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ORIGINAL ARTICLE

# Efficacy and safety of everolimus for patients with focal cortical dysplasia type 2

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## Abstract

**Objective:** This study aimed to evaluate the effectiveness and safety of everolimus in treating seizures associated with focal cortical dysplasia type 2 (FCD 2).

**Methods:** A prospective, crossover, placebo-controlled clinical trial (ClinicalTrials.gov: NCT03198949) enrolled patients aged 4–40 years with pathologically confirmed FCD 2 and a history of ≥3 seizures per month for two out of the 3 months prior to screening. The trial included a 4-week baseline phase, two 12-week core phases, and a 29-week extension phase. Patients received everolimus or placebo in a blinded manner during core phase I, with crossover to the alternate treatment in core phase II. Everolimus dosage started at 4.5 mg/m$^2$/day, targeting a serum level

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of 5–15 ng/mL. The primary outcome was the proportion of patients achieving ≥50% seizure reduction from baseline in the last month of each core phase. Safety profiles were compared between groups.

**Results:** Between May 11, 2017, and June 19, 2020, 21 patients completed the core phases. There was no significant difference in the primary outcome between everolimus and placebo groups (24% vs. 19%, p = 0.66). The patients showed varied responses. Three patients with a pathogenic variant in the *MTOR* gene or no genetic abnormalities achieved seizure freedom with everolimus in the last month of the core phase, while none of the patients with variants in other genes did. Adverse events, such as mucositis or skin ulceration, were more common with everolimus (19/21 vs. 7/21, $p < 0.001$). All adverse events resolved without study drug withdrawal.

**Significance:** Everolimus treatment for 12 weeks did not show overall superiority in reducing seizures compared to placebo. However, it showed promise, mostly in patients with a pathogenic variant in the *MTOR* gene, highlighting the need for further research into patient-specific factors influencing treatment response. The everolimus treatment was generally safe and manageable.

**Plain Language Summary:** This study tested everolimus for reducing seizures in patients with focal cortical dysplasia type 2 (FCD 2). While the drug was not more effective than a placebo for most, few patients showed better results, with some becoming seizure-free. Side effects were common but manageable. More research is needed to understand why certain patients respond better to treatment.

**KEYWORDS**
epilepsy, drug-resistant epilepsy, Everolimus, focal cortical dysplasia, MTOR inhibitors

## 1 | INTRODUCTION

Focal cortical dysplasia (FCD) is a localized congenital anomaly of the cerebral cortex characterized by cortical thickening and abnormal cortical gyration.[1,2] FCD2 is genetically,[3] radiologically,[4] and pathologically[5] different from FCD1. Increasing evidence indicates that FCD2 is an mTORopathy, caused by dysregulation of the mechanistic target of the rapamycin (mTOR) pathway.[6]

FCD2 causes drug-resistant epilepsy.[7] The standard treatment for FCD2 is surgery; however, seizure freedom is achieved only in 50%–70% of such cases.[8–11] Poor surgical outcomes related to incomplete resection and multilobar extent warrant the need for a new treatment option.[12]

The use of mTOR inhibitors is a promising treatment option for FCD2. mTOR signaling pathway is disrupted in patients with FCD2. Somatic and germline variants are reported in genes related to the mTOR signaling pathway, including *MTOR, AKT3, TSC1*, and *TSC2*.[13] Increased S6 phosphorylation in resected brain specimens indicated mTOR protein hyperactivation in FCD2.[6] Seizures and dysmorphic neurons were rescued by an mTOR inhibitor in a mouse model.[14] An mTOR inhibitor is used as an effective anti-seizure drug for another mTORopathy, tuberous sclerosis complex (TSC).[15] Several clinical trials have confirmed the anti-seizure effects of everolimus in TSC.[16–18] However, there has been limited clinical data proving the efficacy of an mTOR inhibitor on FCD2.

**Key points**

- Everolimus treatment for 12 weeks did not show overall superiority in reducing seizures compared to placebo.
- Patients with pathogenic variants in the *MTOR* gene responded well to everolimus.
- Everolimus was generally well tolerated with no serious side effects in patients with FCD2.
- A larger, multicenter study is needed to further explore the full potential and long-term benefits of everolimus in FCD2.

We conducted a clinical trial to investigate the anti-seizure efficacy and safety of everolimus in patients with pathologically confirmed FCD2. To the best of our knowledge, this is the first clinical trial to examine the use of everolimus in patients with FCD2.

## 2 | METHODS

### 2.1 | Patients

Patients were recruited at Severance Children's Hospital, Seoul, South Korea from May 19, 2017 to January 30, 2021. Patients were considered eligible if they met all of the following criteria: (1) a pathologically confirmed diagnosis of FCD2; (2) drug-resistant epilepsy defined as a failure to become seizure-free with adequate trials of two anti-seizure medications; (3) ages of between 4 and 40 years; (4) ≥3 seizures monthly for ≥2 out of 3 months prior to screening while on one or more anti-seizure drugs at a stable dose; and (5) ≥3 seizures during the 4-week baseline phase (Supplementary information—Data S1).

### 2.2 | Study design

This prospective, cross-over, placebo-controlled clinical trial was conducted at Severance Hospital, a tertiary referral center in Seoul, South Korea. The trial included a 4-week baseline phase, two 12-week core phases I and II, and a 29-week extension phase (Figure 1).

During the 4-week baseline phase, habitual seizure type and frequency were determined. A seizure diary was provided.

During the 12-week core phase I, patients received either everolimus (Afinitor®, Novartis Pharma Stein AG, Stein, Switzerland) or a placebo treatment according to their allocation in a blinded manner. The initial dosage was 4.5 mg/m$^2$/d. Titrations were performed to achieve target blood through everolimus concentrations of 5–15 ng/mL. Drugs were administered using 2 mg dispersible tablets. Afinitor or placebo dose reductions and treatment interruptions for 27 days or less were allowed if patients had disabling adverse events. Drug withdrawal was defined as treatment interruption for 28 days or longer. During the following 12-week core phase II, patients were crossed over to alternative treatment. Concomitant anti-seizure drug dosages, mode of vagal nerve stimulation, and ketogenic diet ratios were maintained. Rescue medications, such as rectal diazepam, were allowed.

After the core phases, consenting patients entered the 29-week extension phase. Patients who had been on a placebo during core phase II were switched to open-label everolimus, and those on everolimus during core phase II continued to receive the drug. Further titration was performed in an open manner if the dose or blood trough concentration of everolimus was considered subtherapeutic.

For clinical data collection, an electronic case report form (eCRF) was developed by the Severance Clinical Trials Center. Information on the date of testing, date of birth, sex, age at seizure onset, age at surgery, surgery type, outcome after surgery, seizure frequency, and seizure types were collected. Genetic data on mosaic or germline variants detected in the resected brain were obtained from the previous studies.[6,19]

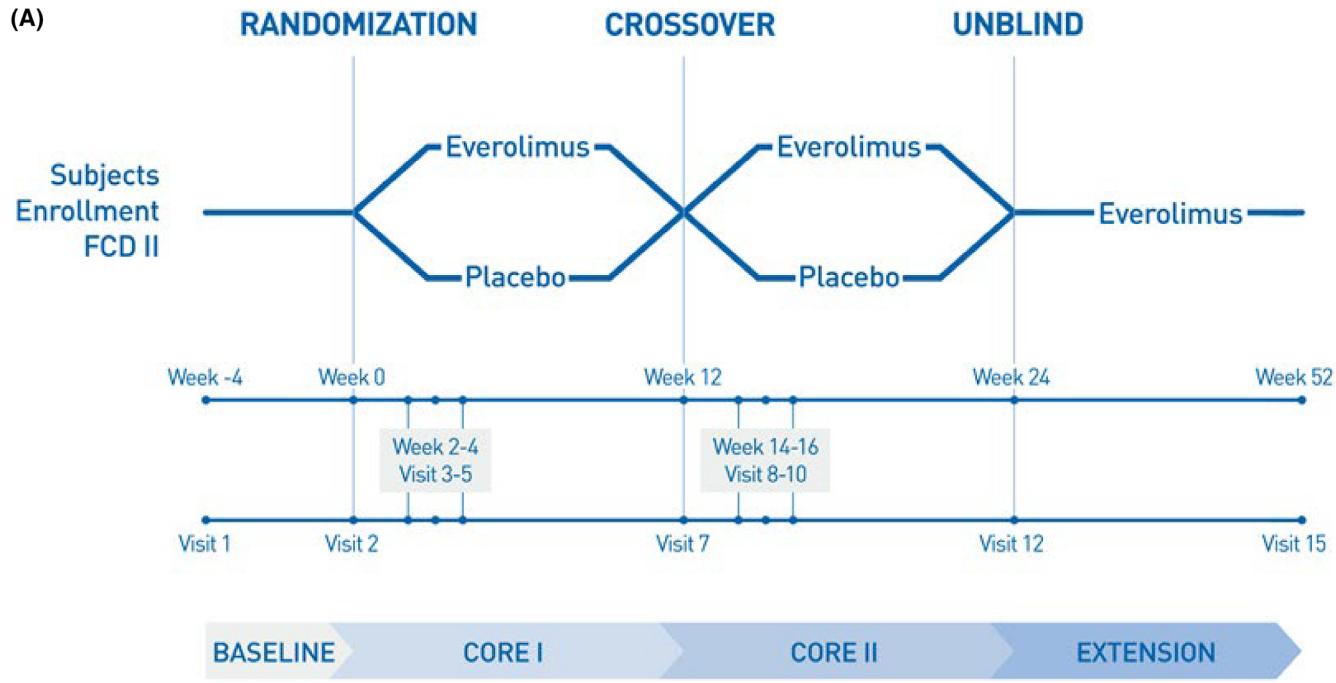
### 2.3 | Randomization and blinding

Patients were randomly and blindly assigned (1:1) to receive everolimus-first or placebo-first treatment using a web-based electronic data capture (EDC) system with the permuted block randomization method (block size = 4). Randomization was performed by a biostatistician at the Severance Clinical Trials Center who was not involved in the rest of the trial. The everolimus and placebo formulations were identical in appearance, packaging, and labeling. All patients, caregivers, guardians, and investigators were blinded to treatment allocation and laboratory test results throughout the core phase except for one investigator who determined the placebo and everolimus dosages every visit during the core phases. This investigator did not have any other involvement in the rest of the trial. The research pharmacy was informed of all patient allocations.

### 2.4 | Outcomes and measures

The seizure frequencies during the core phases were compared to the baseline seizure frequency at 4, 8, and 12 weeks. The primary outcome was a proportion of patients with ≥50% seizure reduction from baseline in the last 4 weeks of the core phase (between Weeks 8 and 12), analyzed at week 12. Secondary outcomes included the ≥90% and 100% responder rates, mean percentage of seizure frequency reduction, and number of seizure-free days. The generalized seizure frequencies were analyzed independently in a similar manner. During the extension phase, seizure frequencies were compared to those of baseline at 28, 40, and 52 weeks.

Patients who experienced a reduction of at least 50% in seizures while taking everolimus in the last month of the core phase compared to that reported during the baseline phase and to those while taking a placebo during the last month of the core phase were classified as good



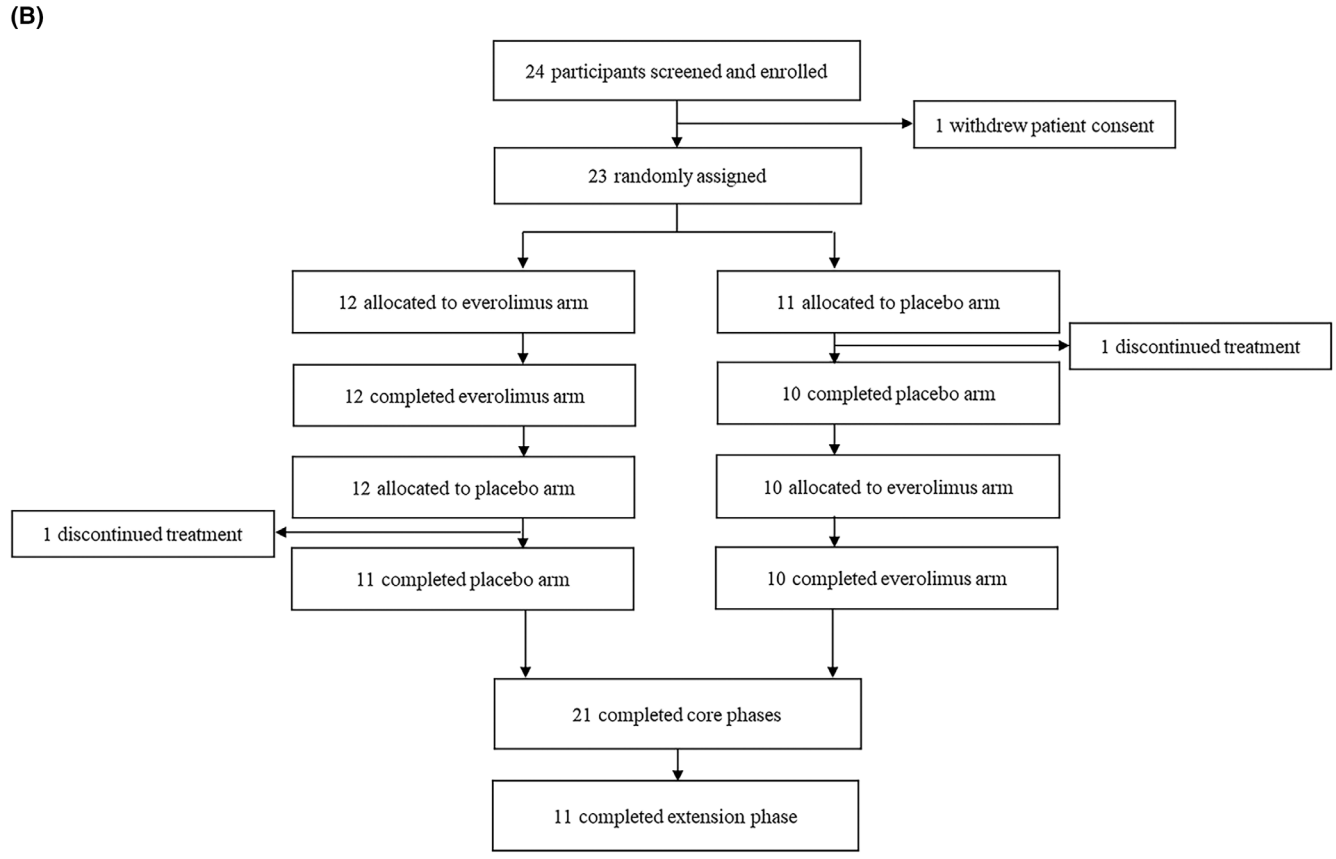




**FIGURE 1** (A) Study design. (B) Trial profile.

responders. The characteristics of these patients were described in detail.

Adverse events were collected at every visit and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03. Serious adverse events (SAEs) were defined as any event that resulted in death, was life-threatening, required inpatient hospitalization or prolonged an existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or

required intervention to prevent permanent impairment or damage.

## 2.5 | Statistical analysis

The planned sample size ($N=23$) was estimated using a simulation approach, giving the study at least an 80% power to detect a 50% difference in response rates between the everolimus and placebo arms based on a two-sided McNemar's test with an alpha level of 0.05. The initial target recruitment was 26 patients, considering a 10% drop-out rate.

For the responder rate, which is a binary outcome, McNemar's test (or Bowker's test) and the generalized estimating equation (GEE) method were used. For seizure frequency and number of seizure days, which are continuous variables, we used a linear mixed model (LMM) based on Grizzle's model. Data during the extension phase were analyzed using the Wilcoxon signed-rank sum test. Univariate logistic regression, Fisher's exact test, and Mann–Whitney test were performed to study the relationship between each variable and outcome. Logistic regression was used if general logistic regression could not be due to a small number of events. Seizure frequency and seizure-free days during the extension phase were analyzed using a Wilcoxon-signed rank test. Adverse events were analyzed using McNemar's test or Bowker's test.

A good responder was defined as someone who had at least a 50% reduction in seizure frequency in the last month of the core phase while on everolimus compared to that from the baseline or on placebo. Related factors were compared between good responders and others in order to identify patient-specific factors related to the treatment outcome.

Data are presented as the median (interquartile range [IQR]), frequency (%, *n*), or estimated probability (95% confidence interval [CI]), as appropriate. All statistical analyses were performed using SAS® ver. 9.4 (SAS Institute, Cary, North Carolina, USA).

## 2.6 | Standard protocol approvals, registrations, and patient consents

The study protocol was approved by the Institutional Review Board of Yonsei University Health System (IRB number: 4–2017-0299) and registered with ClinicalTrials.gov (NCT03198949). Written informed consent was obtained from patients and their parents or legal guardians before study enrollment. The study was conducted in accordance with the Declaration of Helsinki and all local regulations.

# 3 | RESULTS

## 3.1 | Study patients

A total of 24 patients (10 male and 14 female) with pathologically confirmed FCD2 were screened between May 2017 and January 31, 2021. One patient withdrew consent during the baseline period. Twenty-three (9 male, 14 female) patients received the investigational drug and were randomly assigned to receive placebo-first ($N=11$) or everolimus-first treatment ($N=12$). Two patients discontinued the treatment during the core phase. Finally, 21 patients (7 male and 14 female) completed the two core phases (Figure 1).

The median age of the 21 patients was 15 years (13–18 years). The median value of the seizure onset age was 0.8 years (0.3–4.0 years). The majority (13, 62%) of the patients had an early seizure onset at the age of 24 months or younger. All had epilepsy chronically, and the median duration of epilepsy was 13 years (6–26 years). Nine (43%) patients had a previous history of infantile epileptic spasms syndrome.

The median age at surgery was 7.4 years (4.3–13.9 years). All of them underwent surgery between 2005 and 2017. Median years after surgery were 7.7 years (6.3–9.7 years). Transiently, six patients had seizure freedom for a year or longer before recurrence after surgery, but the majority of patients (71%, 15/21) either never achieved seizure freedom or had it for less than a year, indicating an incomplete lesion resection.

Five patients had FCD 2b, and the rest had FCD 2a. All histological diagnoses were made after surgery. Pathogenic variants in genes related to the mTOR signaling pathway were identified in the resected brain in 10 patients: *MTOR* (5), *DEPDC5* (2), *TSC1* (2), and *TSC2* (1). Of note, one patient had a pathogenic variant in the *SCL35A2* gene. Baseline characteristics of the patients are provided in Tables 1 and 2.

## 3.2 | Primary and secondary outcomes

The primary outcomes (≥50% responder rate in the last 4 weeks of the core phase) did not differ between the everolimus and placebo treatments (24% (5/21) vs. 19% (4/21), $p=0.66$). Additional analyses using the generalized estimating equation (GEE) to adjust results for sequence and period effects were performed. Similarly, the estimated probability for ≥50% responder rates did not differ for everolimus and placebo treatments during the 12-week core phases (estimated odds ratio [OR], 2.0; 95% CI, 0.5–8.4; $p=0.37$). None of the 50% responder rates at 4, 8, or 12 weeks differed between everolimus and placebo treatment (Table 3).

**TABLE 1** Baseline patient demographic and clinical characteristics.

| | Patients ($n=21$) |
|---|---|
| Sex (male:female) | 7:14 |
| Median age, years | 15 (13–18, 6–34) |
| Duration of epilepsy, years | 13 (11–16, 6–26) |
| Median age of seizure onset, years | 0.7 (0.4–4.0, 0.0–14.0) |
| Median age at surgery, years | 7.4 (4.3–13.9, 0.5–23) |
| Median year of surgery | 2011 (2009–2012, 2005–2017) |
| History of IESS | 9 (43) |
| History of Lennox–Gastaut syndrome | 7 (33) |
| Patients with visible FCDs on MRI | 9 (43) |
| Median number of concomitant ASMs | 3 (3–4, 2–5) |
| Resective surgery | 21 (100) |
| Multilobar resection | 11 (52) |
| Unilobar resection or lesionectomy | 10 (48) |
| Two-year surgical outcome | |
| Engel class 1 | 3 (14) |
| Engel class 2 | 10 (48) |
| Engel class 3 | 8 (38) |
| History of ketogenic diet or MAD | 17 (81) |
| Corpus callosotomy | 3 (14) |
| Vagal nerve stimulation | 1 (5) |
| Pathology | |
| Focal cortical dysplasia 2a | 16 (81) |
| Focal cortical dysplasia 2b | 5 (24) |
| Identified genetic variants from resected brain | |
| *MTOR* | 5 (24) |
| *DEPDC5* | 2 (10) |
| *TSC1* | 2 (10) |
| *TSC2* | 1 (5) |
| *SLC35A2* | 1 (5) |
| Baseline daily seizure frequency | 1.9 (0.6–5.5, 0.1–11.7) |
| Focal seizures | 21 (100) |
| Focal motor seizures with retained awareness | 11 (52) |
| Focal seizures with impaired awareness | 10 (48) |
| Generalized seizures | 11 (52) |

*Note*: Data are presented as *n* (%) or median (interquartile range, minimum–maximum) values.

Abbreviations: ASM, anti-seizure medication; FCD, focal cortical dysplasia; IESS, infantile epileptic spasms syndrome; MAD, Modified-Atkins diet; MRI, magnetic resonance imaging.

Daily seizure frequency did not differ significantly between everolimus and placebo treatments, although the frequency was consistently lower with everolimus than with placebo (estimated difference, −1.12; 95% CI, −2.24 to 0.18, $p=0.09$). It tended to decline more with everolimus at week 4 (estimated difference, −0.69; 95% CI, −1.89 to 0.51, $p=0.24$), Week 8 (estimated difference, −1.06; 95% CI, −2.91 to 0.80, $p=0.25$), and Week 12 (estimated difference, −1.54; 95% CI, −4.27 to 1.18, $p=0.25$) (Table 3).

The proportion of seizure-free days during the overall core phases did not differ between everolimus and placebo treatments, although seizure-free days were consistently higher on everolimus than with placebo (estimated difference, 0.1; 95% CI, −0.007 to 0.1; $p=0.07$). The proportion of seizure-free days was significantly higher with everolimus compared to that with placebo at week 4 (estimated difference, 0.08; 95% CI, 0.001–0.2; $p=0.048$). This trend tended to be sustained throughout the core phase, but it did not reach statistical significance at Week 8 (estimated difference, 0.04; 95% CI, −0.04–0.12; $p=0.33$) or Week 12 (estimated difference, 0.04; 95% CI, −0.05 to 0.13, $p=0.32$).

There was no difference between everolimus and placebo in the ≥50% responder rates of generalized seizures during the 12-week core phase (estimated OR: 2.6; 95% CI, 0.3–25.2; $p=0.42$). The estimated daily seizure frequency of generalized seizures was lower on everolimus treatment compared to that with placebo, but with no statistical difference (0.7 (95% CI, −0.7 to 2.2) vs. 1.0 (95% CI, −0.5 to 2.4), $p=0.17$). No difference was observed in seizure-free days for generalized seizures between everolimus and placebo (0.6 (95% CI, 0.4 to 0.9) vs. 0.5 (95% CI, 0.2 to 0.8), $p=0.07$) (Supplementary information—Data S1).

All 21 patients agreed to enter the extension phase after completing the core phase. The overall median daily seizure frequency during the overall extension phase reduced from baseline (1.9 (IQR 0.6–5.5) to 1.0 (IQR 0.2–3.9); $p=0.007$). Median daily seizure frequency reduced significantly from baseline at 28 weeks (1.9 (IQR 0.6–5.5) vs. 0.7 (IQR 0.1–3.5), $p=0.005$) and at 40 weeks (1.9 (IQR 0.6–5.5) vs. 1.0 (IQR 0.3–4.8), $p=0.02$), but not at 52 weeks (1.9 (IQR 0.6–5.5) vs. 0.5 (IQR 0.14–3.71), $p=0.11$). The proportion of seizure-free days increased significantly from baseline at 40 weeks (0.4 (IQR 0.4–0.7) vs. 0.5 (IQR 0.03, 0.8), $p=0.045$) and at 52 weeks (0.4 (IQR 0.4–0.7) vs. 0.7 (IQR 0.3–0.9), $p=0.01$). Details are provided in the Supplementary information—Data S1.

## 3.3 | Good responders

Seven (33%, Patients 4, 5, 7, 12, 14, 19, and 24) patients experienced a reduction of at least 50% in seizures while taking everolimus in the last month of the core phase

**TABLE 2** Individual data on epilepsy diagnosis, pathology, and genetic findings related to response to everolimus.

| Patient number | Sex | Onset age, years | Epilepsy duration, years | History of IESS | Generalized tonic seizures | History of IESS | FBTCS or generalized seizures | Age at resection, years | Resection year | Resection location | Duration of post-surgical seizure freedom, years | Years after epilepsy surgery |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 0.2 | 13 | (−) | (−) | (−) | Yes | 3.8 | 2009 | Rt F | 0 | 9.2 |
| 2 | F | 0.0 | 17 | Yes | Yes | Yes | (−) | 8.5 | 2011 | Lt FP | 0 | 8.5 |
| 3 | F | 0.3 | 13 | Yes | Yes | Yes | (−) | 5.4 | 2012 | Lt FT | 0 | 7.6 |
| 4 | M | 0.3 | 18 | Yes | (−) | Yes | Yes | 11.8 | 2009 | Lt FT | 0 | 6.2 |
| 5 | M | 14.0 | 20 | (−) | (−) | (−) | Yes | 23.0 | 2008 | Lt TP | 0 | 11.0 |
| 6 | F | 0.3 | 15 | Yes | Yes | Yes | Yes | 1.8 | 2006 | Lt F | 4.0 | 13.2 |
| 7 | M | 3.8 | 16 | Yes | (−) | Yes | (−) | 10.1 | 2010 | Rt F | 3.0 | 8.9 |
| 8 | M | 0.3 | 14 | Yes | Yes | Yes | (−) | 7.4 | 2012 | Rt FT | 0 | 6.6 |
| 9 | F | 0.0 | 6 | Yes | (−) | Yes | Yes | 0.5 | 2014 | Rt F | 0 | 5.5 |
| 10 | M | 1.0 | 17 | Yes | Yes | Yes | (−) | 3.5 | 2005 | Rt FT | 4.0 | 14.5 |
| 11 | M | 4.0 | 12 | (−) | (−) | (−) | Yes | 12.0 | 2016 | Lt FP | 0 | 4.0 |
| 12 | F | 3.6 | 9 | (−) | (−) | (−) | (−) | 5.5 | 2012 | Rt F | 1.0 | 6.5 |
| 14 | F | 0.3 | 6 | Yes | (−) | Yes | (−) | 2.9 | 2017 | Rt FT | 0.7 | 3.1 |
| 15 | F | 7.0 | 6 | (−) | Yes | (−) | Yes | 8.9 | 2016 | Rt FT | 0.3 | 4.1 |
| 16 | F | 7.0 | 16 | (−) | (−) | (−) | Yes | 12.8 | 2011 | Rt FT | 2.0 | 10.2 |
| 17 | M | 9.0 | 10 | (−) | (−) | (−) | Yes | 10.9 | 2011 | Lt P | 1.0 | 8.1 |
| 18 | F | 5.0 | 13 | (−) | Yes | (−) | (−) | 10.3 | 2012 | Rt F | 0 | 7.7 |
| 19 | F | 0.2 | 14 | (−) | (−) | (−) | Yes | 4.3 | 2011 | Rt F | 0.6 | 9.7 |
| 20 | F | 0.8 | 11 | (−) | (−) | (−) | Yes | 5.0 | 2012 | Lt PO | 0.3 | 7.0 |
| 21 | M | 0.0 | 26 | (−) | (−) | (−) | (−) | 14.3 | 2009 | Lt P | 0 | 11.7 |
| 24 | F | 1.0 | 12 | (−) | (−) | (−) | (−) | 6.7 | 2014 | Lt F | 0.5 | 6.3 |

(Continues)

TABLE 2 (Continued)

| Patient number | Mean seizure frequency per day | | | Seizure frequency reduction, % | | FCD type | Genetic abnormality | | | Everolimus | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Placebo* | Everolimus* | Everolimus compared to baseline* | Everolimus compared to placebo* | | Gene | Variants | Allele frequency, % | Trough concentration, ng/mL | Maximum dose, mg |
| 1 | 0.6 | 0.9 | 0.6 | (−) | 33 | 2a | *MTOR* | c.5930C > A | 1.3 | 5.6 | 10 |
| 2 | 4.7 | 7.0 | 5.6 | (−) | 20 | 2a | | | | 7.0 | 6 |
| 3 | 4.5 | 4.6 | 3.4 | 24 | 26 | 2a | | | | 7.2 | 6 |
| 4 | 23.4 | 30.3 | 3.3 | 86 | 89 | 2a | | | | 7.6 | 10 |
| 5 | 1.0 | 1.1 | 0.5 | 50 | 55 | 2a | *MTOR* | c.4379T > C | 1.6 | 9.2 | 12 |
| 6 | 4.4 | 3.6 | 3.6 | 18 | 0 | 2a | | | | 6.7 | 10 |
| 7 | 0.2 | 0.1 | 0.1 | 50 | 0 | 2a | *DEPDC5* | c.3802C > T | 48.9 | 5.9 | 10 |
| 8 | 6.3 | 7.0 | 7.9 | (−) | (−) | 2a | | | | 13.1 | 8 |
| 9 | 0.9 | 0.5 | 0.8 | 11 | (−) | 2a | *DEPDC5* | c.3406A > T | 50.3 | 6.0 | 10 |
| 10 | 0.4 | 0.2 | 3.3 | (−) | (−) | 2a | *SLC35A2* | c.502C > T | 11.4 | 8.4 | 12 |
| 11 | 0.1 | 0.2 | 0.2 | (−) | 0 | 2b | *TSC1* | c.2630T > A | 3.8 | 6.5 | 12 |
| 12 | 5.4 | 0.0 | 0.5 | 91 | (−) | 2a | | | | 3.5** | 10 |
| 14 | 1.9 | 0.3 | 0.0 | 100 | 100 | 2b | | | | 16.8 | 8 |
| 15 | 6.2 | 5.5 | 6.2 | 0 | (−) | 2a | | | | 5.7 | 12 |
| 16 | 1.6 | 0.5 | 1.6 | 0 | (−) | 2a | | | | 6.2 | 12 |
| 17 | 9.6 | 2.6 | 1.5 | 84 | 42 | 2a | | | | 6.5 | 12 |
| 18 | 8.9 | 10.6 | 7.1 | 20 | 33 | 2a | *TSC2* | c.4639G > A | 1.6 | 9.4 | 10 |
| 19 | 0.8 | 0.7 | 0.0 | 100 | 100 | 2b | *MTOR* | c.4447T > C | 6.6 | 5.7 | 12 |
| 20 | 0.2 | 0.3 | 0.2 | 0 | 33 | 2a | *MTOR* | c.7280T > C | 2.4 | 6.9 | 8 |
| 21 | 0.2 | 0.2 | 0.3 | (−) | (−) | 2b | *TSC1* | c.64C > T | 2.0 | 6.2 | 12 |
| 24 | 2.0 | 7.5 | 0.0 | 100 | 100 | 2b | *MTOR* | c.6644C > T | 7.9 | 4.1** | 10 |

Abbreviations: ASM, anti-seizure medication; F, frontal; F, female; FBTCS, focal to bilateral tonic–clonic seizures; FCD, focal cortical dysplasia; FE, focal epilepsy; IESS, infantile epileptic spasms syndrome; L, left; LGS, Lennox–Gastaut syndrome; M, male; N, number; O, occipital, P, parietal; R, right; T, temporal.

*Seizure frequency during the last month of the core phase. **Two patients had lower than targeted trough levels because caregivers opted not to increase the everolimus dose due to side effects (mucositis in patient 12, rash and mucositis in patient 24) and their satisfaction with the efficacy at the lower dose.

**TABLE 3** Comparison of responder rates, seizure frequency, and number of seizure-free days between everolimus and placebo treatments during the core phase using generalized estimating equation tests and a linear mixed model during the core phase.

| The ≥50% responder rates | | Estimated probability (95% CI) | Estimated OR (95% CI) | *p*-value |
|---|---|---|---|---|
| 12-week analysis | Everolimus | 0.24 (0.02, 0.46) | 1.95 (0.45, 8.42) | 0.37 |
| | Placebo | 0.14 (0.04, 0.36) | Ref. | |
| First 4 weeks (Week 4 or 16) | Everolimus | 0.33 (0.17, 0.56) | 2.12 (0.72, 6.29) | 0.18 |
| | Placebo | 0.19 (0.07, 0.41) | Ref. | |
| Second 4 weeks (Week 8 or 20) | Everolimus | 0.33 (0.17, 0.56) | 1.63 (0.46, 5.81) | 0.45 |
| | Placebo | 0.23 (0.10, 0.46) | Ref. | |
| Third 4 weeks (Week 12 or 24) | Everolimus | 0.24 (0.01, 0.46) | 1.49 (0.33, 6.82) | 0.61 |
| | Placebo | 0.17 (0.06, 0.42) | Ref. | |
| **The ≥90% responder rates** | | **Estimated probability (95% CI)** | **Estimated OR (95% CI)** | ***p*-value** |
| 12-week analysis | Everolimus | N/A | N/A | N/A |
| | Placebo | | | |
| First 4 weeks (Week 4 or 16) | Everolimus | 0.10 (0.02, 0.31) | 2.11 (0.50, 8.96) | 0.31 |
| | Placebo | 0.05 (0.007, 0.27) | Ref. | |
| Second 4 weeks (Week 8 or 20) | Everolimus | 0.13 (0.05, 0.30) | 3.45 (0.26, 46.16) | 0.35 |
| | Placebo | 0.04 (0.003, 0.37) | Ref. | |
| Third 4 weeks (Week 12 or 24) | Everolimus | 0.17 (0.06, 0.42) | 5.08 (0.87, 29.57) | 0.07 |
| | Placebo | 0.04 (0.01, 0.21) | Ref. | |
| **Daily seizure frequency** | | **Estimate (95% CI)** | **Difference (95% CI)** | ***p*-value** |
| 12-week analysis | Everolimus | 2.40 (0.63, 4.17) | −1.12 (−2.42, 0.18) | 0.09 |
| | Placebo | 3.52 (1.75, 5.29) | | |
| First 4 weeks (Week 4 or 16) | Everolimus | 2.50 (0.82, 4.17) | −0.69 (−1.89, 0.51) | 0.24 |
| | Placebo | 3.19 (1.51, 4.87) | | |
| Second 4 weeks (Week 8 or 20) | Everolimus | 2.22 (0.27, 4.17) | −1.06 (−2.91, 0.80) | 0.25 |
| | Placebo | 3.28 (1.33, 5.23) | | |
| Third 4 weeks (Week 12 or 24) | Everolimus | 2.51 (0.22, 4.81) | −1.54 (−4.27, 1.18) | 0.25 |
| | Placebo | 4.05 (1.76, 6.35) | | |
| **Proportion of seizure-free days** | | **Estimate (95% CI)** | **Difference (95% CI)** | ***p*-value** |
| 12-week analysis | Everolimus | 0.48 (0.31, 0.66) | 0.05 (−0.007, 0.12) | 0.08 |
| | Placebo | 0.43 (0.26, 0.60) | | |
| First 4 weeks (Week 4 or 16) | Everolimus | 0.49 (0.31, 0.66) | 0.08 (0.001, 0.16) | **0.048** |
| | Placebo | 0.41 (0.23, 0.58) | | |
| Second 4 weeks (Week 8 or 20) | Everolimus | 0.48 (0.30, 0.66) | 0.04 (−0.04, 0.12) | 0.33 |
| | Placebo | 0.44 (0.26, 0.62) | | |
| Third 4 weeks (Week 12 or 24) | Everolimus | 0.48 (0.31, 0.66) | 0.04 (−0.05, 0.13) | 0.32 |
| | Placebo | 0.44 (0.26, 0.61) | | |

*Note*: Values in bold indicate that there is statistical significance at the level of $p < 0.05$.

compared to that reported during the baseline phase. Among them, five patients (24%, Patients 4, 5, 14, 19, and 24) also showed a 50% or higher reduction in seizure frequency while taking everolimus compared to those while taking a placebo during the last month of the core phase, suggesting an effective anti-seizure effect of everolimus (Figure 2). These five patients could be classified as good responders.

Overall, patients with variants in the *MTOR* gene showed good seizure outcomes. Three (60%, Patients 5, 19, and 24) out of five patients with variants in the *MTOR* gene were good responders, while none of the patients with variants in other genes, including *TSC1*, *TSC2*, and *DEPDC5*, did (Table 2). Patients without identified genetic abnormalities also responded well, and two (20%, Patients 4 and 14) without genetic abnormalities were good responders. Individual data of patients with or without genetic abnormalities are provided in Table 2 and Figure 2.

Particularly, three patients (14%, Patients 14, 19, and 24) achieved seizure freedom in the last month of the core phase while taking everolimus. They were the patients who had seizures nearly every day, and they each had a mean daily seizure frequency of 1.9, 0.8, and 2.0 seizures per day. No similar responses were seen with the placebo.

All three patients had a confirmed pathologic diagnosis of FCD 2b in the resected brain and experienced seizure freedom for a few months, less than a year after surgery, which suggested a correctly located but incomplete removal of the FCD lesion. These three patients were 6, 13, and 14 years old, younger than the median age of the participants in this study, which was 15 years. All of them had focal seizures, and none had tonic seizures or spasms during this study. They either had a pathogenic variant in the *MTOR* gene (Patients 19 and 24) or no genetic abnormalities (Patient 5). These patients experienced sustained responses to everolimus and maintained a seizure-reduction state during the extension phase (Figure 2).

The majority of patients continued to show similar responses to everolimus during the extension phase with those of the core phase. However, one patient (Patient 12) showed a favorable response to everolimus only during the extension phase. During the last months of the core phases, the patient had seizures only on everolimus and none on placebo treatment, suggesting that everolimus was not effective. However, she showed a remarkable seizure reduction during the extension phase, and review of the patient's data showed that she only had clustered seizures and that she incidentally did not have any seizures during the last month of the core phase (Figure 2). During the extension phase, she showed a clear seizure reduction compared to the baseline phase.

### 3.4 | Adverse events

Overall, 43 adverse events occurred in 19 (91%) patients during the core phases. Nineteen patients experienced adverse events with everolimus, while only seven experienced adverse events with placebo (19/21 vs. 7/21, $p < 0.001$). Mucositis (10/21 vs. 0/21, $p = 0.002$) and skin ulceration (7/21 vs. 3/21, $p = 0.046$) occurred more frequently with everolimus.

Treatment emergent adverse events (TEAEs) occurred in 16 (76%) patients. Sixteen patients experienced an adverse event with everolimus, while only two experienced adverse events with placebo ($p < 0.001$). Mucositis and skin ulceration were the common treatment-emergent adverse events (≥10%).

One serious adverse event requiring hospitalization or intervention occurred with everolimus and placebo each (1/21 vs. 1/21; $p = 1.0$). One patient had a serious adverse event, which was mucositis that required an incision and drainage procedure, while on everolimus (Patient 2). Another patient developed pneumonia that required hospitalization in the last month of the core phase after taking placebo for 82 days (Patient 15). All adverse events were resolved without study drug withdrawal. Four (19%) patients underwent dose reduction due to adverse events. Details are provided in Table 4.

## 4 | DISCUSSION

The present study showed that everolimus did not significantly reduce the primary outcome measure of ≥50% seizure reduction compared to placebo during the core phases. This indicates that everolimus may not provide a substantial benefit over placebo for short-term seizure control in patients with FCD2.

However, few secondary outcomes showed promising trends, with an increased proportion of seizure-free days and a non-significant trend toward reduced daily seizure frequency with everolimus necessitating detailed outcome analysis of each individual patient.

In fact, seven (33%) patients experienced a reduction of 50% or higher in seizures in the last month of the core phase while taking everolimus compared to baseline, and five (24%) patients also showed significantly higher seizure reduction of ≥50% compared to baseline and placebo, highlighting that everolimus can be highly effective in some cases, particularly in those with focal seizures and FCD2b, *MTOR* gene variants, and young age.

Patients with pathogenic variants in the *MTOR* gene showed a favorable response to everolimus, with 60% being good responders. This points to a potential genetic biomarker for predicting treatment response. The lack of

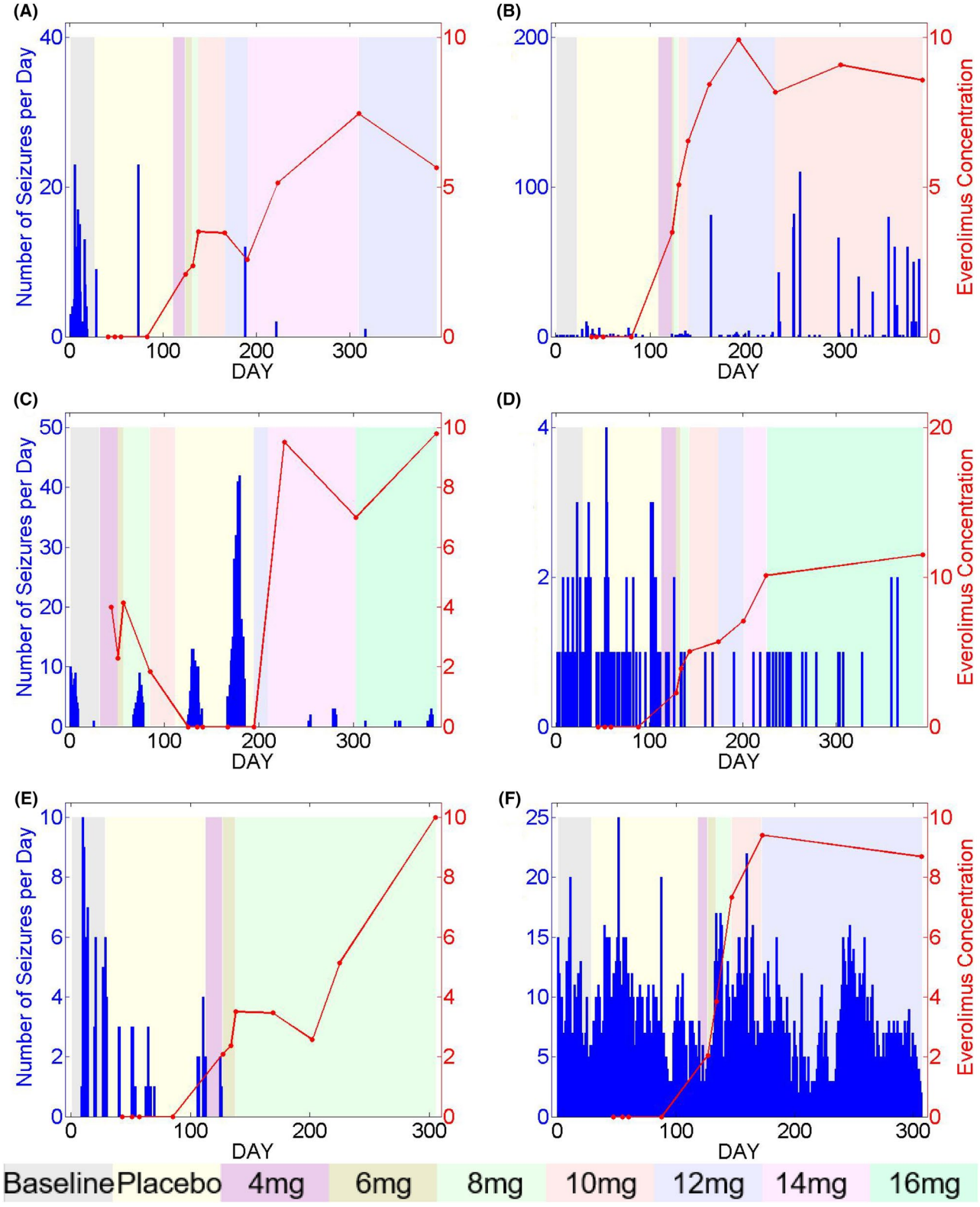



**FIGURE 2** Changes in seizure frequency in individual patients in relation to everolimus dose and concentration. Patients with genetic abnormalities in *MTOR* or without identified genetic abnormalities showed good responses to everolimus. The number of seizures per day (blue bar) reduced with an increase in everolimus concentration (red line). The numbers on the upper margin of the graph represent the dosage of everolimus, while the numbers on the lower margin indicate the study dates. (A) Patient 12 with a negative genetic test. (B) Patient 10 with a pathogenic variant in the *SLC35A2* gene (variant allele frequency [VAF], 11.4%). (C) Patient 24 with a pathogenic variant in the *MTOR* gene (VAF, 7.9%). (D) Patient 19 with a pathogenic variant in the *MTOR* gene (variant allele frequency, 6.6%). (E) Patient 14 with a negative genetic test. (F) Patient 18 with a pathogenic variant in the *TSC2* gene (variant allele frequency, 1.6%).

**TABLE 4** Adverse events related to everolimus and placebo during the core phase ($N=21$).

| | All | Everolimus *n* (%) | Placebo *n* (%) | *p*-value |
|---|---|---|---|---|
| Any adverse events | 19 (91) | 19 (91) | 7 (33) | <0.001 |
| Mucositis | 10 (48) | 10 (48) | 0 | 0.002 |
| Skin ulceration | 7 (33) | 7 (33) | 3 (14) | 0.046 |
| Rash | 2 (10) | 2 (10) | 0 | 0.16 |
| Constipation | 1 (5) | 0 | 1 (5) | 0.32 |
| Cough | 2 (10) | 1 (5) | 1 (5) | 1 |
| Edema | 1 (5) | 1 (5) | 0 | 0.32 |
| Herpes simplex viral infection | 1 (5) | 0 | 1 (5) | 0.32 |
| Lethargy | 1 (5) | 1 (5) | 0 | 0.32 |
| Leukopenia | 1 (5) | 1 (5) | 0 | 0.32 |
| Nasal congestion | 1 (5) | 0 | 1 (5) | 0.32 |
| Pneumonia | 1 (5) | 0 | 1 (5) | 0.32 |
| Upper respiratory infection | 2 (10) | 1 (5) | 1 (5) | 1 |
| Wound complication | 1 (5) | 0 | 1 (5) | 0.32 |
| Treatment emergent adverse events (TEAEs) | 16 (76) | 16 (76) | 2 (10) | <0.001 |
| Mucositis | 10 (47) | 10 (47) | 0 | 0.002 |
| Skin ulceration | 7 (33) | 7 (33) | 2 (10) | 0.03 |
| Rash | 2 (10) | 2 (10) | 0 | 0.16 |
| Lethargy | 1 (5) | 1 (5) | 0 | 0.32 |
| Leukopenia | 1 (5) | 1 (5) | 0 | 0.32 |
| TEAEs leading to drug dose adjustment | | | | |
| Dose reduction | 4 (19) | 4 (19) | 0 | 0.046 |
| Withdrawal | 0 | 0 | 0 | NA |
| Serious adverse events | | | | |
| Any* | 2 (10) | 1 (5) | 1 (5) | 1 |
| Hospitalization | 1 (5) | 0 | 1 (5) | 0.32 |
| Intervention & drainage | 1 (5) | 1 (5) | 0 | 0.32 |
| Life-threatening | 0 | 0 | 0 | NA |
| Death | 0 | 0 | 0 | NA |

Abbreviation: NA, not available; TEAEs, treatment emergent adverse events.

*Two serious events were mucositis (during everolimus treatment) and pneumonia (during placebo treatment). Pneumonia required hospitalization.

response in patients with *TSC1*, *TSC2*, and *DEPDC5* variants suggests that the therapeutic effect of everolimus might be more specific to *MTOR*-related pathophysiology. Interestingly, one of our patients was found to have a mosaic variant in *SLC35A2*, which was recently recognized to cause a different disease entity, mild malformations of cortical development with oligodendroglial hyperplasia (MOGHE).[20] We included this patient since a formal report of his previous pathology indicated that he had FCD2, but further pathologic review was not conducted due to unavailability of the brain tissue. However, since this patient had an epilepsy resection and a diagnosis of FCD2 in 2005, there is a possibility of receiving an incorrect pathologic diagnosis. This was not a problem that we had expected when we started our study, and this finding supports the recent ILAE FCD diagnosis, which recommended an integrated multi-layered FCD classification scheme including genetic findings.[2] As expected, this patient did not respond to everolimus, confirming that patients with disrupted glycosylation would show a different clinical response to everolimus from patients with mTORopathy, even though they both cause drug-resistant epilepsy. With more recent insightful research, differences between MOGHE, FCD1, and FCD2 are becoming better addressed.[21,22]

Why mTOR inhibitors are effective for mTORopathy seems quite straightforward.[23] The *MTOR* gene encodes a key protein in the mTOR signaling pathway, which is involved in cell growth, proliferation, and survival.

Dysregulation of this pathway is known to contribute to the development of FCD2. Everolimus, an mTOR inhibitor, targets this dysregulated pathway, thereby reducing hyperactive signaling and potentially normalizing neuronal activity. The positive response in patients with *MTOR* mutations supports this mechanism of action, suggesting that everolimus directly addresses the underlying pathophysiology in these patients.

In contrast, the anti-seizure effects of everolimus remain less well understood. The reduction in median daily seizure frequency and the increase in seizure-free days during the extension phase compared to the baseline reinforce the idea that longer-term treatment with everolimus might be necessary to observe significant clinical benefits. These findings suggest potential benefits that might become more evident over longer treatment periods in a larger patient group.

Everolimus was associated with a higher incidence of adverse events, particularly mucositis and skin ulceration, compared to placebo. One patient developed severe mucositis, which required incision and drainage. This highlights the need for careful monitoring and management of adverse events in patients undergoing everolimus treatment. Despite the higher rate of adverse events, however, most were manageable, and only a few patients required dose reductions. None required study drug withdrawal due to adverse events. All of the patients agreed to enter the extension phase after completing the core phase, indicating that everolimus is generally well-tolerated with appropriate care. Still, a new mTOR inhibitor with a low adverse event profile with high blood–brain barrier permeability would be appreciated.

## 4.1 | Limitations

This study had several limitations. The small sample size (21 patients completing the core phases) limits the generalizability of the findings. Although the initial sample size was 23, two patients withdrew, and recruiting more was challenging since FCD2 patients often become seizure-free after epilepsy surgery. Additionally, we employed a broad inclusion criterion, enrolling patients who experienced ≥3 seizures per month for at least 2 out of 3 months prior to screening. This may have been a limitation, as low seizure frequency could hinder the detection of significant differences between the drug and placebo. Establishing appropriate inclusion criteria is important for future studies. The sample size for each genetic mutation was small, making it likely that studies of this nature will yield meaningful results only in a multicenter setting. One limitation was the lack of a washout period between the two core phases, which would have been essential given the mechanism of action of everolimus.

Finally, phenotypic heterogeneity and variable lesion characteristics complicated outcome interpretation. All of our patients included in the study had chronic early-onset severe drug-resistant epilepsy, including Lennox–Gastaut syndrome. Early intervention may prevent seizures more effectively than late treatment, as seen in the mouse models of TSC and FCD2.[24,25] Repeated seizures can cause neuronal injury, glial proliferation, and gliosis, which may exacerbate epilepsy and make these lesions non-responsive to everolimus.[26] Furthermore, the wide range of seizure frequencies and types among patients, including those with rare clustered seizures or seizures triggered by specific conditions, may have led to undercounting responders whose changes were less prominent. A seizure diary was used, which can be inaccurate. We also could have undercounted responders who had decreased seizure duration rather than reduced seizure frequency.

In conclusion, we did not observe a greater overall seizure reduction compared to placebo in our patient group following 12 weeks of everolimus treatment, possibly due to the small sample size limiting the detection of significant differences. However, the drug was generally well tolerated with no serious side effects, and several patients, particularly those with *MTOR* gene mutations, demonstrated favorable responses. A larger, multicenter study is needed to further explore the full potential and long-term benefits of everolimus in FCD2 and to better assess its efficacy in this specific patient population.

## AUTHOR CONTRIBUTIONS

Se Hee Kim contributed to study design and conceptualization, data interpretation, writing, and critical approval of the final paper. Hoon-Chul Kang contributed to study design, data interpretation, and critical approval of the paper. Jeong Ho Lee contributed to study design, and critically reviewed and revised the manuscript. Se Hoon Kim reviewed the pathological diagnosis and critically reviewed and revised the manuscript. Yun Ho Roh, Jongsung Hahn, and Kyung Lok Min contributed to study design, data collection, data interpretation, literature search, and statistical analysis. Seok-Jin Lee, Donghwa Yang, Han Som Choi, and Soyoung Park collected data, carried out the initial analyses, contributed to data collection, creation of figures and tables, and literature search. Sang-Guk Lee conducted a drug-level study and contributed to study design and data interpretation. Min Jung Chang contributed to study design, data collection, data interpretation, literature search, writing, statistical analysis, and verifying the underlying

data. Heung Dong Kim contributed to study design and conceptualization, data interpretation, critical approval of the final paper, and funding acquisition. All authors have approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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## CONFLICT OF INTEREST STATEMENT

JHL is the Chief Scientific Officer (CSO) of SoVarGen, a biopharmaceutical company. SHK and KHC have served as paid consultants for SoVarGen. The remaining authors have no conflicts of interest related to the content of this manuscript.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding authors.

## ETHICS STATEMENT

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

## PATIENT CONSENT STATEMENT

Patients or their caregivers agreed to participate in this study and signed informed consent.

## CLINICAL TRIAL REGISTRATION

*Name*: A Study Investigating the Anti-epileptic Efficacy of Afinitor (Everolimus) in Patients With Refractory Seizures Who Have Focal Cortical Dysplasia Type II (FCD II). *The registration number*: NCT03198949. *Date of registration*: May 24, 2018. *Date of first enrollment*: May 25, 2018. *Web link to the registration*: https://www.clinicaltrials.gov/study/NCT03198949?cond=focal%20cortical%20dysplasia&rank=4.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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