	-22.5 <sup>a</sup>	74	6.6
3 <sup>d</sup>	69	-29.6 <sup>a</sup>	72	3.9
4 <sup>e</sup>	65	-31.6 <sup>a</sup>	71	4.5

<sup>a</sup> Significantly greater reduction than placebo ( $p \leq 0.05$ ).

<sup>b</sup> 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).

<sup>c</sup> Same as intent-to-treat population but includes patients who dropped out during dose introduction phase (includes imputation for patients not completing dose introduction).

<sup>d</sup> Intent-to-treat using all post-randomization data with no imputation.

<sup>e</sup> Efficacy evaluable population.

**Table 3.** Reduction from baseline in the Frequency of Complex Partial Seizures (Table 14 relabeled Table 8 from Dr. Sahlroot's review). Note: see comments from Table 2.

(Protocol 912-US)

Population	Zonisamide		Placebo	
	N	Median % Change	N	Median % Change
1 <sup>b</sup>	69	-30.2 <sup>a</sup>	70	-2.75
2 <sup>c</sup>	78	-20.9	72	-0.5
3 <sup>d</sup>	69	-30.2 <sup>a</sup>	70	-2.75
4 <sup>e</sup>	64	-31.1 <sup>a</sup>	68	-0.5

<sup>a</sup> Significantly greater reduction than placebo ( $p \leq 0.05$ ).

<sup>b</sup> 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).

<sup>c</sup> Same as intent-to-treat population but includes patients who dropped out during dose introduction phase (includes imputation for patients not completing dose introduction).

<sup>d</sup> Intent-to-treat using all post-randomization data with no imputation.

<sup>e</sup> Efficacy evaluable population.

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Table 4. Analyses of proportion of responders for population 1. The p-value is computed using the Mantel-Haenszel statistic controlling for center.

Seizure type	% responders		p-value
	Placebo	Zonisamide	
Partial	17	28	0.178
Complex partial	14	30	0.038
All	15	29	0.083

### Trial 912-EUR

This trial used the same basic design as 912-US. The results appear in Tables 5 through 8. The last 3 rows of Table 5 correspond to Table 11, p. 32 in the Effectiveness section of the document under review.

Table 5. Summary of 912-EUR data on percent reduction for population 1. The p-values are two-sided and were calculated from Type III MS using SAS proc GLM with ranks of the efficacy variable as the response and covariates treatment group, treatment center, and the interaction between these covariates.

Variable (% change from baseline)	Seizure Type	Placebo		Zonisamide		p-value
		N	Median	N	Median	
day 29 to 56	partial	66	0.2	67	27.8	0.006
	complex	65	3.6	67	25.2	0.007
	all	66	1.8	67	27.3	0.006
day 57+	partial	66	9.45	66	28.8	0.103
	complex	65	8.2	67	30	0.029
	all	66	9.45	66	30	0.118
day 29+	partial	66	-1.05	67	27.2	0.0176 <sup>†</sup>
	complex	65	-4.3	67	28.2	0.0079 <sup>†</sup>
	all	66	-1.05	67	22.5	0.0247

† primary efficacy analysis

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**Table 6.** Reduction from baseline in the Frequency of All Partial Seizures. The data in this table agrees with the sponsor's summaries in Tables 11- 14 on pp. 32-33 in the Effectiveness section of the document under review. Where the FDA analysis differs from the sponsors, the sponsor's analysis is presented in bold.

(Protocol 912-EUR)

Population	Zonisamide		Placebo	
	N	Median % Change	N	Median % Change
1 <sup>b</sup>	67	-22.5 <sup>a</sup>	66	1.0
2 <sup>c</sup>	70	-20 <sup>a</sup>	68	3
3 <sup>d</sup>	67 (69)	-22.5 <sup>a</sup> (-29.2)	66 (68)	1.0 (-3.3)
4 <sup>e</sup>	65	-22.5 <sup>a</sup>	66	1.0

<sup>a</sup> Significantly greater reduction than placebo ( $p \leq 0.05$ ).

<sup>b</sup> 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).

<sup>c</sup> Same as intent-to-treat population but includes patients who dropped out during dose introduction phase (includes imputation for patients not completing dose introduction).

<sup>d</sup> Intent-to-treat using all post-randomization data with no imputation.

<sup>e</sup> Efficacy evaluable population.

**Table 7.** Reduction from baseline in the Frequency of Complex Partial Seizures. The data in this table agrees with the sponsor's summaries in Tables 11- 14 on pp. 32-33 in the Effectiveness section of the document under review. Where the FDA analysis differs from the sponsors, the sponsor's analysis is presented in bold.

(Protocol 912-EUR)

Population	Zonisamide		Placebo	
	N	Median % Change	N	Median % Change
1 <sup>b</sup>	67	-28.2 <sup>a</sup>	65	4.3
2 <sup>c</sup>	70	-26.9 <sup>a</sup>	68	11.2
3 <sup>d</sup>	67 (69)	-28.2 <sup>a</sup> (-34.8)	65 (68)	4.3 (0.4)
4 <sup>e</sup>	65	-27.2 <sup>a</sup>	64	4.1

<sup>a</sup> Significantly greater reduction than placebo ( $p \leq 0.05$ ).

<sup>b</sup> 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).

<sup>c</sup> Same as intent-to-treat population but includes patients who dropped out during dose introduction phase (includes imputation for patients not completing dose introduction).

<sup>d</sup> Intent-to-treat using all post-randomization data with no imputation.

<sup>e</sup> Efficacy evaluable population.

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Table 8. Analyses of proportion of responders for population 1. The p-value is computed using the Mantel-Haenszel statistic controlling for center.

Seizure type	% responders		p-value
	Placebo	Zonisamide	
Partial	14	28	0.071
Complex partial	15	28	0.132
All	12	28	0.039

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**/S/**

John Lawrence, Ph.D.  
Mathematical Statistician

This review consists of 7 pages of text, tables, and figures.

Concur:

Dr. Jin

Dr. Chi

**/S/**  
**/S/**

cc:

NDA #20-780  
HFD-120/Dr. Katz  
HFD-120/Dr. Capcala  
HFD-120/Dr. Burkhart  
HFD-120/Ms. Ware  
HFD-710/Dr. Chi  
HFD-710/Dr. Jin  
HFD-710/Dr. Hung  
HFD-710/chron

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JUN 3 1999

Zonisamide Capsules (100 mg)  
NDA 20-789

Athena Neuroscience/Elan Pharmaceuticals  
South San Francisco, CA 94080

Reviewer: Iftexhar Mahmood, Ph. D.

Submission Date: August 19, 1998: April 21, 1999

Indication: Epilepsy.

The Sponsor Athena Neuroscience/Elan Pharmaceuticals, has responded to the dissolution specifications set by the FDA.

Dosage Form: Capsules

Strengths: [Redacted]

Apparatus: [Redacted]

Medium: [Redacted]

Speed: [Redacted]

Sponsor's proposed Specifications: Q [Redacted]

FDA's proposed Specifications: Q [Redacted]

The Sponsor plans to continue dissolution testing according to their proposed specifications. The Sponsor claims that at least there was [Redacted] Dissolution profiles of stability batches (694Z03, 694Z04 and 694Z05 and validation Batches 694F01, 694F02 and 694G01) submitted to Dr. Thomas Oliver (chemistry) showed that [Redacted] mean dissolution for all the batches [Redacted]. These data do not support Sponsor's view of Q [Redacted]. Therefore, based on current evaluation of data, the FDA recommends the following:

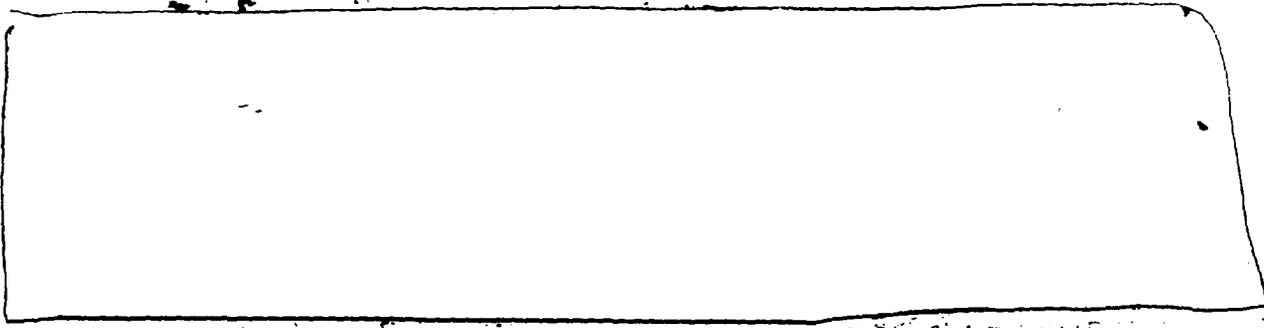
The Sponsor should test their dissolution profiles with specifications of Q [Redacted]

Based on these data a new dissolution specification may be proposed by the Sponsor. (APPENDIX I)

2 pages  
redacted

DRAFT

LABELING



**Recommendation:**

Please send the dissolution specifications and the labeling comments to the Sponsor.

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**/S/** 6/3/99

Ifkhar Mahmood, Ph. D.  
Division of Pharmaceutical Evaluation I

RD/FT initialed by Chandra Sahajwalla, Ph. D.

**/S/** 6/3/99

CC: IND 20-789HFD-120, HFD-860 (Mahmood, Sahajwalla, Mehta), Biopharm-CDR  
(for Drug Files).

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