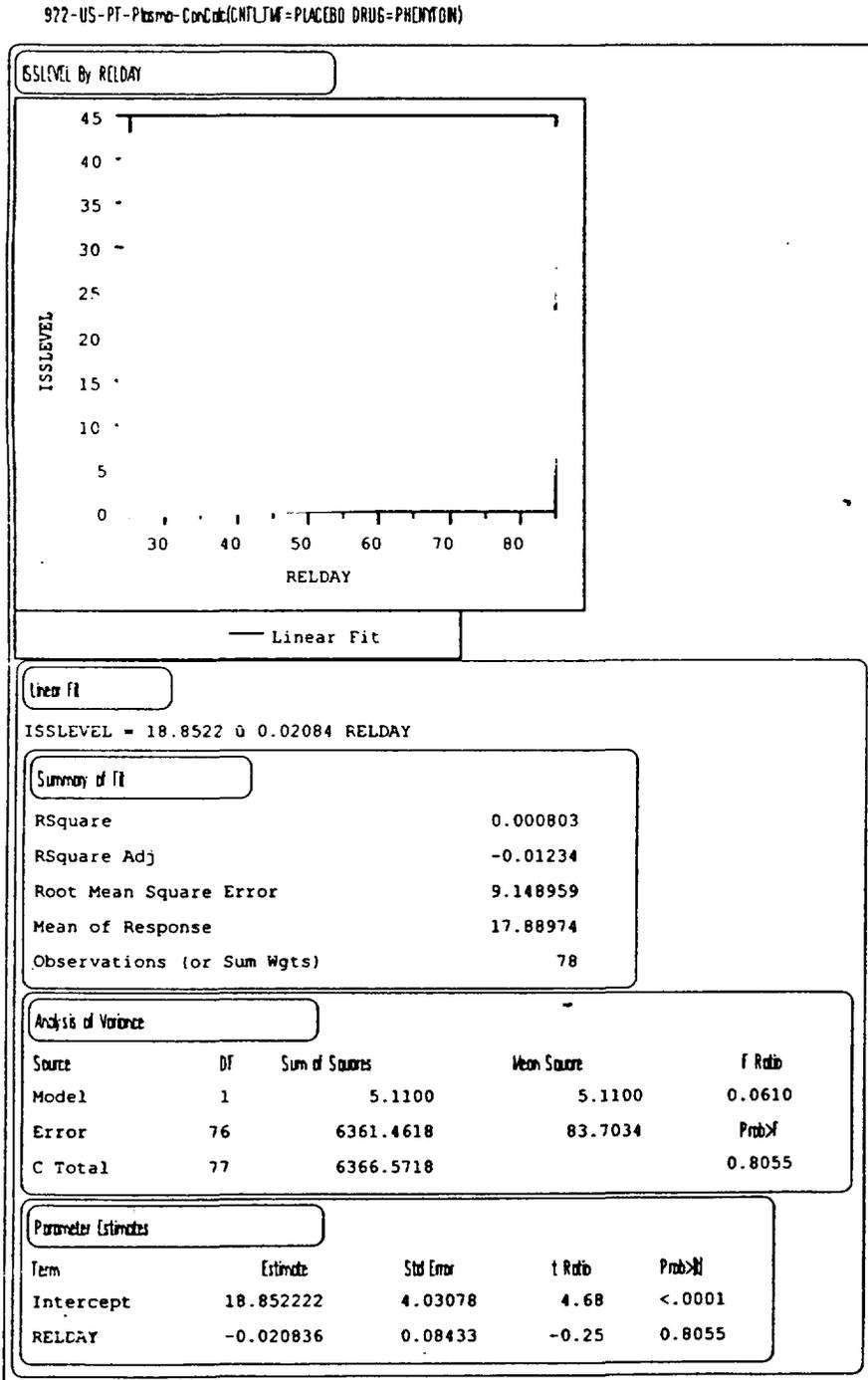


Figure 56

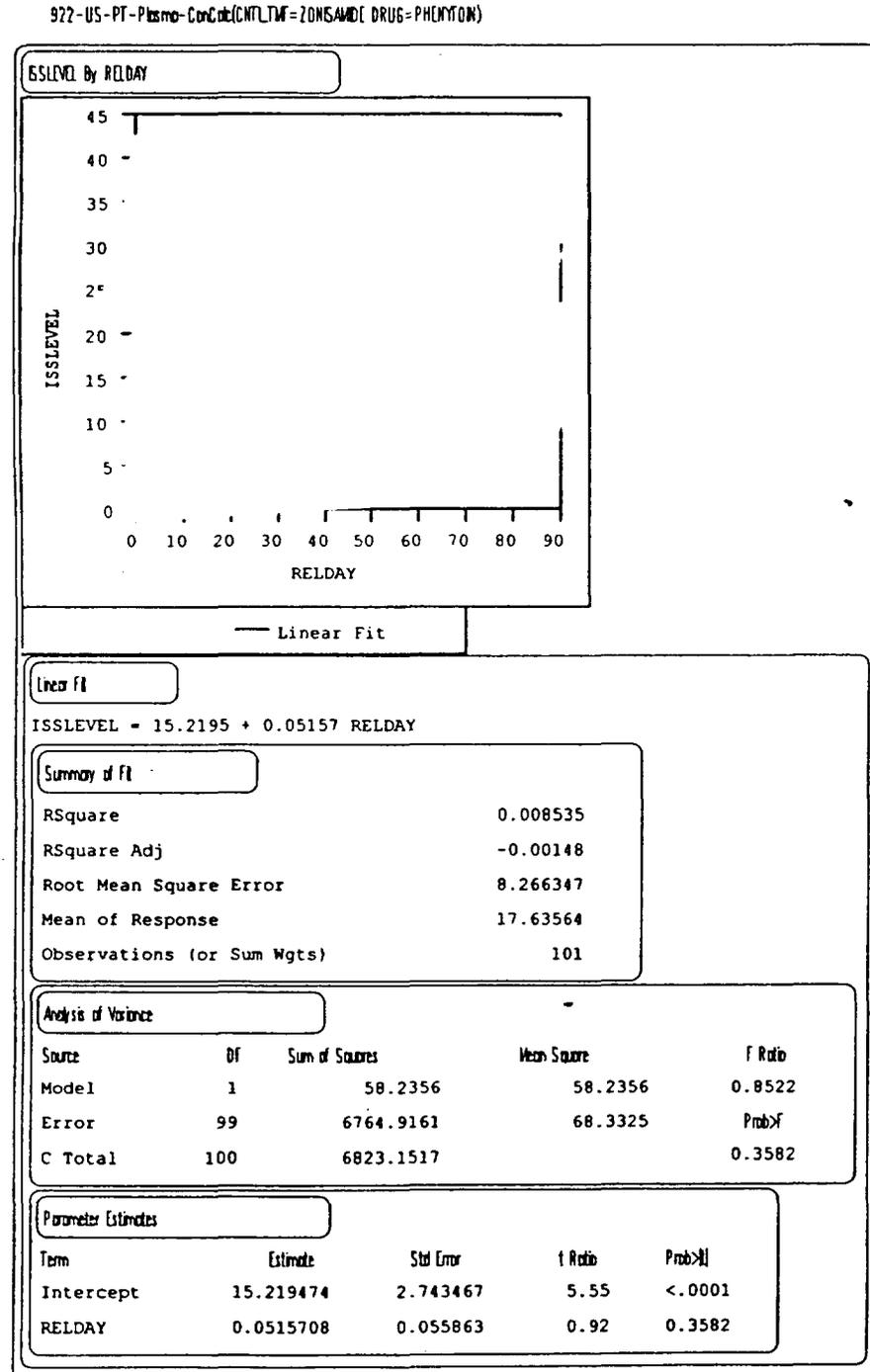
Plasma Level of Phenytoin vs. Relative Study Day for Placebo Subjects in the Controlled Portion of 922-US



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Figure 57

Plasma Level of Phenytoin vs. Relative Study Day for Zonisamide Subjects in the Controlled Portion of 922-US

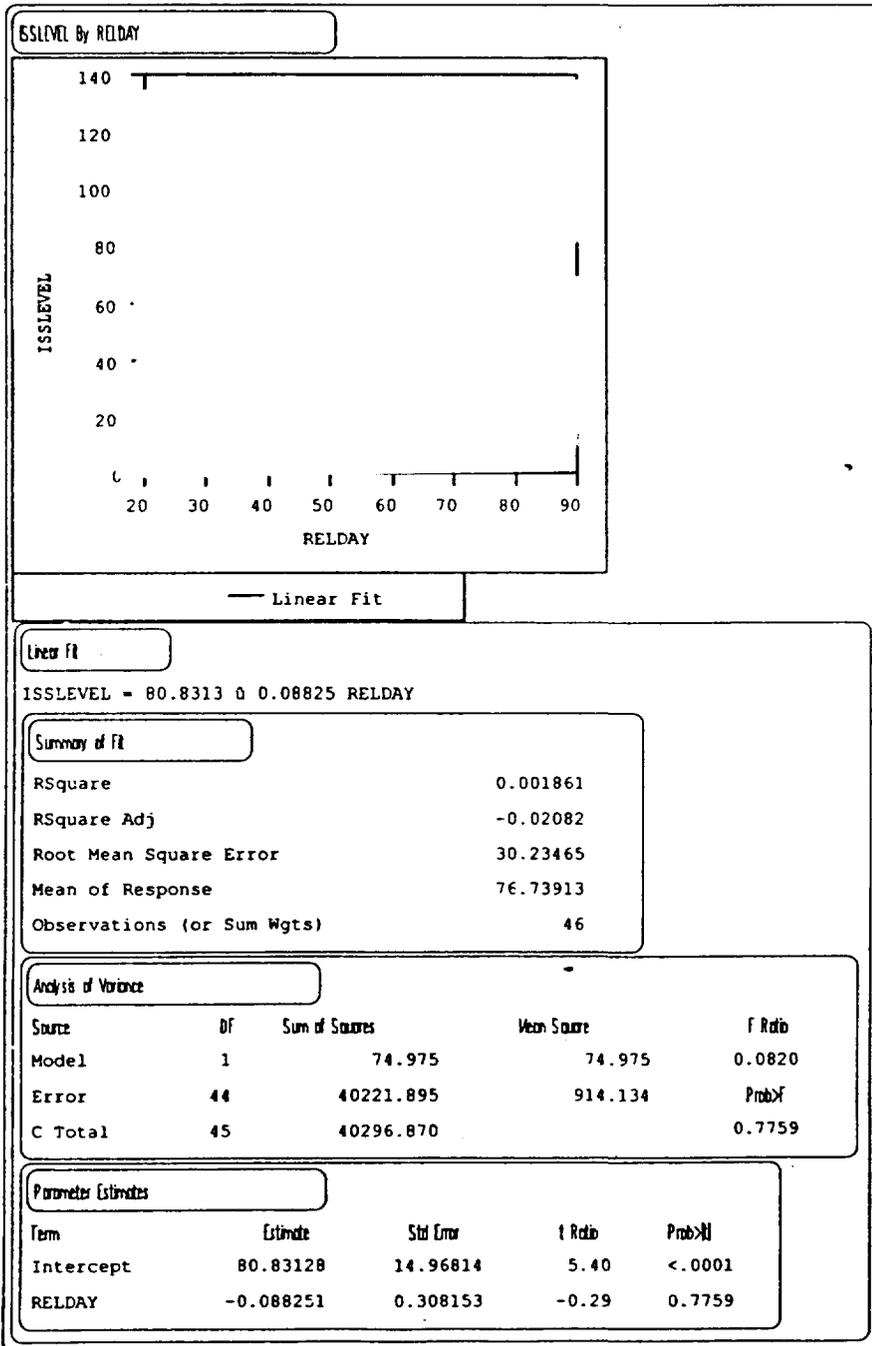


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Figure 58

Plasma Level of Valproic Acid vs. Relative Study Day for Placebo Subjects in the Controlled Portion of 922-US

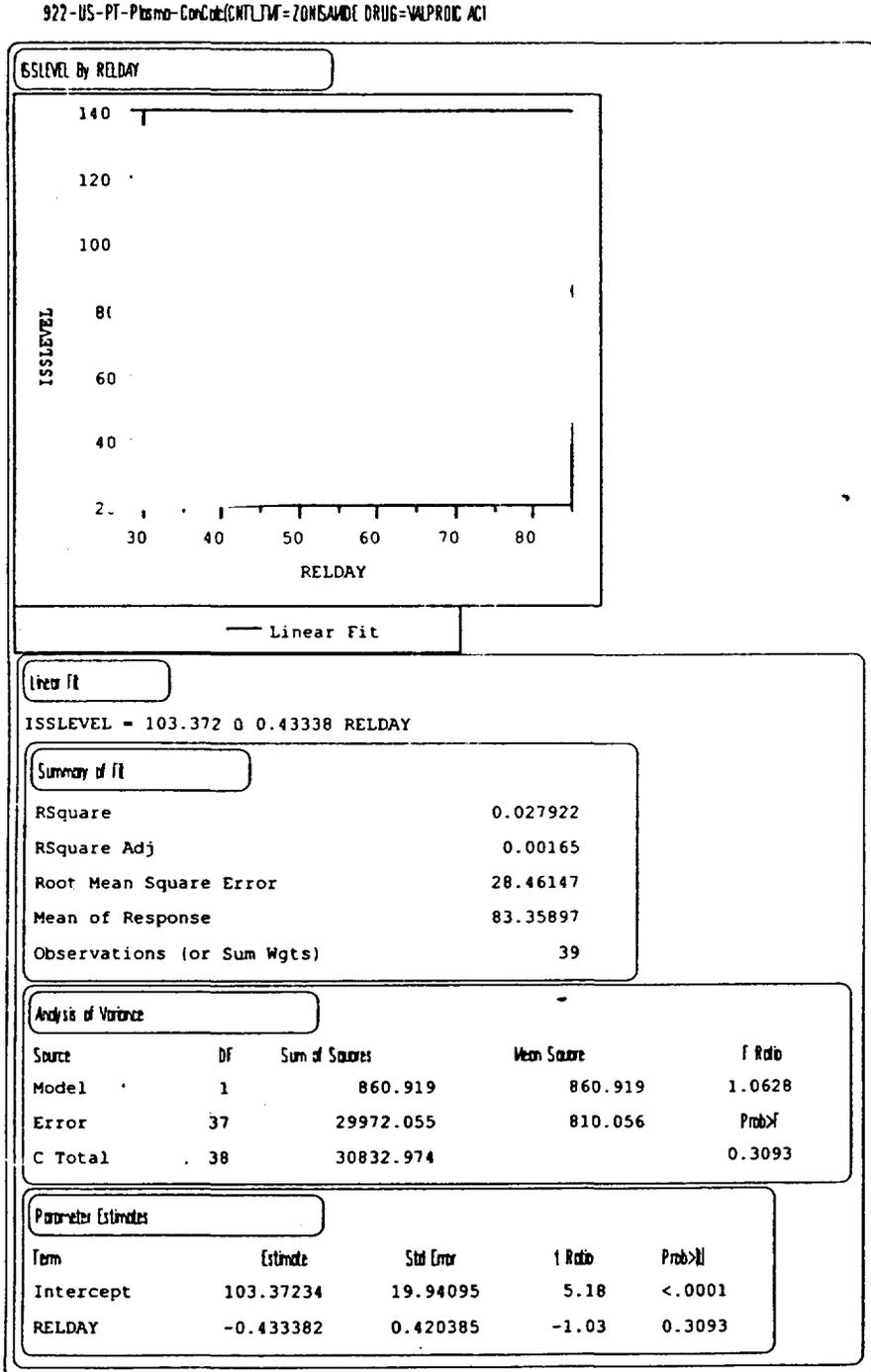
922-US-PT-Plasma-ConCon(CNTLTM=PLACEBO DRUG=VALPROIC ACID)



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Figure 59

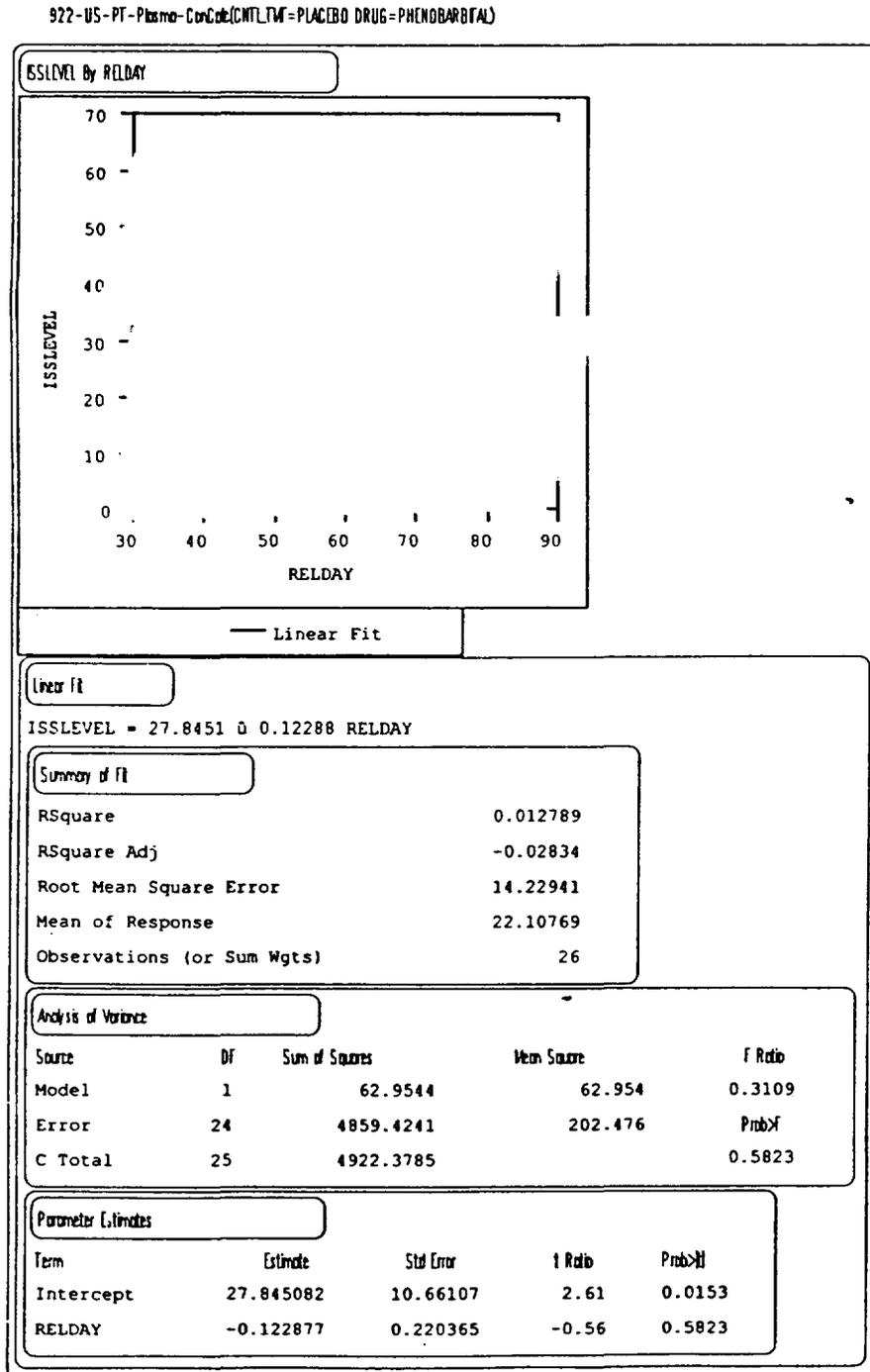
Plasma Level of Valproic Acid vs. Relative Study Day for Zonisamide Subjects in the Controlled Portion of 922-US



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Figure 60

Plasma Level of Phenobarbital vs. Relative Study Day for Placebo Subjects in the Controlled Portion of 922-US

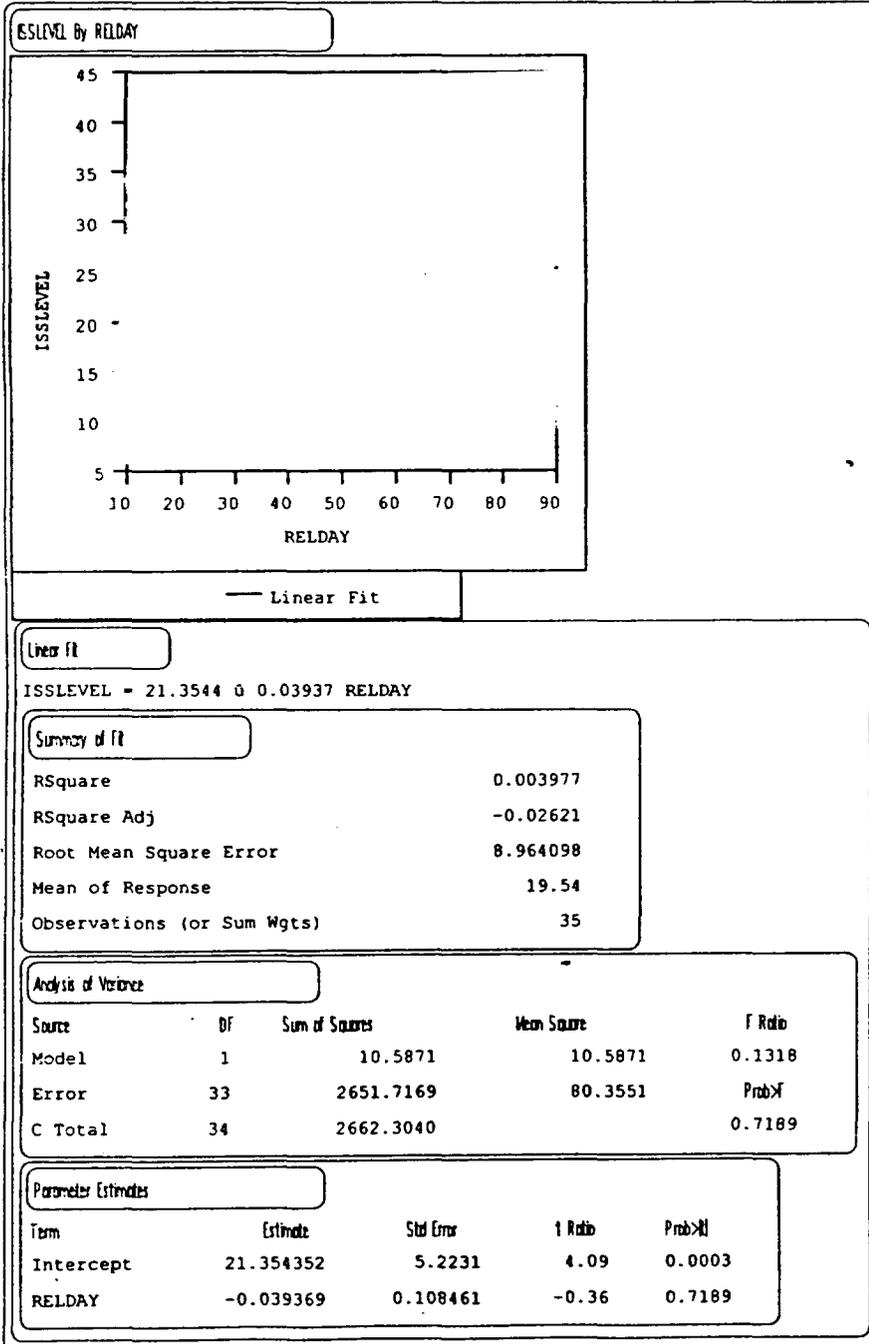


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Figure 61

Plasma Level of Phenobarbital vs. Relative Study Day for Zonisamide Subjects in the Controlled Portion of 922-US

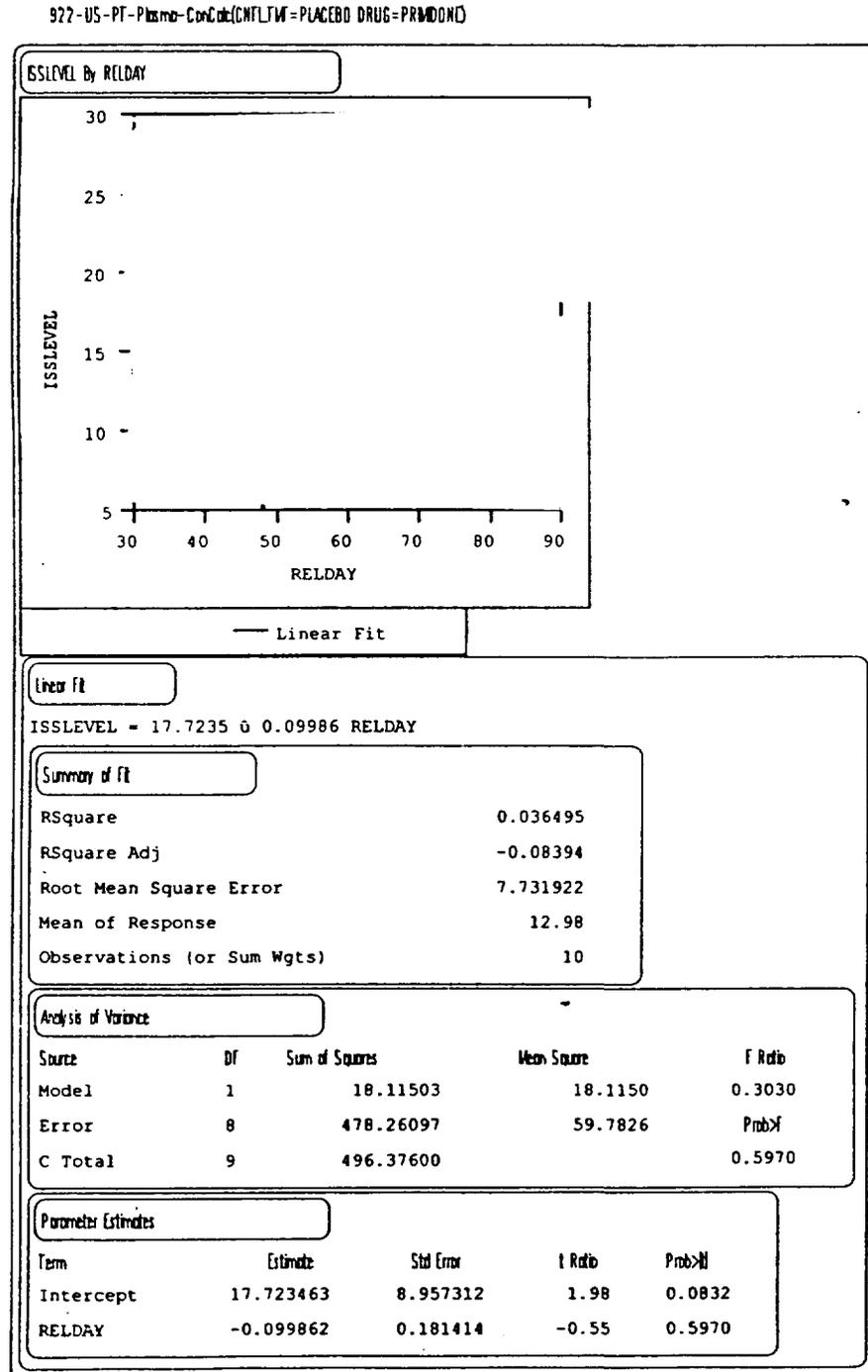
922-US-PT-Plasma-ConCntrlTWF=ZONISAMIDE DRUG=PHENOBARBITAL



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Figure 62

Plasma Level of Primidone vs. Relative Study Day for Placebo Subjects in the Controlled Portion of 922-US

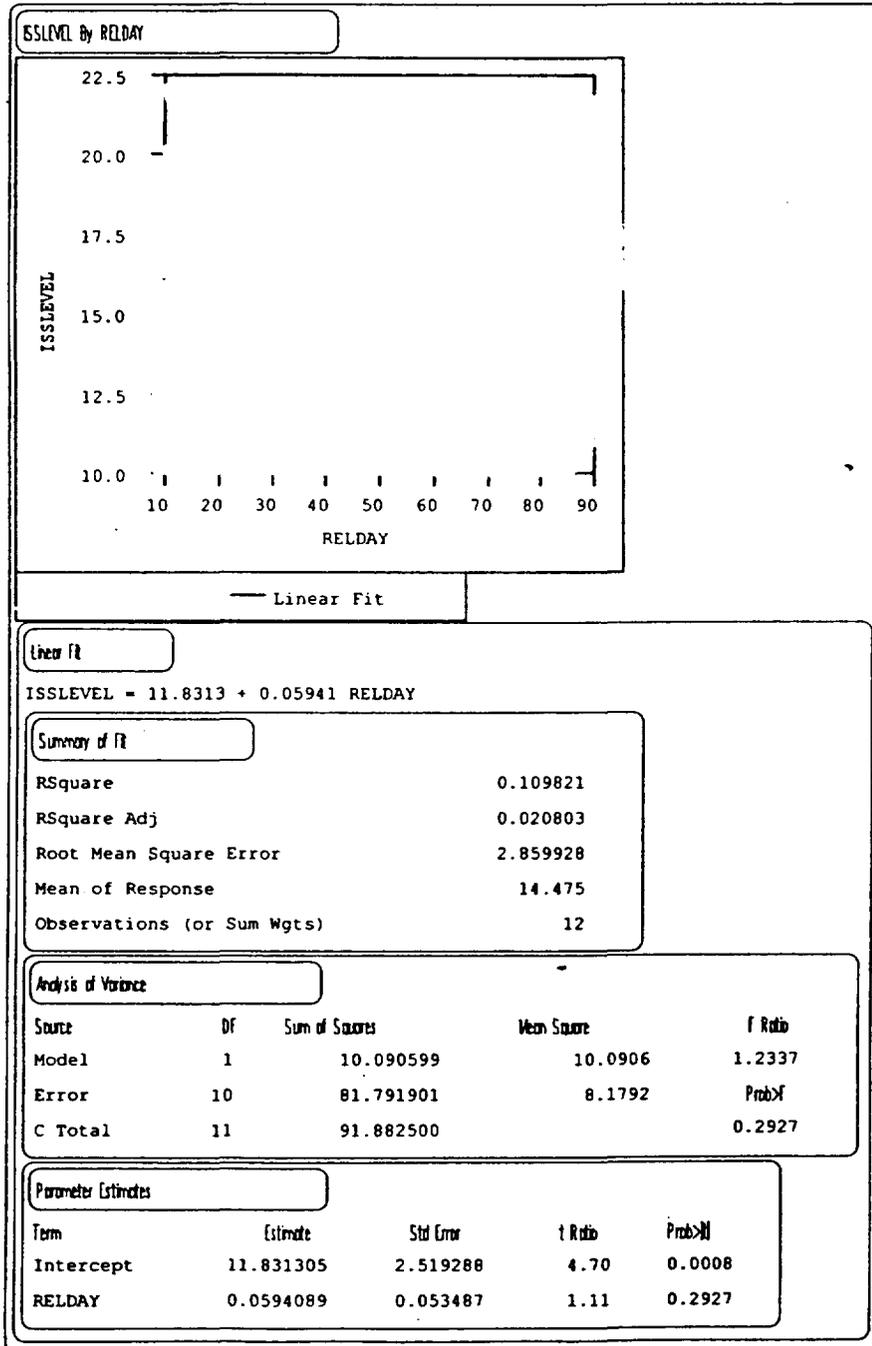


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Figure 63

Plasma Level of Primidone vs. Relative Study Day for Zonisamide Subjects in the Controlled Portion of 922-US

922-US-PT-Plasma-ConCob(CNTLTM=ZONISAMIDE DRUG=PRIMIDONE)

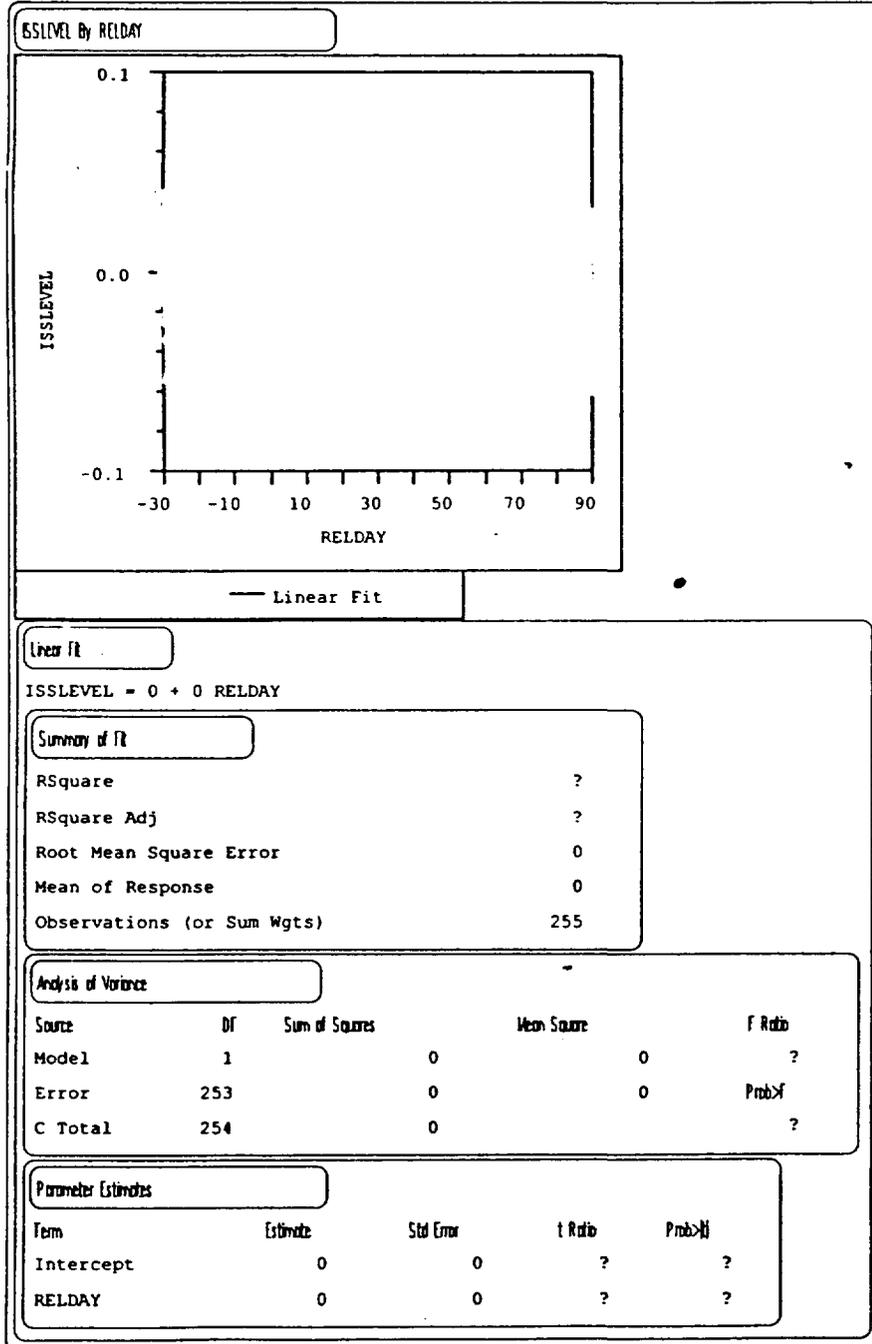


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Figure 64

Plasma Level of Zonisamide vs. Relative Study Day for Placebo Subjects in the Controlled Portion of 922-US

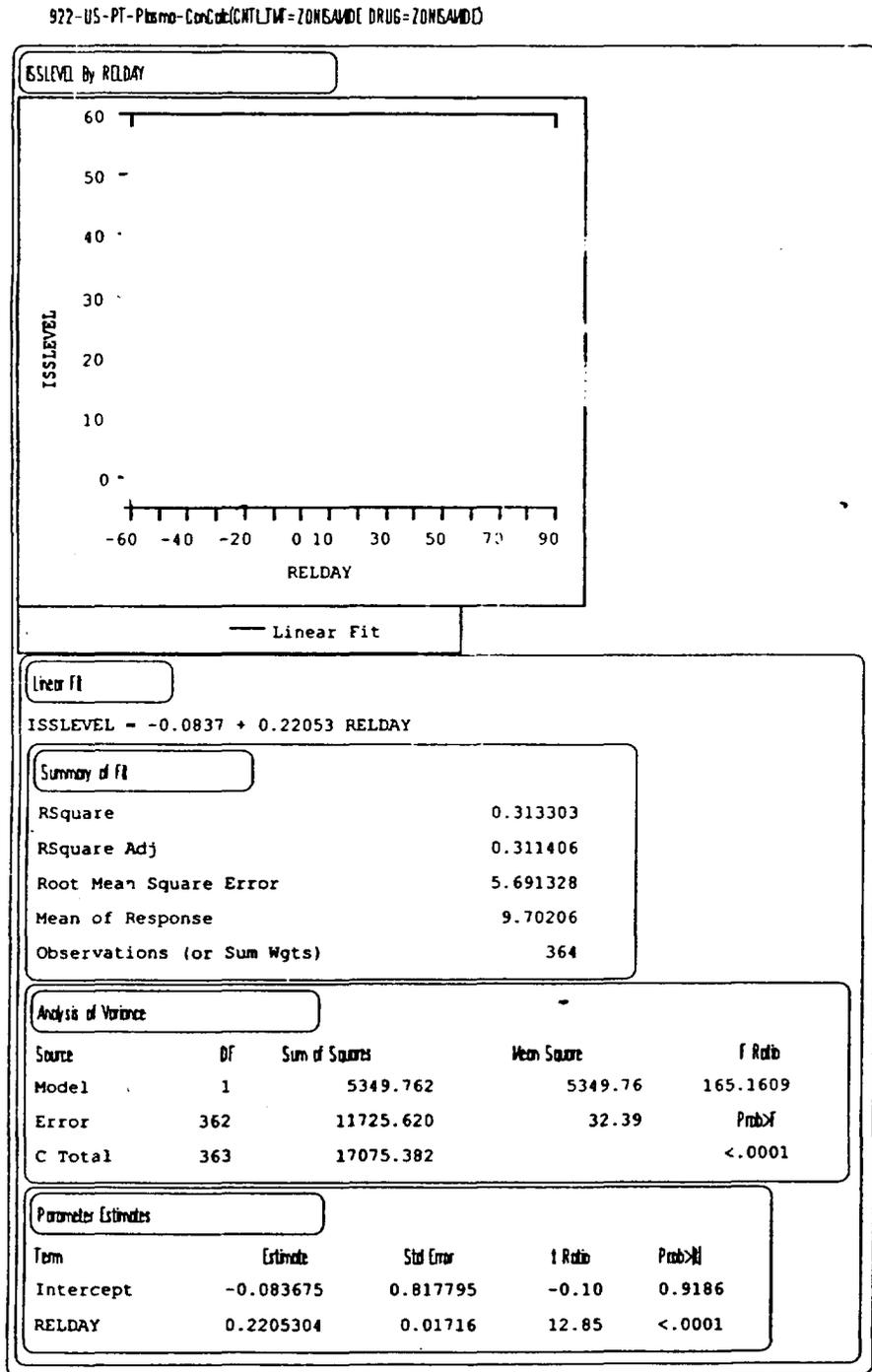
922-US-PT-Plasma-ConCntr(CNTRLTW=PLACEBO DRUG=ZONISAMID)



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Figure 65

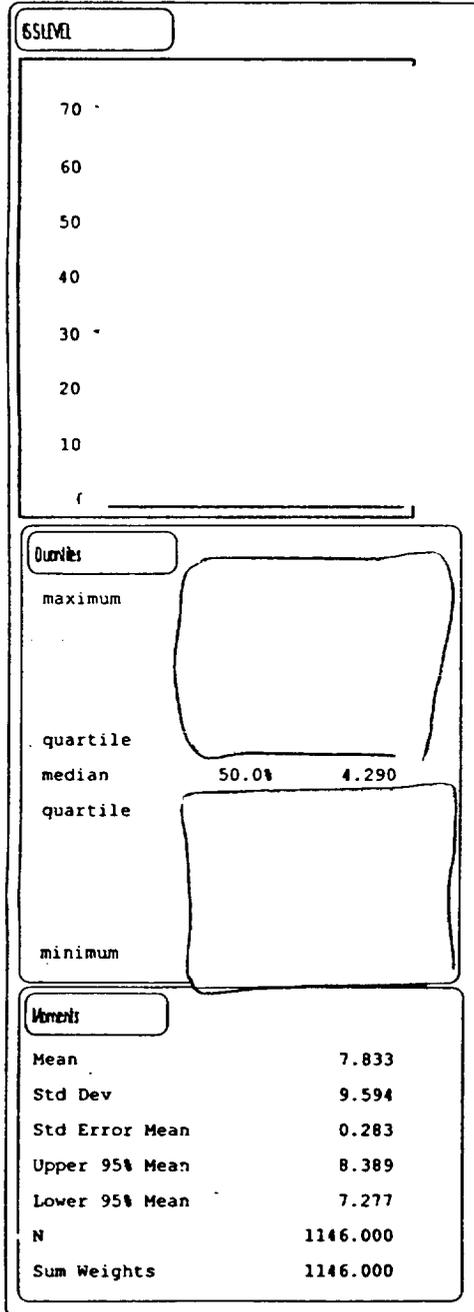
Plasma Level of Zonisamide vs. Relative Study Day for Zonisamide Subjects in the Controlled Portion of 922-US



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Figure 66

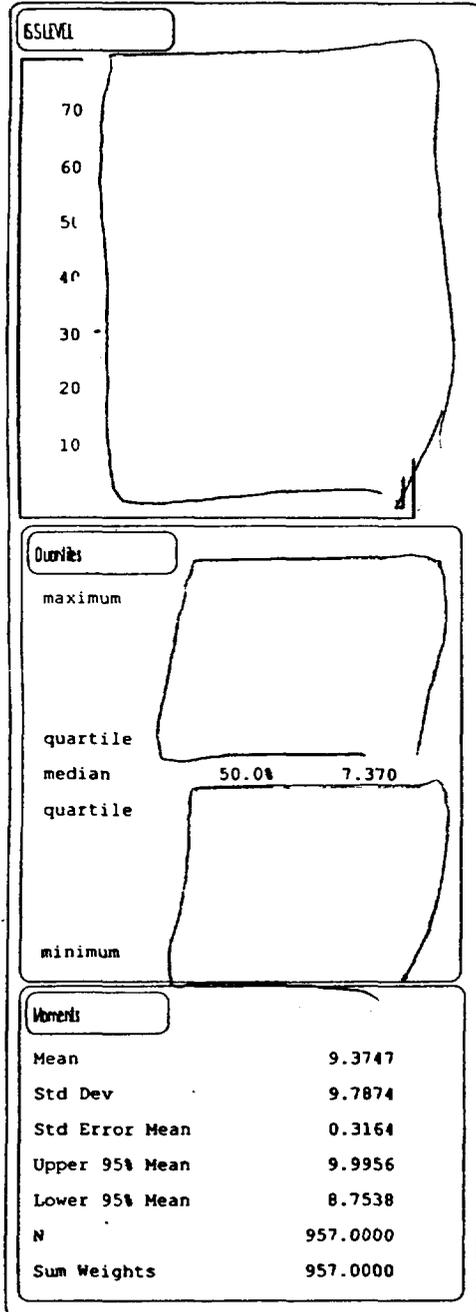
Zonisamide Plasma Levels in 922-US



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Figure 67

Zonisamide Plasma Levels During the Controlled Portion of 922-US



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Review of Clinical Data

Safety Review of the Zonisamide NDA

NDA: NDA 20-789

Sponsor: Dainippon

Drug: Zonisamide

Route of Administration: Oral

Reviewers:
Mike Sevka, M.D.
Judy Racoosin, M.D., M.P.H.
Jim Knudsen, M.D., Ph.D.
Greg Burkhart, M.D., M.S.

Author: Greg Burkhart, M.D., M.S.

Review Completion Date: February 24, 1998

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2-24-98

The Zonisamide NDA was submitted on March 19, 1997. The efficacy review was conducted by Dr. Jim Sherry. The safety review was conducted by members of the division's safety team. Dr. Sevka reviewed the deaths, serious AEs, AEs associated with discontinuations, common AEs, and the overdose and pregnancy experience. Dr. Knudsen examined the accuracy of the data in the NDA and the validity of the AE coding, and reviewed the laboratory, ECG and vital sign data. Dr. Racoosin reviewed the post-marketing surveillance (PMS) experience. I assisted with the review of patient discontinuations, and reviewed and incorporated the findings of each safety reviewer into this safety review document.

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I. Background

A. Development Program

1. Overview of Zonisamide's Clinical Development

Dainippon submitted the NDA on March 19, 1997 with data purported to support a claim that zonisamide is safe and effective in the adjunctive treatment of partial seizures. The NDA describes the experience of 1572 healthy volunteers and patients with exposure to zonisamide.

The administrative history of zonisamide is pertinent to the safety review. The IND was originally held by [redacted] who voluntarily suspended the development program on February 6, 1987 purportedly because of an increased risk of renal calculi. At that time, there were 259 patients enrolled in 5 ongoing studies who were withdrawn from drug.

Prior to the suspension, [redacted] had completed 2 RCTs in 1984, EUR912 and US912. After Dainippon took over development of zonisamide, consultants advised Dainippon that EUR912 did not show evidence of efficacy, and Dainippon initiated RCT 922 completing it in 1994. Study 922 differed significantly in design from EUR912 and US912 in that it titrated to a smaller daily dose.

Other than the concern about renal calculi formation, there were no other striking safety issues in the administrative file. There were several IND safety reports describing patients who developed thrombocytopenia with one report indicating that a patient also developed thrombocytopenia upon rechallenge. [redacted] had also amended the protocols for studies EUR912 and US912 to administer zonisamide by titration after preliminary analyzes showed increased AE occurrence with increased initial dose.

Presumably because of the suspension in the development program by [redacted] that resulted in 259 patients being withdrawn from drug, Dainippon chose to separate the safety experience in the NDA by dividing the development experience into "primary" and "supplementary" databases. The primary database contains the data for 976 patients with zonisamide exposure including the experience from patients in the 3 RCTs and their extensions as well as that from several uncontrolled studies. The supplementary database contains the data for 259 patients who were withdrawn from drug in the terminated studies and patients studied for other indications and healthy volunteers in phase 1 studies.

2. Overall Approach to Safety Surveillance

Because of the concern regarding an increased risk for renal calculi, patients enrolled in the US studies 920, 921, and 922 underwent renal ultrasound at baseline and then at 1 year and study endpoint. For patients in study 922, ultrasound was also performed at the end of 12 weeks so that event occurrence in the zonisamide group could be compared with that for placebo.

Otherwise, the surveillance employed to monitor for AE occurrence was generally passive and similar to that used by most sponsors. Even though the sponsor has chosen to split the data into a primary and supplementary database, the surveillance and follow-up of patients in the supplementary database appears to be consistent with that in the primary.

AEs were defined as new events emerging on treatment or those that if present at baseline had progressed on drug. The sponsor used a modified COSTART dictionary for coding AEs.

3. Foreign Marketing & Post-Marketing Surveillance Experience

Zonisamide was initially marketed in Japan in 1989 and then in Korea in 1992 with the NDA containing data on the PMS experience in Japan. The PMS data can generally be divided into those from (1) spontaneous reports to the sponsor, (2) findings from the *General Survey* which collected data retrospectively on 3906 exposed patients over 1989-1994, and (3) findings from the *Prospective Survey* which is ongoing and provides data on 1512 patients (424 with monotherapy and 1088 with adjunctive therapy) from epilepsy centers in Japan.

The NDA provides a summary of Dainippon's submission to the Japanese regulatory authorities that summarizes the experience from the 1008 patients (including 403 children). This experience was apparently relied upon for Japanese approval. No detailed presentation of the safety experience of these patients was included in the NDA and, while it was not completely clear, the Japanese database does not appear to overlap to any great extent with the current NDA database.

4. Approach to the Review of Safety

The safety review was conducted by several medical officers from the Division's Safety Team. Dr. Knudsen examined the accuracy of the data contained in the NDA as well as the general validity of AE coding. In addition, he specifically reviewed the laboratory, vital sign, and ECG data. Dr. Sevka reviewed the mortality, serious and common AEs, AEs associated with discontinuation, pregnancy and overdose experience, and finally, the findings from studies 920, 921 and 922 that used renal ultrasound to screen for renal calculi. Dr. Racoosin reviewed the data from the PMS experience. I assisted with the

review of the discontinuations, coordinated the overall review, reviewed the overall findings and incorporated each reviewer's written comments into the final document.

B. Animal Findings

According to the sponsor's summary of the preclinical findings, the LCD50 was 1900 mg/kg in rodents and 1000 mg/kg in dogs and monkeys. Symptoms associated with death were nonspecific generally characterized by sedation and ataxia in most animals. In chronic exposure studies in rats, renal calculi were observed but the finding was dismissed by the sponsor because the incidence was purportedly similar to the expected background rate. No findings suggestive of systemic toxicity were reportedly observed in the 52 week dog studies with zonisamide dosed at 30/mg/day. At higher doses (75 mg/kg/day) there was liver enlargement without any histopathological findings. Across species in chronic studies there were increases in BUN without any increases in creatinine, except for one study, where there was a significant increase in creatinine without a change in BUN. In the segment 2 studies, there were dose-related cardiovascular defects in dogs.

C. Safety Issues for Sulfonamides and Carbonic Anhydrase Inhibitors

Zonisamide is a sulfonamide and an inhibitor of carbonic anhydrase. Sulfonamides have been associated with a range of what many experts consider to be idiosyncratic reactions ranging from SJS, TEN to angioedema and serum sickness-type reactions. Carbonic anhydrase inhibitors are associated with renal calculi formation, electrolyte changes and CNS toxicity at high doses.

D. Safety Issues in the Sponsor Proposed Labeling

The proposed labeling identifies several safety issues. In the warning section, the sponsor mentions the apparent increase in renal calculi. They have also included a separate warning on hypersensitivity reactions that mentions urticaria, SJS and TEN based upon PMS experience from Japan.

The labeling does not specifically contraindicate zonisamide in patients who are allergic to sulfonamides.

E. Description of Submission

1. Paper and Electronic

The sponsor submitted a complete paper copy of the NDA as well as electronic files of study reports and the ISS. In addition, some safety data was submitted as SAS transport files for patients included in the primary database.

2. Cutoff Dates for the NDA database and Four Month Safety Update

The cutoff date for reporting deaths at the time of the NDA submission was October 31, 1996 with the cutoff date for serious AEs 4 months earlier. The cutoff date for the project database was 9 months earlier than the death date.

In the 4 month safety update, the cut-off date for both deaths and serious AEs was March 31, 1997 with the cutoff date for the project database 5 months behind.

3. Quality of the Data

To examine the overall validity of the safety data submitted in the NDA, we cross-checked information on the CRFs, listed in data tabulations, patient listings and that on narrative summaries for all deaths and AE dropouts. In general, there were only minor inconsistencies. The narrative summaries were generally limited in clinical detail and appeared to be summaries of the database.

There was inconsistency in the definition used to select the "baseline" laboratory value for analyzes of change from baseline. However, this did not affect our review of patients with clinically significant laboratory findings on study.

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II. Safety Review Findings In the NDA

A. *Description of Patients Included in the Primary Safety Database*

The characteristics of the patients included in the primary safety database was summarized by the sponsor in Table 8h-10. For the most part, demographic characteristics were consistent with that for the indication. The most common adjunctive treatment to zonisamide was carbamazepine/phenytoin which was used in 16% of patients with exposure to zonisamide.

B. *Extent of Exposure in the NDA Development Program*

The NDA described the safety experience for 1572 unique patients with some exposure to zonisamide. Of the 1572 patients, 261 were included in phase 1 studies with 217 exposed to only a single dose. Of the 1355 patients with multidose exposure, 976 were included in the primary safety database including the 269 patients who had zonisamide exposure in the controlled portion of the three RCTs and the 205 placebo patients who were exposed to zonisamide in the RCT extensions.¹

Of the 976 patients in the primary database, 512 were exposed for 6 or more months and 343 were exposed for more than 1 year. When considering exposure by dose, 296 patients were exposed to at least 400 mg per day for over 1 year. There were also 345 patients who had at least one day of a maximum dose of 600-799 mg per day. I estimated this experience at about 300 PYs by using the sponsor's maximum dose by time table. There were also 71 patients who had at least one day at a maximum of 800 mg or above with about 50-100 PYs overall use.²

The supplementary database consists of [redacted] data for 596 patients and healthy volunteers. There were 346 patients in this database from studies that were prematurely terminated or that included patients with seizure types not included in this NDA.³ Of these, 40 had exposure for 1 year or more.

C. *Safety Findings in Phase 1 Studies*

¹Of the 230 placebo patients who entered the three RCTs, 205 went into the extensions.

²Patients counted at a maximum of 800 mg and above certainly had experience at 600-799, however, such exposure was not counted in that description. This approach attempts to give the minimum exposure at a dose, not to be an unbiased estimate of the total exposure at that specific daily doses.

³ There were 11 more patients in phase 1 studies in the supplementary database that were also included in the primary data.

There was 1 death in a 68 year old male occurring more than 30 days after a single zonisamide dose administered in a phase 1 study. There were 4 patients with one or more serious AEs that occurred during phase 1. One of these had hematuria, flank pain and nephrolithiasis that developed 4 days after last use after having been exposed to 400 mg per day for 24 days.

In a multidose pharmacokinetic study in healthy volunteers, an increase from baseline of serum creatinine was observed during the 30 days of zonisamide administration as shown in the Table below. As shown below, follow continued after exposure with patients seemingly obtaining their pretreatment values. Apparently BUNs were not collected. There were no reported clinical events in these healthy subjects and no explanation was offered by the sponsor.

APPENDIX C.7

Protocol B'0-926: An Open-Label, Multiple-Dose, Pharmacokinetic Study of NDA Formulation Zonisamide Capsules in Healthy Volunteers

Clinical Laboratory Results: Serum Chemistry

Chemistry Lab Test (Units)	Protocol Day	Panel	Mean	Median	Standard Deviation	Number	Min	Max
CREATININE (MG/DL)	DAY -1	Panel A	1.09	1.10	0.13	16		
		Panel B	1.05	1.10	0.12	8		
	DAY 8	Panel A	1.19	1.20	0.13	16		
		Panel B	1.14	1.10	0.15	8		
	DAY 15	Panel A	1.28	1.38	0.15	16		
		Panel B	1.24	1.20	0.15	8		
	DAY 22	Panel A	1.31	1.30	0.15	16		
		Panel B	1.24	1.20	0.19	8		
	DAY 29	Panel A	1.37	1.40	0.14	16		
		Panel B	1.30	1.25	0.19	8		
	DAY 36	Panel A	1.24	1.30	0.10	13		
		Panel B	1.19	1.10	0.22	7		
	DAY 56	Panel A	1.09	1.18	0.13	13		
		Panel B	1.10	1.20	0.14	5		
ALBUMIN (G/DL)	Screen	Panel A	4.42	4.45	0.28	16		
		Panel B	4.36	4.40	0.25	8		
	DAY -1	Panel A	4.52	4.58	0.25	16		

SOURCE: IRD-ROSTREIN DATA9304 LABEL.SAS January 23, 1997

APPENDIX C.7 Page 3 of 13

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D. Mortality in the Phase 2/3 Studies

1. All-Cause Mortality

The sponsor reported 22 deaths in the development program at the time the NDA was submitted, with 21 on zonisamide and 1 on placebo. Combining the experience in the

controlled portion of 922, 912EUR and 912US, there was 1 death in placebo (1/230 = 0.43%) and none on zonisamide.

Two additional zonisamide deaths were reported with the safety update (1763 & 1167) who were enrolled in an extension study. (Their dates of death were after the cut-off date for the update but the sponsor reported them anyway.)

Thus, we are aware of 23 deaths that occurred in patients taking zonisamide with 20 of these within 30 days of last use. Of the 3 deaths that were not within 30 days of last use, 1 occurred in phase 1 (noted above.) and another occurred in a patient lost to follow up. This patient was 27 year old male who apparently left the country and presumably did not have a source for continued exposure to the drug. There were no details on his death but it appears to have probably occurred more than 30 days after last use.⁴

Excluding the 3 deaths that happened more than 30 days after last exposure, the 2 deaths reported in the safety update, the 4 deaths in the supplementary database gives 14 deaths in the primary database for which we may have an estimate of person-time. Using the sponsor's estimate of 1000 PYs for the primary database gives an all-cause mortality rate of 1.4 per 100 PYs.⁵

2. Cause-Specific Mortality in Phase 2/3 Studies

As noted above there were 20 deaths counting those in the safety update that were within 30 days of last use. After reviewing the clinical data for these 20 deaths, there were none associated with a hematological, renal, hepatic, or dermatological AE. Individual deaths are summarized in the next two sections.

a) Sudden Unexplained Death

Of the 20 deaths within 30 days of last use, 6 may have been sudden and unexplained (SUD) in our opinion. The sponsor classified 5 of these 6 deaths as SUD, and according to the discussion in the ISS, 3 of these occurred in the primary database giving a SUD rate of 3 per 1000 patient-years. However, based upon the information in the ISS tables, all 6 may have been in the primary data base which would give a rate of 6 per 1000 PYs. The rates with topiramate and tiagabine were 5 and 4 per 1000 person-years, respectively.

All 6 SUDs are summarized below.

Patient 912-99 was a 22 year old male who was found dead in bed. He had been taking zonisamide for about 18 months. The last prescribed dose was 700 mg/day.

⁴ There were 2 additional deaths (912-30/2 and 912-59/10) for which there was insufficient information to verify the date of last use who were counted as 2 of the 18 deaths.

⁵ All-cause mortality was 0.8 per 100 PYs in the tiagabine NDA.

Patient 912-99 (5502/18) was a 55 year old female who was found dead. She was taking zonisamide for 2,641 days with the last dose of 700 mg/day along with another AED.

Patient 810-921 (5575/1522) was a 37 year old male who was also found dead. He was taking zonisamide 400 mg/day. His autopsy was reported as negative.

Patient 810-922 (6128/3123) was a 21 year old female who was found dead in bed. She was taking zonisamide for 629 days with her last dose 700 mg/day. Her autopsy was also reported as negative.

Patient 810-922 (6246/3155) was a 33 year old male who was found dead. He was taking zonisamide for 421 days with the last dose being 300 mg/day. His autopsy was also reported as negative.

Patient 912-30/2 was a 50 year old male waiting to enroll in a compassionate use study. He died suddenly and had been on 500 mg per day for 2.5 years. Exact date of last dose unknown but probably within 30 days.

b) Other Causes

Of the 14 remaining patients whose death was within 30 days of the last dose of zonisamide, 5 deaths may have been related to epilepsy and are summarized below.

Patient 912-6/12 - 35 yo F -found dead in bed with her tongue chewed, presumably from a seizure after receiving 500 mg/day of zonisamide for 46 months.

Patient 912-32/8 - 43 yo M drowned, possibly as a result of a seizure.

Patient 810-921, 5679/1166 - 52 yo M - cardiac arrest while having a generalized tonic-clonic seizure during an ECG after taking zonisamide for 14 months with his last dose being 400 mg/day.

Patient 810-922, 6128/3126 - 67- yo M - experienced 3 tonic-clonic seizures with cardiopulmonary arrest during the 3 seizure after taking zonisamide for 9 months with the last dose 400 mg/day; an autopsy was not performed.

Patient 912-47/19 - 29 yo F- fell from a porch, was impaled on a stake in a planter after taking zonisamide 100 mg/day for 4 days; her plasma levels were below therapeutic levels at the time of her death.

The remaining 9 deaths are summarized below.

Patient 912-58/4 was a 27 year old male who died of pneumonia and cardiac failure 1 week after his last dose of zonisamide (300mg/day). He was on zonisamide for 15 days of treatment.

Patient 912-59/4 was a 33 year old male who also died with a respiratory tract infection 14 days after being hospitalized and discontinuing zonisamide. He had been on zonisamide for 49 days with a final dose of 200mg/day.

Patient 912-59/10 was a 18 year old female who died with a glioblastoma at an unspecified time after stopping zonisamide 300 mg/day following 98 days of use.

Patient 912-99, 5503/20 was a 61 year old female who died of breast carcinoma after taking zonisamide for 2,912 days.

Patient 810-920, 5574/5602 was a 49 year old female hospitalized for pulmonary embolism possibly secondary to thrombophlebitis of the leg after taking zonisamide for about 635 days with a final dose of 600 mg/day.

Patient 810-921, 5650/1088 was a 41 year old male who had a sudden death. His autopsy demonstrated a large subarachnoid hemorrhage. He took zonisamide for 149 days with a final dose of 600 mg/day.

Patient 810-921, 5652/1490 was a 48 year old male with a history of postictal depression. He committed suicide by a gunshot wound to the head after postictal paranoia developed after a seizure. He took zonisamide for 5 days at dose of 100 mg/day.

Safety update deaths

Patient 810-921, 5579/1763 was a 50 year old male who drowned after being swept out to sea while swimming. He had taken zonisamide for more than 2 years in protocol 810-921 and had been seizure free for 2.5 years. His last dose was 400mg/day along with carbamazepam at 1800mg/day.

Patient 810-921, 5679/1167 was 25 year old male who fell from a roof requiring hospitalization and respirator support for 3 days prior to expiring. He had been titrated up to 500mg/day of zonisamide from 400mg/day and was also taking carbamazepam 700mg/day.

E. Serious AEs

Neither the ISS nor the safety update enumerated the total number of patients who experienced one or more serious AEs. In the sponsor's table of serious AEs in the NDA, we counted 273 serious AEs with 60 serious AEs reported in the update.

1. Serious AE Risk in the RCTs

In study 922, there was no material difference in serious AE occurrence between zonisamide and placebo during the controlled portion. For zonisamide, there were 7 serious AEs that occurred in 7 patients (7/118 = 6% of patients had a serious AE). For placebo, there were there were 6 serious AEs that occurred in 6 patients (6/85 = 7% of patients had a serious AE). The serious AEs with zonisamide consisted of a thyroid nodule, recurrence of anal fistula, nausea/vomiting/anorexia, pneumonia, status epilepticus, severe ataxia, and paranoia/delirium. Of these 7 patients, 2 dropped out of study because of this event (bolded above).

In study 912US, there was about a 2.5 fold increase in overall serious AE occurrence with zonisamide. In the zonisamide group, there were 11 serious AEs that occurred in 8 patients on zonisamide so that 10.3% of patients assigned zonisamide had at least one serious AE ($8/78 = 10.3\%$). In the placebo group, there were 3 serious AEs that occurred in 3 patients ($3/74 = 4.0\%$ of patients had a serious AE). Of the 8 patients with serious AEs on zonisamide, the events consisted of depression/suicide attempt, cholestatic hepatitis, stroke, fractured leg, hallucinations/anxiety, intermittent tachycardia, cholecystitis, psychosis/attempted suicide. The patient with hepatitis continued drug with resolution of symptoms/findings. The patient with cholecystitis had it at baseline.

In study 912EUR, there were no serious AEs with placebo. For zonisamide, there were 2 serious AEs occurring in 2 patients ($2/73 = 2.7\%$). For the 2 patients with serious AEs on zonisamide, the events consisted of exanthema and hospitalization for seizure control.

2. Clinical Characteristics of Serious AEs in the Development Program Observed During Zonisamide Use

Epilepsy related events accounted for the largest proportion of serious AEs followed by events in the genitourinary, the CNS and cardiovascular systems. There were 10 patients who were identified by the sponsor with at least 1 status event with 1 patient dying during the event. There may have been 2 other patients not classified as status who died during the event (patient numbers 912-47/19 and 912-6/12). Both events were apparently unwitnessed and resulted in death.

The sponsor may have classified any renal calculi occurrence as serious. In the ISS and safety update, there were 26 patients who had at least one serious AE attributed to renal calculi. Of these, 9 were symptomatic with 1 patient hospitalized. In addition to the 26 patients, 5 more developed echogenic foci on ultrasound with 1 patient withdrawn from study. Overall, 7 patients were described as passing stones with 6 of these symptomatic.

There were 6 patients who attempted suicide (1 completed) and 12 patients coded by the sponsor as having a psychotic event, 8 patients coded with depression, 8 patients classified as having paranoid episodes (separate from the patients with a psychotic event), and 3 patients with hallucinations. Four patients had serious AEs that were coded as confusion. Three patients had serious AEs coded as ataxia.

Of the 12 patients identified by the sponsor as having events consistent with psychosis, all were hospitalized and 6 were discontinued from drug. One of the patients was enrolled in study 922 where the event occurred in the extension. One of the 10 patients had a positive rechallenge but continued drug at a lower dose.

Of the 8 patients classified by the sponsor as having paranoia, 7 were hospitalized. One

occurred in the controlled portion of 922. Of the three patients who were identified as having hallucinations, there was 1 positive rechallenge.

Across the development program, there were 5 cases of rash that were considered serious, none of which were classified by the sponsor as SJS or TEN. However, the clinical details and follow-up of these cases was limited for most. (Summarized below.)

There were 3 cases of a hematological event that was classified as serious with no confirmed cases of aplastic anemia or agranulocytosis. Two of these cases are summarized below. The third case, which was mentioned in the background section who had thrombocytopenia on rechallenge (912-201-358), could not be located. There were no serious events consistent with hepatic failure. There was one case of renal failure apparently cause by rhabdomyolysis resulting from status. Summaries for these cases follow.

Serious Hematological AEs

#179 (Protocol 912-CU) 5503/20 - breast cancer, anemia, death - 61 yo F - breast cancer reported after 1,306 days of zonisamide and anemia reported after 1,758 days of zonisamide and throughout compassionate use; also on carbamazepam 1000mg/day; zonisamide was stopped one day prior to death due to adverse events which were not specified in the narrative; discussion of hematologic lab values were not included in the narrative. While the patient had underlying cancer, we do not know much about the stage of cancer or the event that has been coded as anemia.

#160 (Protocol 16 wk baseline control) 912-44/3 - neutropenia - 38 yo M - developed progressive neutropenia on Day 38 and withdrawn due to neutropenia after 46 days of zonisamide therapy; was on 500mg/day zonisamide at time of withdrawal; also on phenytoin 500mg/day; medical history significant for neutropenia on carbamazepam; WBC counts were 3,800-1wk before study; 4,400- 3 wks into study; 2,300- Day 38 ; 2,100- Day 43; 4,700- Day 82 (normalized).

Serious Hepatic AEs

#56 (Protocol 912-US) 912-12/26 - 23 yo M - cholestatic hepatitis - diagnosed with cholestatic hepatitis on Day 6 while on zonisamide 100mg/day (plasma conc. = 2.1 ug/ml); concomitant drugs included carbamazepam 2000mg/day and phenytoin 330mg/day; developed rising alkaline phosphatase on Day -13 up to 560 U/L on Day 9 then falling to 227 U/L on Day 26 and normalizing to 117 U/L on Day 56; SGOT was elevated to 88 U/L on Day 7 rising to 100 U/L on Day 9 and normalizing to 23 by Day 26; SGPT was elevated at 82 on Day 1, peaking at 122 on Day 7 and normalizing to 10 by Day 56; zonisamide dose on Day 56 was 500mg/day (plasma conc. = 9.0 ug/ml). This event resolved on drug.

Serious Genitourinary AEs

#40 (Protocol 810-922) 5575/3144 - 33 yo M - dilantin toxicity, acute renal failure - took zonisamide during double-blind phase and continued on zonisamide 400mg/day in the open-label phase; on Day 296 (21 weeks into open-label) was noted to have signs of drug toxicity with phenytoin serum level of 36.7 ug/ml and was hospitalized and noted to have BUN of 39 mg/dL, creatinine of 6 mg/dL, and hemoglobin of 15.3 g/dL but discharged from hospital with phenytoin level of 14.4 ug/ml; returned to hospital 3 days later with nausea, vomiting, tiredness and confusion and was noted to have BUN of 97 mg/dL, creatinine of 12 mg/dL, hemoglobin of 11.3 g/dL, and leucocytosis; his condition was determined to be acute renal failure as a result of prior seizures that led to significant rhabdomyolysis and transient renal insufficiency; discharged from hospital with BUN of 52 mg/dL and creatinine of 3.0 mg/dL; continued on phenytoin 400 mg/day and zonisamide 400mg/day. Additional information was presented in the 4-month safety update for this patient which indicates that 1) the renal failure was thought to be due to phenytoin toxicity, 2) zonisamide was temporarily stopped during the second hospitalization (3 days); patient was without problems 3 weeks later at follow-up; patient continued in the study at the same zonisamide dose with concomitant phenytoin 400mg/day and Trilafon 8mg/day.

Serious Dermatological AEs

#42 (Protocol 810-922) 5581/3073 - 28 yo M - taking zonisamide 400/day; hospitalized on Day 574 during open-label portion of study with pruritic rash; left arm became inflamed and profusely drained and antibiotics started; had started lamotrigine on Day 530 but discontinued at hospitalization; concomitant medications included valproic acid 3500 mg/day and carbamazepam 1300 mg/day during double-blind with valproic acid tapered beginning Day 509 of open-label; patient also noted to have echogenic focus in the left kidney at screening and echogenic focus with shadowing at 12 months viewed as no change from screen when compared to screen.

#63 (Protocol 912-EUR) - 912-32/8 - exanthema - 43 yo M - on zonisamide during double-blind treatment; hospitalized with severe itching exanthema with urticaria all over the body 9 days after starting double-blind; zonisamide was discontinued and the rash resolved in 40 days; patient also taking primidone 1000mg/day; no further description provided in the narrative.

#148 (Protocol 912-US-EXT) - 912-12/25 - pruritic rash and periorbital edema - 28 yo F - on placebo during double-blind without AEs; on zonisamide 600mg/day when hospitalized and withdrawn on Day 66 from the open-label segment because of pruritic rash and periorbital edema; treated with prednisone 50mg/day, Benadryl 200mg/day, Atarax 100mg/day and discharged 4 days later with rash resolving about 1 week after zonisamide was stopped.; considered severe and drug-related by the investigator; also on concomitant carbamazepam 1000mg/day.

#162 (Protocol 16 Week Baseline Controlled) - 912-55/10 - rash - 41 yo F - on zonisamide 600mg/day when developed a pruritic confluent maculopapular rash on Day 38 and withdrawn from study on Day 43; considered severe and drug-related by the investigator; the sponsor states that there is no evidence to suggest that this case met the usual criteria for a serious event but was reported

as such by the investigator in response to pay special attention to events regarding skin.

#187 (Protocol 912-72) - 912-72/3 - allergic rash - 40 yo M - on zonisamide 400mg/day; developed a moderately severe allergic facial rash on Day 29 and hospitalized; zonisamide was stopped and the rash cleared within a few days; zonisamide 400mg/day was restarted on Day 36 but the narrative does not comment on recurrence of rash; concurrent AEDs were carbamazepin 700mg/day and clonazepam 3mg/day.

F. Discontinuations

1. Overall Dropout Irrespective of Cause

The sponsor did not enumerate the total number of dropouts or given a breakdown by cause focusing instead on patients who discontinued for AEs.

We reviewed the individual study reports for the RCTs to examine overall patient dropout. In study 922, there was no material difference in dropout by group either in the crude rate or when examining Kaplan-Meier curves. The zonisamide group lost 15% of assigned patients by day 48 while placebo lost 15% by day 50.

For US912 and EUR912, the zonisamide groups had significantly greater dropout than placebo in both studies. For the US study, the zonisamide group had lost 10% by day 21 while placebo had lost 10% by day 64.

2. AE Dropout

In the ISS, 287 patients were identified by the sponsor as dropping out for AE occurrence. The sponsor enumerated the most common causes of dropout as follows: 33 patients with "irritability", 86 patient with "somnolence, fatigue and/or ataxia", 31 patients with "concentration loss or difficulty", and 27 patients with "memory loss or other cognitive impairment".

Overall, there were 77 patients who dropped out of the RCTs because of AE occurrence. There was little difference in the AE dropout rates between zonisamide and placebo groups in study 922. In placebo, 8.2% (7/85) dropped out for AEs during weeks 1-12 and additional 6.9% (5/72) dropped out for AEs during weeks 13-20 when started on zonisamide. In the zonisamide group, 11.9% (14/118) dropped out for AEs during weeks 1-20. In studies US912 and EUR912, there were higher AE dropout rates with zonisamide. Across the RCTs, AE dropout appeared to correlate with increasing dose with 12 of the 18 patients reaching 800 mg dropping out.⁶

⁶ Although not well described in the ISS, these 18 patients at 800 mg or more may have all been in US912.

In the RCTs, the most common COSTARTs associated with dropout were somnolence, ataxia, fatigue, anorexia, irritability, dizziness, forgetfulness, trouble concentrating and confusion. There was one patient who dropped out with a rash (912-12/30). There no dropouts associated with hematological, hepatic or renal events that we could identify in the review.

Across the development program, the COSTART associated with dropout were generally consistent with the experience in the RCTs. There was one case of moderately severe anemia (summarized below) that did not contain sufficient clinical details for a full description and there was no follow up of the case. There were also several cases of serious skin rash that provided little follow-up.

Hematological AEs Associated with Dropout

912-201-358/ 2057 (page 249) - anemia - 16 yo M - withdrawn from study due to anemia after 166 days of treatment with zonisamide 200mg/day; baseline hemoglobin was 12.2 g/dL which fell to 6.9 g/dL on the day of withdrawal; cause of anemia was unknown but patient was treated with iron; the sponsor indicates that there are no details of follow-up. According the data in the NDA, the Hemoglobin was 10.2 on day 144. The value of 6.9, which was noted in the narrative, was not in the database. WBC and platelets were normal on day 144 but not reported for the day of dropout.

Dermatological AEs Associated with Dropout

912-5/ 6 (page 257) - edema, pharyngitis and rash - 36 yo F - experienced edema, pharyngitis and rash on Day 102 of zonisamide 200mg/day treatment; zonisamide was discontinued and the events resolved by Day 111; patient was not taking any other medication at the time of zonisamide discontinuation; considered moderate and drug-related by the investigator.

912-12/ 29 (page 231) - pruritic rash - 46 yo F - on placebo without AEs during double-blind phase; developed pruritic rash on Day 130 of open-label period and was withdrawn by the investigator while on zonisamide 500mg/day after 132 days of treatment; rash was treated with Benadryl and resolved within a few days after zonisamide discontinuation; rash considered moderate and drug-related by the investigator; concomitant medication included carbamazepam 1400mg/day and phenobarbital 30mg/day; was hospitalized for exacerbation of seizures the day after zonisamide discontinuation; during hospitalization phenobarbital was replaced with phenytoin 300mg/day.

912-12/ 30 (page 210) - rash - 55 yo M - withdrawn from study on Day 26 because of mild rash while taking zonisamide 300mg/day; rash cleared a few days after discontinuation; plasma zonisamide levels were 10.4 ug/ml on Day 21 and 15.8 ug/ml on Day 28; concomitant medications were carbamazepam 1300 mg/day and ibuprofen 600mg/day; also developed increased irritability and double vision after about 2 weeks of treatment.

912-13/ 31 (page 231) - decreased appetite, macular rash, swollen hands and feet, muscle aches, slowness of thought - 39 yo F - was on placebo during

double-blind phase; discontinued open-label period after 49 days of treatment with zonisamide because of AEs; decreased appetite by Day 17 on 200mg/day, slowness of thought by Day 31, macular rash by Day 46, swollen hands and feet and muscle aches by Day 47; on zonisamide 400mg/day at time of discontinuation; rash and slowness of thought resolved before zonisamide discontinuation without medical intervention.; concomitant medications were carbamazepam 1000mg/day and phenytoin 400mg/day.

912-45/ 13 (page 243) - rash - 30 yo M - developed severe rash on study Day 70 and was withdrawn from study by the investigator on Day 78; patient was taking zonisamide 500mg/day and phenytoin 400mg/day; rash resolved 4 weeks after zonisamide discontinuation; no previous medical history of rash or allergies; rash considered severe and related by the investigator.

912-69/ 3 (page 254) - erythematous rash - 25 yo M - developed severe generalized erythematous rash after taking zonisamide 200mg/day for 14 days; concomitant medications were phenytoin 400mg/day and primidone 750mg/day; rash considered drug-related by the investigator; one week after zonisamide was discontinued developed dizziness and ataxia attributed to phenytoin.

5575/ 1521 (page 222) - rash - 33 yo F - discontinued zonisamide (dose not specified) after developing a red pruritic rash over trunk and extremities on Day 8 of treatment; treated with diphenhydramine and rash resolved in 3 days; concomitant medication included valproic acid 3750mg/day; medical history significant for asthma and allergic reaction (rash) to aspirin, co-trimoxazole, phenytoin and PCN.

5579/ 5764 (page 216) urticaria - 43 yo M - developed urticaria after 26 days of treatment with zonisamide 400mg/day and was discontinued from the study on Day 27 with the urticaria resolving the following day; plasma zonisamide levels were 4.8 ug/ml on Day 15 and 4.4 ug/ml on Day 29; concomitant medications were phenytoin 400mg/day and clonazepam 1.5mg/day.

5652/ 1483 (page 227) - fatigue, rash, burning throat - 44 yo F - discontinued zonisamide (dose not specified) due to fatigue, rash, burning throat after 88 days of treatment; diphenhydramine treatment was ineffective; phenobarbital 60mg/ day was a concomitant drug but was tapered to discontinuation by Day 43; past medical history significant for allergic rash to carbamazepam and phenytoin.

5652/ 1489 (page 228) - rash - 32 yo M - discontinued zonisamide 400mg/day treatment on Day 29 due to a rash which appeared on Day 28; treated with diphenhydramine and rash resolved by Day 39; carbamazepam 1800mg/day was concomitant.

5968/ 1653 (page 230) - dermatitis - 42 yo F - decided to discontinue zonisamide treatment on Day 27 because of dermatitis which appeared on Day 16 when being given 200mg/day and was treated with diphenhydramine while zonisamide was increased to 400mg/day; zonisamide was tapered with last dose given on Day 36; carbamazepam 1000mg/day and lorazepam 1-2mg prn for seizure flurry were concomitant.

912-6/9 (page 262) - rash - 37 yo F - experienced a rash on Day 7 of zonisamide 400mg/day treatment; rash resolved on Day 14 but zonisamide was discontinued on Day 16; phenobarbital 120mg/day and phenytoin 400mg/day were concomitant.

912-202-64/ 2109 (page 250) - rash - 24 yo F - discontinued from study on Day 14 while on zonisamide 200mg/day due to a mild rash on her elbow, wrist, ankles and legs which first appeared on Day 4 while taking zonisamide 100mg/day; rash resolved on Day 22; phenytoin 300mg/day was concomitant.

G. AEs in Controlled Studies

1. Common AE Occurrence in the Primary and Supplementary Databases

The table below shows the number and percent of patients reporting AEs across the RCTs and has been condensed from the sponsors Table 8h-17b (S8 Vol 314 P60). It lists AEs which occurred in zonisamide-treated patients at a frequency of 1% and were 2 times greater than in placebo.

AEs in Placebo-controlled Trials		
AE	Zonisamide (N = 269) n (%)	Placebo (N = 230) n (%)
Stomach pain or irritation	20 (7.4)	4 (1.7)
Diarrhea	14 (5.2)	6 (2.6)
Constipation	8 (3.0)	2 (0.9)
Mouth of throat dry	7 (2.6)	2 (0.9)
Ataxia	45 (16.7)	13 (5.7)
Dysarthria	21 (7.8)	5 (2.2)
Forgetfulness	19 (7.1)	5 (2.2)
Nystagmus	14 (5.2)	6 (2.6)
Confusion	15 (5.6)	3 (1.3)
Paresthesia	13 (4.8)	3 (1.3)
Irritability	31 (11.5)	12 (5.2)
Depression	20 (7.4)	7 (3.0)

Trouble concentrating	22 (8.2)	2 (0.9)
Anxiety	15 (5.6)	6 (2.6)
Paranoia	5 (1.9)	1 (0.4)
Hallucination	4 (1.5)	0 (0.0)
Cough	4 (1.5)	1 (0.4)
Rash	8 (3.0)	3 (1.3)
Skin laceration	9 (3.3)	1 (0.4)
Diplopia	24 (8.9)	10 (4.3)
Dysguesia	6 (2.2)	1 (0.4)
Male sexual dysfunction	3 (1.8)	0 (0.0)

While most of the events that seem to be related to zonisamide use are not unexpected and, in fact, are similar to those seen with topiramate, the increases GI events and cough was somewhat unexpected. There was no discussion of these events in the ISS.

a) AE Occurrence by Age, Gender, Dose, and Time in the Primary Database

The sponsor examined the effect of age, gender, dose and time on AE occurrence across the primary database. A separate analysis across the RCTs was not performed making the findings difficult to interpret since there was no comparison with placebo.

The effect of plasma concentration was also examined in the ISS, but in a pooled analysis. Studies also varied as to timing of measurement and there were no AEs which when incident required measurement of plasma levels.

2. AE Occurrence in Study 922

In the sponsor's Table 20, which is shown below, all AEs that occurred in 2 or more patients in any one treatment group are listed. We have bolded AEs that occurred in 1% or greater of patients assigned zonisamide and that were 2 fold greater than placebo over weeks 1-12.

Table 20 Treatment-Emergent Adverse Events Reported in Two or More Patients in Any Treatment During Weeks 1-5, 1-12, and 13-20

Weeks 1-5

Weeks 1-12

Weeks 13-20

Body System Adverse Event	Grp A	B1	B2	Grp A	B1+ B2	Grp A	B1+ B2
	(PLB) (N= 85) N(%)	(ZNS) (N= 60) N(%)	(ZNS) (N= 58) N(%)	(PLB) (N= 85) N(%)	(ZNS) (N= 118) N(%)	(ZNS) (N= 72) N(%)	(ZNS) (N= 95) N(%)
BODY AS A WHOLE	26 (30.6)	11 (18.3)	11 (19.0)	39 (45.9)	41 (34.7)	16 (22.2)	15 (15.8)
Headache	10 (11.8)	3 (5.0)	6 (10.3)	11 (12.9)	11 (9.3)	4 (5.6)	1 (1.1)
Fatigue	8 (9.4)	2 (3.3)	3 (5.2)	12 (14.1)	11 (9.3)	7 (9.7)	3 (3.2)
Viral Illness	2 (2.4)	2 (3.3)	2 (3.4)	8 (9.4)	8 (6.8)	2 (2.8)	1 (1.1)
Ache/ pain	3 (3.5)	2 (3.3)	2 (3.4)	5 (5.9)	6 (5.1)	2 (2.8)	1 (1.1)
Weight Change	3 (3.5)	0 (0.0)	1 (1.7)	4 (4.7)	5 (4.2)	3 (4.2)	2 (2.1)
Tension Headache	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	3 (2.5)	0 (0.0)	0 (0.0)
Edema	2 (2.4)	1 (1.7)	0 (0.0)	4 (4.7)	2 (1.7)	0 (0.0)	0 (0.0)
Asthenia	5 (5.9)	0 (0.0)	0 (0.0)	5 (5.9)	1 (0.8)	0 (0.0)	1 (1.1)
Allergy	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	1 (0.8)	0 (0.0)	0 (0.0)
Drug Toxicity	2 (2.4)	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)	1 (1.4)	0 (0.0)
Thirst	1 (1.2)	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)	1 (1.4)	0 (0.0)
Fever	2 (2.4)	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	1 (1.1)
Surgery	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	1 (1.4)	2 (2.1)
Trauma	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)	1 (1.4)	2 (2.1)
DIGESTIVE SYSTEM	21 (24.7)	13 (21.7)	12 (20.7)	32 (37.6)	45 (38.1)	20 (27.8)	14 (14.7)
Anorexia	3 (3.5)	4 (6.7)	5 (8.6)	8 (9.4)	17 (14.4)	9 (12.5)	3 (3.2)
Nausea And/ or Vomiting	8 (9.4)	4 (6.7)	3 (5.2)	15 (17.6)	14 (11.9)	7 (9.7)	4 (4.2)
Diarrhea	2 (2.4)	2 (3.3)	1 (1.7)	3 (3.5)	11 (9.3)	0 (0.0)	1 (1.1)
Stomach Pain/ irritation	1 (1.2)	3 (5)	1 (1.7)	1 (1.2)	9 (7.6)	3 (4.2)	2 (2.1)
Mouth/ throat Dry	1 (1.2)	1 (1.7)	3 (5.2)	1 (1.2)	6 (5.1)	1 (1.4)	0 (0.0)
Stomatitis	1 (1.2)	0 (0.0)	2 (3.4)	1 (1.2)	3 (2.5)	2 (2.8)	0 (0.0)
Abdominal Distress	3 (3.5)	0 (0.0)	1 (1.7)	4 (4.7)	2 (1.7)	0 (0.0)	2 (2.1)
Constipation	1 (1.2)	0 (0.0)	0 (0.0)	2 (2.4)	1 (0.8)	1 (1.4)	2 (2.1)
Gingivitis	0 (0.0)	0 (0.0)	1 (1.7)	2 (2.4)	1 (0.8)	2 (2.8)	2 (2.1)
Dental Abnormalities	1 (1.2)	0 (0.0)	0 (0.0)	3 (3.5)	0 (0.0)	1 (1.4)	2 (2.1)
HEMIC & LYMPHATIC SYST DISORDER	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	2 (2.1)
Purpura	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	2 (2.1)
MUSCULOSKELETAL SYSTEM	13 (15.3)	5 (8.3)	7 (12.1)	14 (16.5)	20 (16.9)	6 (8.3)	7 (7.4)
Myalgia	5 (5.9)	2 (3.3)	1 (1.7)	5 (5.9)	5 (4.2)	1 (1.4)	2 (2.1)
Soft Tissue Injury	3 (3.5)	1 (1.7)	2 (3.4)	3 (3.5)	5 (4.2)	3 (4.2)	1 (1.1)
Back Pain	2 (2.4)	0 (0.0)	1 (1.7)	2 (2.4)	4 (3.4)	2 (2.8)	3 (3.2)
Arthralgia	1 (1.2)	1 (1.7)	1 (1.7)	1 (1.2)	2 (1.7)	0 (0.0)	0 (0.0)

Muscle Spasm/ stiffness	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)
Muscle Injury	2 (2.4)	0 (0.0)	1 (1.7)	2 (2.4)	1 (0.8)	0 (0.0)	1 (1.1)
Fracture	1 (1.2)	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
NERVOUS SYSTEM	23 (27.1)	20 (33.3)	16 (27.6)	39 (45.9)	61 (51.7)	31 (43.1)	21 (22.1)
Somnolence	8 (9.4)	11 (18.3)	3 (5.2)	13 (15.3)	18 (15.3)	5 (6.9)	2 (2.1)
Dizziness	7 (8.2)	6 (10)	4 (6.9)	12 (14.1)	16 (13.6)	7 (9.7)	9 (9.5)
Ataxia	3 (3.5)	2 (3.3)	4 (6.9)	6 (7.1)	12 (10.2)	5 (6.9)	3 (3.2)
Dysarthria	2 (2.4)	2 (3.3)	2 (3.4)	4 (4.7)	9 (7.6)	5 (6.9)	2 (2.1)
Insomnia	3 (3.5)	4 (6.7)	2 (3.4)	6 (7.1)	8 (6.8)	5 (6.9)	0 (0.0)
Nystagmus	1 (1.2)	0 (0.0)	1 (1.7)	3 (3.5)	7 (5.9)	2 (2.8)	3 (3.2)
Forgetfulness	1 (1.2)	1 (1.7)	0 (0.0)	3 (3.5)	6 (5.1)	4 (5.6)	3 (3.2)
Paresthesia	1 (1.2)	0 (0.0)	1 (1.7)	4 (4.7)	5 (4.2)	1 (1.4)	1 (1.1)
Tremor	3 (3.5)	1 (1.7)	1 (1.7)	7 (8.2)	4 (3.4)	2 (2.8)	3 (3.2)
Confusion	2 (2.4)	1 (1.7)	1 (1.7)	2 (2.4)	3 (2.5)	3 (4.2)	2 (2.1)
Lethargy	1 (1.2)	0 (0.0)	2 (3.4)	2 (2.4)	2 (1.7)	2 (2.8)	0 (0.0)
Perception Disorder	0 (0.0)	0 (0.0)	1 (1.7)	1 (1.2)	2 (1.7)	0 (0.0)	0 (0.0)
Epileptic Seizure	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.2)	1 (0.8)	0 (0.0)	1 (1.1)
Incr Seizure Activity	1 (1.2)	0 (0.0)	0 (0.0)	2 (2.4)	1 (0.8)	1 (1.4)	1 (1.1)
Motor Function Slowed	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Twitching	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.2)	1 (0.8)	2 (2.8)	0 (0.0)
Status Epilepticus	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	2 (2.1)
Fall	1 (1.2)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperkinesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.1)
PSYCHOBIOLOGIC FUNCTION	9 (10.6)	7 (11.7)	8 (13.8)	16 (18.8)	31 (26.3)	16 (22.2)	8 (8.4)
Depression	3 (3.5)	2 (3.3)	1 (1.7)	5 (5.9)	8 (6.8)	2 (2.8)	0 (0.0)
Irritability	2 (2.4)	2 (3.3)	2 (3.4)	6 (7.1)	7 (5.9)	2 (2.8)	0 (0.0)
Anxiety	1 (1.2)	1 (1.7)	2 (3.4)	2 (2.4)	5 (4.2)	1 (1.4)	1 (1.1)
Slowness of Thought	3 (3.5)	0 (0.0)	2 (3.4)	4 (4.7)	4 (3.4)	5 (6.9)	4 (4.2)
Trouble Concentrating	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	4 (3.4)	2 (2.8)	0 (0.0)
Hallucination	0 (0.0)	1 (1.7)	1 (1.7)	0 (0.0)	3 (2.5)	0 (0.0)	0 (0.0)
Emotional Lability	1 (1.2)	1 (1.7)	0 (0.0)	5 (5.9)	3 (2.5)	3 (4.2)	1 (1.1)
Hostility	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	2 (1.7)	0 (0.0)	1 (1.1)
Paranoia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)
Behavioral Changes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)	1 (1.4)	0 (0.0)
Apathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.8)	0 (0.0)
RESPIRATORY SYSTEM	11 (12.9)	9 (15)	6 (10.3)	20 (23.5)	29 (24.6)	8 (11.1)	12 (12.6)
Rhinitis	7 (8.2)	7 (11.7)	3 (5.2)	13 (15.3)	17 (14.4)	5 (6.9)	7 (7.4)
Cough	1 (1.2)	0 (0.0)	2 (3.4)	1 (1.2)	5 (4.2)	0 (0.0)	2 (2.1)

Sinusitis	1 (1.2)	1 (1.7)	1 (1.7)	2 (2.4)	4 (3.4)	1 (1.4)	0 (0.0)
Pharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	4 (3.4)	1 (1.4)	2 (2.1)
Dyspnea	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	2 (1.7)	0 (0.0)	0 (0.0)
Bronchitis	2 (2.4)	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
SKIN & APPENDAGES	7 (8.2)	11 (18.3)	11 (19)	16 (18.8)	33 (28.0)	9 (12.5)	7 (7.4)
Skin Laceration	1 (1.2)	1 (1.7)	2 (3.4)	1 (1.2)	9 (7.6)	1 (1.4)	2 (2.1)
Rash	2 (2.4)	2 (3.3)	3 (5.2)	3 (3.5)	7 (5.9)	1 (1.4)	0 (0.0)
Abrasion	1 (1.2)	3 (5)	0 (0.0)	2 (2.4)	4 (3.4)	0 (0.0)	1 (1.1)
Diaphoresis	0 (0.0)	1 (1.7)	1 (1.7)	0 (0.0)	3 (2.5)	0 (0.0)	0 (0.0)
Puncture Wound	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)
Skin Nodules	0 (0.0)	1 (1.7)	1 (1.7)	0 (0.0)	2 (1.7)	0 (0.0)	1 (1.1)
Abscess	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)
Nail Disorders	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)
Alopecia	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)
Burn	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)
Mycotic Infection	0 (0.0)	1 (1.7)	0 (0.0)	2 (2.4)	2 (1.7)	2 (2.8)	0 (0.0)
Acne	0 (0.0)	1 (1.7)	0 (0.0)	2 (2.4)	1 (0.8)	1 (1.4)	0 (0.0)
Cyst	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	1 (0.8)	0 (0.0)	0 (0.0)
Pruritus	2 (2.4)	0 (0.0)	0 (0.0)	4 (4.7)	0 (0.0)	1 (1.4)	0 (0.0)
SPECIAL SENSES	7 (8.2)	7 (11.7)	5 (8.6)	10 (11.8)	20 (16.9)	8 (11.1)	9 (9.5)
Diplopia	4 (4.7)	2 (3.3)	2 (3.4)	4 (4.7)	8 (6.8)	3 (4.2)	4 (4.2)
Blurred Vision	3 (3.5)	0 (0.0)	2 (3.4)	3 (3.5)	4 (3.4)	2 (2.8)	2 (2.1)
Dysgeusia	0 (0.0)	1 (1.7)	1 (1.7)	1 (1.2)	4 (3.4)	1 (1.4)	0 (0.0)
Tinnitus	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)
Otalgia	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	2 (1.7)	1 (1.4)	0 (0.0)
Conjunctivitis	1 (1.2)	1 (1.7)	0 (0.0)	1 (1.2)	1 (0.8)	1 (1.4)	2 (2.1)
UROGENITAL SYSTEM	5 (5.9)	1 (1.7)	1 (1.7)	12 (14.1)	7 (5.9)	3 (4.2)	3 (3.2)
Menstrual Disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	2 (1.7)	1 (1.4)	0 (0.0)
Urinary Tract Infection	3 (3.5)	1 (1.7)	0 (0.0)	3 (3.5)	1 (0.8)	1 (1.4)	0 (0.0)
Renal Calculi	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.5)	1 (0.8)	0 (0.0)	0 (0.0)
Polyuria	1 (1.2)	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	1 (1.1)

As before, cough and GI symptoms were increased on zonisamide. Skin rash occurrence was not as strongly associated with zonisamide use.

a) AE Occurrence by Age, Gender, Dose, and Time in Study 922

The sponsor examined the effects of age on AE occurrence in study 922 [Appendix

C.15.2 (weeks 1-12) and C.15.3 (weeks 13-20)]. Below is a table condensed from Appendix C.15.2 which lists AEs observed in at least 3% of patients on zonisamide. For the most part, there were too few patients for comparison. The only finding, of note, was that ataxia was associated with zonisamide use in the older age group.

AEs by Age in Study 810-922 For Weeks 1 -12				
	12 - 40 year age group		>40 - 65 year age group	
	Placebo (Group A) N = 62 n (%)	Zonisamide (Groups B1 + B2) N = 82 n (%)	Placebo (Group A) N = 21 n (%)	Zonisamide (Groups B1 + B2) N = 34 n (%)
Tension Headache	0 (0.0)	3 (3.7)	0 (0.0)	0 (0.0)
Anorexia	7 (11.3)	13 (15.9)	1 (4.8)	4 (11.8)
Nausea and/or Vomiting	14 (22.6)	6 (7.3)	1 (4.8)	8 (23.5)
Diarrhea	2 (3.2)	7 (8.5)	1 (4.8)	4 (11.8)
Stomach Pain/ Irritation	0 (0.0)	7 (8.5)	1 (4.8)	2 (5.9)
Mouth/ Throat Dry	0 (0.0)	3 (3.7)	0 (0.0)	3 (8.8)
Stomatitis	1 (1.6)	1 (1.2)	0 (0.0)	2 (5.9)
Soft Tissue Injury	2 (3.2)	2 (2.4)	1 (4.8)	3 (8.8)
Back Pain	0 (0.0)	3 (3.7)	2 (9.5)	1 (2.9)
Somnolence	11 (17.7)	12 (14.6)	2 (9.5)	5 (14.7)
Dizziness	11 (17.7)	10 (12.2)	1 (4.8)	6 (17.6)
Dysarthria	4 (6.5)	7 (8.5)	0 (0.0)	2 (5.9)
Ataxia	4 (6.5)	5 (6.1)	1 (4.8)	7 (20.6)
Nystagmus	2 (3.2)	7 (8.5)	1 (4.8)	0 (0.0)
Tremor	7 (11.3)	2 (2.4)	0 (0.0)	2 (5.9)
Forgetfulness	2 (3.2)	4 (4.9)	0 (0.0)	2 (5.9)
Confusion	2 (3.2)	1 (1.2)	0 (0.0)	2 (5.9)
Depression	3 (4.8)	5 (6.1)	1 (4.8)	3 (8.8)
Slowness of Thought	3 (4.8)	2 (2.4)	0 (0.0)	2 (5.9)
Anxiety	2 (3.2)	2 (2.4)	0 (0.0)	3 (8.8)

Trouble Concentrating	0 (0.0)	4 (4.9)	0 (0.0)	0 (0.0)
Hallucination	0 (0.0)	3 (3.7)	0 (0.0)	0 (0.0)
Paranoia	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.9)
Sinusitis	2 (3.2)	2 (2.4)	0 (0.0)	2 (5.9)
Cough	0 (0.0)	3 (3.7)	1 (4.8)	1 (2.9)
Rash	1 (1.6)	6 (7.3)	2 (9.5)	1 (2.9)
Skin Laceration	1 (1.6)	6 (7.3)	0 (0.0)	3 (8.8)
Abrasion	1 (1.6)	4 (4.9)	1 (4.8)	0 (0.0)
Diplopia	4 (6.5)	8 (9.8)	0 (0.0)	0 (0.0)
Blurred Vision	3 (4.8)	2 (2.4)	0 (0.0)	2 (5.9)
Dysguesia	0 (0.0)	2 (2.4)	0 (0.0)	2 (5.9)
Tinnitus	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.9)

The sponsor also examined the effect of gender [weeks 1-12 in Appendix C.15.4 (weeks 1-12) and C.15.5 (weeks 8-12)]. As with age, the following table focuses on AEs that occurred in at least 3% of patients on zonisamide over weeks 1-12. As before, there were limited numbers of patients for many cells. There were no striking findings except for possibly insomnia where females were at increased risk but males were not.

AEs by Gender in Study 810-922 For Weeks 1 -12				
	Male		Female	
	Placebo (Group A) N = 35 n (%)	Zonisamide (Groups B1 + B2) N = 69 n (%)	Placebo (Group A) N = 50 n (%)	Zonisamide (Groups B1 + B2) N = 49 n (%)
Weight Change	4 (11.4)	1 (1.5)	0 (0.0)	4 (8.2)
Tension Headache	0 (0.0)	1 (1.5)	0 (0.0)	2 (4.1)
Nausea and/or Vomiting	9 (25.7)	6 (8.7)	6 (12)	8 (16.4)
Anorexia	3 (8.6)	8 (11.6)	5 (10)	9 (18.4)
Diarrhea	2 (5.7)	8 (11.6)	1 (2)	3 (6.1)
Stomach Pain/ Irritation	0 (0.0)	6 (8.7)	1 (2)	3 (6.1)

Mouth/ Throat Dry	0 (0.0)	2 (2.9)	1 (2)	4 (8.2)
Somnolence	4 (11.4)	13 (18.8)	9 (18)	5 (10.2)
Dysarthria	1 (2.9)	6 (8.7)	3 (6)	3 (6.1)
Insomnia	3 (8.6)	2 (2.9)	3 (6)	6 (12.2)
Ataxia	0 (0.0)	4 (5.8)	6 (12)	8 (16.4)
Nystagmus	1 (2.9)	3 (4.4)	2 (4)	4 (8.2)
Trouble Concentrating	0 (0.0)	3 (4.4)	0 (0.0)	1 (2)
Depression	1 (2.9)	1 (1.5)	4 (8)	7 (14.3)
Cough	0 (0.0)	4 (5.8)	1 (2)	1 (2)
Dyspnea	1 (2.9)	0 (0.0)	0 (0.0)	2 (4.1)
Skin Laceration	1 (2.9)	6 (8.7)	0 (0.0)	3 (6.1)
Rash	0 (0.0)	4 (5.8)	3 (6)	3 (6.1)
Diaphoresis	0 (0.0)	3 (4.4)	0 (0.0)	0 (0.0)
Diplopia	3 (8.6)	4 (5.8)	1 (2)	4 (8.2)

There was no analysis of AE risks by dose or plasma concentration for study 922.

H. Laboratory Findings

1. Collection of Laboratory Data in the Development Program

Laboratory analyte evaluations were performed at baseline, at specified intervals during the different studies and at study endpoint or termination. In addition, evaluations occurred every 6 months in the extension studies.

In the RCTs, the final laboratory evaluation was at week 12 for EUR912 and US912, and at week 20 for 922. For US study 912, laboratory evaluation was conducted at weeks 1, 2, 4, 8, and 12, and in 922 at 5, 7, 12, and 20.

2. Sponsor's Approach To Analyzing the Laboratory Data

For laboratory data for patients in the primary database, the sponsor conducted a pooled analysis for the full dataset and then for the RCTs separately. The RCT analysis focused on selected laboratory tests. These analyses focused on mean changes as well as

on patients who developed clinically meaningful laboratory changes during treatment. To define clinically significant lab values, the sponsor used the values in a table presented at the FDA workshop on good review practices for safety. The effect of dose was examined by using the patient's modal dose over the study period.

Laboratory data for patients in the supplementary database were presented as simple line listings.

3. FDA Approach to the Review of Laboratory Data

In addition to examining the sponsor's findings for the primary database, clinically significant changes were examined for each RCT separately and as reported in the safety update. The line listings for patients in the supplementary database were also reviewed. Patient narratives and CRF tabulations were examined for patients who died, dropped out for AEs or had serious AEs.

4. Overall Findings

a) Change from Baseline in RCTs

The sponsor's table 8h-33 (volume 314 in NDA) shows the mean baseline and endpoint values as well as the percentage change in the means for selected analytes (did not include sodium, potassium or chloride). There were statistically significant increases in creatinine and alkaline phosphatase, and a decrease in phosphorus.

b) Clinically Significant Changes in the RCTs

Sponsor's appendix 8h-A.26 shows the percentage of patients by treatment group who developed a clinically significant laboratory value who also had a normal baseline value. For some studies, specifically study 922, the sponsor used the endpoint instead of the maximum value. The decrease in phosphorous noted in the mean change analysis was reflected by a larger percentage of patients on zonisamide who developed clinically significant decreases. The incidence of hematuria was no different between zonisamide and placebo.

The table indicates that only one patient across the RCTs had a clinically significant increase in creatinine. However, based upon our review of the individual study reports for each RCT, there should have been 3 patients included in this table. In our review of the CRF tabulations for the patient identified as having a creatinine of 7, this appears to have been laboratory error since subsequent BUNs and creatinines were all normal.

In review of deaths, dropouts and serious AEs, we found no patients with clinically significant SGOT or ALP values, or decreases with phosphorous. We could find no patients with any evidence of decreased renal function.

There were two patients who developed thrombocytopenia on zonisamide and none on placebo.

Subject 3142 [redacted] a 28YOF enrolled in group A had a baseline value (day1) of 297000. On study day 130 (dose of zonisamide recorded as 400 mg) the platelet count was 119000.

3201: No information is available.

Finally, one patient was reported to have a hemoglobin of 3.7 g/dl, but we could not locate any information on this patient including the ID number.

c) Mean Changes and Clinically Significant Changes in Study 922

We also examined study 922 separately. There was a statistically decrease in WBC and increases in alkaline phosphatase, creatinine, uric acid and chloride.

From baseline to week 12, the mean WBC decrease was about 300 for zonisamide compared to an increase of about 300 in placebo. The mean increase in alkaline phosphatase value was 4 IU/L in zonisamide compared to no change in placebo. Creatinine increased from 0.99mg/dl to 1.1mg/dl in zonisamide with no change in placebo. Chloride increased from a mean of 104 mm/L to 106 mm/L while there was no change in placebo.

Of the 117 patients assigned zonisamide and for which there were corresponding laboratory data, 14 (12%) had clinically significant increases in alkaline phosphatase at week 12, compared to 2 patients (2.4%) in placebo. Nine patients⁷ exposed to zonisamide had clinically significant leukopenia at week 20. Since the sponsor focused on week 20 we could not tell if there were any cases with placebo in the first 12 weeks. (Placebo patients switched to drug after 12 weeks.) There were no cases of agranulocytosis or aplastic anemia. Of the 9, none discontinued. Four of the more typical cases of leukopenia are summarized below.

Patient number 3029 [redacted] a 44YOF (supplemental data from appendix D22.1, volume 71, p.207) had a WBC count of 6100 on day 1 not 3700 as shown in the table. On day 183, after approximately 133 days of exposure to the 400 mg dose of zonisamide, the WBC count was reported to have decreased to 2900 . The dose of zonisamide recorded at that time was 400 mg. The WBC count was 3700 after 6 months.

⁷ Eight were shown in the table but patient 3046 [redacted] from group B1 listed in volume 77 developed a clinically significantly decrease in WBC 2600 by day 50.

3072 [redacted] (data from volume 71, p.69) was a 33YOM enrolled in group A. His baseline (day 1) WBC count was 3200. After exposure to a 400 mg dose of zonisamide (how long), the WBC count was reported to be 2700. Follow up values were unavailable. There were no other changes in the hemogram.

3019 [redacted] (data from volume 71, p.326) was a 67YOF enrolled in group A. Her baseline (day 1) WBC count was 3900. After exposure to a 400 mg dose of zonisamide (how long), the WBC was 2800. Follow up values were unavailable. There were no other changes in the hemogram.

3040 [redacted] (data from volume 71, p.408) was a 60YOF enrolled in group B2. Her baseline WBC count was 3000. After exposure to a 400 mg dose of zonisamide her reported WBC count was 2600. Follow up values were unavailable. Small changes relative to baseline also occurred in HGB, RBC and platelet counts. The AED regimen of this patient was not available. No follow-up of the patient's course was provided.

d) Patients that Dropped out with Clinically Significant Laboratory Values

Across the development program, the number of patients who had abnormal lab values at study stop was not provided.

According to the sponsor, no patient was discontinued from an uncontrolled or controlled zonisamide trial conducted by Dainippon because of an abnormal laboratory value. There were, however, discontinuations from studies conducted by [redacted]

Discontinuations due to abnormalities in chemistry analytes

Patient 912-75/5 is mentioned in the supplemental ISS database. She was a 43YO, who weighed 52 kg. She withdrew after 84 days of zonisamide exposure due to elevation in alkaline phosphatase levels to 291 IU/L. This rise continued after withdrawal reaching a peak of 323 IU/L 4 months later. Baseline values were recorded as 182 IU/L. The investigator suspected vitamin D deficiency and started treatment with supplements. Follow-up information is unavailable. Concurrent medications used by this patient, known to result in defects in the production of 25-(OH)D3 such as phenytoin and phenobarbital, were not discussed.

Discontinuations due to abnormalities in hematological analytes

Patient number 2057 (912-201-358) dropped out with a Hg of 6.9 g/dl on the day of withdrawal. Discussed in the dropout section.

Patient 912-44/3 (16WK Baseline Contr Study), a 38YOM was withdrawn after 46 days of zonisamide therapy due to neutropenia. At that time he was receiving 500mg/day of zonisamide. Before the study the WBC count was 4400 with 50% neutrophils. On day 43 the count was 2100 with 6%

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neutrophils. Upon dechallenge, the WBC count normalized to 4700 on day 82. Concomitant medication was phenytoin, 500mg/day. Blood chloride values were 105 mEq/L at baseline increasing to 111 mEq/L on day 38, decreasing to 105 Meq/L upon dechallenge. The investigator considered the severe neutropenia to be possibly related to zonisamide administration. He had a similar to carbamazepine therapy. This case has been published (Epilepsy Res 1993;14:165-73).

Patient number 1188 (912-103-044) was enrolled in an open label non-US study. This 29-year old French woman had leukopenia and neutropenia on day 56. Dose of zonisamide on this day was 800mg/day; duration of exposure unknown. Her baseline value was $7.5 \times 10^9/L$, decreasing to 2.2 on day 56. The values returned to within the normal range following dechallenge (day 61). Other concurrent AEDs were primidone 1000mg/day and valproic acid 2000mg/day. Both the investigator and monitor considered these events clinically important and possibly related to zonisamide.

I. ECG Findings

The ISS included a short statement that there were no clinically significant ECG findings in the development program. No summary data or patient listings were provided in the ISS.

For some phase 1 studies, ECGs were apparently performed. We also checked the protocols for the 3 RCTs, and it appears that only US912 collected ECG data.

In study US912, ECGs were scheduled for screening and week 12 at the end of the double blind period. In the individual study report for 912, there was a table summarizing the ECG findings for the study. According to the report, there were no patients with clinically significant ECGs changes. In reviewing the table, we found it confusing in that it summarized findings for the following time points, "screening" and "baseline". Thus, we are not sure if these were on-treatment results.

Across the development program, no patients were reported to have dropped out because of an abnormality in the ECG. There was one report of a serious or potentially serious adverse event in study report 912-USA, (volume 79).

Patient 912-15/18, a 49 YOM weighing 72.3kg (no height given) had intermittent tachycardia reported as a serious adverse event on day 13, from the beginning of the double-blind phase. The ZNS dose at the onset of the event was 400mg/day. His condition was monitored in the hospital cardiac unit. No further follow-up information is available. His concomitant was primidone, 1000mg/day.

J. Vital Signs

Sitting blood pressure, pulse, temperature and respiratory rate were monitored in most studies. Potential postural changes in BP were not examined. There were no patients

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who were reported to have dropped out of study for an abnormality of any vital sign. The proportions of subjects in the 3 pooled RCTs with potentially clinically significant changes in vital signs, are displayed in the table which follows (sponsor's table 8h-34 in volume 314). There were no statistically or clinically significant differences between the treatment groups.

No patients dropped out from either zonisamide or placebo in the RCTs. Three patients dropped out for weight loss after switching from placebo to zonisamide. These 3 patients are summarized below.

Patient 3024, a 47 year old female (55kg;62") reported a mild weight loss of 2.3 kg over a 4 week period. She had been exposed to ZNS for 140 days. The dose at the time of the event was 400 mg/day. There were numerous concomitant medications listed; seven to be exact. One of these included dexedrine, 10 mg/day.

Patient 3056, a 14 year old male (12.5kg; height not given) reported a weight loss (no values) after 106 days of therapy. The dose of ZNS at the time of withdrawal was 400mg/day. Concomitant medications included phenytoin 300mg/day and gabapentin, 2400mg/day. If the numbers have been correctly reported by the sponsor in the case of this 14 year old 12kg boy, the dose would be high.

Patient 3083, a 37 year old female lost 1.9 kg at 400mg/day.

Weight change was reported as a treatment emergent adverse event in 3.0 % (8/269) of patients assigned zonisamide and 2.2 % (5/230) on placebo.

Across the rest of the patients in the primary database 14 additional patients with zonisamide exposure dropped out for weight loss. The narrative summaries were examined (volume 314). Eight of the 14 were women. Women lost an average of 12-14kg prior to discontinuation while males lost an average of 6kg. The largest weight loss was 20kg in a 78kg female after 182 days of ZNS exposure. Of the 14 patients, 2 discontinued before week 20. Decreased appetite or anorexia were reported, in addition to the weight loss, by approximately one half of the subjects who discontinued.

K. Overdose Experience

The ISS identified 2 patients in the development program who intentionally ingested zonisamide in suicide attempts. Both recovered and were reported to have had confusion and sedation. The sponsor also described a literature report of another suicide attempt where the patient survived but was comatose for 10 hours.

L. Renal Calculi in the Development Program

The sponsor provided a separate section in the ISS that described renal calculi occurrence separately for studies conducted by [redacted] and Dainippon. Most of these cases were reviewed under the serious AE section. Since ultrasound was used in Dainippon clinical studies, we will review the findings from those studies in this section.

1. Dainippon Clinical Trials

Studies 920, 921 and 922, all conducted in the US, performed renal ultrasounds at baseline and 1 year, and at study endpoint. Findings from the ultrasounds were used to identify new calculi formation, the development of echogenic foci that were not conclusively calculi, and to follow calculi that were present at baseline.

In 922, ultrasounds were also conducted after 12 weeks of treatment so that the incidence of renal calculi could be compared with that in placebo.⁸ However, such a comparison was not provided in the ISS. Based upon our review, it appears that 2 placebo patients were diagnosed with renal calculi compared to none in the zonisamide group.

Across the 3 studies, there were 501 patients treated with zonisamide counting the 72 who crossed over from placebo in 922 after 12 weeks. Of these 501 patients, 20 were diagnosed with renal calculi. The clinical significance of some of these events was already discussed in the serious AE section.

One confusing aspect to the sponsor's description of renal calculi occurrence across the NDA was that the total number of patients considered to have developed incident calculi was not consistently reported. In the serious AE section where the sponsor stated that calculi were considered serious, 26 patients were identified. In the separate section on calculi provided by the sponsor in the ISS, 13 patients were reportedly diagnosed with calculi from [redacted] studies with 20 diagnosed in Dainippon studies giving 33 total patients.

M. Pregnancy Exposure in the NDA

Of the 9 pregnancies described in the ISS, reports 4 ended as normal births with one of child having hypospadias. There were 2 therapeutic abortions and 3 spontaneous abortions.

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ON ORIGINAL**

⁸ One study center in study 922 substituted KUB X-rays for ultrasounds.

III. Other Experience with Zonisamide

A. Post-Marketing Experience in Japan

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1. Sources of Post-Marketing Data

a) The General Survey

The *General Survey* (n=3,906) was a retrospective collection of clinical information from patients who received zonisamide. It was conducted by the sponsor's medical service representatives between the years 1989-1994. The survey included patients who had been treated for partial or generalized seizures; however, there were no specific inclusion/exclusion criteria. The method used by the sponsor to identify patients was not discussed, but it appears that physicians voluntarily enrolled patients in a retrospective manner after being approached by company representatives.

The following data were collected:

- patient background;
- concurrent antiepileptic drugs (AEDs);
- frequency and severity of seizures with outcome;
- adverse events;
- global evaluations.

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Data was collected from a predetermined number of patients to ensure a certain sample size (the goal was 4000 patients) after patients had been on zonisamide therapy. Verbatim terms (physician or patient generated) for adverse drug reactions (ADRs) were converted to preferred terms using modified COSTART dictionary.

b) Prospective Survey

The *Prospective Survey* (n=1512; 424 monotherapy, 1088 add-on therapy) enrolled patients at the time zonisamide treatment was started. Twenty epilepsy centers (presumably in Japan) are participating. The study was initiated in 1989 and is ongoing at present. The data presented in the NDA summarize the experience through 12/95.

The population included in the survey consisted of children or adults with a history of partial or generalized seizures. Patients were enrolled irrespective of seizure severity and included patients receiving zonisamide as monotherapy or as adjunctive therapy. There was also little information about patient enrollment and we do not know if every

patient with exposure to zonisamide at each center over the study period was enrolled. The survey aimed to follow patients for at least one year on therapy, but the extent of follow up in the survey was not described. The following information was collected:

- medical history;
- type of epilepsy, frequency, severity, duration of seizures, and age of onset;
- neuropsychological findings;
- history of treatment with other AEDs;
- effects on seizure frequency;
- electroencephalographic (EEG) findings;
- adverse events, clinical laboratory test results, and plasma drug concentration.

Verbatim terms (physician or patient generated) for adverse drug reactions (ADRs) were converted to preferred terms using modified COSTART dictionary.

c) Spontaneous Reporting

The sponsor collected spontaneous reports of AEs reported in Japan with the NDA summarizing those AEs rated as serious by the physician. The criteria used to define seriousness were not discussed.

2. Sponsor's Approach to Describing the PMS Experience

For each data source, the sponsor summarized the number of serious AEs by preferred term and body system. Two separate discussions of the PMS data were provided. One focused on events considered "unexpected" (not in the Japanese zonisamide labeling). The second discussion was based upon a review of the PMS data by the [redacted] [redacted] medical monitor. This review focused on deaths, serious skin and hematological events, and the experience from pregnancy exposure.

There were a number of limitations to the sponsor's approach. First, none of the summary data identified the number of patients with a particular event. Thus, while we could see the number of patients with thrombocytopenia, we could not tell how many patients were accounting for selected combinations of events.

Second [redacted] review of the PMS data was difficult to follow. We were not certain exactly how events were identified nor what methods were used in the review. The case synopses provided by [redacted] did not indicate from which source of PMS data the event was captured. Some events appear to have been recoded by [redacted]. For example, there were no aplastic anemia reports in the summary data for the 3 sources of PMS data, yet the [redacted] review identified several cases. The review also seemed to have additional information that was not in the AE reports that could be important to whether some events may be related to zonisamide use. For example, in one of the possible cases of

aplastic anemia, it was reported by [redacted] that zonisamide was discontinued after the bone marrow was performed that was interpreted as consistent with recovery. The bone marrow was performed well after abnormalities in RBCs, WBCs and platelets had been diagnosed and were shown to be improving. Thus, if zonisamide was discontinued after improvement, this would not seem to be a good case. We do not know how the [redacted] reviewer obtained this information since it was not on the AE report.

Finally, there was limited documentation for the estimated use since approval in Japan. In response to our query, the sponsor developed a second estimate based upon IMS data. However, there was limited documentation of the basis for the second estimate.

3. Findings from PMS

a) General Survey - All Reported AEs

Dainippon Table 8f-4 "Incidence of Adverse Events by Body System and Preferred Term in the General Survey" summarizes the extent of AE occurrence. Somnolence, anorexia, nausea/vomiting, and psychiatric disorder occurred in at least 1.5% of the patients. Potentially serious AEs included vesiculobullous rash (43/3906 [1.1%]) and leukocytopenia (8/3906 [0.2%]). As noted above, the report did not break down the AEs by severity.

Leukopenia was reported in 0.2%, increased GGT in 1% and increased alkaline phosphatase in 0.4% of patients exposed to zonisamide in the retrospective survey.

b) Prospective Survey - All Reported AEs

Dainippon Table 8f-6 "Incidence of Adverse Events by Body System and Preferred Term in the Prospective Survey" summarizes AE occurrence in the prospective survey. Somnolence, anorexia, abnormal GPT/GGPT, nausea/vomiting, slowness of thought, psychiatric disorder, irritability, apathy, ataxia, weight loss, headache, and malaise occurred in at least 1.5% of the patients. Potentially serious AEs included vesiculobullous rash (21/1512 [1.4%]) and leukocytopenia (4/1512 [0.3%]); however, the report of the prospective survey did not break down the AEs by severity.

Leukopenia was reported in 0.3%, increased GGT in 1%, increased alkaline phosphatase in 1.1% and an abnormal SGOT in 1.4% of the patients in the prospective survey.

c) Serious AE Occurrence Across the PMS Experience

Dainippon Table 8f-7 "Incidence of Serious Adverse Drug Reactions" summarizes the number of serious AEs by organ system across the three sources of PMS data (general survey, prospective survey, and spontaneous reporting). The highest numbers of AEs fell into the skin and appendage (35) and the leukocyte and reticuloendothelial (16) systems.

The AE terms in Dainippon Table 8f-7 appear to more specific than the terms generally included in the tables for the general and prospective surveys. For example, in Table 8f-4, there were 41 reports of vesiculobullous rash while in Table 8f-7, the term *vesiculobullous rash* is not listed.

As noted in table 8f-7, in the general survey there were 4 separate terms that were reported consistent with serious skin reactions (rash-2, erythema multiforme - 1, and muco-cutaneo-ocular syndrome - 1). The number of patients represented by these reports is not clear, but certainly two of the terms can be used to describe SJS. There was one case of erythema reported from the prospective survey. There were at least 14 cases of serious skin rashes that were coded as SJS and 2 cases coded as TEN. When the medical monitor reviewed all serious skin rashes, there more cases of SJS and TEN identified. These are discussed in more detail in section (e).

In the general survey there were two reports consistent with serious hematological reactions (decreased IgA - 1, thrombocytopenia - 1). In the prospective survey there was one case of granulocytopenia. No follow-up was provided for this patient.

There were 5 cases of agranulocytosis and 3 cases of thrombocytopenia from spontaneous reporting.

There were seven cases of serious hepatic function disorder submitted as spontaneous reports. In comparison, in the general survey there was one case of serious hepatic function disorder, accounting for 0.03% of AE reported. In the prospective survey there were no cases of serious hepatic function disorder reported.

d) Unexpected-ADRs

Dainippon Table 8f-15 "Unexpected Adverse Drug Reactions" summarizes AEs not included in Japanese labeling by body/ organ system and severity. This table is difficult to interpret because it is not clear which of the unexpected AEs were reported spontaneously, and which were reported as part of the general or prospective surveys.

e) Review