

Evaluation of safety and efficacy of zonisamide in adult patients with partial, generalized, and combined seizures: an open labeled, noncomparative, observational Indian study

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Abstract: A prospective, multicentric, noncomparative open-label observational study was conducted to evaluate the safety and efficacy zonisamide in Indian adult patients for the treatment of partial, generalized, or combined seizures. A total of 655 adult patients with partial, generalized, or combined seizures from 30 centers across India were recruited after initial screening. Patients received 100 mg zonisamide as initiating dose as monotherapy/adjunctive therapy for 24 weeks, with titration of 100 mg every 2 weeks if required. Adverse events, responder rates, and seizure freedom were observed every 4 weeks. Efficacy and safety were also assessed using Clinicians Global Assessment of Response to Therapy and Patients Global Assessment of Tolerability to Therapy, respectively. Follow-up was conducted for a period of 24 weeks after treatment initiation. A total of 655 patients were enrolled and received the treatment and 563 completed the evaluation phase. A total of 20.92% of patients received zonisamide as monotherapy or alternative monotherapy and 59.85% patients received zonisamide as first adjunctive therapy. Compared with baseline, 41.22% of patients achieved seizure freedom and 78.6% as responder rate at the end of 24 week study. Most commonly reported adverse events were loss of appetite, weight loss, sedation, and dizziness, but discontinuation due to adverse events of drug was seen in 0.92% of patients. This open label real-world study suggests that zonisamide is an effective and well-tolerated antiepileptic drug in Indian adults for treatment of partial, generalized as well as combined seizures type. No new safety signals were observed.

Keywords: zonisamide, partial onset seizures, generalized seizures, responder rate, monotherapy, adjunctive therapy

Introduction

Epilepsy is one of the most common serious neurological disorders, affecting more than 50 million people worldwide.¹ It has been estimated that approximately 80% of them are in developing countries.² The overall prevalence of epilepsy in India is reported as 1%, which is slightly higher in the rural areas (1.9%).² Approximately two-thirds of the patients experience simple or complex partial (focal) seizures, whereas the remaining one-third experience generalized seizures.³ Uncontrolled seizures can lead to a wide variety of consequences, including shortened lifespan, neuronal death, excessive bodily injury, physiological dysfunction, neuropsychological and psychiatric impairment, and social disability.⁴

The goal of epilepsy management currently is to maximize the quality of life of patients, by minimizing the seizure episodes, with the least possible therapy-related



adverse effects.⁵ Pharmacological therapy is the most common approach for the management of epilepsy. In the past two decades, several new antiepileptic drugs (AEDs), including gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, and zonisamide, have been introduced with the objective of improving efficacy, tolerability, and ease of use compared with the classical AEDs (ie, carbamazepine, valproic acid, phenytoin, phenobarbital, primidone, ethosuximide, and benzodiazepines). However, this makes the drug selection process quite challenging. Although seizures can be controlled in approximately 60%–70% of patients with the first or second AED, regardless of the drug used, failure to respond to the first two AEDs may suggest refractoriness.³

Zonisamide is a benzisoxazole derivative with a unique chemical structure that differs structurally from other AEDs. It is considered as one of the preferred AEDs among the new-generation AEDs owing to its potent broad spectrum of efficacy, once-daily dosing, good tolerability, and potential for weight loss.⁵ Zonisamide has demonstrated safety and efficacy in a wide variety of epilepsy and seizure types, including both partial and generalized seizures, with over 2 million patient-years of exposure internationally, over the past 18 years of its existence.⁶ Zonisamide has International League Against Epilepsy Level A evidence as initial monotherapy for efficacy in adults with partial onset seizures.⁷ Furthermore, several clinical studies have reported that zonisamide is an effective and well-tolerated therapy in everyday clinical settings similar to that observed in clinical trials.⁸ However, all these studies were conducted in the USA and Europe and included patients with partial onset seizures with or without secondary generalization.

Taking this as background, we evaluated the efficacy and safety of zonisamide in Indian adult patients with partial, generalized, and combined seizures in real-world treatment situations and everyday clinical practice.

Methods

Design and patients

This was a prospective, multicentric, open-labeled, noncomparative, postmarketing surveillance study conducted across 30 centers in India. Patients with partial (simple partial, complex partial, and secondary generalized), generalized (tonic-clonic seizures, tonic seizures, and atypical absence seizures), or combined seizures, who satisfied all the inclusion/exclusion criteria were enrolled in the study. The study was conducted under conditions of normal clinical practice where the available data corresponding to certain specific and clinically relevant parameters were captured at regular time points (baseline, 4 weeks interval and 24 weeks). Baseline demography, physical examination, weight, vital

signs, medical history, including history of patient's seizures, seizure type and epilepsy syndrome, seizure frequency, prior treatment, and AED prescription were recorded. Informed consent was obtained, and the patient's eligibility was assessed prior to the enrolment. The study was conducted in accordance with the ethical code of conduct laid out by the Declaration of Helsinki, Good Clinical Practice guidelines, and Indian Council of Medical Research guidelines. The protocol and statement of informed consent were approved by the Institutional Ethics Committee of each center. [ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT01283256.

The inclusion criteria were as follows: male or female subjects, aged 18–75 years, previously treated or untreated with AEDs, diagnosed with partial seizures (simple partial seizures, complex partial seizures, and secondary generalized tonic-clonic seizures), generalized seizures (tonic-clonic seizures, tonic seizures, and atypical absence seizures), or combined seizures (mixed). Patients had to have computed tomography or magnetic resonance imaging done within the past 10 years that ruled out a progressive cause of epilepsy. Females of childbearing potential must have a negative pregnancy test at screening and enrollment and be willing to use medically acceptable forms of contraception for the duration of the study and for 1 month following discontinuation of the study drug.

Patients with history of seizures of nonepileptic origin, drug or alcohol abuse, kidney stones, or hypercalciuria, psychiatric disorders requiring electroconvulsive therapy in past 6 months, suicide attempt within past 6 months, or noncompliance with psychotropic medications were excluded. Those with significant past or present medical disorders, mental disorder, or any progressive neurological disorder (eg, infection, multiple sclerosis, or tumor), clinically significant metabolic acidosis, any known hypersensitivity to the study drug, zonisamide, or hypersensitivity to sulfonamides were also excluded.

Additionally, patients who were receiving zonisamide therapy, any investigational new drug, carbonic anhydrase inhibitors (acetazolamide), or mono-amine oxidase inhibitors, in the past 3 months before screening were also excluded from the study. Furthermore, addition of any other AED during the study period called for exclusion of the patient from the study.

Treatment

Patients were treated with zonisamide according to the approved package insert⁹ and as per the discretion of the physician. Zonisamide therapy was initiated as 100 mg tablets once-daily after meals before bedtime, which is minimum recommended dosage for epilepsy patient aged >18 years

in India. The dose was up-titrated by 100 mg every 2 weeks till each individual patient reached the maintenance dose, depending on the dose which achieved seizure control. However, the maximum recommended and allowed dose in the study was 600 mg/day.

Efficacy assessments

After the baseline-screening visit (day 0), the patients were followed-up at the end of weeks 4, 8, 12, 16, 20, and 24 (end of study visit). A window period of ± 2 days was permitted for the follow-up visit. During each visit, a complete general examination and clinical evaluation of efficacy parameters were carried out.

The primary efficacy end-point was a median percentage reduction in seizure frequency over a period of 24 weeks. Seizure activity was recorded by the subject or relative/caretaker in the patient diary provided, from day 1 through the end of the study. The secondary efficacy end-points were percentage responder rate and seizure-free patients over a period of 24 weeks. A subject was classified as a responder if there was $\geq 50\%$ reduction in the frequency of seizures, regardless of seizure type, for a period of 24 weeks when on a stable dose of zonisamide. The Clinicians Global Assessment of Response to Therapy (CGART) was assessed by the clinician on a seven-point scale as compared to baseline rated as follows: 1= excellent response, 2= good response, 3= average response, 4= no response, 5= minimally poor response, 6= poor response, and 7= very poor response.¹⁰ In addition, the subgroup analysis of responder rate, seizure-free patients at 24 weeks, and adverse events was performed in accordance with major concomitant AEDs such as carbamazepine, valproate, phenytoin, and levetiracetam.

Safety assessments

All adverse events, either spontaneously reported by the patients, or noted by the physician were recorded during the study period. The nature and severity of the adverse effects, if any, were also recorded. Patient Global Assessment of Tolerability to Therapy (PGATT) was assessed by the patient on a four-point rating scale as follows: 1= excellent tolerability, 2= good tolerability, 3= average tolerability, and 4= poor tolerability.¹¹ At every visit, concomitant medications received by each patient were reviewed to assess the likelihood of any adverse events.

Treatment compliance

All patients included in the study were asked to bring back the remaining medication/empty strips during the next visit and the number of tablets/empty strips was counted to check

for patient compliance. If the patient had not consumed more than 80% of the total prescribed medication during every visit, then the patient was termed as “noncompliant” and was not included in the efficacy analysis.

Statistical methods for data analysis

Data from all the centers were pooled for analysis. Two populations were retained for analysis. These were the intention to treat (ITT) population, corresponding to all included patients who met the eligibility criteria, and the per protocol (PP) population, corresponding to all patients in the ITT population who completed the study.

Measurement data were expressed as mean and standard deviation, and categorical data were expressed as median and range, and nominal data were expressed as numbers and percentages. Measurement data were analyzed using one-way analysis of variance (repeat measures), whereas ranking/qualitative data were analyzed using Friedman test. Proportions of patients who were seizure-free before enrollment and those after study completion were analyzed using paired *t*-test. For all statistical tests, a *P*-value equal to 0.05 was considered significant.

Results

Baseline characteristics

Of the total 659 patients who consulted a participating neurologist, 655 patients fulfilled the criteria for inclusion in the study (ITT population). The demographic characteristics and clinical features of the study population are given in Table 1. Four patients were excluded from the study due to lack of data. Totally, 563 patients completed the 24 week study period (PP population), whereas 92 discontinued (Figure 1).

At the start of zonisamide therapy, the median seizure frequency was three seizures/month (range: 1–120). Zonisamide was administered as first-line therapy in 137 patients (20.92%), whereas it was administered as add-on therapy in 518 patients (79.08%). Among patients who received zonisamide as add-on therapy, approximately 59.85% of the patients received it as first add-on therapy, 16.03% as second add-on, 2.44% as third add-on, and 0.76% of patients as fourth add-on (Figure 2). The median dose of zonisamide used during the study was 200 mg/day. Prior to starting zonisamide, 105 patients had been treated unsuccessfully with at least two AEDs, 16 with three AEDs, and five with four AEDs. The most frequently used concomitant AEDs during the study are shown in Figure 3. These include carbamazepine (25.65% patients), valproate (24.73%), phenytoin (24.12%), levetiracetam (14.05%), benzodiazepines (12.52%), and lamotrigine (1.68%).

Table 1 Demographic and clinical features of study population

	Total population (N=655)
Age, mean \pm SD (years)	33.24 \pm 13.22
Sex, n (%)	
Male	392 (59.85%)
Female	263 (40.15%)
Past medical history, n (%)	
Epilepsy	12 (1.83)
Psychiatric disorders	0 (0.00)
CVA	3 (0.46)
Allergy	1 (0.15)
Valproate allergy	0 (0.00)
Hypertension	21 (3.21)
CVD	6 (0.92)
Diabetes	12 (1.83)
Alcohol	8 (1.22)
Smoking	22 (3.36)
Hypercholesterolemia	5 (0.76)
CHD	3 (0.46)
Seizure type, n (%)	
Simple partial	48 (7.33)
Complex seizures	179 (27.33)
Secondary GTC	124 (18.93)
Generalized TC	200 (30.53)
Generalized tonic	46 (7.02)
Atypical absence seizures	4 (0.61)
Mixed seizures	54 (8.24)
Duration of epilepsy (months), n (%)	
0–12	171 (26.11)
12–24	133 (20.31)
24–36	73 (11.15)
36–48	51 (7.79)
48–60	45 (6.87)
>60	182 (27.79)
Seizure features, n (%)	
Pre-ictal phase	222 (33.89)
Consciousness impaired	437 (66.72)
Motor symptoms	417 (63.66)
Sensory symptoms	163 (24.89)
Autonomic symptoms	92 (14.05)
Psychic symptoms	66 (10.08)

Abbreviations: CHD, congestive heart disease; CVA, cerebrovascular accidents; CVD, cerebrovascular disorders; GTC, generalized tonic clonic; TC, tonic clonic; SD, standard deviation.

Efficacy

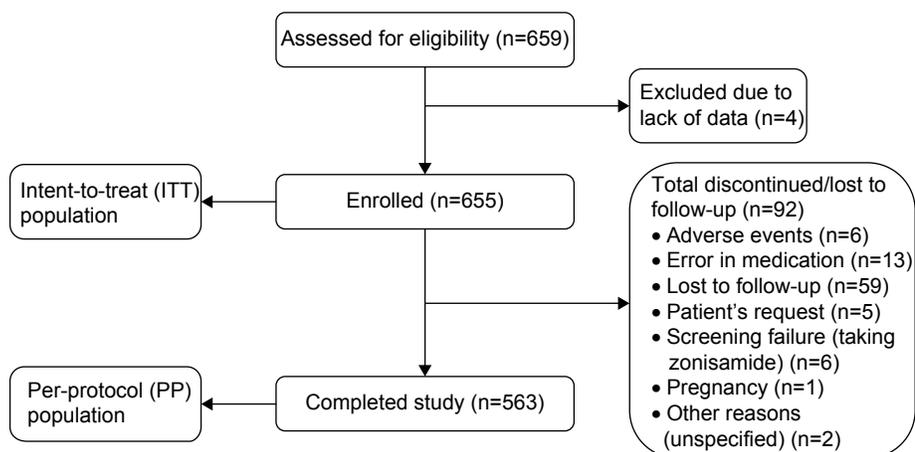
There was a statistically significant reduction in seizure frequency at each follow-up visit compared to baseline ($P < 0.0001$), with a maximum percentage reduction of 91.5% at week 24 ($P < 0.0001$, Figure 4). The mean change in seizure frequency from baseline was -3.98 (95% CI -3.39 to -4.57). Among responders, seizure frequency was reduced from 4.52 ± 8.13 seizures/month at baseline to 0.21 ± 0.78 at 24 weeks, with mean change from baseline of -3.74 .

In the ITT population, percentage of patients who showed some significant reduction in seizure frequency was 93%, whereas 7% of the patients showed no statistically significant change. In the PP population, approximately 95% of the patients showed statistical reduction in the seizure frequency and approximately 5% of the patients showed no significant change in seizure frequency.

Responder rate (defined as percentage of patients whose seizure frequency decreased by $\geq 50\%$ compared with baseline) was 78.6%; approximately 41.22% of the patients achieved seizure freedom after 24 weeks of zonisamide therapy (Figure 4).

The responder rate was not clinically different with respect to concomitant antiepileptic medication used. Responder rate was higher for Valproate (89.51%) and lower for Phenytoin (67.09%). However, number of patients who achieved seizure freedom was lowest for patients receiving carbamazepine (30.4%) and highest for those receiving phenytoin (44.9%) (Table 2).

The efficacy with zonisamide treatment assessed by the clinician on a seven-point CGART scale was “good” to “excellent” in 89.83% of the patients at week 24 (Figure 5). “Average response” was observed in 3.92% of the patients, whereas 6.24% patients had “no response” or “poor response”.

**Figure 1** Flow diagram of the study.

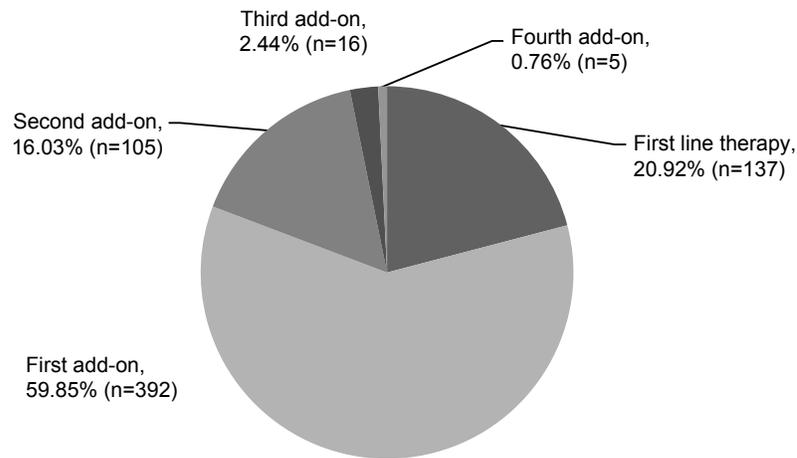


Figure 2 Type of zonisamide therapy administered.

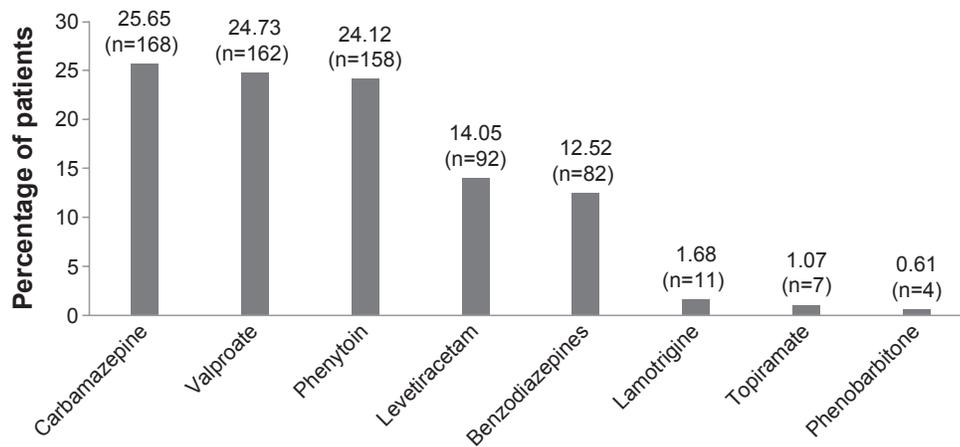


Figure 3 Concomitant antiepileptic drugs used during the study.

Notes: The data included patients who received concomitant medication to monotherapy (n=392) and as combination therapy (105 patients received dual therapy, 16 patients received triple therapy, and five patients received four-drug therapy).

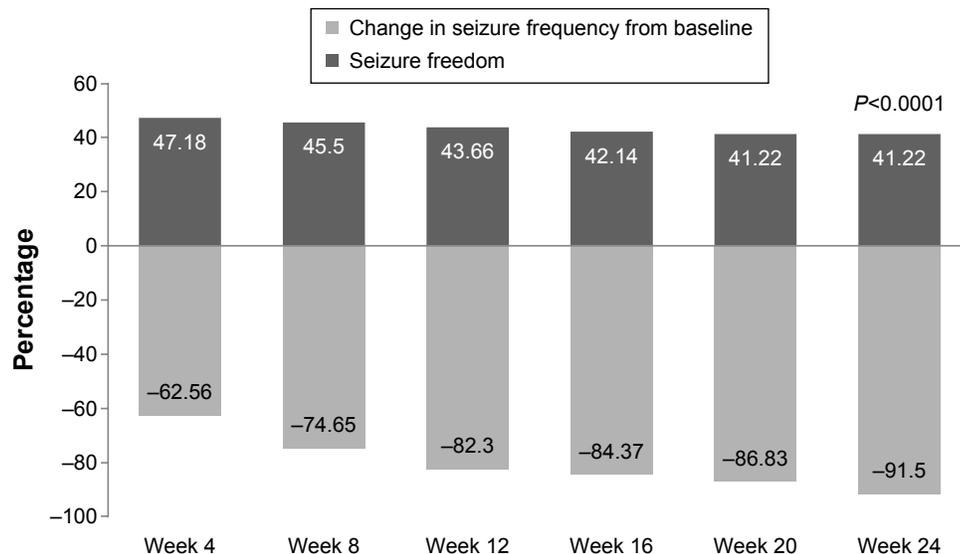


Figure 4 Percent change from baseline in seizure frequency and seizure freedom.

Table 2 Treatment response as a function of concomitant AED

	Seizure freedom at 24 weeks, %	Responder rate at 24 weeks, %
Zonisamide + carbamazepine (n=168)	30.4	69.64
Zonisamide + valproate (n=162)	33.64	89.51
Zonisamide + phenytoin (n=158)	44.9	67.01
Zonisamide + levetiracetam (n=92)	35.9	79.35

Abbreviation: AED, antiepileptic drug.

Safety and tolerability

A total of 114 adverse events (17.4%) were reported in 112 subjects (Table 3). Majority of these events were of mild-to-moderate intensity. The most commonly reported adverse events were loss of appetite (7.3%), weight loss (3.5%), sedation/somnolence (2.1%), and dizziness (2%). Increased seizure frequency was reported in three patients (0.5%) and rashes in two patients (0.3%). Aggressive behavior and sleep disturbance, mild rash and skin itching, fever, and headache were reported in one patient each. There was no death, disability, or hospitalization required for any of the adverse events. Furthermore, none of the events was due to over-dosage, or was congenital or malignant in nature. No history of clinical relevant metabolic acidosis or oligohydrosis was reported.

There was no incidence of kidney stone reported, possibly due to the short duration of study. Six patients (0.92%) discontinued therapy due to adverse events. The tolerability of zonisamide assessed by patients on a four-point PGATT

Table 3 Adverse events (AEs) reported during the study

Serial number	AE	Frequency, n (%)
1	Loss of appetite	48 (7.33)
2	Weight loss	23 (3.51)
3	Sedation	14 (2.14)
4	Dizziness	13 (1.98)
5	Irritability	7 (1.07)
6	Increased seizure frequency	3 (0.46)
7	Rash	2 (0.31)
8	Aggressive behavior and sleep disturbance	1 (0.15)
9	Mild rash and itching over skin	1 (0.15)
10	Viral fever	1 (0.15)
11	Headache	1 (0.15)
	Total adverse events	114 (17.40)
	Total patients	112 (17.10)

scale was “good” to “excellent” in 93.75% of the patients at week 24 (Figure 6).

Discussion

This is the first observational postmarketing study comprising the largest patient pool to assess the safety and efficacy of zonisamide in Indian patients in real-world clinical settings. All other studies evaluating effects of zonisamide in real-world clinical settings were conducted mainly in Europe. In India, zonisamide has been approved as monotherapy or adjunctive therapy in patients with primary generalized seizures and partial seizures, and in Europe as monotherapy in adult patients with newly diagnosed partial seizures and adjunctive therapy in children aged ≥6 years and adults with partial seizures with or without secondary generalization.

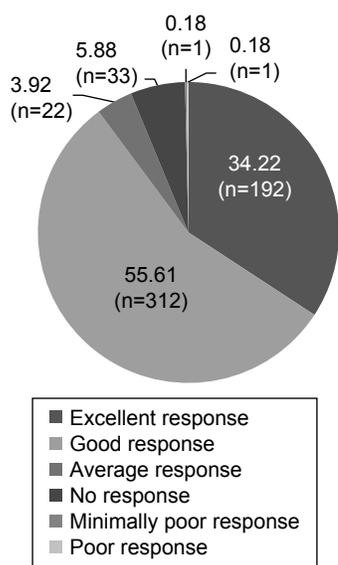


Figure 5 Clinicians Global Assessment of Response to Therapy (CGART) at week 24, n=561.

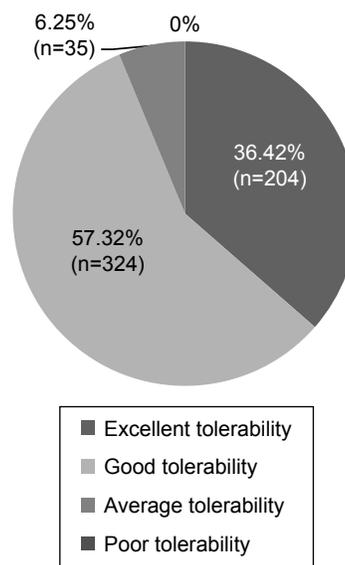


Figure 6 Patients Global Assessment of Tolerability to Therapy (PGATT) at week 24, n=560.

The primary outcome of this study was impressive with more than approximately 80% of patients achieving $\geq 50\%$ reduction in seizure frequency, whereas seizure freedom was achieved in approximately 41% of patients after 24 weeks of zonisamide treatment. The responder rate and proportion of patients who achieved seizure freedom with zonisamide were 40.9% and 15%, respectively, in ZEUS;¹² 79% and 34% in ZADE study;¹³ 65.9% and 25.6% in OZONE study;¹⁴ and 79.7% and 43.6% in ZOOM study.¹⁵ This difference may be attributable to inclusion of patients with less severe and less refractory epilepsies in our study. Median seizure frequency at baseline was three seizures/month in this study, which was lower than that reported in previous randomized trials and studies conducted in real-world clinical settings.^{12–20} Moreover, approximately 17% of the patients in this study were not taking any AEDs while 80% were taking only one or two AEDs. Furthermore, mean duration of epilepsy in patients included in this study was approximately 5 years, which was again lower than that reported in other observational studies (approximately 23 years in ZEUS, 18 years in OZONE study, and 15 years in ZADE study). Another possible reason may be inclusion of patients with partial, generalized, and combined seizure type in comparison with previous studies which included patients with partial onset seizures.

In a Phase III multicenter randomized-controlled trial, Baulac et al²¹ compared efficacy and safety of zonisamide 300 mg/day and carbamazepine 600 mg/day monotherapy for 26–78 weeks in adults with newly diagnosed partial epilepsy. The study showed that 79.4% of the patients in PP population and 69.4% in ITT population were free of seizures at 26 weeks in the Zonisamide group, as compared to 83.7% of the patients in PP population and 74.7% in ITT population in the Carbamazepine group. These findings further support the notion that zonisamide may provide greater efficacy in newly diagnosed or less refractory patients of epilepsy.

The overall efficacy of zonisamide treatment as assessed by the clinician on a seven-point CGART scale was “good” to “excellent” in approximately 89.83% of the subjects.

With regard to safety, the study demonstrated that zonisamide was well-tolerated, with adverse events reported in approximately 17% of patients. This rate was lower than that reported in previous randomized-controlled trials and observation studies.^{12–21} The most common adverse events reported were decrease in appetite, weight loss, sedation, and dizziness. No cases of renal stone, metabolic acidosis, and oligohydrosis were reported. Most of the AEs were of mild-to-moderate intensity with no death, disability, or inpatient hospitalization required for any of the adverse events.

Discontinuation due to adverse effects of drug was seen in only 0.92% patients.

Despite the inherent limitations of an open label, non-comparative, and observational study design, the results of this study provide some useful clinical information. We were able to gather data across a broad age range from a relatively large group of epilepsy patients with a wide spectrum of both partial onset seizures and generalized seizures. However, long-term efficacy and safety of zonisamide could not be assessed owing to short duration of study.

Conclusion

This real-world data in clinical settings do suggest that zonisamide is an effective and well-tolerated AED for the treatment of partial, generalized, and combined seizures in the Indian population. Zonisamide is found to be effective in various seizure types which could be due to its potent broad spectrum action.^{22,23} The long half-life of zonisamide (63–69 hours) allows once-daily dosing, which could enhance adherence to therapy. Some AEDs such as carbamazepine, valproate, oxcarbazepine, gabapentin, and pregabalin are associated with weight gain, in contrast zonisamide is found to reduce appetite and help with weight loss. Hence, it could be advantageous in some patients when administered as combination therapy with these AEDs.^{5,24} However, a 24 week observational study is relatively short time to judge effectiveness of zonisamide and further long-term studies can be considered in future. The results of this study support the use of zonisamide as well-tolerated and efficacious agent for treatment of partial onset and generalized seizures. Zonisamide can be considered by physicians as a potential AED as monotherapy or adjunctive therapy to achieve seizure control in their epileptic patients in their real-world clinical settings.

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Disclosure

All authors asides from Dr Amitabh Dash received an investigator fee for the study. Dr Amitabh Dash is an employee of Eisai Co. Ltd. The authors report no other conflicts of interest in this work.

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