FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

Everolimus dosing recommendations for tuberous sclerosis complex–associated refractory seizures

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Summary

Objective: The present analysis examined the exposure-response relationship by means of the predose everolimus concentration (C_{min}) and the seizure response in patients with tuberous sclerosis complex–associated seizures in the EXIST-3 study. Recommendations have been made for the target C_{min} range of everolimus for therapeutic drug monitoring (TDM) and the doses necessary to achieve this target C_{min}.

Methods: A model-based approach was used to predict patients' daily C_{min}. Time-normalized C_{min} (TN-C_{min}) was calculated as the average predicted C_{min} in a time interval. TN-C_{min} was used to link exposure to efficacy and safety end points via model-based approaches. A conditional logistic regression stratified by age subgroup was used to estimate the probability of response in relation to exposure. A multiplicative linear regression model was used to estimate the exposure-response relationship for seizure frequency (SF). An extended Cox regression model was used to link exposure to the time to first adverse event.

Results: There was a strong, consistent, and highly significant relationship between everolimus exposure and efficacy, measured by TN-C_{min} and SF, regardless of patient's age and concomitant use of cytochrome P450 3A4 (CYP3A4) inhibitors/inducers. Results of an extended Cox regression analyses indicated that

twofold increases in TN-C_{min} were not associated with statistically significant increases in the risk of stomatitis or infections.

Significance: The recommended TDM is to target everolimus C_{min} within a range of 5-7 ng/mL initially and 5-15 ng/mL in the event of an inadequate clinical response, and safety is consistent with previous reports. Starting doses depend on age and the concomitant use of CYP3A4/P-glycoprotein inducers/inhibitors.

KEYWORDS
dose, refractory, seizures, TDM, TSC

1 | INTRODUCTION

Tuberous sclerosis complex (TSC) is a rare autosomal dominant multisystem disorder, resulting from mutations in one of the *TSC* genes, *TSC1* or *TSC2*. Epilepsy is the most common neurologic symptom of TSC and occurs in 80%-90% of patients.[1,2] Approximately two-thirds of patients experience seizure onset in the first year of life, often as infantile spasms or partial seizures.[3,4] In adults with TSC and no prior history of seizures, nearly 12% develop epilepsy at some point in time.[3] The management of TSC-associated refractory seizures may include antiepileptic drugs (AEDs), ketogenic diet, epilepsy surgery, and vagus nerve stimulation.[5] However, existing treatments are often ineffective and >60% of patients develop treatment-refractory seizures.[4]

Dysregulation and hyperactivation of the mechanistic target of rapamycin (mTOR) pathway are responsible for the pathophysiology of TSC. This has led to the use of mTOR inhibitors to treat the various manifestations of TSC. Everolimus, an mTOR inhibitor, has been approved by regulatory authorities for treatment of TSC-associated subependymal giant cell astrocytoma (SEGA), angiomyolipomas, and epilepsy (European Union approval).[6–8] A recent phase 3 study, EXIST-3 (EXamining everolimus In a Study of Tuberous sclerosis complex), compared the efficacy and safety of 2 trough exposure levels (C_{min}) of adjunctive everolimus with placebo in patients with TSC and treatment-resistant focal epilepsy.[9] Based on the positive results of this trial, the European Commission approved everolimus as an adjunctive treatment for patients aged 2 years and older with refractory partial-onset seizures associated with TSC.[9] Findings from the EXIST-3 study showed that everolimus led to a statistically significant and clinically meaningful reduction in seizure frequency (SF) and response rate with a favorable benefit-risk profile that improves with ongoing treatment.[8] In this study, everolimus trough concentration (C_{min}) was found to be correlated with seizure outcomes (response rate and median percentage reduction in SF).[8]

Key Points

- Epileptic seizures are one of the most common presenting symptoms of TSC, affecting 80%-90% of patients; >60% of patients with TSC develop treatment-refractory seizures
- Dysregulation and hyperactivation of the mTOR pathway are responsible for the pathophysiology of TSC; this led to the use of everolimus, an mTOR inhibitor for the treatment of various manifestations of TSC
- The EXIST-3 study demonstrated a strong, consistent, and highly statistically significant relationship between everolimus PK exposure and seizure frequency response or postbaseline seizure frequency across all age groups
- Everolimus is primarily metabolized by CYP3A4 and is a substrate of the PgP transporter; many of the AEDs typically used in patients with TSC and seizures are either inducers or substrates of these enzymes, and hence monitoring of everolimus blood C_{min} levels is recommended to optimize therapy
- The recommendation based on the present results is to target a concentration range of everolimus of 5-15 ng/mL for patients with TSC-associated refractory seizures
- The safety of everolimus is consistent with the known safety profile of everolimus in TSC

In patients with TSC, a substantial variability of everolimus C_{min} levels was observed. This is likely due to everolimus being metabolized by cytochrome P450 3A4 (CYP3A4) and is a substrate of the P-glycoprotein (PgP) transporter. Many of the AEDs typically used in these patients are either inducers or substrates of these enzymes. Other medications can inhibit the activity of the CYP P450 system, and thereby inhibit the clearance of everolimus. In addition, volume of

distribution and metabolism change with advancing age; this effect is especially prominent in a pediatric population. Therefore, monitoring of everolimus blood C_{min} levels may provide important clinical information and allow for optimization of therapy. In the previously reported studies in TSC patients with SEGA, durable response rates were achieved with everolimus by targeting C_{min} of 5-15 ng/mL.[6,10,11] We evaluated the effect of age on the pharmacokinetic (PK) profile of everolimus and exposure-response relationship in patients with TSC-associated refractory seizures. Based on the results of PK and exposure-response analyses, recommendations for the target C_{min} range for therapeutic drug monitoring (TDM) in patients with TSC-associated refractory seizures of different age groups and the doses to achieve the target C_{min} have been explored.

2 | MATERIALS AND METHODS

The details of the EXIST-3 study design have been reported previously.[8] Briefly, EXIST-3 was a 3-arm, prospective, randomized, multicenter, double-blind, placebo-controlled, phase 3 study comparing the efficacy and safety of 2 everolimus treatment arms targeting either low everolimus exposure (3-7 ng/mL; LE) or high everolimus exposure (9-15 ng/mL; HE) with a placebo arm, in patients with TSC who had refractory partial onset seizures and were on a stable regimen of AEDs prior to the start of everolimus treatment. The study included an initial 8-week baseline phase, followed by an 18-week core phase, and a 48-week extension phase. Patients were randomly assigned to placebo, LE, and HE arms. Patients were stratified by age subgroups (<6 years, 6 to <12 years, 12 to <18 years, and ≥18 years). Everolimus was taken daily with food or consistently without food according to label prescriptions. As the safety of everolimus was well known, only C_{min} was collected in this study with the primary aim of the TDM. PK samples were excluded if they were not taken under the correct time window, impacted by vomiting episodes, or not a steady state. Because of the exclusion of unlikely values and the review of results by an expert PK scientist, the observed C_{min} was considered the true C_{min}. Dose adjustments to attain the target C_{min} were performed during the first 6 weeks of the core phase, and as needed during the subsequent 12-week maintenance period. The primary efficacy end point was change from baseline in SF for each of the 2 everolimus C_{min} target ranges compared with placebo after the 12-week maintenance period of the core phase. SF corresponds to the ratio between the number of seizures and the number of days on which seizure information was known within the same period of time (baseline or maintenance phase). The change of SF from baseline was expressed both as response rate and as median percentage reduction in SF.[8] A patient was considered to be a responder if the patient

achieved ≥50% reduction from baseline in average weekly partial onset SF during the maintenance period of the core phase. Independent ethics committees and/or local ethics review boards approved the protocol, and all patients or their guardians provided written informed consent.

2.1 | PK analysis

Clinical sites collected blood samples prior to the administration of that day's study medication (trough PK) in all patients during the 6-week titration period of the core phase and forwarded them to a central laboratory for determination of everolimus C_{min}. After the completion of the titration period, patients continued their current dose level during the 12-week maintenance period. Trough PK blood samples were collected every 4 weeks during the maintenance period. In addition, trough everolimus levels were collected every 2 weeks after any everolimus dose adjustments as well as after any initiation, discontinuation, or dose adjustment of a CYP3A4/PgP inducer/inhibitor. PK statistical analyses were performed on those PK samples obtained prior to dose administration, 20-28 hours after the patient's last dose, at steady state, and in the absence of vomiting within 4 hours after previous dose.

Based on the dose-proportionality characteristics of everolimus, a modified power model[12] was used to predict a daily C_{min}. The power model was expressed as a linear mixed effect model with a random effect to account for interpatient variability and the patient's daily leading dose and age subgroup as fixed effects to capture the impact of the most immediate dose on the concentration levels adjusted by the patient's age. Both the C_{min} and leading dose parameters were transformed into logarithmic scale prior to the modeling step. The age subgroup (<6 years, 6 to <12 years, 12 to <18 years, and ≥18 years) reflected the strata used at the time of randomization.

Time-normalized C_{min} (TN-C_{min}) was an estimate of the daily C_{min} for a patient averaged over a time interval. Time-normalized C_{min} was linked to the efficacy or safety end point measured over the same time interval. A conditional logistic regression model stratified by age subgroup was used to estimate the probability of an efficacy response in relation to exposure. The model estimated the odds of a response per a twofold increase in everolimus exposure. A linear regression model was used to estimate postbaseline SF in relation to exposure over the 12-week maintenance period of the core phase. The model was multiplicative in nature, as both variables (postbaseline SF and TN-C_{min}) were transformed in logarithmic scale. Based on this model, the minimum efficacious everolimus concentration was predicted. The minimum efficacious concentration refers to the minimum everolimus concentration that resulted in a level of efficacy higher than that experienced by patients on the placebo arm in terms of SF reduction. To characterize the exposure-

safety relationship, the time to first event of the selected adverse events (AEs) in relation to everolimus exposure was estimated using an extended Cox model, stratified by age subgroup, with TN-C_{min} as a time-varying covariate over 4 prespecified time intervals. The 4 time intervals were defined according to the study design: the titration and maintenance periods of the core phase and the titration and maintenance periods of the extension phase. Using everolimus exposure as a time-dependent covariate allowed a better characterization of the impact of any change in everolimus exposure over time due to dose titration or interruption.

3 | RESULTS

A total of 366 patients were randomized to receive placebo (n = 119), LE everolimus (n = 117), or HE everolimus

(n = 130). Detailed patient baseline characteristics have been reported previously.[8] The median age of patients in the LE arm was 9.7 years (range = 2.2-56.3 years), and in the HE arm it was 10.1 years (range = 2.3-50.5 years). Eighty-two percent of the study population was <18 years of age. Overall, the demographic and disease characteristics were well balanced among the treatment arms. Body surface area (BSA) was noted to increase up to the age of 18 years, and thereafter remained relatively stable (Figure S1).

3.1 | C_{min} during the core phase

The BSA-adjusted median dose received by patients in the LE arm was 5.2 mg/m^2/d (range = 1.3-14.5 mg/m^2), and in the HE arm it was 7.5 mg/m^2/d (range = 1.4-24.4 mg/m^2). The median C_{min} values for the LE and HE arms were similar at week 1. Over time, median C_{min} values for the LE
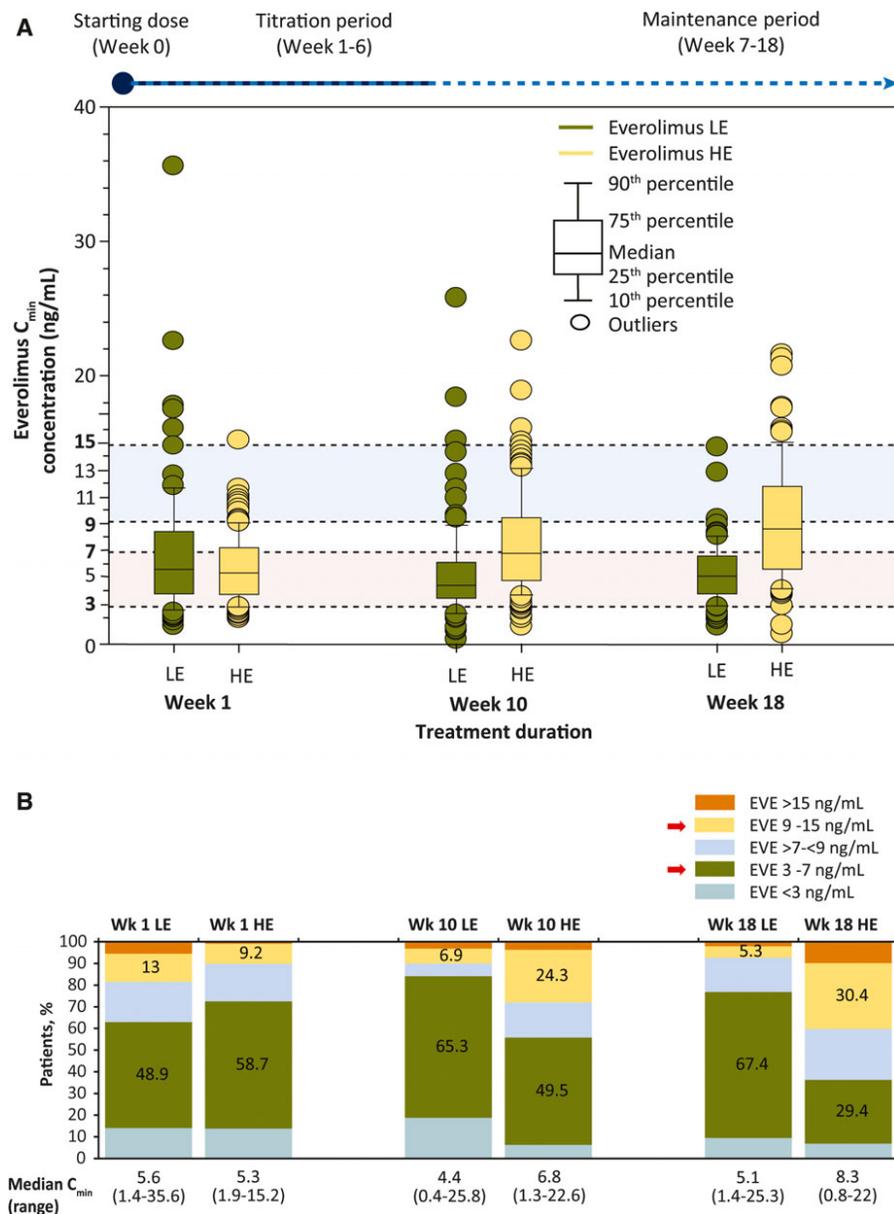

FIGURE 1 Everolimus observed C_{min} concentrations (ng/mL) during the core phase. A, Observed C_{min} by randomized everolimus treatment arms. HE, high exposure; LE, low exposure. This figure shows that everolimus LE arm achieved the target C_{min} of 3-7 ng/mL starting at week 1, with the median C_{min} maintained within the target range during the core phase. The everolimus HE arm had similar C_{min} values as the LE arm at week 1 because the same starting doses were administered to both treatment arms, and then gradually increased toward the end of the core phase. Overlapping but notable differences were seen in the exposures achieved in the everolimus LE and HE arms. B, Proportion of patients by exposure ranges based on everolimus (EVE) observed C_{min}. This figure displays the proportion of patients with their observed everolimus C_{min} ranges during the core phase. The majority of the patients had their everolimus C_{min} within the target trough range of 5-15 ng/mL. The red arrows denote the 2 exposure ranges of everolimus patients who were targeted to achieve LE, 3-7 ng/mL and HE, 9-15 ng/mL

and HE arms increased gradually until the end of the core phase due to dose titrations (Figure 1). The median C_{min} observed at the end of the core phase in patients randomized to the LE arm was 5.1 ng/mL (range = 1.4-25.3 ng/mL), and in the HE arm it was 8.3 ng/mL (range = 0.8-22.0 ng/mL). There was an overlap in C_{min} range across different arms, but notable differences in the exposures were achieved in the LE and HE arms (Figure 1A). The majority of patients had their C_{min} within the range of 5-15 ng/mL (Figure 1B). Approximately 60% of patients in the HE arm were found to be below the lower limit of the target C_{min} range (9 ng/mL) at week 18 (Figure 1B). In all age ranges, there is a trend indicating an increase in C_{min} with increasing doses (Figure 2).

3.2 | Effect of age and concomitant use of CYP3A4 inducers on everolimus C_{min}

There was a large interpatient variability in the dose-normalized C_{min} that decreased with increasing age (Figure S2). Irrespective of the assigned exposure group, median dose-normalized C_{min} was higher for the patients who were in the younger age groups, whereas the values were similar for patients who were age ≥ 12 years. Figure S2 and Table S1 show that concomitant administration of a CYP3A4/PgP inducer decreased the median dose-normalized C_{min} of everolimus in all age groups.

3.3 | C_{min}-efficacy relationship analysis

A trend indicative of better SF response and better percentage SF reduction from baseline at higher TN-C_{min} values

was evident (Figure 3A-C). The response rates were 29.9% (n = 147, 95% confidence interval [CI] = 22.7%-38.0%) in the exposure range of 3-7 ng/mL compared with 44.2% (n = 52, 95% CI = 30.5%-58.7%) and 50% (n = 30, 95% CI = 31.3%-68.7%) in the exposure ranges of >7 to <9 ng/mL and 9-15 ng/mL, respectively. The response rate in patients with TN-C_{min} < 3 ng/mL was similar to that of patients in the placebo arm (14.0% vs 15.0%, respectively). Similarly, the median percentage reduction from baseline in SF was 35.6% (n = 147, 95% CI = 24.4%-41.9%) in the exposure range of 3-7 ng/mL compared with 39.7% (n = 52, 95% CI = 28.0%-62.8%) and 47.7% (n = 30, 95% CI = 36.5%-66.3%) in the exposure ranges of >7 to <9 ng/mL and 9 to 15 ng/mL, respectively. A conditional logistic regression stratified by age subgroup showed that a twofold increase in TN-C_{min} was associated with a 2.17-fold increase (95% CI = 1.339-3.524) in the odds of a response. In addition to TN-C_{min}, baseline SF was also a significant factor (with an odds ratio of 0.978, 95% CI = 0.959-0.998), indicating that patients with higher baseline SF had more difficulty becoming a responder.

3.4 | Minimum efficacious concentration

Results of a linear regression model predicting the log of absolute SF during the maintenance period of the core phase indicated that for a twofold increase in TN-C_{min} there was a statistically significant 28% reduction (95% CI = 12%-42%) in postbaseline SF. Both baseline SF and TN-C_{min} were significant factors.

Based on this multiplicative linear regression model, it was predicted that a TN-C_{min} of 5.3 ng/mL was the lowest
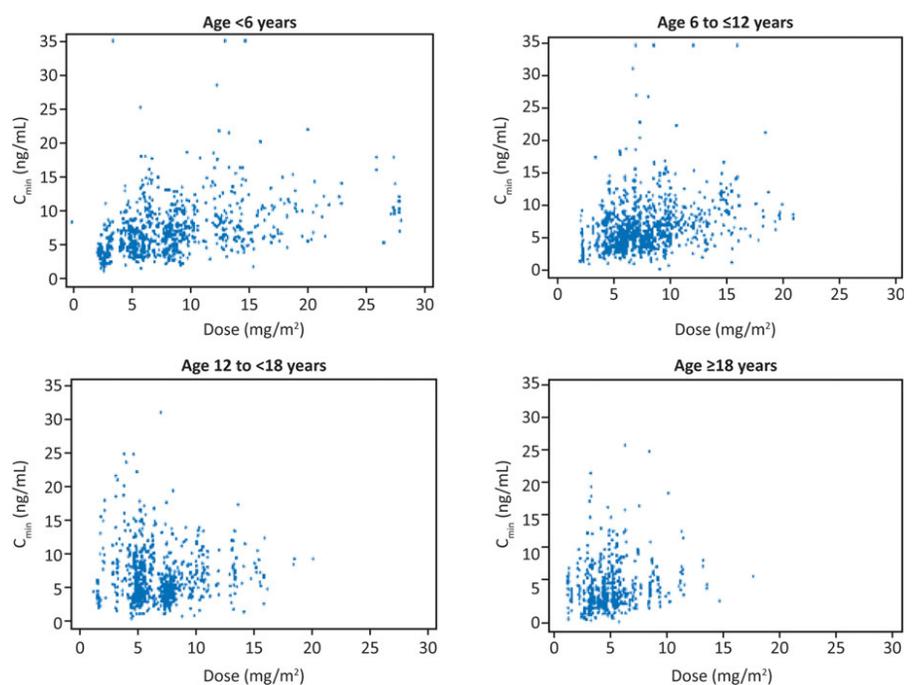

FIGURE 2 Relationship between predose everolimus concentrations (C_{min}) and dose (mg/m^2) in patients with tuberous sclerosis complex (TSC)-associated seizures in all age ranges. This figure shows a trend indicating an increase in predose everolimus C_{min} with increase in doses for patients with TSC seizures across all the age ranges
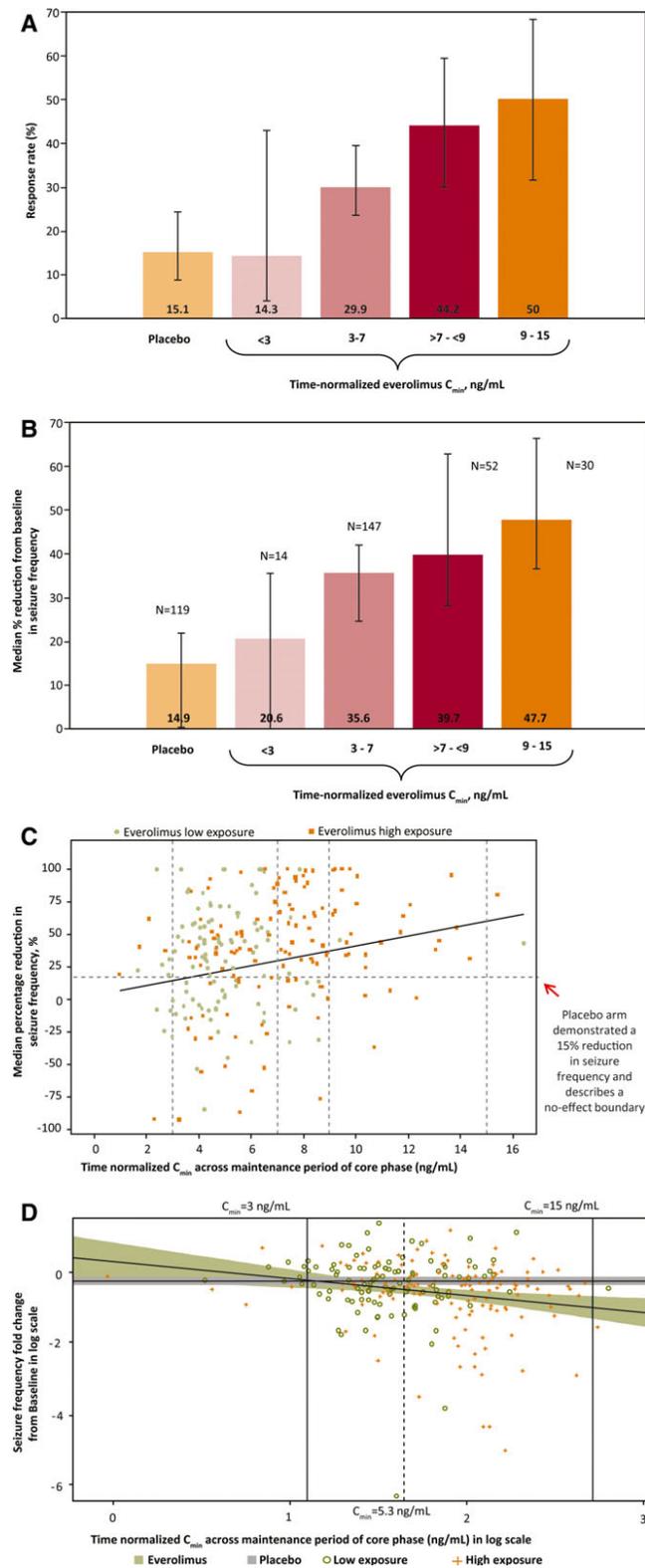
FIGURE 3 Everolimus exposure-response relationships. A, Effect of everolimus time-normalized (TN)-C_{min} on response rate. Error bars represent 95% confidence intervals of median. TN-C_{min} denotes an estimated average of C_{min} across the maintenance period of the core phase. This figure shows an improvement in seizure response rates with an increase in everolimus TN-C_{min}. Reduction in seizure frequency (SF) among patients with an average exposure of <3 ng/mL was similar to that in patients treated with placebo. B, Effect of everolimus TN-C_{min} on median percentage reduction in SF. Error bars represent 95% confidence intervals of median. This figure depicts an improvement in the median percentage reduction in SF with increase in everolimus TN-C_{min}. Reduction in SF among patients with an average exposure of <3 ng/mL was similar to that in patients treated with placebo. C, Relationship between median percentage reduction in SF and TN-C_{min}. The straight line in the figure stands for a linear regression. This figure depicts the percentage reduction in SF with increase in everolimus TN-C_{min} in both everolimus low-exposure and high-exposure arms. The modeling data confirm that a twofold increase in TN-C_{min} reduced postbaseline SF by 28%. D, Baseline-adjusted change of SF by TN-C_{min} during the maintenance period of the core phase. This figure presents a model-based approach to determine the lowest TN-C_{min} for which a response in SF (represented by fold change from baseline in SF) was statistically different between everolimus and placebo. The predicted fold change from baseline in SF for patients taking placebo was presented as a straight line at −0.25 with light gray colored 95% confidence interval (CI) representing the 15% reduction in SF demonstrated in the placebo treatment arm with zero exposure to everolimus. The predicted fold change from baseline reduction in SF for patients taking everolimus increases as TN-C_{min} increases. A TN-C_{min} of 5.3 ng/mL was considered the lowest everolimus exposure level for which 95% CI of predicted change from baseline SF (0.537-0.695) did not overlap with the 95% CI of predicted change from baseline SF of placebo (0.696-0.879), indicating this as the lower bound of the therapeutic range

did not overlap with the 95% CI of predicted change from baseline SF in patients treated with placebo (0.696-0.879; Figure 3D).

3.5 | C_{min}-safety relationship

AEs were consistent with the known safety profile of everolimus. The most frequently reported AEs of any grade in our study were stomatitis (placebo, 9%; LE, 55%; HE, 64%), diarrhea (placebo, 5%; LE, 17%; HE, 22%), and nasopharyngitis (placebo, 16%; LE, 14%; HE, 16%).[8] The nature and pattern of AE frequencies during the core phase were similar for patients with TN-C_{min} exposures in the LE and HE groups (Table S2). Stomatitis of grade 3 or 4 severity was reported in 3% of patients in the LE group and 4% of patients in the HE group. The other most frequent grade 3 or 4 AEs reported with everolimus (occurring in >2 patients) included neutropenia (LE, 2%; HE, 2%), pneumonia (LE, 1%; HE, 2%), and irregular

everolimus exposure for which the reduction from baseline in SF was higher than the expected reduction in patients taking placebo. It was with an everolimus exposure of 5.3 ng/mL that the 95% CI of predicted change from baseline SF in patients treated with everolimus (0.537-0.695)

TABLE 1 Number and percentage of patients reporting adverse events of special interest by time-normalized C_{min} range (≥5% frequency)

Adverse event, n (%)	<3 ng/mL, n = 15	3 to <5 ng/mL, n = 89	5-15 ng/mL, n = 139	>15 ng/mL, n = 2	Placebo, n = 119
Cytopenia	2 (13)	8 (9)	7 (5)	2 (100)	9 (7.6)
Dyslipidemia in pediatric population [<18 years old]	1 (7)	13 (15)	16 (12)	1 (50)	5 (5.2)[a]
Hemorrhages	0 (0)	6 (7)	16 (12)	0 (0)	4 (3.4)
Hyperglycemia/new onset of diabetes	0 (0)	15 (17)	23 (17)	1 (50)	9 (7.6)
Hypersensitivity	0 (0)	12 (14)	23 (17)	0 (0)	8 (6.7)
Hypophosphatemia	1 (7)	1 (1)	0 (0)	0 (0)	0 (0)
Female infertility [including amenorrhea]	0 (0)	4 (5)	3 (2)	1 (50)	4 (10.8)[b]
Postnatal developmental toxicity	0 (0)	1 (1)	1 (1)	1 (50)	2 (2.1)[a]
Stomatitis	7 (47)	52 (58)	84 (60)	2 (100)	11 (9.2)

[a]Percentage calculated based on the number of patients aged <18 years (n = 97 for the placebo arm).
[b]Percentage calculated based on the number of female patients aged 10-55 years (n = 37 for the placebo arm).

menstruation (HE only, 2%). Although the percentage of patients reporting AEs of special interest (AESIs) was lower at TN-C_{min} < 3 ng/mL than those reporting at higher TN-C_{min}, the percentages of patients reporting AESIs at TN-C_{min} ranges of 3 to <5 ng/mL and 5-15 ng/mL were similar (Table 1). Results of extended Cox regression analyses of the time to first event of stomatitis and infections and infestations versus TN-C_{min} indicated that TN-C_{min} was associated with an increase in the risk of either of these events during the core phase (stomatitis: hazard ratio [HR] = 1.092, 95% CI = 0.866-1.376; infections and infestations: HR = 1.060, 95% CI = 0.85-1.33). However, these effects were not statistically significant.

4 | DISCUSSION

Everolimus is eliminated in humans primarily by metabolism via CYP3A4.[13] The activity of CYP3A4 is extremely weak or absent in the fetus and begins to increase after birth to reach 30%-40% of the adult activity after 1 month and 50% of adult levels between 6 and 12 months of age.[14–19] As the CYP3A4 isozyme capacity starts maturing in newborns to full capacity during adolescence, clearance of everolimus also changes with age. Due to the different rates of increase in body size and liver enzyme capacity with age, patterns of change in everolimus clearance with age are different based on whether clearance is normalized to BSA. Because BSA increases up to the age of 18 years and thereafter remains largely constant (Figure S1), differences in the everolimus clearance across different age ranges were observed in our study. Based on dose-normalized C_{min} values in patients of different age ranges, everolimus clearance values were lower in patients of age ranges 1 to <3 years and ≥3 to <6 years, whereas everolimus clearance values normalized to BSA were lower in patients

of age ranges ≥12 to <18 years and ≥18 years. Dose-normalized C_{min} (C_{min}/dose) is inversely related to apparent clearance, and so the relationship between dose-normalized C_{min} and age is a mirror image of the relationship between clearance and age. The patterns of the change in everolimus clearance with age, using dose-normalized C_{min} as the surrogate, were similar in patients with TSC-associated SEGA[20] and patients with TSC-associated refractory seizures. In addition to the effect of age on everolimus blood concentrations, patients with TSC-associated refractory seizures receive concomitant administration of CYP3A4 enzyme-inducing AEDs (EIAEDs), which might affect the clearance of everolimus in blood. As expected, patients with concomitant administration of CYP3A4/PgP inducers had lower dose-normalized C_{min} across all age ranges. Because both age and use of CYP3A4 EIAED concomitant medication can impact everolimus clearance, TDM is recommended to maintain C_{min} within a target concentration range for patients with TSC seizures. A target concentration range of 5-15 ng/mL is recommended for the following reasons. (1) The time-normalized C_{min} of 5.3 ng/mL was the threshold concentration, above which the 95% CI of predicted change from baseline SF does not overlap with the 95% CI of predicted change from baseline seizure of placebo patients, and hence this indicates that C_{min} of 5.3 ng/mL is the lower bound of the therapeutic range. (2) In addition, the seizure response was numerically superior at the TN-C_{min} range of 5-15 ng/mL than <5 ng/mL and a higher C_{min} was associated with a better seizure response. Also, there were limited data on C_{min} values >15 ng/mL, which limited the ability to assess the safety of C_{min} exposure >15 ng/mL, and hence this indicates an upper bound of the therapeutic range, at least preliminarily until further results should become available. (3) Although the percentage of patients reporting AESI was lower at TN-C_{min} < 3 ng/mL than those reporting at higher TN-C_{min}, the

TABLE 2 Recommended starting dose for treatment of patients with tuberous sclerosis complex–associated seizures

Age range, y	Without the concomitant administration of CYP3A4/PgP inducer	With the concomitant administration of CYP3A4/PgP inducer
<6	6 mg/m^2	9 mg/m^2
≥6	5 mg/m^2	8 mg/m^2

CYP3A4, cytochrome P450 3A4; PgP, P-glycoprotein.

percentages of patients reporting AESIs at TN-C_{min} ranges of 3 to <5 ng/mL and 5-15 ng/mL were similar. No notable differences in overall safety were observable across the 3-15 ng/mL C_{min} exposure range. (4) The majority of observed C_{mins} in this study were in the range of 5-15 ng/mL, the safety and tolerability profile of everolimus observed in the study was consistent with prior experience in the TSC setting,[7,10] and the grading (severity) of most events was modest (typically grade 1 or 2).[8]

It was observed at week 1 of the core phase in the EXIST-3 study that the median C_{min} for adult patients was <5 ng/mL and was the lowest among patients of other ranges. To provide a simpler age-based starting dose scheme and to increase the C_{min} level after the starting dose for adult patients, a starting dose scheme, based on 2 categories of age rather than 3, has been proposed; a starting dose of 6 mg/m^2 is recommended for patients aged <6 years and 5 mg/m^2 for those ≥6 years of age, who are not receiving EIAEDs or other CYP3A4/PgP inducers. For those who are receiving concomitant CYP3A4/PgP inducers (carbamazepine,

oxcarbazepine, phenobarbital, phenytoin, primidone, clobazam, topiramate), a dose of 9 mg/m^2 is recommended for those aged <6 years and 8 mg/m^2 for those ≥6 years of age (Table 2). In addition, a flexible titration dose scheme of 1-4 mg is recommended, in comparison to the fixed 2-mg titration dose (or 4 mg for patients with concomitant use of a CYP3A4/PgP inducer) used in the EXIST-3 study. The fixed 2-mg titration dose could be too low for some patients (eg, patients with larger body size and/or patients with high everolimus clearance). The flexible titration dose scheme could potentially reduce the number of titration steps to attain a C_{min} within the target range. The recommended starting dose and titration dose scheme of 1-4 mg based on simple dose proportionality is supported by a simulation (Figure 4) predicting that 25-75 percentile of the predicted C_{min} is within the target 5-15 ng/mL range after 1-2 dose titrations. We illustrate the use of the 1- to 4-mg flexible titration dose with 2 examples. For a patient who receives a starting dose of 4 mg/d and achieves a steady state concentration of 4 ng/mL, to reach everolimus concentration >5 ng/mL (eg, 6 ng/mL), the new dose would be 6 mg/d (an increase by 2 mg/d). Similarly, if a patient receives a starting dose of 8 mg/d and achieves a steady state concentration of 4 ng/mL, the new dose would be 12 mg/d (an increase of 4 mg/d).

In conclusion, the present results demonstrate that targeting an everolimus C_{min} within the range of 5-7 ng/mL initially and 5-15 ng/mL in the event of an inadequate clinical response has a favorable risk-benefit profile in patients with TSC-associated refractory seizures. Starting doses to achieve such a target TDM range with flexible titration
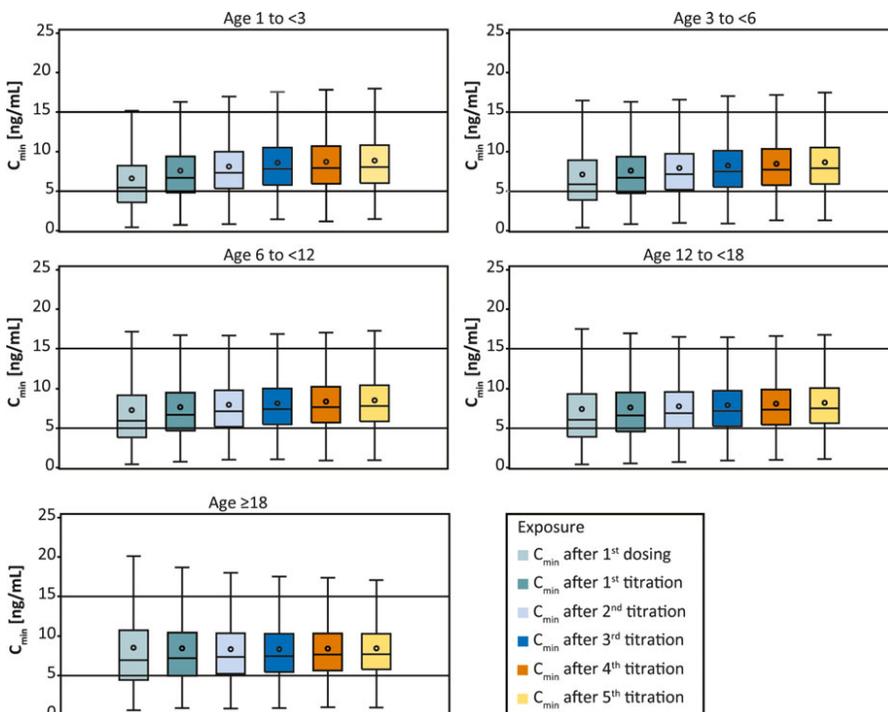

FIGURE 4 Box plots of predicted predose everolimus concentration (C_{min}) after the starting dose and over 5 dose titrations by age range based on the recommended starting dose scheme. Recommended starting dose scheme: 6 mg/m^2/d and 5 mg/m^2/d for patients aged <6 years and 5 mg/m^2/d for patients > or = 6 years ≥ 6 years, respectively. Titration dose scheme: 1-4 mg. The figure shows that 25-75 percentile of the predicted C_{min} was within the target 5-15 ng/mL range after 1-2 dose titrations

increments of 1-4 mg are recommended based on age and status of CYP3A4/PgP inducers.

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SUPPORTING INFORMATION

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