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Short-term efficacy and safety of zonisamide as adjunctive treatment for refractory partial seizures: A multicenter open-label single-arm trial in Korean patients

Kyoung Heo [a], Byung In Lee [a,*], Sang Do Yi [b], Yong Won Cho [b], Dong Jin Shin [c], Hong Ki Song [d], Ok Joon Kim [e], Sung-Pa Park [f], Sung Eun Kim [g], Sang Ho Kim [h], Jun Hong Lee [i], Kyu-Sik Kim [i], Se-Jin Lee [j]

[a] Department of Neurology, Severance Hospital, Seoul, Republic of Korea
[b] Department of Neurology, Keimyung University Dongsan Medical Center, Daegu, Republic of Korea
[c] Department of Neurology, Gachon Medical School Gil Medical Center, Incheon, Republic of Korea
[d] Department of Neurology, Kangdong Sacred Heart Hospital, Seoul, Republic of Korea
[e] Department of Neurology, Bundang CHA Hospital, Seongnam, Republic of Korea
[f] Department of Neurology, Kyungpook National University Hospital, Daegu, Republic of Korea
[g] Department of Neurology, Inje University Haeundae Paik Hospital, Busan, Republic of Korea
[h] Department of Neurology, Dong-A University Hospital, Busan, Republic of Korea
[i] Department of Neurology, National Health Insurance Corporation Ilsan Hospital, Koyang, Republic of Korea
[j] Department of Neurology, Yeungnam University Medical Center, Daegu, Republic of Korea

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ABSTRACT

Objective: To evaluate the efficacy and safety of adjunctive zonisamide (ZNS) therapy in Korean adults with uncontrolled partial epilepsy.
Methods: Study patients had an average of at least one seizure per 4-week (averaged over a 12-week historical baseline) despite the use of one to three antiepileptic drugs. The starting dose of ZNS was 100 mg/day, and was increased to 200 mg/day after 2 weeks. During the 12-week maintenance period, the dose of ZNS was adjusted to 200–400 mg/day based on the physicians' discretion. The global evaluation scale (GES) and quality of life (QOLIE-31) were also evaluated.
Results: A total of 121 patients were enrolled, of which 88 patients completed the study. The median percent reduction in weekly seizure frequency over the treatment period was 59.0%. The ≥50% and ≥75% responder rates were 57.3% and 38.5%, respectively. Seizure freedom over the treatment period was observed in 25 patients, but seizure freedom throughout the 16-week treatment period was attained in only 16 patients. On investigator's GES, 84 patients were considered improved, with 33 patients showing marked improvement. In QOLIE-31 scale, seizure worry improved significantly but emotional well-being deteriorated. Treatment-emergent adverse events (AEs) were reported in 80 patients. The most common AEs were dizziness (28.1%), somnolence (24.0%), anorexia (18.2%), headache (14.0%), nausea (13.2%), and weight loss (10.7%). Twenty-two patients discontinued the trial due to drug-related AEs.
Conclusions: Our results suggest that adjunctive ZNS therapy for the treatment of refractory partial epilepsy, though efficacious, is associated with significant tolerability problems.

1. Introduction

Zonisamide (ZNS) has been approved for broad-spectrum use in Japan since 1989 and in Korea since 1991, while it was licensed as an adjunctive drug for the treatment of partial seizures much later in the USA (2000) and Europe (2005).

ZNS's main pharmacological effects are due to the blockade of neuronal voltage-gated sodium channels and low-voltage-activated (T-type) calcium channels.[1] ZNS has a favorable pharmacokinetic profile. It is rapidly absorbed from the gastrointestinal tract, and peak plasma concentrations are achieved within 2–5 h after oral dosing. Oral bioavailability is close to 100%, and the kinetics are linear after the administration of a single dose of 200–800 mg.[2] Steady-state plasma concentrations are achieved within 14 days of

* Corresponding author at: Department of Neurology, Yonsei University College of Medicine, Severance Hospital, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Republic of Korea. Tel.: +82 2 2228 1603; fax: +82 2 393 0705.
E-mail address: bilee@yuhs.ac (B.I. Lee).

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commencing treatment and are maintained over time, with a peak-trough fluctuation of only 14% on twice-daily dosing.[3] Although inactivation of ZNS occurs predominantly by hepatic metabolism involving CYP3A4-mediated reduction, this drug neither induces nor inhibits hepatic cytochrome P450 isoenzymes that are implicated in the metabolism of several antiepileptic drugs (AEDs).[4] However, enzyme-inducing AEDs increase its clearance, an interaction that may necessitate a dosage increase, but which will also permit more rapid attainment of steady-state ZNS concentrations. Otherwise, ZNS is essentially devoid of clinically significant interactions with other AEDs, oral contraceptives and, indeed, all other classes of therapeutic agents investigated to date.[5]

The efficacy and safety of ZNS in partial epilepsy have been demonstrated in several pre-registration, randomized, double-blind, placebo-controlled studies in which this drug was administered as adjunctive therapy in drug-resistant epileptic patients with partial epilepsy.[6–9] Long-term open studies as well as double-blind, placebo-controlled studies have demonstrated that ZNS has a good efficacy and tolerability profile, supporting its use as an adjunctive therapy for adult epileptic patients.[10–15] A long-term open-label study[13] in 317 patients with refractory partial epilepsy who completed a fixed-dose, randomized, double-blind, add-on trial[4] showed that patient retention rates at 1, 2, and 3 years were 65.3%, 44.5% and 28.8%, respectively, comparable to those reported for other AEDs. In indirect comparisons of new AEDs based on meta-analysis of placebo-controlled add-on trials, ZNS had a middle ranking in terms of both response and withdrawal rates.[16,17]

In this study, we report the results of a pragmatic trial aimed at assessing the efficacy and safety of ZNS as an add-on therapy in patients suffering from partial seizures not adequately controlled despite treatment with up to three other AEDs. We also report the impact of ZNS on health-related quality of life. We used an open-label methodology, very similar to routine clinical practice, with regard to inclusion criteria and dose escalation.

2. Methods

2.1. Study population

Patients 15 years or older with partial seizures, whether or not secondarily generalized, were eligible for enrolment. Patients had to have presented with an average of at least one partial seizure per 4 weeks (averaged over a 12-week period preceding study entry) despite the use of one or three AEDs. Partial seizures were classified according to the Commission on the Classification and Terminology of the International League against Epilepsy.[18] Patients were not allowed to be taking more than three concomitant AEDs at the time of study entry, with benzodiazepines being considered AEDs if taken on a daily basis for any indication. The AED regimen was required to have been stable for at least 4 weeks prior to study entry. Laboratory values less than two times the upper normal limits of serum ALT, AST, total bilirubin, BUN, or creatinine levels were allowed. Patients were excluded if they had diseases or conditions expected to unduly complicate management or evaluation. These included serious psychiatric disorders within the past 5 years, uncountable seizures or a history of convulsive status epilepticus within the last year, presence of known psychogenic nonepileptic seizures within the last year, progressive degenerative neurological disease, a history of nephrolithiasis, previous exposure to ZNS, participation in another clinical study of an investigational drug or device within 12 weeks of the selection visit, a history of questionable compliance to scheduled visits or medication intake, pregnant or lactating females, females of childbearing potential unwilling to utilize a medically acceptable birth control method, and visual field defects relevant to vigabatrin as a previous or concomitant AED.

2.2. Study design

This therapeutic confirmatory Phase IV open-label, single-arm study of patients with partial seizures began with a 12-week historical baseline period followed by a 16-week treatment period

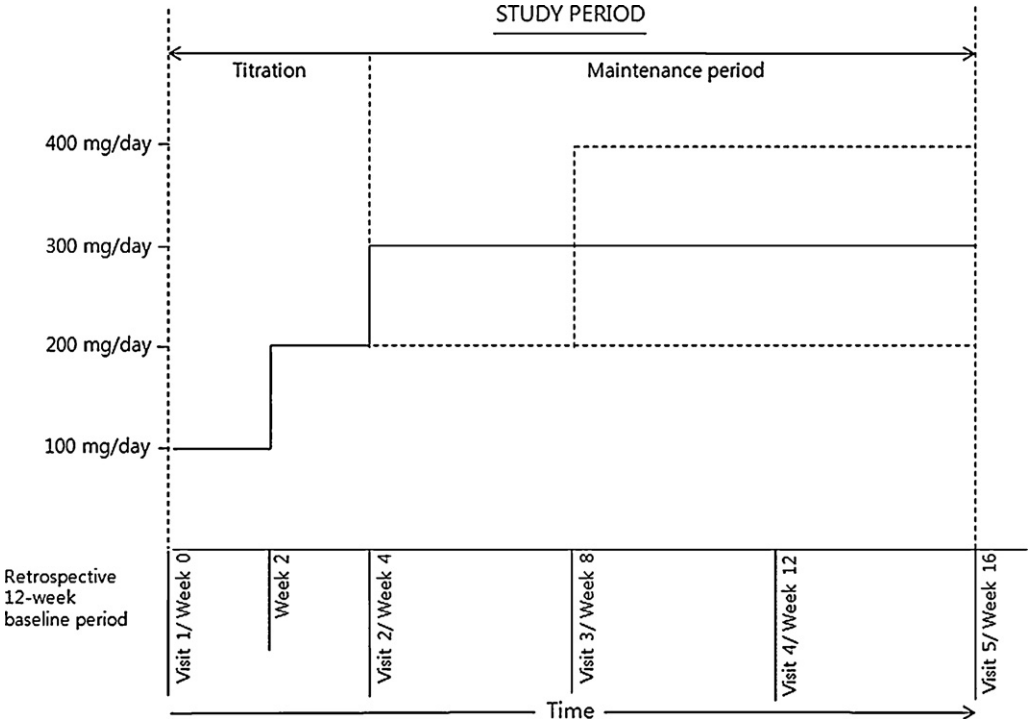

Fig. 1. Study design.

in 10 Korean centers. Prior to study commencement, the study protocol was approved by the Institutional Review Board of each participating center. It was conducted according to the International Conference on Harmonisation guidelines and the Declaration of Helsinki.

The study was divided into an up-titration period (first 4 weeks) and a maintenance period (last 12 weeks) as shown in Fig. 1. At visit 1 (week 0), investigators obtained patients' written informed consent, collected demographic data and medical/surgical histories, and performed physical and neurological examinations, including vital signs and body mass. During the 4-week up-titration period, patients initially received ZNS 100 mg/day (V1) (administered *qd*). The dose was increased to 200 mg/day (administered *bid*) after 2 weeks and could be increased to 300 mg/day (administered *bid*) after an additional 2 weeks (V2) at the discretion of the investigator if it was clinically necessary to achieve maximum benefit. During the 12-week maintenance period, the ZNS dose was allowed to be increased from 200 mg/day to 300 mg/day or from 300 mg/day to 400 mg/day at V3 (week 8) if seizure control was insufficient, and decreased on a single occasion in patients who were receiving 300 mg/day if poorly tolerated. At week 16, patients made a fifth and final visit on completion of the study, at which time final data were collected. Those who elected not to continue ZNS therapy had their dose reduced gradually. Patients recorded the date, number, and type of seizures on a daily record card; each investigator coded the seizures experienced by his or her patients. Adverse events (AEs) were recorded at each visit based on spontaneous patient reports, investigator observations, responses to standard questions asked by the investigator, and events recorded on the patient daily record card.

2.3. Prior and concomitant therapy

The history of previous AEDs was investigated. For the purposes of study evaluation, the patients' concomitant AEDs had to remain constant during the study. Additional medication was allowed to be prescribed for the well-being of the patient; however, medication (other than AEDs) affecting the central nervous system was to be avoided unless the patient had been on a stable dose for at least the last 6 months before the first visit. Concomitant medication was maintained at the same stable dose throughout the study.

2.4. Efficacy and safety measurements

Efficacy end points were based on the frequency of seizures during the 16-week treatment period (titration and maintenance) compared with the 12-week baseline period as well as retention rate. The primary efficacy variables were the percent reduction from baseline in seizure frequency per week and the retention rate at week 16, defined as the number of subjects still treated with ZNS at the end of the 16-week treatment period divided by the number of patients in the intent-to-treat (ITT) population. Other efficacy variables included the median reduction in the frequency of seizures and seizure days per week, the responder rates, and the number of seizure-free patients. For patients who did not complete the 16-week treatment period, data up to withdrawal were used in the analysis of efficacy.

Other variables included global evaluation of disease evolution and quality of life. A validated Korean version of the original Quality of Life in Epilepsy Questionnaire (QOLIE-31) instrument[19,20] was filled in at the selection visit and at the end of the 16-week treatment period or upon early withdrawal. Following the completion of treatment, the investigator provided a global evaluation scale rating to assess the overall change in the severity of the patient's illness compared to the start of study medication. The rating was based on overall clinical impression (marked improvement, moderate improvement, slight improvement, no change, slight worsening, moderate worsening, and marked worsening). Safety was assessed according to AEs, physical and neurological examinations, and laboratory evaluations at visit 1 (week 0) and visit 5 (week 16). Physical examinations included measurement of vital signs.

2.5. Statistical methods

Safety analyses were performed on the ITT population, which included all patients who took at least one dose of ZNS. However, four patients who discontinued the study at the early stage without any post-treatment seizure count were not included in the efficacy analyses based on seizure count during the treatment period. Study variables were summarized by descriptive statistics: mean, median, standard deviation, Q1 and Q3, range for continuous variables, and frequency tables for categorical variables. Baseline characteristics (gender, age, etiology of epilepsy, history of epilepsy, previous and concomitant AEDs) and ZNS exposure were summarized descriptively for the ITT population. We used the paired *t*-test, Wilcoxon's signed rank test, Wilcoxon's rank sum test, or Kruskal–Wallis test to analyze continuous variables and the χ^2 test or McNemar's test to examine categorical variables.

3. Results

3.1. Demographics

A total of 121 patients were enrolled and formed the ITT population (Table 1). Of these, 69 (57.0%) were male and 52 (43.0%) were female. Patients' ages ranged from 16 to 69 years, with a mean age (±S.D.) of 37.7 (±11.2) years. All patients were Korean. The mean age (±S.D.) at onset of epilepsy was 21.2 (±12.5) years and the mean duration (±S.D.) of epilepsy was 19.0 (±11.8) years. The etiology of epilepsy was unknown in 55.4% of patients or attributed to hippocampal sclerosis including a history of significant brain insult or dual pathology (11.6%), cranial trauma (9.9%), atrophic change without a history of significant brain insult (9.1%), cerebral infection (1.7%), malformation of cortical development (2.5%), cerebral palsy without a history of significant brain insult (2.5%), vascular malformation (1.7%), stroke (1.7%), tuberous sclerosis (1.7%), perinatal injury (0.8%), neurofibromatosis (0.8%), and mental retardation without a history of significant brain insult (0.8%). The median (Q1–Q3) baseline seizure frequency was 0.50 (0.25–0.92) per week. The median (Q1–Q3) seizure days were 0.42 (0.25–0.83) per week. Ninety-three (76.9%) patients presented with at least one complex partial seizure, 37 (30.6%) patients with at least one secondarily generalized tonic–clonic seizure, and 13 (10.7%) patients with at least one simple partial seizure during the baseline 12-week period. Regarding the history of previous AED treatment, 54 (44.6%) patients had taken two or more AEDs prior to entry to this study. The majority (85.1%) of patients entered the trial on two or three concomitant AEDs. The most frequently used concomitant AEDs were lamotrigine, valproic acid, topiramate, and levetiracetam.

Of the 121 patients, 88 (72.7%) completed the 16-week treatment and 33 discontinued the study. Twenty-three patients withdrew due to an AE, three withdrew because of a lack of efficacy, and seven withdrew for other reasons (protocol violation in five, loss of follow-up in one, and withdrawal of consent in one). The trial began on February 04, 2008 and finished on August 30, 2010.

The 121 patients who took one or more doses of ZNS received the treatment for a mean duration (±S.D.) of 94.3 (±35.9) days within the study period. The mean daily dose (±S.D.) of ZNS during

Table 1
Baseline demographic and clinical characteristics of the 121 enrolled patients.

Parameter	Value
Age, years (mean ± S.D.)	37.7 ± 11.2
Gender, male (%)	57.0
Body weight, kg (mean ± S.D.)[a]	65.7 ± 14.0
Height, cm (mean ± S.D.)[a]	164.9 ± 8.7
Body mass index, kg/m^2 (mean ± S.D.)[a]	24.0 ± 4.0
Age at onset, years (mean ± S.D.)	21.2 ± 12.5
Epilepsy duration, years (mean ± S.D.)	19.0 ± 11.8
Weekly partial seizure frequency	
Mean ± S.D.	1.16 ± 2.3
Median	0.50
Interquartile range (Q1–Q3)	0.25–0.92
Min–max	0.25–21.0
No. of previous antiepileptic drugs (AEDs), *n* (%)	
0	36 (30)
1	31 (26)
2	23 (19)
3	15 (12)
4	13 (11)
≥5	3 (2)
Previous AEDs taken by ≥10% of patients, *n* (%)	
Valproic acid	35 (29)
Carbamazepine	25 (21)
Topiramate	23 (19)
Pregabalin	17 (14)
Phenytoin	16 (13)
Clonazepam	13 (11)
Oxcarbazepine	13 (11)
No. of concomitant AEDs, *n* (%)	
1	18 (15)
2	58 (48)
3	45 (37)
Concomitant AEDs taken by ≥10% of patients, *n* (%)	
Lamotrigine	61 (50)
Valproic acid	50 (41)
Topiramate	43 (36)
Levetiracetam	41 (34)
Carbamazepine	31 (26)
Oxcarbazepine	20 (17)
Pregabalin	13 (11)

[a] These data were obtained from analysis of 113 patients.

the 16-week treatment period was 233 (±61) mg, with a median daily dose of 261 mg/day. The mean daily dose (±S.D.) of exposure over the last 8 weeks of the individual titration period for subjects completing the study was 297 (±69) mg (range, 200–400 mg).

3.2. Efficacy

The four patients who discontinued the study (AE in two patients, withdrawal of consent in one patient, and lack of efficacy in one patient) without any seizure counts after baseline were not included in the efficacy analysis. A total of 117 patients were therefore analyzed. Overall, 90 patients (76.9%) experienced a reduction from baseline in seizure frequency per week over the study period; during the last 12 weeks, 84 patients (71.8%) experienced a reduction from baseline. In the ITT population ($n = 117$), the median (Q1–Q3) percent reduction in seizure frequency was 59.0% (Q1–Q3, 8.3–89.6%) over the treatment period (range, −3260.0 to 100.0%) ($p < 0.001$); during the last 12 weeks ($n = 102$), the median (Q1–Q3) percent reduction in seizure frequency was 68.5% (Q1–Q3, 18.0–96.3%) over the last 12-week treatment period (range, −4100.0 to 100.0%) ($p < 0.001$). The frequency of seizures decreased from a median (Q1–Q3) of 0.50 (Q1–Q3: 0.33–1.00) per week during the baseline period to a median of 0.25 (Q1–Q3: 0.06–0.88) per week over the treatment period. The median seizure frequency was 0.25 per week during the initial 4 weeks ($n = 117$, median reduction from baseline = 53.8%), remained at 0.24 per week during weeks 4–8 ($n = 102$, median reduction from baseline = 68.4%), then was 0.00 per week during weeks 8–12 ($n = 91$, median reduction from baseline = 100.0%), and remained at 0.23 during the last 4 weeks ($n = 89$, median reduction from baseline = 84.8%), as shown in Fig. 2.

Over the treatment period, 57.3% (67/117) of patients had a 50% or greater reduction in seizures count, 38.5% (45/117) had at least a 75% reduction, and 21.4% (25/117) of patients had a 100% reduction. During the last 12 weeks, 54.7% (64/117) of patients had a 50% or greater reduction, 39.3% (46/117) had a 75% or greater reduction, and 21.4% (25/117) of patients had a 100% reduction. However, seizure freedom was obtained for a mean of only 6.1 weeks (2.0–12.1 weeks) in nine patients (AEs in six patients, protocol violation in two patients, and loss of follow-up in one patient). The mean weekly baseline seizure frequency (±S.D.) of 16 patients with seizure freedom completing the study was 0.34 (±0.19) which was significantly lower than 1.32 (±2.54) of the other patients ($n = 101$) ($p < 0.001$). The mean number of life-time AEDs (previous and concomitant) of 16 patients with seizure freedom completing the study was 3.0 (±1.8) (range, 1–7) which tended to be lower compared with 3.9 (±1.8) (range, 1–8) of the other patients ($n = 101$) ($p = 0.054$). The mean daily dose of exposure over the last 8 weeks of the individual titration period for 16 patients with seizure freedom completing the study was 256 (±63) mg (range, 200–400 mg) which

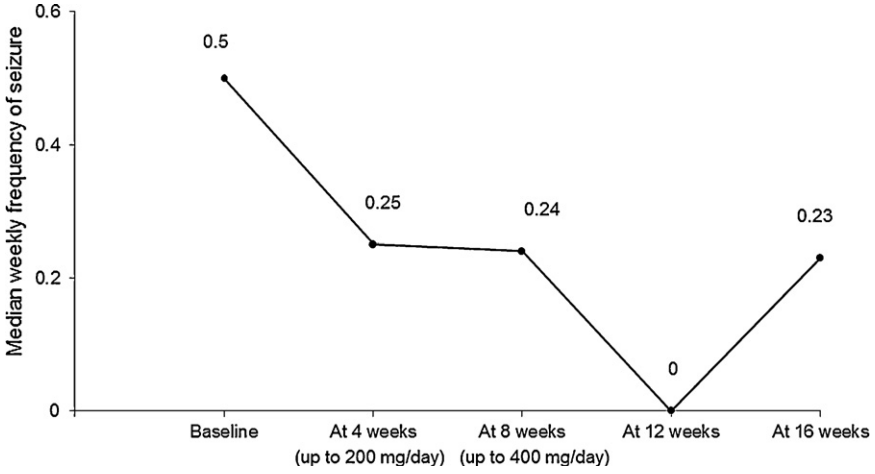

Fig. 2. Median weekly frequency of seizure.

was significantly lower than 306 (±67) mg (range, 200–400 mg) for 72 patients without seizure freedom completing the study ($p = 0.009$).

The median (Q1–Q3) percent reduction in seizure days was 59.3% (Q1–Q3, 5.4–90.1%) over the treatment period (range, −2420.0 to 100.0%) ($p < 0.001$); during the last 12 weeks, the median (Q1–Q3) percent reduction in seizure days was 73.0% (Q1–Q3, 15.7–95.1%) over the treatment period (range, −3050.0 to 100.0%) ($p < 0.001$). The frequency of seizure days decreased from a median (Q1–Q3) of 0.42 (Q1–Q3: 0.33–0.83) per week during the baseline period to a median of 0.24 (Q1–Q3: 0.06–0.79) per week over the treatment period.

At V3 (week 8), the ZNS dose was increased up to 300 or 400 mg in 25 patients because of insufficient seizure control; four patients had a 75% or greater reduction and three patients had a reduction of 50% or greater but less than 75%, while the remaining 18 patients had less than 50% reduction over the treatment period.

3.3. Global evaluation scale and QOLIE-31

According to the investigators, 69.4% of patients showed improvement (marked, 27.3%; moderate, 28.1%; (Q1–Q3, 8.33–89.6%) slight, 14.0%), while 17.4% of patients showed no change and 4.1% of patients worsened (moderate in two patients and marked in three patients). However, the total QOLIE-31 score did not improve. Seizure worry improved significantly ($p = 0.013$), but emotional well-being deteriorated ($p = 0.007$). Health status showed a tendency to improve ($p = 0.086$) (Table 2). Of the 97 patients evaluable for quality of life analysis, 49 (50.5%) experienced improvement in their overall QOLIE-31 score.

3.4. Safety

Two hundred and four treatment-emergent AEs were reported in 80 patients [(66.1%; mean frequency of 2.6 (±1.8) per person]. Fifty-one patients (63.8%) had two or more AEs. AEs that emerged in 3% or more of patients during the treatment period are listed in Table 3. The most commonly reported AEs were dizziness (28.1%), somnolence (24.0%), anorexia (18.2%), headache (14.0%), nausea (13.2%), and weight loss (10.7%). The majority (99.5%) of treatment-emergent AEs were mild to moderate in intensity. There were no significant differences in the proportion of patients with AEs (1 AED, 61.1%; 2 AEDs, 67.2%; 3 AEDs, 66.7%) and the mean frequency per person of AEs [1 AED, 0.9 (±0.9); 2 AEDs, 1.8 (±2.0); 3 AEDs, 1.8 (±2.1)] according to the number of concomitant AEDs. Nine patients reported AEs leading to a reduction in the ZNS dose. Twenty-three patients discontinued the trial due to drug-related AEs except for one patient [mean frequency, 2.7 (±1.9) per person; somnolence ($n = 8$), dizziness ($n = 7$), nausea and vomiting ($n = 7$), headache ($n = 5$), anorexia ($n = 5$), decreased weight ($n = 5$), asthenia ($n = 4$), amnesia or impaired judgment ($n = 2$), abdominal pain ($n = 2$), and tremor, palpitation, pyrexia, abulia, insomnia, rash, paresthesia, etc. in each one (permitting duplication)]. Five patients discontinued the trial within the first 4 weeks, 12 patients between 4 and 8 weeks, and five patients during the last 8 weeks (range, 0.7–13.1). Thirteen patients (59.1%) had two or more AEs. Two patients experienced serious AEs (multiple injuries due to a traffic accident and acute diverticulitis, respectively). These serious AEs were not considered to be related to ZNS treatment. Psychiatric AEs occurred in six patients (depression in two patients, abulia in two patients, and agitation, anxiety, and insomnia, respectively, in three individual patients). None of patients developed nephrolithiasis.

Neurological examination revealed nervous system abnormalities in 9.1% of patients at baseline; overall, no relevant changes were observed during treatment. Significant decreases in mean body weight and body mass index were found (65.7–64.0 kg; 24.2–23.5 kg/m^2, $p < 0.001$). Body weight decreases of at least 5% from baseline occurred in 22 patients (range −3.5 to −10.0 kg; representing a weight decrease of 5.7–15.5% from baseline), and increases of at least 5% occurred in another two patients (range 3.3–6.3 kg; representing a weight increase of 6.3–7.6% from baseline). There was no significant difference between the proportions of patients who showed significant changes (normal to abnormal or abnormal to normal) in laboratory values of pre- and post-treatment (data not shown).

Table 2
Mean QOLIE-31 changes ($n = 97$).

Domain/item	Baseline mean (S.D.)	Change mean (S.D.)	p value
Seizure worry	47.1 (25.3)	5.5 (21.1)	0.013
Overall QOL	54.1 (15.7)	−0.0 (18.6)	0.989
Emotional well-being	58.6 (20.0)	−5.9 (20.9)	0.007
Energy/fatigue	47.0 (19.8)	−1.4 (17.5)	0.433
Cognitive functioning	65.9 (20.6)	−0.2 (19.5)	0.905
Medication effects	53.9 (28.7)	−0.6 (26.4)	0.819
Social function	52.8 (25.9)	2.5 (24.0)	0.315
Total score	56.3 (16.2)	−0.2 (12.9)	0.888
Health status	53.2 (20.2)	3.7 (21.2)	0.086

Table 3
Treatment-emergent adverse events occurring in 3% or more of enrolled patients (intent-to-treat population).

Adverse event	N (%)
Dizziness	34 (28.1)
Somnolence	29 (24.0)
Anorexia	22 (18.2)
Headache	17 (14.0)
Nausea	16 (13.2)
Weight loss	13 (10.7)
Asthenia	8 (6.6)
Amnesia and impaired judgment	6 (5.0)
Constipation	5 (4.1)
Fatigue	4 (3.3)

4. Discussion

The protocol in the present study followed the usual pattern of community-based clinical practice in that the dose adjustment of AED was flexible and patients with less severe epilepsy (median baseline seizure frequency, 0.5 per week) were recruited.

As expected, the efficacy results of this Korean open-label trial exceeded the results reported by placebo-controlled, double-blinded clinical trials[6–9] that reported significant increases in reduction in median seizure frequency (up to 41%) and responder rates (35–42%) following ZNS 400–600 mg/day.[21] During the 16-week treatment, ZNS reduced the weekly frequency of seizures by a median of 59.0%; 57.3% of patients experienced a reduction in seizures of ≥50%, 38.5% had a reduction of 75% or greater, and 21.4% showed seizure freedom, although only 13.7% maintained seizure freedom for the treatment period. A total of 90 patients (76.9%) experienced a reduction from baseline in seizure count. The median percent reduction in seizure days was 59.3%. These figures suggest that ZNS is efficacious as an adjunctive drug for the treatment of partial seizures although considering less refractory population in this study and overwhelming heterogeneity of non-comparative studies like this study.[22]

The most common AEs in this study were dizziness, somnolence, anorexia, headache, and nausea, consistent with those reported in previous placebo-controlled trials. Furthermore, the number of patients (66.1%) who experienced treatment-emergent AEs were comparable or slightly lower: 67.9%, 70.9%, and 81.4% for patients receiving ZNS 100 mg/day, 300 mg/day, or 500 mg/day,

respectively, in a placebo-controlled trial;[9] 77.9% from pooled data of placebo-controlled trials;[21] and 74.4% in a short-term, open-label, single-arm trial.[23] The rate of premature withdrawal (19.0%) was comparable with that (19.3%) reported from pooled data of placebo-controlled trials[21] and slightly higher than the 15.3% reported for a multicenter, short-term (19 weeks), open-label, single-arm, add-on trial.[23] Therefore, the proportion of patients who withdrew because of AEs was relatively high compared with the proportion of patients with AEs, which suggests that ZNS can cause significant AE-related problems in a specific population. This result may be related to the occurrence of multiple AEs in patients. The rates of each AE were higher than those based on pooled data from placebo-controlled trials (dizziness, 28.1% vs. 13.3%; somnolence, 24.0% vs. 15.3%; anorexia, 18.2% vs. 9.6%; headache, 14.0% vs. 6.4%; nausea 13.2% vs. 8.4%).[21] Although detailed data are not available regarding the total number of AEs in placebo-controlled trials, patients with AEs in this study may have had more AEs per person. The mean number of AEs among the 80 patients with AEs was 2.6 and the percentage of patients with more than one AE was 63.8%. Furthermore, the mean number of AEs in 22 patients with drug-related AEs that led to their premature withdrawal from the study was 2.7 and the percentage of patients with more than one AE was 59.1%. The high incidence of multiple AEs in patients may contribute adversely to the patients' overall safety despite the mild to moderate degree of severity of each individual AE. Premature withdrawal occurred more frequently between 4 and 8 weeks than the first 4 weeks (titration period), and nine patients withdrew prematurely due to AEs despite a seizure-free state. The high incidence of both multiple AEs and premature withdrawal may be related to the greater number of concomitant AEDs (37.2% with three concomitant AEDs) and the more rapid than optimal titration schedule. However, there were not significant differences in the proportion of patients with AEs and the frequency per person of AEs according to the number of concomitant AEDs, and only five of 22 patients prematurely withdrew ZNS due to drug-related AEs during the titration period. In fact, the high efficacy but significant tolerability problems associated with ZNS that were found in this study appear to reflect the high rate of improvement in the investigators' global evaluation scale and the improvement in seizure worry without changes or deterioration in the other QOLIE scales.

Our results demonstrate that ZNS is effective in adult Korean subjects with uncontrolled partial epilepsy when administered at optimized doses of up to 400 mg/day, as evidenced by the high efficacy results, although these data were obtained only for short-term period. However, adjunctive ZNS therapy was associated with tolerability problems in a significant number of patients, as evidenced by the high rates of premature withdrawal and multiple AEs per patient.

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