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Committee for Medicinal Products for Human Use (CHMP)

Zonegran

(zonisamide)

Procedure No. EMEA/H/C/000577/P45 024

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

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I. Executive Summary:

As requested by the EMEA in a fax dated 23rd September 2008 and in accordance with Article 45 of Regulation EC No 1901/2006 as amended, Eisai Ltd has submitted the following clinical studies, for assessment:

1. Open – label, baseline controlled and compassionate use (add on therapy) for the treatment of partial seizures - 720-02385-96
2. Extension of study 720-02385-96 EXT – Treatment of Partial Seizures - 720-02385-96-EXT
3. Open – label study to evaluate the Pharmacokinetics Profile and Safety of Zonisamide in Paediatric Subjects with Epilepsy - AN46046-225
4. Open – label, Extended Treatment Safety Study of Zonisamide in children with Epilepsy – AN46046-226
5. Open – label, dose titration Assessment of Slow, low dose Titration of zonisamide in patients with Partial Seizures – ZNS-401
6. Open – label, Multicentre Study to evaluate 25mg and 50mg for the initiation of therapy in Patients with Epilepsy –ZNS-501
7. Open – label, Multicentre, Safety and Efficacy Study of Zonisamide in Patients with Progressive Myoclonic Epilepsy – ZNS-502
8. Open – label, Dose-Ranging Study of Zonisamide in Patients with Neuropathic Pain – ZNS-503

The current SPC of Zonegran contains no other information than that the safety and efficacy of Zonegran in children and adolescents below the 18 years of age has not been established and therefore is its use in this age category is not recommended.

The majority of the studies cited above included subjects in the age range from 12-18 years of age i.e. studies 720-02385-96 (1), 720-02385-96-EXT (2), ZNS-401 (5), ZNS-501 (7) and study ZNS-502 (8). Also in the study in neuropathic pain (ZNS-503) the age range was 12-65 years. It is not clear how many of the patients in these studies were between 12-18 years of age, which dose they used and which adverse events were observed. This might provide useful safety information that might be included in the SPC for prescriber if zonegran is used in this age group. Therefore the MAH should either provide an integrated safety analysis of these studies for this age category or given a justification of its absence. Study AN46046-225 concerned a PK study in 33 subjects between 5-15 years of age. Twenty-one subjects were between 5-11 years of age and 12 subjects were 12-15 years of age. Each subject was titrated to a maximum tolerated dose during a period of approximately 7 weeks starting at 1 mg/kg/day which was gradually increasing up to 12 mg/kg/day or a maximum of 600 mg/day. This also may be useful information that could be mentioned in section 5.1 of the SPC.

Study AN46046-226 was the open label extension of study of AN46046-225. In subjects aged 5-11 years, the daily dose ranged from 9.0 mg/kg/day to 14.6 mg/kg/day, and in subjects aged 12-18 years, it ranged from 6.4 mg/kg/day to 10.1 mg/kg/day.

It appears that an increase in seizure frequency was observed which is rather unexpected i.e. at the initial visit, subjects aged 5-11 years had a median seizure frequency on 30 seizures per month, compared with 2 seizures per month in subjects aged 12-18 years. At the final visit, subjects aged 5-11 years had a median seizure frequency of 40 seizures per month, compared with 4 seizures per month in subjects aged 12-18 years. This requests an explanation. In addition 10 non fatal Saes were reported in 5 subjects (four aged 5 – 11 years and one aged 12 – 18 years). Two of these, namely, encephalopathy and grand mal convulsion were considered by the investigators to be related to zonisamide and both events resolved following a

reduction in the zonisamide dosage. Point is that as with other AEDs a proportion of patients are worsening instead of an improving in seizure frequency. . This should be mentioned in the SPC.

CHMP CONCLUSIONS:

- Following assessment of these studies, overall, the conclusions of the MAH are endorsed as far as efficacy is concerned.
  For safety an integrated safety analysis is expected for the age category of 12-18 years of age i.e. for the studies where subjects were included from 12 years of age the safety data should be integrated unless the company can justify the absence of such integrated safety analysis.
- Following assessment of studies 720-02385-96, 720-02385-96EXT, ZNS-401, ZNS-501 and ZNS-503, the adverse event of headache should be added to the product information of Zonegran and the MAH is requested to submit a Type II variation to do so.
- Following assessment of studies 720-02385-96 and 720-02385-96EXT, the adverse event of rhinitis should be added to the product information of Zonegran and the MAH is requested to submit a Type II variation to do so.

- Study AN46046-225 concerned a PK study in 33 subjects between 5-15 years of age. Twenty-one subjects were between 5-11 years of age and 12 subjects were 12-15 years of age. Each subject was titrated to a maximum tolerated dose during a period of approximately 7 weeks starting at 1 mg/kg/day which was gradually increasing up to 12 mg/kg/day or a maximum of 600 mg/day. In the open label extension study (AN46046-226) for subjects aged 5-11 years, the daily dose ranged from 9.0 mg/kg/day to 14.6 mg/kg /day and for subjects aged 12-18 years from 6.4 mg/kg/day to 10.1 mg/kg/day. This may be useful information that could be mentioned in section 5.1 of the SPC whereas the PK data may be mentioned in 5.2.

  It appears that an increase in seizure frequency was observed in study AN46046-226 which is rather unexpected. An explanation is requested.

  Further an increase in seizure frequency was observed in a proportion of patients in the studies. This is not unexpected in epilepsy studies. However this should be mentioned in the SPC.

- These studies are mainly small and are open label with no placebo or active comparator arms and so results should be interpreted with caution.
- None of these 8 studies discussed in this Assessment Report have any data on the long term use of zonisamide in the paediatric population, nor on the effect of zonisamide on the growth and development of children, nor on the effect of zonisamide on puberty.

Further research and studies is ongoing in support of an indication for zonisamide in the paediatric population as part of FUM It is noted that there is currently a study ongoing (E2090-044-312) to further investigate the use of zonisamide in the paediatric and adolescent population, the final clinical study report of which is expected in January 2011. The MAH has stated that this date is an estimate based on predicted recruitment rate and could move 6 months either way.

II. Scientific overview and discussion:

Overview: Zonegran (zonisamide) is a novel sulphonamide with weak carbonic anhydrase inhibitory activity, chemically unrelated to other anti-epileptic agents. It has a blocking action on voltage sensitive sodium and calcium channels, thereby disrupting synchronized neuronal firing, reducing the spread of seizure discharges and disrupting subsequent epileptic activity. It also has a modulatory effect on

GABA-mediated neuronal inhibition as well as a variety of other effects, which may contribute to its pharmacological effects.

Worldwide Marketing Authorization Status:

Zonisamide is approved for marketing in several countries/regions including Japan, South Korea, the United States, the European Union, Switzerland, Australia, and the Philippines. Zonisamide was licensed in Japan and South Korea in 1989 and 1990 respectively, under the tradename Excegran. Excegran is approved in Japan and Korea as monotherapy and adjunctive therapy in the treatment of partial and generalized seizures in adults and children. Zonegran was licensed in the United States in 2000 and is approved in the US as adjuvant therapy for the treatment of partial seizures in patients 16 years and older. Zonegran was granted a license in the European Union as adjuvant therapy for partial seizures in adults on 10 March 2005 (via the centralized procedure), in Switzerland on 19 October 2006, in Australia on 31 July 2007 and in the Philippines on 28 August 2007.

Zonegran is available in most locations as either a 25, 50, or 100 mg capsule, intended for either once a day or twice daily dosing. In Japan, as well as Korea, Excegran is also available as a 20% powder formulation.

Table #1 lists the worldwide marketing authorization status and launch dates of zonisamide.

Table #1 Worldwide Marketing Authorization Status for Zonisamide

COUNTRY	DATE OF MARKET AUTHORIZATION	LAUNCH DATE	TRADE NAME
Japan	31 March 1989	16 June 1989	Excegran
South Korea	28 May 1990	02 June 1992	Excegran
US	27 March 2000	May 2000	Zonegran
Mexico	19 July 2002	Unknown	Zonegran
Austria	10 March 2005	Jan 2006	Zonegran
Belgium	10 March 2005	Pending	Zonegran
Bulgaria	10 March 2005	Pending	Zonegran
Cyprus	10 March 2005	Pending	Zonegran
Czech Republic	10 March 2005	Pending	Zonegran
Denmark	10 March 2005	January 2006	Zonegran
Estonia	10 March 2005	Pending	Zonegran
Finland	10 March 2005	July 2007	Zonegran
France	10 March 2005	January 2006	Zonegran
Germany	10 March 2005	June 2005	Zonegran
Greece	10 March 2005	Pending	Zonegran
Hungary	10 March 2005	December 2007	Zonegran

Table #1 Worldwide Marketing Authorization Status for Zonisamide			
COUNTRY	**DATE OF MARKET AUTHORIZATION**	**LAUNCH DATE**	**TRADE NAME**
Iceland	10 March 2005	March 2007	Zonegran
Ireland	10 March 2005	August 2005	Zonegran
Italy	10 March 2005	October 2006	Zonegran
Latvia	10 March 2005	Pending	Zonegran
Lithuania	10 March 2005	Pending	Zonegran
Liechtenstein	10 March 2005	Pending	Zonegran
Luxembourg	10 March 2005	Pending	Zonegran
Malta	10 March 2005	Pending	Zonegran
Netherlands	10 March 2005	Pending	Zonegran
Norway	10 March 2005	November 2006	Zonegran
Poland	10 March 2005	Pending	Zonegran
Portugal	10 March 2005	March 2008	Zonegran
Romania	10 March 2005	Pending	Zonegran
Slovak Republic	10 March 2005	July 2008	Zonegran
Slovenia	10 March 2005	Pending	Zonegran
Spain	10 March 2005	April 2006	Zonegran
Sweden	10 March 2005	January 2006	Zonegran
UK	10 March 2005	July 2005	Zonegran
Switzerland	19 October 2006	November 2006	Zonegran
Australia	31 July 2007	Pending	Zonegran
Philippines	28 August 2007	Pending	Zonegran
India	26 September 2007	Pending	Zonegran

Assessment of Clinical Studies:

1. Study 720-02385-96

Clinical Study Report
February 21, 1997

MAH STUDY SYNOPSIS

Title
Overall Report of a Historical-Controlled 16-Week Multicenter Study of the Efficacy and Safety of Zonisamide (CI-192) in Medically Refractory Patients with Partial Seizures (USA) (Protocols 912-39 through 42, 44 through 47, and 55)

Study Dates
18 April 1985 to 26 January 1987

Study Objectives
To determine the effectiveness, plasma levels, and safety of zonisamide in medically refractory patients with partial seizures.

Study Design
This study was a multicenter, outpatient, non-blinded study that evaluated zonisamide as adjunctive therapy in the treatment of medically refractory patients with partial seizures.

The trial included a 12-week baseline-control period in which patients continued to receive one to three other antiepileptic drugs (phenytoin, carbamazepine, valproic acid, ethosuximide, and phenobarbital or primidone), and a 16-week treatment period in which each patient received zonisamide daily in two equally divided doses every 12 hours in addition to their other antiepileptic drugs. During the treatment period, zonisamide was increased gradually from an initial dose of 1.5 mg/kg/day up to 6 mg/kg/day during the first month of treatment. Additional adjustments were based on clinical response providing the daily dosage of zonisamide did not exceed the smaller of 20 mg/kg or the amount producing a plasma concentration of 40 µg/mL.

The primary measure of the effectiveness of zonisamide was the median percent reduction from baseline in the frequency of partial seizures. A secondary criterion was the proportion of patients responding, a response being defined as at least a 50% reduction in frequency. Further measures of efficacy were physician and patient global assessments.

The patients kept a daily record of the number and description of seizures they experienced, including the description and duration of each seizure. Clinic visits were scheduled monthly during the baseline phase, weekly during the first month of treatment, every two weeks during the second month of treatment, and monthly thereafter. Safety was evaluated based on the following variables: adverse events, clinical laboratory tests (hematology, scrum chemistry), vital signs, ECG, and physical and neurologic examinations.

Study Population
A total of 180 patients with refractory partial seizures, alone or secondarily generalized, were selected for study and included 85 women and 95 men. They ranged in age from 12 to 67 years and in weight from 40.9 to 118.2 kg. Median seizure rates prior to the study were 9.3 partial seizures/month and 5.6 complex partial seizures/month.

Patient Disposition
One patient died and a further 38 patients withdrew from the study, 8 because of lack of efficacy, 22 because of adverse events, and 8 for other reasons. One hundred forty-one patients (78.3%) completed the study and 137 of these continued into a separately reported extended-treatment phase.

Efficacy Results

The median percent reduction in each seizure type is shown in the table below.

Change from Baseline in Seizure Frequency (Weeks 5-16)

Seizure Type	N	Median % Change
All Partial Seizures	160	-39.3
Complex Partial Seizures	154	-40.6
All Seizures	160	-36.5

Reference: Appendices B.11, B.12, B.13

Sub-group analysis by age, sex, race and study site failed to reveal any important differences in efficacy between the sub-groups.

The proportion of responders is shown in the following table.

Treatment Responders

Seizure Type	Responders	Non-Responders	Total	% Responders
All Partial Seizures	62	98	160	38.8
Complex Partial Seizures	60	94	154	39.0
All Seizures	61	99	160	38.1

Reference: Appendix B.26

The proportion of responders is similar for each seizure type and is consistent with the median reductions in seizure frequency.

The design of the study was such as to allow dose to be titrated to achieve a satisfactory clinical response. It is therefore not surprising that no clear dose-response pattern may be perceived in the results.

The global assessments as reported by both physicians and patients are recorded in the table below.

Physician and Patient Global Assessments at the End of Treatment Compared to Baseline

Rating	By Physician (N=167)		By Patient (N=168)	
	N	%	N	%
Marked Improvement	51	31	49	29
Slight Improvement	17	10	26	15
No Change	62	37	51	30
Worse	37	22	42	25

Reference: Appendix B.39

It is clear that both physicians and patients perceived zonisamide to be valuable in the majority of cases.

Safety Results

The most commonly reported treatment-emergent adverse events are shown in the following table. Treatment-emergent adverse events were most commonly associated with the nervous system (71.7% of patients), body as a whole (48.3%), psychobiologic function (47.2%) and the digestive system (45.6%). The most common treatment-emergent adverse events included dizziness (26.1%), somnolence (25.0%), and nausea and/or vomiting (23.9%). The majority of these adverse events were rated as mild or moderate in severity.

Summary of Most Common Treatment-Emergent Adverse Events (TEAE) Occurring in More Than 10% of Patients

Body System/Adverse Events	**Zonisamide (N=180)**	
	N	**%**
Nervous System		
Somnolence	45	25.0
Dizziness	44	24.4
Confusion	30	16.7
Ataxia	30	16.7
Dysarthria	25	13.9
Lethargy	24	13.3
Body as a Whole		
Headache	40	22.2
Fatigue	35	19.4
Digestive System		
Nausia and/or Vomiting	43	23.9
Anorexia	37	20.6
Psychobiologic Function		
Irritability	29	16.1
Slowness of Thought	22	12.2
Respiratory System		
Rhinitis	25	13.9
Special Senses		
Diplopia	23	12.8
Blurred Vision	20	11.1

Reference: Appendix B.42

The majority of adverse events were reported as mild or moderate and occurred during the first 28 treatment days. Adverse events were reported with similar frequency by men and women and by patients of different age groups.

One patient (912-47 #19) died during the study. Death resulted from the underlying seizure disorder. In addition to one death, serious adverse events were reported for three patients.

Twenty-two patients discontinued zonisamide therapy prematurely because of an adverse event. Most adverse events leading to premature discontinuation first occurred during the dose introduction period, and were primarily related to the nervous system.

One case of renal calculi was reported.

Other Safety Assessments

There were no systematic trends in laboratory values. A few mild, transient abnormalities in clinical laboratory values occurred in some individuals during the study. With the exception of one instance of neutropenia, none was considered clinically significant nor cause for concern.

No trends or clinically important findings were noted in the physical examinations or electrocardiograms. Neurological examinations and electroencephalograms were consistent with

antiepileptic drug therapy and a diagnosis of partial seizures. Zonisamide treatment was associated with weight loss, particularly during the first 28 days of treatment.

MAH Conclusions

- Zonisamide treatment was associated with a reduction in the frequency of simple and complex partial seizures when given as adjunctive therapy to patients with refractory epilepsy.

- Zonisamide was well tolerated by this patient group.

CHMP COMMENTS:

- This clinical trial was an open label study and not a randomised one.
- This study was carried out in patients between the ages of 12 and 67 years. It is not clear how many of these patients were in the 12 to 18 year old age group.
- The above mentioned conclusions of the MAH are endorsed.
- Following assessment of this study, the adverse events of headache and rhinitis should be added to the product information for Zonegran.

2. Study 720-02385-96 EXT:

MAH STUDY SYNOPSIS

Title
Efficacy and safety report of the extended phase of a baseline-controlled 16-week multicenter study of the efficacy and safety of zonisamide (CI-912) in medically refractory patients with seizures (USA)

Study Dates
November 19, 1985 to August 25, 1987

Study Objectives
To obtain additional data on the safety and efficacy of zonisamide in the long-term treatment of medically refractive patients with partial seizures.

Study Design
This study was the long-term open extension to a multicenter, outpatient, non-blinded study that evaluated zonisamide as adjunctive therapy in the treatment of medically refractory patient with partial seizures.

Patients continued to receive one to three other antiepileptic drugs (phenytoin, carbamazepine, valproic acid, ethosuximide, and phenobarbital or primidone) together with zonisamide in two equally divided doses every 12 hours. Dosage adjustments were based on clinical response providing the daily dosage of zonisamide did not exceed the smaller of 20 mg/kg or the amount producing a plasma concentration of 40 μg/mL.

The primary measure of the effectiveness of zonisamide was the percent reduction from baseline in the frequency of partial seizures . A secondary measure was the proportion of patients responding, response being defined as a 50% reduction in frequency.

Clinic visits were scheduled 3-monthly.

Safety was evaluated based on the following variables: adverse events, clinical laboratory tests, EEG, ECG, and physical and neurologic examinations.

Study Population
A total of 137 patients with refractory partial seizures, alone or secondarily generalized, entered the extension phase of the study. These included 72 men and 65 women. They ranged in age from 12 to 67 years and in weight from 41 to 118 kg.

Patient Disposition

Investigators were not consistent in their classification of the reasons for discrimination. As there was no predetermined treatment period for this extension, it was not technically possible for a patient to complete the study. It is probable that most of the patients described by the investigators as "completed" were in fact discontinued when the study was terminated.

Summary of Discontinuation Information

	All Patients (N=137)	
Reason	N	%
Study Completed	25	18.2
Lack of Efficacy	15	10.9
Seizure Exacerbation	2	1.5
Adverse Event	9	6.6
Lack of Compliance	2	1.5
Personal	4	2.9
Surgery	3	2.2
Lost to Follow Up	2	1.5
Other*	75	54.7
Total	137	100.0

* These patients were discontinued when the study was terminated
Eight patients transferred to a compassionate-use protocol.
Cross-reference: Appendix B.4

Efficacy Results

The median reduction in seizure frequency is summarized in the table below.

Overall Median Percent Reduction in Seizure Frequency from Baseline

Seizure Type	N	N Missing	Median	Minimum	Maximum
Complex Partial	119	11	-65.2	-99.2	477
All Partial	129	1	-64.9	-99.7	385
All Seizures	129	1	-64.9	-99.7	384

Cross-reference: Appendix B.8

The proportion of responders at each time interval is presented below.

Proportion of Responders						
Time Interval	**Complex Partial Seizures**		**All Partial Seizures**		**All Seizures**	
	N	**%**	**N**	**%**	**N**	**%**
Months 5-7	49/108	45	53/120	44	55/122	45
Months 8-10	42/87	46	44/95	46	44/96	45
Months 11-13	38/68	55	38/74	51	37/77	48
Months 14-16	29/55	52	31/63	49	31/63	49
Months >16	14/35	40	16/40	40	17/40	42

Cross-reference: Appendices B.9, B.10, B.11

It is clear that, by either measure, long-term zonisamide therapy was associated with a reduction in seizure activity compared to baseline.

Safety Results

The most commonly reported treatment-emergent adverse events are shown in the following table.

Adverse Events Occurring in ≥ 5% Patients*		
Body System/COSTART Term	**No. of Pts**	**%**
Nervous System		
Dizziness	31	22.6
Somnolence	21	15.3
Dysarthria	18	13.1
Ataxia	15	10.9
Tremor	15	10.9
Confusion	11	8.0
Increase seizure activity	9	6.6
Lethargy	9	6.6
Coordination abnormal	7	5.1
Forgetfulness	7	5.1
Nystagmus	7	5.1
Psychobiologic Function		
Slowness of thought	14	10.2
Irritability	12	8.8
Anxiety	10	7.3
Trouble concentrating	9	6.6
Depression	7	5.1
Body as a Whole		
Headache	24	17.5
Fatigue	18	13.1
Weight change	12	8.8
Digestive System		
Anorexia	24	17.5
Nausea and/or vomiting	19	13.9
Diarrhea	7	5.1
Stomach pain/irritation	7	5.1
Respiratory System		
Rhinitis	21	15.3
Special Senses		
Diplopia	19	13.9

* Menstrual disorder was reported in 9.2% of the 65 female patients

Cross-reference: Appendix B.18

Treatment-emergent adverse events were most commonly associated with the nervous, psychobiologic and digestive systems and with the body as a whole. The most common treatment-emergent adverse events included dizziness (22.6%), headache (17.5%), anorexia (17.5%), somnolence (15.3%), and rhinitis (15.3%). The majority of these adverse events were rated as mild or moderate in severity.

Adverse events were reported with similar frequency by men and women and by patients of different age groups.

No deaths occurred during the extension. Twelve patients reported serious or potentially serious adverse events including three cases of renal calculi.

Nine patients discontinued zonisamide therapy because of an adverse event.

Other Safety Assessments
No systemic changes in laboratory variable were seen. A few mild, transient abnormalities in clinical laboratory values occurred in some individuals during the extension but none gave cause for serious concern.

No trends or clinically important findings were noted in the physical examinations or electrocardiograms. Neurological examinations and electroencephalograms were consistent with antiepileptic drug therapy and a diagnosis of partial seizures.

MAH Conclusions

- Long-term zonisamide treatment was associated with a reduction in the frequency of simple and complex partial seizures when given as adjunctive therapy to patients with refractory epilepsy.

- Zonisamide was well tolerated by this patient group

CHMP COMMENTS:

- This study is an open ended, open label extension of study 720-02385-96 with no control group and as such is of limited value for the assessment of efficacy.
- The study population was between 12 and 67 years of age and it is not clear how many of the patients were in the paediatric and adolescent population.
- The investigators were not consistent in their classification of the reasons for discontinuation of the patients from the study.
- The above mentioned conclusions of the MAH are endorsed.
- Following assessment of this study, as with study 720-02385-96, the adverse events of headache and rhinitis should be added to the product information for Zonegran.

3. Study AN46046-225:

MAH SYNOPSIS

Name of Company: Elan Pharmaceuticals, Inc. **Name of Finished Product:** Zonegran ™ **Name of Active Ingredient:** Zonisamide (1,2-benzisoxazole – 3-methanesulfonamide, AD-810)	**Individual Study Synopsis** **Page 1 of 7** **Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**

Title of Study:	Safety and Pharmacokinetic Study of Zonisamide (Zonegran™) Administered to Children With Epilepsy (Protocol AN46046-225)
Date of Protocol:	July 24, 2000
Date of Amendment 1:	November 3, 2000
Date of Amendment 2:	April 5, 2001
Publication (reference):	None
Study Period:	
Date of Study Initiation:	October 2, 2000 **Date of Last Observation:** August 14, 2001
Phase of Development:	II
Study Objective:	The primary study objective was to characterize the safety and pharmacokinetics of zonisamide in pediatric subjects with epilepsy.

2. SYNOPSIS (cont.)

Name of Company: Elan Pharmaceuticals, Inc. **Name of Finished Product:** Zonegran ™ **Name of Active Ingredient:** Zonisamide (1,2-benzisoxazole – 3-methanesulfonamide, AD-810)	**Individual Study Synopsis** **Page 2 of 7** **Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**

Methodology: This was a Phase II, multicenter, open-label, pharmacokinetic (PK) study designed to evaluate the PK profile and safety of zonisamide in pediatric subjects with epilepsy. All subjects were to be screened within 14 days prior of receiving their first dose of zonisamide. For analysis purposes, subjects were grouped based on their age at the time of entry into this study: Group 1 consisted of subjects aged 5 through 11 years, and Group 2 consisted of subjects aged 12 through 15 years. At least six subjects in each age group were to be on either carbamazepine or phenytoin as part of their stable antiepilepsy drug (AED) regimen. Subjects were enrolled to provide an approximately equal distribution of subject ages within each of the two age groups.

Study days were calculated relative to the date when study drug was first administered (defined as Day 1). Each subject was to be titrated to a maximum tolerated dose during a period of approximately 7 weeks (Days 1 through 48), starting at 1 mg/kg/day (based on weight at screening) and gradually increasing up to 12 mg/kg/day or a maximum of 600 mg/day. If a subject could not tolerate any dose level during the titration period, the dose could be decreased in increments of 1 mg/kg/day until a tolerated dose was reached.

Following screening, study visits were to occur on Days 1, 13, 28, 40, 48, 60, and study termination (Day 67 or early termination). Vital signs, weight measurements, and adverse event (AE) and concomitant medication assessments were to be performed at every visit except for Day 1. Pharmacokinetic (PK) profiles, physical examinations, clinical laboratory testing, and electrocardiograms (ECGs) were to be performed on Days 13, 40, and 60, following at least 12 days of stable zonisamide dosing. Steady-state serum zonisamide concentration–time profiles were evaluated at dose levels of 1, 7, and 12 mg/kg/day in order to

describe the pharmacokinetics of zonisamide at low, moderate, and high doses in the pediatric population. A post-study visit was to be conducted on approximately Day 67, 1 week after the last dose of study drug.
Number of Subjects: Of 33 subjects enrolled into this study at four centers in the United States, 21 subjects completed the study.
Diagnosis and Main Criteria for Inclusion: Males or females aged 5 through 15 years who had a clinical diagnosis of epilepsy and were on a stable dose of up to two other AEDs.
Test Product, Dose and Mode of Administration: Zonisamide in 12.5-mg, 25-mg, 50-mg, or 100-mg capsules was to have been administered orally at the dose prescribed by the investigator. Zonisamide doses were to be administered every 12 hours twice daily. However, for those subjects whose weight was between 15 and 18 kg, zonisamide could be administered once daily until the subject was titrated to a dose that could be administered twice daily.
Duration of Treatment: Planned duration of treatment was approximately 9 weeks (60 days).
Reference Therapy, Dose, and Mode of Administration, Batch No.: No reference therapy was administered.

2. SYNOPSIS (cont.)

Name of Company: Elan Pharmaceuticals, Inc. **Name of Finished Product:** Zonegran ™ **Name of Active Ingredient:** Zonisamide (1,2-benzisoxazole – 3-methanesulfonamide, AD-810)	**Individual Study Synopsis** **Page 3 of 7** **Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**

Criteria for Evaluation:

Pharmacokinetics: Steady-state PK parameters of zonisamide included the following: time to observed maximum concentration (T_{max}), observed maximum concentration (C_{max}), area under the curve to last quantifiable concentration ($AUC_{0\text{-}last}$), area under the curve to 12 hours ($AUC_{0\text{-}12hr}$), apparent oral clearance (CL/F), and total body weight-normalized apparent oral clearance (CL/F/TBW).

Safety: Safety was assessed by the use of concomitant medications; reported and observed AEs; results of clinical laboratory measurements, vital signs, physical examinations, 12-lead ECGs, and global assessments.

Statistical Methods: In general, data were summarized across all subjects and by age group (5–11 years and 12–15 years). Descriptive statistics were calculated for all parameters (counts and percentages for categorical data; N, mean, standard deviation [SD], median, minimum, and maximum for continuous data).

In addition, PK parameters were summarized by the absence or presence of known or expected inducers of zonisamide metabolism (carbamazepine, fosphenytoin, oxcarbazepine, pentobarbital, phenobarbital, phenytoin, primidone). Descriptive statistics were calculated for all parameters. When appropriate, statistical tests were performed for selected parameters (e.g., comparing the two age groups with respect to PK parameters). Dose proportionality (twice daily dosing only) was assessed, by age group and the absence or presence of inducers (if appropriate), by determining the ratio of geometric means and associated 90% confidence intervals of dose adjusted C_{max} and AUC values, using the 7 mg/kg dose level as the reference.

Safety was assessed using the safety evaluable population, defined as all subjects who took at least one dose of study drug. Mean dose at the final PK visit (in mg/kg/day) in this study

was calculated. All AEs were listed by subject and were mapped to body systems and preferred terms using the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) dictionary. Treatment-emergent AEs (TEAEs) were summarized by age group, relationship to study drug, and maximum severity, and whether a subject was taking a concomitant enzyme-inducing AED at any time during the study. Serious adverse events (SAEs) and AEs that resulted in discontinuation were summarized, listed, and described in subject narratives.

Clinical laboratory results and changes from baseline were summarized by age group. In addition, clinical laboratory results were classified as below, within, or above reference ranges at baseline and at each clinic visit, and were summarized in shift tables. Additional analyses of bicarbonate and chloride were performed, including categorical analyses and shift tables. Vital signs were listed by subject and summarized by age group using descriptive statistics; these summaries included both changes from baseline and categorical changes. Physical examination results were listed and ECG results were listed and summarized. Concomitant medications were summarized and listed.

Global assessments of seizure control at baseline and at the final visit were listed.

2. SYNOPSIS (cont.)

Name of Company: Elan Pharmaceuticals, Inc. **Name of Finished Product:** Zonegran ™ **Name of Active Ingredient:** Zonisamide (1,2-benzisoxazole – 3-methanesulfonamide, AD-810)	**Individual Study Synopsis Page 4 of 7** **Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**

SUMMARY OF RESULTS

Disposition and Demographics: A total of 33 subjects were enrolled in the study and received zonisamide (21 subjects aged 5–11 years, 12 subjects aged 12–15 years). Of these 33 subjects, 21 (63.6) subjects completed the study. Overall, the mean age at baseline was 10 years. Nineteen subjects were male, and 14 subjects were female. Thirty-two subjects were white, and one subject was black. Thirty-one subjects provided PK data that was included in the PK analysis.

Total Daily Dose and Concomitant Medications: The mean total daily dose for individual subjects aged 5-11 years ranged from less than 0.8 to 13.2 mg/kg/day at the final PK assessment. The corresponding range of mean doses for individual subjects aged 12-15 years was 2.0 to 12.3 mg/kg/day at the final PK assessment. The overall maximum mean dose was 9.6 mg/kg/day; 9.3 mg/kg/day for 5-11 year old subjects and 10.0 mg/kg/day for 12-15 year old subjects.

All subjects took a CNS medication during the study; otherwise, the most commonly used medications were cough/cold preparations. The most frequently reported (≥5 subjects) concomitant AEDs were topiramate, lamotrigine, levetiracetam, and phenytoin. Sixteen subjects (eleven aged 5–11 years and five aged 12–15 years) were taking inducers of zonisamide metabolism (carbamazepine, fosphenytoin, oxcarbazepine, pentobarbital, phenobarbital, phenytoin, or primidone) as part of their AED regimen.

Pharmacokinetics: In both non-induced and induced subjects receiving zonisamide twice-daily, mean zonisamide serum concentration-time profiles appeared dose-dependent, and showed relatively small peak-trough fluctuations over each 12-hour evaluation period. Serum zonisamide concentrations were higher in non-induced compared to induced subjects at the same dose level.

At each dose level and by age group and inducer status, relatively comparable mean

zonisamide serum concentration-time profiles were observed for each gender, indicating little or no apparent gender differences.

Subjects aged 5–11 years receiving 1 mg/kg/day zonisamide by a once-daily regimen had generally comparable mean steady-state C_{max} and T_{max} values compared to subjects of the same age group receiving 1 mg/kg/day using a twice-daily regimen.

Across the three dose levels, non-induced subjects aged 5–11 years taking zonisamide twice-daily had lower steady-state maximum (C_{max}) and cumulative ($AUC_{0\text{-}12hr}$) zonisamide serum exposure values than subjects aged 12 – 15 years, but the differences did not achieve statistical significance (i.e., $p > 0.05$). Mean CL/F and CL/F/TBW values were lower and higher, respectively, in the younger age group compared to the older age group, but again the differences did not typically achieve statistical significance.

Although the study was not powered to definitively assess dose-proportionality, for non-induced subjects of both age groups, greater than dose-proportional increases in zonisamide C_{max} and $AUC_{0\text{-}12hr}$ values (i.e., ratio of geometric means <68%) were observed between

2. SYNOPSIS (cont.)

Name of Company: Elan Pharmaceuticals, Inc.	**Individual Study Synopsis Page 5 of 7**	
Name of Finished Product: Zonegran ™	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use Only)**
Name of Active Ingredient: Zonisamide (1,2-benzisoxazole – 3-methanesulfonamide, AD-810)	**Volume:** **Page:**	

Pharmacokinetics (cont.):
the 1 and 7 mg/kg/day dose levels; however, the 7 and 12 mg/kg/day dose levels were approximately dose-proportional (i.e., ratios of geometric means and associated 90% confidence intervals falling between or only slightly outside 80– 125%). Zonisamide pharmacokinetic parameters for non-induced subjects are summarized below.

Summary of Selected Steady-State Zonisamide Pharmacokinetic Parameters (Non-Induced Subjects) Following Twice-Daily Dosing.

Age Group (yr)	Dose (mg/kg/day)		C_{max} (μg/mL)	$AUC_{(0\text{-}12hr)}$ (μg hr/mL)	CL/F/TBW (mL/hr/kg)	CL/F (mL/hr)
5 – 11	1.0	N	5	5	5	5
		Mean	2.05	20.2	27.2	740
		CV%	30.5	31.7	36.5	23.1
12 – 15	1.0	N	6	6	6	6
		Mean	2.76	28.8	17.8	855
		CV%	14.7	17.7	19.9	20.5
5 – 11	7.0	N	9	9	9	9
		Mean	21.82	232.3	16.2	380
		CV%	28.6	27.7	28.1	33.0
12 – 15	7.0	N	7	7	7	7
		Mean	28.49	315.0	11.5	540
		CV%	19.8	22.2	18.4	20.3
5 – 11	12.0	N	6	6	6	6

		Mean	38.07	414.4	15.3	387
		CV%	25.5	29.6	23.4	21.8
12 – 15	12.0	N	6	6	6	6
		Mean	49.94	549.9	11.4	513
		CV%	21.2	22.3	21.2	22.3

For induced pediatric subjects receiving twice-daily dosing, lower steady-state maximum (C_{max}) and cumulative ($AUC_{0\text{-}12hr}$) zonisamide serum exposure values, and higher CL/F and CL/F/TBW values, were observed relative to non-induced pediatric subjects. Mean CL/F/TBW values ranged from 29 – 130% higher in induced compared to non-induced subjects. For induced pediatric subjects, steady-state maximum (C_{max}) and cumulative ($AUC_{0\text{-}12hr}$) zonisamide serum exposure values appeared to be comparable between subjects aged 5 – 11 years and 12 – 15 years, with no statistically significant differences observed. Mean CL/F and CL/F/TBW values appeared lower and comparable, respectively, in the younger age group compared to the older age group, but again none of the differences achieved statistical significance.

2. SYNOPSIS (cont.)

Name of Company: Elan Pharmaceuticals, Inc.	**Individual Study Synopsis Page 6 of 7**	
Name of Finished Product: Zonegran ™	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use Only)**
Name of Active Ingredient: Zonisamide (1,2-benzisoxazole – 3-methanesulfonamide, AD-810)	**Volume:** **Page:**	

Pharmacokinetics (cont.):
Dose-proportionality findings in induced subjects of both age groups were reasonably consistent with those noted in non-induced subjects. Zonisamide pharmacokinetic parameters for induced subjects are summarized below.

Summary of Selected Steady-State Zonisamide Pharmacokinetic Parameters (Induced Subjects) Following Twice-Daily Dosing.

Age Group (yr)	Dose (mg/kg/day)		C_{max} (µg/mL)	$AUC_{(0\text{-}12hr)}$ (µg hr/mL)	CL/F/TBW (mL/hr/kg)	CL/F (mL/hr)
5 – 11	1.0	N	9	9	9	9
		Mean	1.52	13.9	41.5	1108
		CV%	39.2	43.2	36.8	35.9
12 – 15	1.0	N	2	2	2	2
		Mean	1.27	12.2	41.0	2087
		CV%	11.0	7.7	7.7	20.6
5 – 11	7.0	N	11	11	11	11
		Mean	17.53	173.0	22.1	589
		CV%	27.1	28.7	34.2	35.7
12 – 15	7.0	N	3	3	3	3
		Mean	16.71	176.3	20.8	880
		CV%	22.8	24.4	28.4	20.5
5 – 11	12.0	N	5	5	5	5
		Mean	31.18	326.4	19.7	499
		CV%	26.3	29.8	29.8	27.4
12 – 15	12.0	N	2	2	2	2
		Mean	35.79	385.5	15.6	783
		CV%	5.6	6.2	6.2	21.4

Safety Results: All 33 subjects reported at least one treatment-emergent AE. The body system most commonly affected was the body as a whole, with 26 (78.8%) subjects reporting at least one event in this system. The majority of treatment-emergent AEs were mild to moderate in intensity. There were no discernable differences in AEs reported by subjects in the different age groups (5- 11 year olds and 12-15 year olds). Severe AEs were reported by five (15.2%) subjects. A total of 27 (81.8%) subjects reported at least one treatment-related, treatment-emergent AE, 17 (81.0%) subjects aged 5-11 years and 10 (83.3%) subjects aged 12-15 years. Overall, the most frequently reported (≥5 subjects) treatment-related, treatment-emergent AEs were somnolence (30.3%), anorexia (27.3%), asthenia (21.2%), and dizziness and nervousness (15.2% each).

2. SYNOPSIS (cont.)

Name of Company: Elan Pharmaceuticals, Inc. **Name of Finished Product:** Zonegran ™ **Name of Active Ingredient:** Zonisamide (1,2-benzisoxazole – 3-methanesulfonamide, AD-810)	**Individual Study Synopsis Page 7 of 7** **Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**

Safety Results (cont.):

Sinusitis was the only AE reported more frequently (>2 subjects difference) by subjects who received inducers than by subjects who did not receive inducers. Ten subjects were prematurely withdrawn from the study due to AEs. Three SAEs (2 non-fatal convulsions and 1 fatal grand mal convulsion leading to respiratory failure) were reported in two subjects.

There were more changes from baseline in chemistry results than in either hematology or urinalysis. LDH, sodium, and bicarbonate were consistently decreased from baseline and alkaline phosphatase, BUN, and chloride were consistently increased from baseline. A considerable proportion of subjects (57.6%; 19 of 33) had bicarbonate levels below the reference range at some time during treatment. There was a somewhat higher percentage of subjects aged 5-11 years (61.9%; 13 of 21) than subjects aged 12-15 years (50.0%; 6 of 12) who had bicarbonate levels below the reference range at any time during treatment.

There were some indications of a tendency for overall mean decreases in blood pressure and for mild orthostatic changes with the higher doses; however, decreases in blood pressure readings were minimal. There was a tendency in age groups to see more of an indication of an increase in blood pressure in the 5-11 year olds and a decrease in blood pressure in the 12-15 year olds.

Mean changes in pulse from Baseline tended to be decreases, but mean changes in pulse from each day's pre-dose tended to be increases. Due to the unequal distribution and small sample size, the vital sign results should be interpreted with caution.

Physical examination results were generally unremarkable and no clinically significant abnormalities were seen in ECGs conducted during the study. Global assessments of seizure control showed that two-thirds of the subjects had an improved assessment of seizure control.

Conclusions:

- Zonisamide was found to be generally safe and well tolerated in pediatric epileptic subjects aged 5–15 years.
- Zonisamide PK was observed to be dose-dependent in subjects.
- There were no apparent gender differences in zonisamide pharmacokinetics in subjects.
- Lower zonisamide exposure and increased clearance was observed in subjects receiving known or expected inducers of zonisamide metabolism.
- For non-induced subjects, steady-state zonisamide serum exposure was lower and CL/F/TBW values were higher in the 5-11 year age group (using a mg/kg-based dosing regimen) than in the 12-15 year age group, but the differences were not statistically significant.
- For induced subjects, generally comparable steady-state zonisamide serum exposure and CL/F/TBW values were observed between age groups using a mg/kg-based dosing regimen.

Date of Final Report: February 02, 2002

Date of Amended Report: April 07, 2004

CHMP COMMENTS:
• The above mentioned conclusions of the MAH are endorsed. • It is noted that there appears to be a higher percentage of patients aged 5 to 11 (61.9%, 13 of 21) than patients aged 12 to 15 (50%, 6 of 12) who had bicarbonate levels below the reference range at any time during treatment. • Following assessment of this study, there are no amendments required to the product information.

4. Study AN46046-226:

MAH SYNOPSIS

Name of Company: Elan Pharmaceuticals, Inc. **Name of Finished Product:** Zonegran ™ **Name of Active Ingredient:** Zonisamide (1,2-benzisoxazole – 3-methanesulfonamide, AD-810)	**Individual Study Synopsis** **Page 1 of 5** **Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**
Title of Study: Open-Label, Extended Treatment Safety Study of Zonisamide (Zonegran™) Administered to Children with Epilepsy (Protocol AN46046-226) **Date of Protocol:** July 24, 2000 **Date of Amendment 1:** October 10, 2001		
Publication (reference): None		
Study Period: **Date Study Initiation:** February 8, 2001 **Date of Last observation:** March 20, 2002		
Phase of Development II		
Study Objective: The primary objective was to characterize the long -term safety of zonisamide in paediatric subjects with epilepsy.		
Methodology: This was a Phase II, open-label, extension study designed to evaluate the longterm safety of zonisamide in pediatric subjects with epilepsy who had initiated treatment with zonisamide in Study AN46046-225. For analysis purposes, subjects were grouped based on their age at the time of entry into Study AN46046-226: Group 1 consisted of subjects aged 5 through 11 years, and Group 2 consisted of subjects aged 12 through 18 years.		

2. SYNOPSIS (cont.)

Name of Company: Elan Pharmaceuticals, Inc. **Name of Finished Product:** Zonegran ™ **Name of Active Ingredient:** Zonisamide (1,2-benzisoxazole – 3-methanesulfonamide, AD-810)	**Individual Study Synopsis** **Page 2 of 5** **Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**

Methodology (cont.): Amendment 1, issued on October 10, 2001, changed the study duration from 12 months to 6 months. The final visit for Study AN46046-225 was considered to be the initial visit for this study. Additional study visits for safety assessment were to be conducted monthly for the first 3 months, and a final visit was to be conducted at 6 months. For those subjects who treatment in this study beyond d Month 6 prior to implementation of Amendment 1, an additional visit was to be conducted at Month 9 and/or Month 12. As a result of this, all study data are summarized in this report through Month 12.

Vital signs, adverse event (AE) and concomitant medication assessments, physical examinations (including weight), and clinical laboratory testing were to be performed at every visit. Seizure frequency was to be assessed and electrocardiograms (ECGs) were to be performed at the initial and the final visits. Upon completion of this study, subjects were to be given the opportunity to enroll in study AN46046-354 to continue long-term treatment with zonisamide.

Number of Subjects: 29

Diagnosis and Main Criteria for Inclusion: Males or females aged 5 through 18 years who had a clinical diagnosis of epilepsy, had a satisfactory clinical course in Study AN46046-225, and did not experience adverse events that would make continued dosing with zonisamide unsafe.

Test Product, Dose, and Mode of Administration: Zonisamide in 12.5-mg, 25-mg, 50-mg, or 100-mg capsules was to have administered orally at the dose on which the subject was stable in Study AN46046-225 (1 mg/kg/day to 12 mg/kg/day, up to a maximum of 600 mg/day). Zonisamide doses were to be administered approximately every 12 hours twice daily.

Duration of Treatment: Planned duration of treatment was 6 months.

Reference Therapy, Dose and Mode of Administration, Batch No: No reference therapy was administered.

Criteria for Evaluation:

Safety: Safety was assessed by the use of concomitant medications; reported and observed AEs; and results of clinical laboratory measurements, vital signs, physical examinations (including weight) and 12-lead electrocardiograms (ECGs).

Pharmacokinetics and efficacy: Zonisamide blood samples for pharmacokinetics analysis were to be drawn at Months 3 and 6. Seizure frequency was to be assessed at the initial (Day 1) and final (Month 6 or at the time of early termination) visits. A global assessment of the subject's seizure control by a parent or legal guardian was to be obtained at the final visit (Month 6 or at the time of early termination).

2. SYNOPSIS (cont.)

Name of Company: Elan Pharmaceuticals, Inc. **Name of Finished Product:** Zonegran ™ **Name of Active Ingredient:** Zonisamide (1,2-benzisoxazole – 3-methanesulfonamide, AD-810)	**Individual Study Synopsis** **Page 3 of 5** **Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**

Statistical Methods: In general, data were summarized across all subjects and by age group (5-11 years and 12-18 years). Descriptive statistics were calculated for all parameters (counts and percentages for categorical data; N, mean, standard deviation [SD], median, minimum, and maximum for continuous data). All subjects enrolled in this study had previously participated in a zonisamide study for the treatment of pediatric epilepsy (Study AN46046-225). Subjects in this study were to continue the zonisamide dose on which they were stable in Study AN46046-225. Therefore, all subjects enrolled in this study were considered to be safety evaluable, and were included in all safely analyses. Inferential statistics were not calculated for safety data.

Prior to Protocol Amendment 1, which shortened the duration of the study from 12 months to 6 months, many subjects had completed ≥9 months of treatment in this study. Therefore, it was determined that all data should be summarized as well as listed; all data through Month 12 were summarized and listed in this report.

Mean exposure to zonisamide (in days) in this study, as well as mean cumulative exposure to zonisamide (including exposure in Study AN46046-225), were calculated. All AEs were listed by subject. AEs were mapped to body systems and preferred terms using the Coding Symbols for Thesaurus of Adverse Reaction terms (COSTART) dictionary. AEs that began prior to Day 1 (i.e., those that begun during Study AN46046-225) were categorized as "ongoing" AEs, provided that the stop date occurred after Day 1 or if the stop date was missing. AEs that began on or after Day 1, as well as any ongoing AEs that increased in frequency or worsened in severity on or after Day 1, were categorized as "new" AEs. AEs were summarized by age group, relationship to study drug, and maximum severity; these summaries were completed for new AEs only and new and ongoing AEs combined. AEs were also summarized by age group and whether a subject was taking a concomitant enzyme-inducing AED at any time during the study. Serious adverse events (SAEs) and AEs that resulted in discontinuation were summarized, listed, and described in subject narratives. Clinical laboratory results and changes from baseline (Study AN46046-225) were summarized by age group using descriptive statistics. In addition, clinical laboratory results were classified as below, within, or above reference ranges at baseline and at each clinic visits, and were summarized in shift tables. Additional analyses of bicarbonate and chloride were performed, including categorical analyses and shift tables. Bicarbonate levels (either below or within normal limits of reference range) were used to group subjects for additional shift tables of certain chemistry parameters. Vital signs were listed by subject and summarized by age group using descriptive statistics; these summaries included both changes from baseline (Study AN46046-225) and categorical changes. Physical examination and ECG results were listed. Concomitant medications were summarized and listed.

Seizure frequency per month and change from initial visit in seizure frequency per month were summarized descriptively (N, mean, SD, median, minimum, and maximum) by age group and overall. Global assessments of seizure control at baseline (recorded for subjects at baseline of study AN46046-225) and at the final visit were summarized descriptively (number and percentage of subjects).

2. SYNOPSIS (cont.)

Name of Company: Elan Pharmaceuticals, Inc. **Name of Finished Product:** Zonegran ™ **Name of Active Ingredient:** Zonisamide (1,2-benzisoxazole – 3-methanesulfonamide, AD-810)	**Individual Study Synopsis** **Page 4 of 5** **Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**

Statistical Methods: (contd.)

Serum zonisamide concentrations obtained from blood samples drawn at the Month 3 and Month 6 visits were listed but not summarized. Data from the samples from this study may be pooled with the pharmacokinetic data from studies AS46046-225 and AN46046-354 and other studies as appropriate). If conducted, the results of this analysis will be reported separately.

SUMMARY OF RESULTS

Disposition and Demographics: A total of 29 subjects were enrolled in the study and received zonisamide (20 subjects aged 5-11 years, 9 subjects aged 12-18 years). Of these 29 subjects, 24 (82.8%) completed the study. The mean age at the initial visit was 10 years. There were 17 male and 12 female subjects.

Exposure and Concomitant Medications: Overall, the mean total daily dose ranged from 9.0 to 12.9 mg/kg/day during the study. In subjects aged 5-11 years, it ranged from 9.0 mg/kg/day to 14.6 mg/kg/day, and in subjects aged 12-18 years, it ranged from 6.4 mg/kg/day to 10.1 mg/kg/day.

The overall mean exposure to zonisamide in this study was 259 days. The mean exposure in 5-11 year old subjects was 254 days, compared to 272 days in 12-18 year old subjects. Cumulative exposure to zonisamide (Studies AN46046-225 and -226 combined) was a mean of 323 days overall. The mean cumulative exposure in 5-11 year old subjects was 317 days, compared to 338 days in 12-18 year old subjects.

Concomitant medications affecting the central nervous system (CNS) were used by all subjects. Anti-infectives and dietary supplements were both used by 48% of subjects. The most frequently reported (≥ 5 subjects) concomitant AEDs were levetiracetam, lamotrigine, topiramate, phenytoin sodium, and oxcarbazepine.

Efficacy Results: The seizure frequency data were markedly non-normally distributed. At the initial visit, subjects aged 5-11 years had a median seizure frequency on 30 seizures per month, compared with 2 seizures per month in subjects aged 12-18 years. At the final visit, subjects aged 5-11 years had a median seizure frequency of 40 seizures per month, compared with 4 seizures per month in subjects aged 12-18 years. Results of the global assessment of seizure control, assessed at baseline in Study AN46046-225 and the final visit of Study AN46046-226, indicated that 13 of 29 (44.8%) subjects had average or better seizure control at baseline, compared to 18 of 25 (72.0%) at the final visit. However due to the small sample size and the large variance in data at the initial and final visits, meaningful conclusions cannot be drawn regarding seizure frequency in this study.

2. SYNOPSIS (cont.)

Name of Company: Elan Pharmaceuticals, Inc. **Name of Finished Product:** Zonegran ™ **Name of Active Ingredient:** Zonisamide (1,2-benzisoxazole – 3-methanesulfonamide, AD-810)	**Individual Study Synopsis** **Page 5 of 5** **Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**

Safety Results: All 29 subjects reported at least one treatment-emergent AE. The body systems most commonly affected were body as a whole and nervous system, each with 23 subjects (79.3%) [16 (80.0%) and 17 subjects (85.0%) aged 5-11 years, respectively, and 7 (77.8%) and 6 subjects (66.7%) aged 12-18 years, respectively] reporting events in these systems. The majority of treatment-emergent AEs were mild to moderate in severity. A total of 8 (27.6%) subjects reported 12 new severe AEs (9 different events). No subject was discontinued from the study due to an adverse event and no subject died during the study or within 30 days of the last dose of zonisamide.

A total of 24 (82.2%) subjects had reports of treatment-related, treatment-emergent AEs, 17 (85.0%) subjects aged 5-11 years and 7 (77.8%) subjects aged 12-18 years.

Ten new serious, nonfatal AEs were reported in five subjects; two of the events were considered to be related to zonisamide.

In general, few subjects experienced laboratory abnormalities that were evaluated by the investigator as clinically significant, and no subject was prematurely withdrawn from the study due to laboratory abnormalities. Overall 75.0% of subjects had bicarbonate levels that were below the normal reference range at any time during the study. A smaller proportion (28.6%) of subjects had chloride values that were above the normal reference range at any time during the study.

Overall, vital sign results were generally unremarkable.

MAH Conclusions: Long-term treatment with zonisamide was found to be generally safe and well tolerated in pediatric epileptic subjects aged 5-18 years.

Date of Final Report: 28 March, 2004

CHMP COMMENTS:

- There were only 29 subjects enrolled in this study, of which only 24 completed the study.
- Due to the small sample size and the large variance in data at the initial and final visits and the lack of a placebo arm in this study, meaningful conclusions, in this study, cannot be drawn.
- Ten new non fatal SAEs were reported in 5 subjects (four aged 5 – 11 years and one aged 12 – 18 years). Two of these, namely, encephalopathy and grand mal convulsion were considered by the investigators to be related to zonisamide and both events resolved following a reduction in the zonisamide

dosage.

- Laboratory data show a tendency for a low bicarbonate level and high chloride level to occur more often in 5 – 11 year olds than in 12 – 18 year olds.
- The overall exposure to zonisamide in this study was 259 days, with the mean exposure in 5-11 year old subjects of 254 days and of 272 days in 12-18 year olds. The cumulative exposure to zonisamide (studies AN46046-225 and 226 combined) was a mean of 323days overall with 317 days exposure in the 5-11 year olds and 338 days in the 12-18 year olds. This period of time is not considered to be regarded as long term exposure. Therefore the conclusion of the MAH that long term treatment with zonisamide was found to be generally safe and well tolerated in paediatric epileptic subjects aged 5 – 18 years should be interpreted with caution and further studies would be required to confirm this statement.
- There are no amendments required to the product information following assessment of this study.

5. Study ZNS – 401:

MAH **Synopsis**

Name of Company: Elan Pharmaceuticals, Inc. **Name of Finished Product:** Zonegran ™ **Name of Active Ingredient:** zonisamide	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**
Title of Study: Open-Label Dose Titration Assessment of the Clinical Utility of a Slow. Low Dose Titration Schedule of Zonegran™ in the Initiation of Therapy in patients with Partial Seizures		
Principal Investigator: Investigators for this multi-center study are listed in Section 16.4.		
Study Centers: This study was conducted at 41 sites in 1 country (U.S)		
Publication (reference): Burdette DE. Overall effectiveness of zonisamide therapy on a slow, low dose titration schedule [abstract]. Epilepsia 2000;41;(suppl 7):108-109. Penovich P. Slow titration with zonisamide: beneficial effects in tolerability, Epilepsia 2000;41(suppl):106-107.		
Study Period: Date First Subject Enrolled: 27 January 1999 Date Last Visit Completed: 19 September 2000	**Phase of Development:** III-b	
Primary Objective: The primary objective of this study based on the protocol was: 1. To evaluate a slow, low dose titration schedule of zonisamide in the initiation of treatment in patients with partial seizures		

Secondary Objective: The secondary objectives of this study based on the protocol were:

1. To evaluate the safety and clinical response of patients taking zonisamide in combination with other AEDs such as Neurontin®, Lamictal®, Topamax®, and Gabatril®

2. To evaluate the safety of the lower dosage strengths (i.e. 25 and 50 mg daily) when used to initiate therapy, specifically the frequency of adverse events and body weight changes.

3. To evaluate the efficacy of zonisamide as measured by:

- the reduction in seizure frequency as recorded in a daily seizure diary
- changes in seizure type and duration as recorded in a daily seizure diary
- changes in subject and physician global assessment.

Primary Objective: The primary objective of this study based on the revised Statistical Analysis Plan was:

1. To evaluate the safety of the lower dosage strength of zonisiamide (i.e. 25 and 50 mg) when used in the initiation of treatment, specially the frequency of adverse events and body weight changes.

Secondary Objective: The secondary objectives of this study based on the revised Statistical Analysis Plan were:

Name of Company: Elan Pharmaceuticals, Inc. **Name of Finished Product:** Zonegran ™ **Name of Active Ingredient:** zonisamide	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**

1. To evaluate the efficacy of zonisamide as measured by the reduction in seizure frequency between the Screening Phase and the Maintenance Phase as recorded on the daily diary.

2. To evaluate the efficacy of zonisamide as measured by the subject global assessments of antiepileptic therapy and life in general as well as the investigator global assessment of antiepileptic therapy at Week 12 as compared to baseline (Week 0)

3. To evaluate changes in the duration of seizures between the Screening and Maintenance Phases.

Methodology: This open-label single treatment study was conducted with no placebo or active comparator groups. Subjects were enrolled in a 4-week Screening Phase during which they recorded seizure frequency without zonisamide treatment. Those that met inclusion criteria were enrolled and zonisamide treatment was initiated with a slow, low dose titration beginning at 25 mg daily and increasing up to the maximum tolerated dose of 400 mg daily during the 8-week Titration Phase. The maximum tolerated dose was continued through the 4-week Maintenance Phase. Study Visits were at the end of titration (Week 8) and maintenance (Week 12). Subjects had the option to continue and receive up to 800 mg daily in the Extension Phase, with study visits every 3 months.

Number of Subjects

Planned: 200 subjects

Analyzed: 243 subjects in the Intent-To-Treat Population were the basis for the safety analysis. 196 subjects (who completed the Week 12 Visit) in the evaluable population were the basis for the efficacy analysis. 171 subjects continued into the Extension Phase, those continuing to receive study drug at each study visit were the basis for safety and efficacy evaluations during the Extension Phase.

Diagnosis and Main Criteria for Inclusion: Male or female subjects 12 years of age or older with partial seizures that were receiving one or two daily chronic antiepileptic drugs and required the addition of another daily antiepileptic drug to their regimen entered the Screening Phase. To be enrolled in the treatment phases, subjects must have had at least one partial seizure during the Screening Phase.

Test Product, Dose, and Mode of Administration:

Zonegran ™ (zonisamide) 25, 50 and 100 mg capsules taken orally.

Duration of Treatment: The Screening and Maintenance Phases were each to be 4 weeks in duration. The Titration Phase was planned to last 8 weeks. The median duration of the Titration and Maintenance Phases was 84 days (25^{th} and 75^{th} percentile: 79, 89). The median duration of the Extension Phase was 378 days (25^{th} and 75^{th} percentile: 231, 486).

Reference Therapy, Dose, and Mode of Administration, Batch number: No placebo or active comparator reference treatment was included in this study.

Name of Company: Elan Pharmaceuticals, Inc. **Name of Finished Product:** Zonegran ™ **Name of Active Ingredient:** zonisamide	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**

Criteria for Evaluation:

Efficacy (Primary): The primary efficacy criterion was seizure frequency as recorded in a daily diary.

Effective (Secondary): The secondary efficacy criteria were changes in the seizure type or duration as recorded in a daily diary and changes in subject and physician global assessments of antiepileptic therapy and the subject global assessment of life in general at Week 12 compared to Week 0.

Safety: Safety was evaluated by the frequency of adverse events and body weight changes.

Statistical Methods: Sample size: Sample size and power calculations were not used in this study. Approximately 200 subjects with partial epilepsy were to be enrolled.

Statistical Analysis: Summary statistics were provided for number and type of seizures from seizure diaries, zonisamide dose and duration of treatment, subject compliance, subject and investigator global assessments, body weight. Adverse events and reasons for discontinuation were listed and summarized. The 95% confidence intervals were calculated for the percent of subjects that experienced a ≥ 50% decrease in seizure frequency from the Screening Phase for overall, simple partial, complex partial and other seizures at the end of Maintenance Phase and at each examined Extension Visit period. The 95% confidence intervals were computed for mean body weight changes at Week 8 and 12. The 95% confidence intervals were also computed for the mean global assessment change at the same time points. No inferential statistics were done.

Summary of Results:

Efficacy: The frequency of seizures overall and partial seizures in particular was substantially decreased by zonisamide during this study. The seizure frequency decreased relative to baseline at the end of the Maintenance Phase and continued throughout the Extension Phase for each of these types of seizures. A significant number of subjects experienced a decrease of at least 50% in their seizure frequency following treatment with zonisamide at their maximum tolerated dose, up to 400 mg daily (Maintenance Phase) or up to 800 mg daily (Extension Phase). No change in the duration or type of seizure was apparent with zonisamide treatment.

Name of Company: Elan Pharmaceuticals, Inc.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Zonegran ™	**Volume:**	
Name of Active Ingredient: zonisamide	**Page:**	

Percent of Subjects with a ≥ 50% Decrease in Seizure Frequency (95% Confidence Interval) by Seizure Type from the Screening Phase During Treatment with Zonisamide (Evaluable and Extension Population)

	All Seizures	Simple Partial	Complex Partial	Other
Maintenance Phase	48.5% (41.4, 55.5)	53.2% (42.2, 64.2)	51.0% (43.1, 58.9)	69.7% (58.6, 80.8)
Extension Visit 1	53.5% (46.0, 61.0)	63.6% (52.0, 75.2)	60.7% (52.5, 69.0)	61.7% (49.4, 74.0)
Extension Visit 2	58.6% (50.6, 66.6)	77.2% (66.3, 88.1)	62.1% (53.2, 70.9)	56.6% (43.3, 69.9)
Extension Visit 3	57.3% (48.3, 66.2)	73.3% (60.4, 86.3)	58.7% (48.6, 68.8)	73.8% (60.5, 87.1)
Extension Visit 4	56.4% (46.4, 66.4)	66.7% (51.3, 82.1)	59.7% (48.4, 71.7)	72.7% (57.5, 87.9)

Note: Ninety day (90) seizure frequency observed for each extension visit period was prorated to 28 days prior to calculation of percent change from 28-day screening phase.

Safety: The adverse event profile following administration of zonisamide were generally consistent with data from the package insert. The most frequent treatment adverse events (occurring in > 10% of subjects) during the Titration and Maintenance Phases of the study were dizziness, somnolence, headache, abnormal thinking, asthenia, anorexia, accidental injury and nausea. With the exception of accidental injury, these adverse events were those most frequently considered dug related by the investigator. The most frequent treatment-emergent adverse events (occurring in > 10% of subjects) during the Extension Phase of the study were abnormal thinking, infection, anorexia, weight loss, insomnia and somnolence. Abnormal thinking, weight loss and anorexia were those most frequently (> 10% of subjects) considered study drug related by the investigator.

Subjects that withdraw from treatment during the Titration and Maintenance Phases frequently did so at dose of 100 mg daily or less. Those that withdraw during the Extension Phase frequently attained doses of 400 to 600 mg daily. Somnolence, dizziness and nausea, that were more frequent in the Titration and Maintenance Phases of the study were less frequent in the Extension Phase and may become less troublesome over time with continued therapy. Adverse events such as weight loss that may develop over time may be observed more frequently with longer zonisamide treatment.

Treatment with zonisamide in subjects with partial epilepsy resulted in small, but significant decreases in body weight from baseline. The mean body weight of the 243 subjects in the ITT population was 74.6 kg at baseline with a decrease in mean body weight from baseline at Week 8 of -0.7 kg (95% confidence interval of -1.1, -0.4) and at Week 12 of -1.0 kg (95% CI: -1.3, -0.6). Overall, the mean body weight of the subjects declined over the course of the extension from a mean of 74.7 kg at baseline with a decrease in mean body weight from the baseline at Visit 1 of -2.1 kg (95% confidence interval of -2.8, -1.5) and at Visit 2 of -2.8kg (95% CI: -3.7, -1.9) at Visit 3 of -3.4 kg (95% CI of -4.6, -2.3) and Visit 4 of -3.8 kg (95% CI -5.3, -2.3)

MAH Conclusions:

Zonisamide, titrated to the maximum tolerated dose in subjects with partial epilepsy, resulted in a decrease in seizure frequency of 50% or more in a significant percentage of the evaluable, ITT, and extension populations. This applied to overall seizures as well as simple partial, complex partial and other seizures.

The subject and investigator global assessments of AED therapy and the subject global assessment of life in general showed a small, but significant improvement following zonisamide treatment.

Treatment with zonisamide in subjects with partial epilepsy resulted in small, but significant decreases in body weight from baseline that, during the Titration and Maintenance Phases (medium duration 84 days), were mean decreases of < 1 kg and, during the first 4 visits of the Evaluation Phase (medium duration 378 days), were a mean decrease between 2 and 4 kg. Zonisamide treatment in subjects with partial epilepsy was generally well tolerated.

CHMP COMMENTS:

- This study was an open label, single treatment study which was conducted with no placebo or active comparator groups.
- The subjects included in this trial were aged 12 years and older and so it is not clear how many of these subjects were in the paediatric and adolescent population.
- The above mentioned conclusions of the MAH are endorsed.
- As discussed, following assessment of studies, 720-02385-96 and 720-02385-96EXT and in addition, following assessment of this study, the adverse event of headache should be added to the product information for Zonegran.

6. Study ZNS-501:

MAH SYNOPSIS

Name of Company: Elan Pharmaceuticals, Inc.	**Individual Study Synopsis** **Page 1 of 4**	
Name of Finished Product: Zonegran®	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use Only)**
Name of Active Ingredient: zonisamide	**Volume:** **Page:**	

Title of Study: A Multicenter, Open-Label, Safety Study to Evaluate the Use of 25 mg and 50 mg ZONEGRAN® (zonisamide) in the Initiation of Therapy in Patients with Epilepsy

Date of Protocol: 13 April 2000

Investigators: A total of 26 investigative centres enrolled patients in this study. A complete listing and description of all Investigators and study centres is included in Appendix 17.1.4.

Publication (reference): None

Study Period (dates of study)		**Phase of Development**
Date Study Initiated	**Date of Last Observation**	Phase 3
30 August 2000	23 January 2002	

Primary Objective: The primary objective of this study was:

To assess the safety of the 25 and 50 mg dosage strengths when used in the initial titration of Zonegran®. Safety was determined by the number of adverse events (AEs) and the body weight changes during the initial titration.

Methodology: This was an open-label, multicenter study in patients ≥ 12 years of age with a diagnosis of epilepsy. Those who met the criteria and were enrolled in the study began their titration at 25 or 50 mg of zonisamide depending on their weight. The patient was titrated to the 100 mg dose over 2 to 8 weeks. Patients returned to the clinic once they reached the 100 mg dosage for the Completion Visit. Adverse events, body weight, and any changes to concomitant anti-epileptic drug (AED) medications were to be recorded.

Number of Patients: Approximately 300 patients were initially planned. Upon evaluation of the rate of enrolment, it was decided to terminate the study with 147 patients at 26 sites enrolled with 143 included in the intent-to-treat (ITT) population.

Diagnosis and Main Criteria for inclusion:

Male or female patients ≥ 12 years of age with a confirmed diagnosis of epilepsy

Name of Company:	**Individual Study Synopsis**	
Elan Pharmaceuticals, Inc.	**Page 2 of 4**	
Name of Finished Product:	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use Only)**
Zonegran®		
Name of Active Ingredient:	**Volume:**	
zonisamide	**Page:**	

Test Product, Dose, and Mode of Administration:

Zonegran® in 25 or 50 mg capsules taken orally.

Duration of Treatment: From 2 to 8 weeks

Reference Therapy, Dose, and Mode of Administration, Batch No.: None

Criteria for Evaluation: Safety assessed by monitoring AEs and concomitant medication usage, and measuring the change of weight from Screening to Completion of Visit.

Statistical Methods:

Analysis population: One population, the ITT population, is used for all summaries and analyses of study data

Demographic characteristics: Demographic characteristics of age, gender, race, height, and weight are summarized using descriptive statistics.

Safety: Adverse events and serious adverse events (SAEs) are summarized by body system and preferred term using the Coding Symbol for a Thesaurus of Adverse Reaction Terms (COSTART), presenting frequency of subject incidence and percentages. The change in body weight is measured from the Screening Visit to the Completion Visit. Body weights obtained at the Screening and Completion Visits are summarized using descriptive statistics as well as the change from screening to completion. The magnitude of this change is evaluated using a 95% confidence interval. Concomitant medication taken during the study are listed by patient and summarized by World Health Organization Anatomical Therapeutic Chemical Classification for Drugs (WHO ATC) code and drug name.

Summary of Results:

Efficacy: Not Applicable

Safety:

- There were no deaths. There were 3 SAEs, two of which led to study drug discontinuation. Two of these SAEs were seizures and the third was colitis. No SAE was assessed by the Investigator as study drug related.
- The overall incidence of AEs (number of patients experiencing at least one event) regardless of the relationship to study drug was 82 (57.3%).
  - The body system with the highest incidence of AEs was Body As A Whole 41 (28.7%), then Nervous System 37 (25.9%), followed by Digestive System 23 (16.1%), Respiratory System 12 (8.4%), and skin and Appendages 10 (7.0%).
  - Overall, the AE occurring with the highest incidence was headache (12.6%), followed by somnolence (8.4%) and then asthenia (6.3%).
  - There was a total of 182 AEs reported by 82 patients during the study.

Name of Company:	**Individual Study Synopsis**

Safety (continued)

- The dose level at which AEs occurred can be summarized as follows:
  - Thirty-nine patients had a total of 67 AEs at the 25 mg/day dose level. The AE reported by the highest number of patients at this dose was headache. It occurred in 7 patients.
  - Twenty-four patients had a total of 40 AEs at the 50 mg/day dose level. The AE with the highest incidence was headache in 5 patients.
  - Six patients had a total of 9 AEs at the 75mg/day dose level. No AE occurred more than once at this dose level.
  - Thirty-three patients had a total of 47 AEs at the 100 mg/day dose level. The AE with the highest incidence was headache. It occurred in 9 patients.
  - Seven patients had a total of 16 AEs at doses higher than 100 mg/day. The AEs with the highest incidence were dizziness, somnolence, and insomnia. Each of these AEs occurred in 2 patients.
- There were 81 AEs occurring in 51 patients that were considered by the Investigator to be study drug related. The most frequent study drug related AE was somnolence which was experienced as an AE 13 times by 12 patients.
- Approximately 11% (16/143) of the patients discontinued study drug because of AEs. The total number of AEs that led to discontinuation was 22.
- The body systems with the highest incidence of AEs leading to discontinuation were the Nervous System and Body as a Whole. The Nervous System had 5 patients having a total of 6 AEs. The AEs included convulsion and Grand Mal convulsion, somnolence, emotional lability, tremor, and abnormal gait. The Body as a Whole System had 5 patients having a total of 6 AEs. The AEs in this system included chest pain, headache, overdose, abdominal pain, and allergic reactions.
  - Other AEs leading to study discontinuation were in the Digestive System (nausea, anorexia, dyspepsia, and colitis), Skin and Appendages (urticaria, and rash), Metabolic and Nutritional Disorders (hypernatremia), Urogenital System (urinary tract infection), Cardiovascular System (tachycardia), and Special Senses (tinnitus).
  - The AEs most commonly associated with discontinuation in this study were headache, rash and convulsion
- There was no significant change in patient weights during the study (95% CI = -0.1, 0.6). No patient reached the protocol defined AE of a 10% weight loss.

Name of Company: Elan Pharmaceuticals, Inc.	**Individual Study Synopsis** **Page 4 of 4**	
Name of Finished Product: Zonegran® **Name of Active Ingredient:** zonisamide	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**
Pharmacokinetics and Pharmacodynamics: Not Applicable **MAH Conclusions:** Due to the smaller than planned sample size, the safety results should be interpreted cautiously. • There was no significant change in patient weights during the study (95% CI = -0.1, 0.6). No patient reached the protocol defined AE of a 10% weight loss. • This study showed that the gradual titration of Zonegran® beginning at 25 or 50 mg/day was safe and resulted in few AEs.		
Date of Report: 01 October 2003		

CHMP COMMENTS:

- This trial enrolled patients of 12 years and upwards and it is not clear how many of these were in the 12 to 18 age population.
- The clinical trial is of open label design.
- It was intended to enrol 300 patients, however, only 147 patients were enrolled with 143 included in the intent to treat population and so therefore the conclusion of the MAH, that due to the smaller than planned sample size, the safety results should be interpreted cautiously, is endorsed.
- As discussed in studies 720-02385-96, 720-02385-96EXT and ZNS-401, the adverse event of headache should be added to the product information for Zonegran.

7. Study ZNS – 502:

MAH SYNOPSIS

Name of Company: Elan Pharmaceuticals, Inc.	**Individual Study Synopsis** **Page 1 of 4**	
Name of Finished Product: Zonisamide **Name of Active Ingredient:** Zonisamide (1,2-benzisoxazole – 3-methanesulfonamide, AD-810)	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**

Title of Study: A Multicenter, Open-Label, Safety and Efficacy Study of Zonegran® (Zonisamide) in Patients With Progressive Myoclonic Epilepsy

Date of Protocol: 22 June 1999

Date of Amendment 1: 25 August 1999

Date of Amendment 2: 18 November 1999

Investigators and Study Centers: A total of 20 study centers in the United States participated in this study; patients were enrolled at 16 of these centers. A complete list of investigators and study centers locations is provided in Section 6, Table 1.

Publication (reference): Vossler, DG. Multicenter, open-label, safety and efficacy study of zonisamide in patients with progressive myoclonic epilepsy. Neurology. 2002;April (3 Suppl): 58.

Study Period (dates of study):

Date of First Treatment: 8 March 2000 **Date of Last Observation:** 23 July 2001

Phase of Development: Phase IV

Primary Objectives: The primary objectives of this study were to: (1) assess the safety of zonisamide when used for patients with progressive myoclonic epilepsy as determined by the number of adverse events (AEs), change in body weight, and laboratory tests including zonisamide levels; (2) evaluate the efficacy of zonisamide as measured by 50% reduction in myoclonic seizures as recorded in the daily seizure diary; and (3) evaluate the efficacy of zonisamide as measured by the reduction in seizure frequency, type and duration as recorded in the daily seizure diary.

Methodology: This was a Phase IV, open-label, single-arm, multicenter safety and efficacy study of patients with a diagnosis of progressive myoclonic epilepsy (PME). Planned enrollment was approximately 50 patients. The study design included a screening (baseline) period, titration period, maintenance period, and tapering period. Patients who met the entry criteria were provided a daily seizure diary to record frequency of seizures during the 2-week screening period. Following completion of this screening period, patients were dispensed zonisamide at the Baseline Visit (Week 0). The initial dose of zonisamide treatment (mg/day) depended upon the patient's weight (≤40 kg or >40 kg). For each of the weight groups, the initial target dose of zonisamide was 0.4 mg/kg/day and could be titrated to 6 mg/kg/day over an 8-week period. The dose was increased on a weekly basis until the patient reached the maximum tolerated dose (as determined by the investigator) or the 6 mg/kg/day maximum (400 mg/day). Patients who could not tolerate a dose increase were to return to the previous dose level. An 8-week maintenance period followed the titration period. Upon completion of the maintenance period, patients returned to the clinic for the Final Efficacy Visit.

Name of Company: Elan Pharmaceuticals, Inc. **Name of Finished Product:** Zonisamide **Name of Active Ingredient:** Zonisamide (1,2-benzisoxazole – 3-methanesulfonamide, AD-810)	**Individual Study Synopsis** **Page 2 of 4** **Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**
If the patient wished to continue zonisamide therapy after this study (by either entering another investigational study or taking commercially available zonisamide), the patient was allowed to exit this study upon completion of the Final Efficacy Visit procedures and zonisamide was not tapered. If the patient wished to discontinue zonisamide therapy, the patient was tapered off zonisamide therapy over 2 weeks and returned to the clinic for an End of Tapering Visit. The duration of treatment in this study was 16 weeks for patients not tapering and 18 weeks for those tapering off zonisamide therapy.		
Number of Patients: 30 patients were enrolled and 20 patients completed the study.		
Diagnosis and Main Criteria for Inclusion: Male and female patients 5 years of age or older who had as their primary form of epilepsy a diagnosis of PME (as defined by the International Classification of Epilepsies and Epileptic Syndromes - Progressive Myoclonus Epilepsies). Patients with myoclonic seizures refractory to other antiepileptic drugs (AEDs) were the target study population. Patients selected for study were not to be taking more than three chronic daily AEDs.		
Test Product, Dose, and Mode of Administration: Zonisamide was administered according to the patient's weight. Patients who weighed ≤40 kg were started at 12.5 mg/day (0.4 mg/kg/day) and patients who weighed >40 kg were started at 25 mg/day (0.4 mg/kg/day). Doses were titrated on a weekly basis until patients reached their effective dose or up to a maximum dose of 200 mg/day (6 mg/kg/day) or 400 mg/day (6 mg/kg/day) for patients weighing ≤40 kg or >40 kg, respectively.		
Duration of Treatment: Duration of treatment was 16-18 weeks.		
Reference Therapy, Dose, and Mode of Administration, Batch No.: No reference therapy was administered.		
Criteria for Evaluation: The efficacy parameters were a 50% or 75% reduction in myoclonic seizures, median percent reduction in seizures, number of patients who were seizure free, and number of patients with increases in seizures during the maintenance period. Patient and investigator global assessments of seizure control and patient well being were also measured. Safety was assessed by evaluation of adverse events, changes in body weight, clinical laboratory tests, and zonisamide serum concentration.		
Statistical Methods: All seizure count analyses called for comparison (paired tests) between the baseline period (Week -2 to Week 0) and the maintenance period (Week 8 to Week 16). The seizure diaries returned at Week 0 and Week 16 defined these two periods. Patients either counted their daily seizures over each 24-hour period or using 10-minute counts three times a day (morning, afternoon, and evening). Means of each type of count were calculated for the baseline period and the maintenance period so that each individual had a baseline period mean and a maintenance period mean.		

Name of Company: Elan Pharmaceuticals, Inc.	**Individual Study Synopsis** **Page 3 of 4**	
Name of Finished Product: Zonisamide **Name of Active Ingredient:** Zonisamide (1,2-benzisoxazole – 3-methanesulfonamide, AD-810)	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**

For the patients who counted their seizures for 10 minutes three times a day, seizure data were analyzed for the morning, afternoon, and evening 10-minute counts as well as for an average 10-minute count across the morning, afternoon, and evening observations. For those patients reporting seizures per 24 hours, the 24-hour counts were used for analysis. To enable seizure data to be analyzed for the study population as a whole, the 24-hour counts were also converted to 10-minute counts and combined with the average of morning, afternoon, and evening 10-minute counts to create a converted 10-minute count. Seizure data are reported for each of these count types (i.e. morning 10-minute count; afternoon 10-minute count; evening 10-minute count; average of 10-minute morning, afternoon, and evening counts; 24-hour counts; and converted 10-minute counts) in the efficacy tables; however, the focus in this report is on the converted 10-minute count analyses.

AEs and clinical laboratory test results were summarized using descriptive statistics (counts and percentages for categorical variables and number [N], mean, and standard deviation [SD] for continuous variables). Treatment-emergent adverse events (TEAEs) were summarized by body system and COSTART code, using patient and event counts. Body weight was summarized for the study population as a whole and by age group (≤18 or >18 years) and compared between baseline and Final Efficacy Visit using a paired t-test.

Summary of Results:

Efficacy: Efficacy results based on converted 10-minute myoclonic seizure counts are as follows. Patients with baseline counts greater than zero and non-missing maintenance period seizure events were included in percent reduction calculations (n = 20). Ten of these 20 patients (50%) achieved a 50% reduction in mean myoclonic seizure counts from baseline to maintenance period; and 6 of these 20 (30%) achieved a 75% reduction. The median percent reduction in seizure counts from baseline to maintenance period was 54.5%. The number of patients who were seizure free or who experienced an increase in seizures from baseline to maintenance period was also determined. For this analysis, patients with missing seizure count data during baseline or maintenance periods were not included; however, patients reporting zero seizures at baseline were included (n = 21). Six of these 21 patients (28.6%) had an increase in seizure counts and 4 of these 21 patients (19%) were seizure free during the maintenance period. Patient and investigator global assessments reflected an improvement in seizure control that was statistically significant ($p < 0.05$, paired t-test).

Safety: A total of 27 patients had one or more TEAE. TEAEs that occurred in 10% or more of the study population were: anorexia (27%), asthenia (23%), somnolence (23%), fever (20%), infection (17%), rash (17%), constipation (13%), convulsions (13%), increased cough (13%), accidental injury (13%), nervousness (13%), diarrhea (10%), and vomiting (10%). Sixteen patients had treatment-related TEAEs. Treatment-related TEAEs occurring in 10% or more of the patients were anorexia (23%), somnolence (17%), asthenia (13%), and nervousness (10%). Most TEAEs were mild or moderate in intensity. One death occurred and although this 9-year-old girl had been in critical condition one year prior to entering this study and was first hospitalized during this study prior to receiving study drug, the investigator considered her elevated liver enzymes and multisystem organ failure related to study drug.

Name of Company: Elan Pharmaceuticals, Inc. **Name of Finished Product:** Zonisamide **Name of Active Ingredient:** Zonisamide (1,2-benzisoxazole – 3-methanesulfonamide, AD-810)	**Individual Study Synopsis** **Page 4 of 4** **Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**
Five additional patients had nonfatal serious adverse events (SAEs); none of these were considered treatment related. Five patients withdrew from the study due to TEAEs. The weight of patients over 18 years of age decreased with borderline statistical significance ($p = 0.0525$) during the study. Those patients 18 years of age or younger maintained a stable weight during the study ($p = 0.6738$). Other than for the patient who died from multisystem organ failure, there were no notable clinical laboratory findings.		
Conclusions: Zonisamide appears to be safe and generally well tolerated in subjects with myoclonic epilepsy. However, due to the fact that the study was small and open-label in design, caution should be used when interpreting the results. The observed AE profile appeared to be consistent with what has been previously described for commercially available zonisamide. Further research to establish the efficacy and tolerability of zonisamide in patients with myoclonic epilepsy may be warranted.		
Date of Report: 12 April 2004		

CHMP COMMENTS:

- The above mentioned conclusions of the MAH are endorsed.
- This study was a small, open label study and caution should be used when interpreting the results.
- There was one death during this study which occurred in a 9 year old girl. She had been in a critical condition one year prior to entering the study and was first hospitalised prior to receiving study medication, however, the investigator considered that her elevated liver enzymes and multisystem organ failure to be related to study medication.
- As stated by the MAH, further research to establish the efficacy and tolerability of zonisamide in patients with Progressive Myoclonic Epilepsy would be warranted.

8. <u>Study ZNS – 503:</u>

<u>MAH SYNOPSIS</u>

Name of Company: Elan Pharmaceuticals, Inc.	**Individual Study Table Referring to Part of the**	**(For National Authority Use Only)**

Name of Finished Product: Zonegran®	**Dossier**	
Name of Active Ingredient: zonisamide	**Volume:** **Page:**	

Title of Study: A Pilot Dose-range Finding Study of Zonegran® (zonisamide) in Patients with Neuropathic Pain Conditions

Principal Investigator: Investigators for this 3-center study are listed in Section 16.4.

Study Centers: This study was conducted at 3 sites in the United States.

Publication (reference): Backonja M, Galer B. Zonisamide for neuropathic pain: a pilot study. Poster presented at: Zonegran Scientific Exhibit at the American Epilepsy Society Annual Meeting, December 3, 2000, Los Angeles, CA. Elan Pharmaceuticals 2000;26 27.

Study Period: **Date First Subject Enrolled:** 31 January 2000 **Date Last Visit Completed:** 15 March 2001	**Phase of Development:** IV

Primary Objectives: The primary objectives of this study were:

1. To evaluate the patient tolerability and safety (i.e., laboratory tests, including zonisamide levels, and frequency of adverse events) of Zonegran use in subjects with neuropathic pain conditions.
2. To determine the target dose range of Zonegran for future study of effectiveness in treating subjects with neuropathic pain conditions.

Secondary Objectives: The secondary objectives of this study were:

To evaluate the efficacy of Zonegran, either alone or as adjunctive therapy, in subjects with neuropathic pain conditions as determined by changes in the following:

- Patient Daily Diary (The average weekly pain score was determined by the subject's assessment of daily pain, recorded in the Patient Daily Diary, and the average calculated over the 7-day period)
- Pain Relief Scale
- Pain qualities as rated by the Neuropathic Pain Scale
- Pain assessment as rated by the Wisconsin Brief Pain Inventory, and
- Investigator Global Assessment.

Methodology: This was an open-label, dose-titration, 3-center, Phase IV study for male or female subjects, aged 12 years or older, weighing at least 35 kg and diagnosed with daily neuropathic pain that had persisted for a minimum of 3 months. The study consisted of a screening phase (Week -1); a 1-week baseline Screening Period, during which subjects recorded their daily pain score in the Patient Daily Diary (Week 0); and a 12-week treatment phase consisting of an 8-week dose Titration Period (Weeks 1 through 8), a 2-week dose Maintenance Period (Weeks 9 and l0), and a 2-week Tapering Period (Weeks 11 and 12).

Number of Subjects

Planned: up to 20 subjects

Analyzed: 34 subjects in the Intent-to-Treat Population, 34 subjects in the Safety Population

Name of Company: Elan Pharmaceuticals, Inc.	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use Only)**
Name of Finished Product: Zonegran®	**Volume:**	
Name of Active Ingredient: zonisamide	**Page:**	
Diagnosis and Main Criteria for Inclusion: Subjects diagnosed with daily neuropathic pain that had persisted for a minimum of 3 months (documented by patient's signs and symptoms, neurologic exam, and a minimum score of 4 from average pain intensity score derived from the Patient Diary) were eligible for participation in the study if they met the inclusion and exclusion criteria as stated in the protocol.		
Test Product, Dose, and Mode of Administration: Zonegran 25-mg, 50-mg, and 100-mg capsules taken orally. The capsules were packaged in high density polyethylene bottles with child-resistant closures. For subjects weighing more than 40 kg, the dose was initiated at 25 mg daily and was titrated to a maximum daily dose of 800 mg. For subjects weighing between 35 and 40 kg, the dose was initiated at 25 mg every other day and was titrated to a maximum daily dose of 400 mg. For all subjects, if a dose was not tolerated, then the dose was reduced to the previous level, and the subject was maintained on this dose as their maximum tolerated dose. The dose tapering schedule required tapering the dose for all subjects completing the study. The medication was to be withdrawn by reducing the dose by 50% for 2 weeks, then stopping therapy.		
Duration of Treatment: The Titration Period, during which doses were titrated to the maximum tolerated dose, was 8 weeks in duration (Weeks 1-8). The Maintenance Period, during which subjects received a stable maintenance dose, was 2 weeks in duration (Weeks 9 and 10). The Tapering Period, during which the doses were tapered, was 2 weeks in duration (Weeks 11 and 12).		
Reference Therapy, Dose, and Mode of Administration, Batch Number: No placebo or active comparator reference was included in this study.		

Name of Company:	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Elan Pharmaceuticals, Inc.		
Name of Finished Product:		
Zonegran®	**Volume:**	
Name of Active Ingredient:	**Page:**	
zonisamide		

Criteria for Evaluation:

Safety (Primary): Evaluation of the tolerability and safety of Zonegran was the primary objective of the study. Criteria for evaluating safety were clinically significant changes in vital signs (blood pressure and pulse) and laboratory tests (hematology, blood chemistry, urinalysis, zonisamide levels), and the occurrence of treatment-emergent adverse events as spontaneously reported by patients or noted by the Investigator.

Efficacy (Secondary): Evaluation of the potential efficacy of Zonegran, either alone or as adjunctive therapy, was a secondary objective of this study. The efficacy of Zonegran was determined on the basis of changes from Baseline at each visit in subjects' assessments of daily pain recorded in the Patient Daily Diaries; subjects' assessments of pain relief at Weeks 8 and 10; and changes from Baseline at Weeks 8 and 10 in subjects' assessment of pain using the Wisconsin Brief Pain Inventory and Neuropathic Pain Scale and in the Investigator Global Assessment of patients' disease status.

Pharmacokinetics and Pharmacodynamics: Zonisamide levels were determined as part of the safety analysis.

Statistical Methods: Two analysis populations were defined for enrolled subjects who took at least 1 dose of Zonegran. The intent-to-treat (ITT) analysis population included ITT subjects who had at least 1 on-drug efficacy evaluation, while the safety analysis population comprised all ITT subjects who had follow-up safety information. Study populations were summarized by site and overall for all enrolled subjects. Descriptive statistics were used to summarize age, gender, race, body weight, and height for the safety analysis population. The number (and percentage) of patients who had adverse events beginning during the Titration, Maintenance, or Tapering Periods were displayed by preferred term. Vital signs (blood pressure and pulse) and body weight and changes from Baseline were summarized using descriptive statistics. Baseline was the last measurement taken prior to the first dose of open-label Zonegran. Laboratory data were listed. Efficacy measurements included daily pain scores (from diary), Pain Relief Scale, Neuropathic Pain Scale, Wisconsin Brief Pain Inventory, and Investigator Global Assessment. Analyses of efficacy measurements were based on the ITT analysis population. Descriptive statistics were displayed at Baseline and each study week in addition to changes from Baseline for total scores and individual items, where applicable. Ninety-five percent confidence intervals were calculated at each time point on the mean changes from Baseline for each summarized measure. Numbers and percentages of patients in each category were displayed in addition to mean values for scales with 5 or fewer categories.

Summary of Results:

Dose: One of the objectives of the study was to determine the target dose range of Zonegran in treating subjects with neuropathic pain conditions. According to the protocol, if a dose was not tolerated, then the dose was reduced to the previous level, and the subject was maintained on his/her maximum tolerated dose. The most common maintenance doses were between 350 and 450 mg per day, received by 47.4% of subjects at Week 9 and by 44.4% of subjects at Week 10.

Efficacy: Treatment with zonisamide generally resulted in mean decreases (improvement) in pain scores. For the Patient Daily Diary, mean pain ratings decreased from Baseline at all time points from Weeks 1 to 7 and Weeks 8 to 12. For the Pain Relief Scale, 5 subjects each at Weeks 8 and 10 had a much improved or complete relief response. Four of these subjects had a history of various neuropathies and 1 had reflex sympathetic dystrophy of the left lower leg, left arm twitch, and right forearm numbness. For the Neuropathic Pain Scale, the mean total score decreased from Baseline at the Week 8 and Week 10 visits. In addition, there were decreases for most of the 10 subparameters that make up this assessment tool at Weeks 8 and 10. For the Wisconsin Brief Pain Scale Inventory, there were mean decreases from Baseline at Week 8 in 10 of the 12 parameters and at Week 10 in 7 of the 12 parameters that make up this Inventory. For the Investigator Global Assessment, 4 subjects improved at the Week 8 visit, and a total of 5 subjects had improved at the Week 10 visit, for a total of 6 unique subjects between the 2 time periods. The types of neurological history for these subjects who improved were varied.

Safety: The type of adverse events reported during this trial appear consistent with the adverse event profile in the current Zonegran prescribing information. Adverse events that occurred in more than 10.0% (4 or more subjects) included: thinking abnormal (29.4%), asthenia (26.5%), nausea (26.5%), pain (26.5%), dizziness (23.5%), somnolence (20.6%), dyspepsia (17.6**%),** headache (17.6%), paresthesia (14.7%), rash (14.7%), anorexia (11.8%), constipation (11.8%), diarrhea (11.8%), insomnia (11.8%), pruritis (11.8%), and rhinitis (11.8%). There were no deaths during the study. Five (14.7%) subjects experienced 5 serious adverse events, none of which were considered related to Zonegran treatment. A total of 8 (23.5%) subjects withdrew from the study due to adverse events. The adverse events that led to subject withdrawal also appeared consistent with the adverse event profile in the current Zonegran prescribing information. There were no apparent effects of Zonegran therapy on vital signs or laboratory values. Changes in physical exam findings from the Screening Visit to the end of the study may be more likely to be an indication of the underlying disease of diabetic neuropathy than an effect of Zonegran therapy.

Conclusion: Zonegran appeared safe and well tolerated in this patient population. The results of this trial suggest that further evaluation of Zonegran in subjects with neuropathic pain is warranted, since treatment generally resulted in improvement in pain scores and some subjects clearly demonstrated a positive clinical response during therapy.

CHMP COMMENTS:

- The conclusions of the MAH are endorsed.
- This study was a small, open label study with no placebo or active comparator.
- The age of the study population was 12 years and older and it is not clear how many of the subjects were in the paediatric population.
- As discussed by the MAH, further evaluation of Zonegran in patients with neuropathic pain is warranted.
- As discussed in studies 720-02385-96, 720-02385-96EXT, ZNS-401 and ZNS-501, following assessment of this study, the adverse event of headache should be added to the product information for Zonegran.

CHMP CONCLUSIONS:

- Following assessment of these 8 studies, overall, the conclusions of the MAH are endorsed.
- Following assessment of studies 720-02385-96, 720-02385-96EXT, ZNS-401, ZNS-501 and ZNS-503, the adverse event of headache should be added to the product information of Zonegran and the MAH is requested to submit a Type

II variation to do so.

- Following assessment of studies 720-02385-96 and 720-02385-96EXT, the adverse event of rhinitis should be added to the product information of Zonegran and the MAH is requested to submit a Type II variation to do so.
- These studies are mainly small and are open label with no placebo or active comparator arms and so results should be interpreted with caution.
- In some of these studies the study population is 12 years of age and upwards and it is unclear as to how many of the study subjects are in the paediatric / adolescent population.
- None of these 8 studies discussed in this Assessment Report have any data on the long term use of zonisamide in the paediatric population, nor on the effect of zonisamide on the growth and development of children, nor on the effect of zonisamide on puberty.
- Further research and studies would be required to support an indication for zonisamide in the paediatric population.
- It is noted that there is currently a study ongoing (E2090-044-312) to further investigate the use of zonisamide in the paediatric and adolescent population, the final clinical study report of which is expected in January 2011. This date is an estimate based on predicted recruitment rate and could move 6 months either way.