Sirolimus for epilepsy in children with tuberous sclerosis complex
A randomized controlled trial

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ABSTRACT

Objective: To investigate whether mammalian target of rapamycin complex 1 (mTORC1) inhibitors could reduce seizure frequency in children with tuberous sclerosis complex (TSC).

Methods: Due to slow inclusion rate, target inclusion of 30 children was not reached. Twenty-three children with TSC and intractable epilepsy (age 1.8–10.9 years) were randomly assigned (1:1) to open-label, add-on sirolimus treatment immediately or after 6 months. Sirolimus was titrated to trough levels of 5–10 ng/mL. Primary endpoint was seizure frequency change during the sixth month of sirolimus treatment.

Results: Intention-to-treat analysis showed sirolimus treatment resulted in 41% seizure frequency decrease (95% confidence interval [CI] −69% to +14%; $p = 0.11$) compared to the standard-care period. Per protocol analysis of 14 children who reached sirolimus target trough levels in the sixth sirolimus month showed a seizure frequency decrease of 61% (95% CI −86% to +6%; $p = 0.06$). Cognitive development did not change. All children had adverse events. Five children discontinued sirolimus prematurely.

Conclusions: We describe a randomized controlled trial for a non–antiepileptic drug that directly targets a presumed causal mechanism of epileptogenesis in a genetic disorder. Although seizure frequency decreased, especially in children reaching target trough levels, we could not show a significant benefit. Larger trials or meta-analyses are needed to investigate if patients with TSC with seizures benefit from mTORC1 inhibition. This trial was registered at trialregister.nl (NTR3178) and supported by the Dutch Epilepsy Foundation.

Classification of evidence: This study provides Class III evidence that sirolimus does not significantly reduce seizure frequency in children with TSC and intractable epilepsy. The study lacked the precision to exclude a benefit from sirolimus. *Neurology®* 2016;87:1–8

GLOSSARY

AED = antiepileptic drug; **CI** = confidence interval; **DSMB** = data safety monitoring board; **IQR** = interquartile range; **mTORC1** = mammalian target of rapamycin complex 1; **TSC** = tuberous sclerosis complex.

Tuberous sclerosis complex (TSC) causes epilepsy in 80%–90% of patients, often starting in infancy.[1] Current treatment options include antiepileptic drugs (AEDs), epilepsy surgery, ketogenic diet, and vagus nerve stimulation.[2–4] Approximately two-thirds of patients do not reach adequate seizure control.[1] Cognitive development is negatively affected by epilepsy.[5,6]

TSC is caused by mutations in *TSC1* or *TSC2*,[7,8] resulting in upregulated activity of mammalian target of rapamycin complex 1 (mTORC1).[9] This upregulation disrupts neuronal migration and differentiation, causing regions of dyslaminated cortex, called cortical tubers, and dysplastic neurons throughout the brain.[10] Although the neurologic phenotype in TSC can be partly explained by the structural brain abnormalities, animal studies show that increased mTORC1 activity in the absence of anatomical abnormalities is sufficient to induce epilepsy.[11] Treatment with mTORC1 inhibitors can fully rescue this phenotype,[12] suggesting that mTORC1 inhibitors might be useful for targeted treatment of epileptogenesis in TSC.

Clinically used mTORC1 inhibitors include sirolimus and its derivative everolimus. Everolimus decreased subependymal giant cell astrocytoma and angiomyolipoma volume in patients with TSC.[13,14] Both sirolimus and everolimus may decrease seizure frequency (table e-1 at Neurology.org). A prospective study showed clinically relevant seizure frequency reduction in 12/20 patients with TSC treated with everolimus.[15] However, because seizure frequency can fluctuate spontaneously, lack of a control group hampers interpretation of this study.[16,17]

We performed a randomized controlled crossover trial assessing the therapeutic benefit of sirolimus on seizure frequency in children with TSC and intractable epilepsy.

METHODS Participants. Children between 3 months and 12 years with definite clinical diagnosis of TSC[18] were eligible for inclusion if they had at least 1 epileptic seizure per week and were resistant to at least 2 AEDs. Children with severe renal dysfunction, infection, or surgery less than 6 weeks before randomization were excluded. All data were collected at the ENCORE-TSC Expertise Centre, Erasmus MC–Sophia Children's Hospital in Rotterdam, the Netherlands.

Standard protocol approvals, registrations, and patient consents. The national and local institutional ethics review boards approved the trial protocol (registration number MEC-2010-362). The trial was performed in agreement with the Declaration of Helsinki (2008) and Good Clinical Practice guidelines. Oral and written informed consent was obtained from parents before randomization. This trial is registered at the Dutch Trial Register, reference number NTR3178. For the study protocol see http://www.erasmusmc.nl/encore/Poliklinieken/tubereuze-sclerose-complex/wetenschondtsc/klinondtsc/Onderzoeksprotocol_RATE_studie_versie_3_20-01-2012.pdf/?view=active.

Study design and treatment allocation. Patients participated for 12 months and were randomly assigned in a 1:1 fashion to receive add-on sirolimus treatment during the first or second period of 6 months, in a crossover design. Sample size was calculated based on an estimated baseline seizure frequency of 20 seizures per month, with an SD of 22, based on historical data. A power of 90% with an α level of 0.05 could show a minimal treatment effect of 0.75 SD on the primary outcome with 26 participants. Assuming a 10% dropout rate, target inclusion number was 30.

Patients received 1 mg/mL sirolimus oral solution (Rapamune; Pfizer, New York, NY), monitored and released through the Erasmus MC pharmacy. Sirolimus was titrated to blood trough levels of 5–10 ng/mL. Starting dose was based on body weight. Target trough levels were reached as quickly as possible, by adjusting the dose based on trough levels 1 week, 2 weeks, and 1 month after starting sirolimus (e-Methods at Neurology.org).

Administration was once a day, at a set time. In case of adverse events of grade 2 or higher, sirolimus was stopped until the adverse event resolved or reached grade 1 (e-Methods). AEDs taken at baseline were continued throughout the trial. Dose adjustments were made for cotreatment with CYP3A4-inducing AEDs. Parents and the patients' treating physicians were discouraged from changing AED regimens unless this would cause significant morbidity.

Randomization and masking. A random allocation sequence, computer generated with permuted block design (block size 4) and stratified by age (3–12 months, 1–4 years, 5–11 years), was provided by the Erasmus MC Department of Biostatistics. The neuropsychologist and neurophysiologist were masked to treatment.

Study procedures and outcomes. Primary outcome was seizure frequency, assessed by a daily seizure diary filled out by the parents, starting 1 month before randomization to determine baseline seizure frequency.

Secondary outcomes for epilepsy included proportion of responders to sirolimus and seizure severity. A responder was classified as having ≥50% reduction of seizure frequency in the last month of either study period relative to baseline. Children with secondarily generalized seizures were compared to measure change in seizure severity. The number of status epilepticus episodes in either period was also compared.

Another secondary outcome included analysis of EEGs made at baseline and 6 and 12 months. Thirty-minute EEG registrations were performed on a BrainRT system (OSG bvba, Rumst, Belgium) using 19 silver-silver chloride cup electrodes placed on the scalp and referenced to Fz electrode according to the 10–20 International System and analyzed by an experienced clinical neurophysiologist. Sampling frequency was 500 Hz, bandpass filter was 0.16–70 Hz. Impedances were kept <5 kΩ. Amplitudes and frequencies of waveforms were measured manually using a longitudinal bipolar montage and by EEG spectral analysis after fast Fourier transformation. Epileptiform activity was measured by spike index, presence of electrodecrements, and percentage of generalized epileptiform abnormalities. Spike index was assessed by the average percentage of 1-second bins showing spikes in 10-second epochs. Amplitude of delta activity was measured to determine encephalopathy (amplitude ≥200 μV). Other measurements included presence and frequency of occipital rhythm and presence of hypsarrhythmia.[19] EEG data were complete for 21 participants.
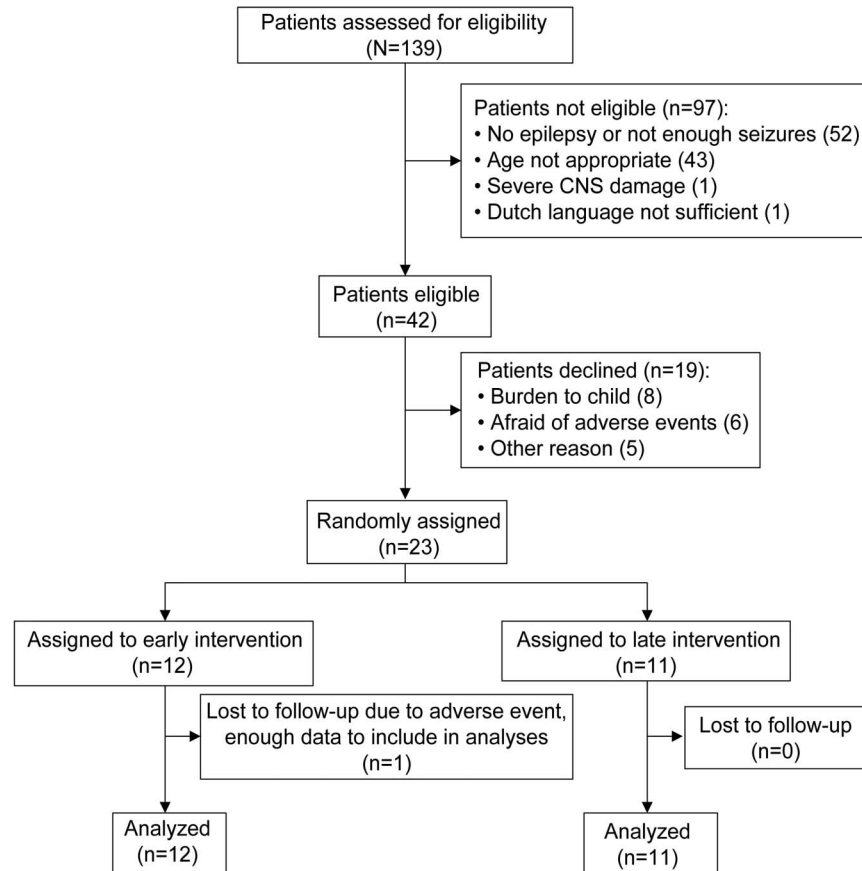
Secondary outcomes also included cognitive development and behavior. Neuropsychological assessments and questionnaires were performed at baseline and 6 and 12 months, and were selected to assess specific problematic behaviors in TSC.[20,21] Assessments included cognitive development (Bayley Scales of Infant and Toddler Development or Wechsler Preschool and Primary Scale of Intelligence), adaptive behavior (Vineland Screener, 2008), sensory processing (Short Sensory Profile-NL, 2006), autistic features (Social Responsiveness Scale, 2007), and emotional and behavioral problems (Child Behavior Checklist, 2000). All participants were assessed by the same licensed neuropsychologist.

Blood samples were taken at baseline and 6 and 12 months for all participants and every visit during sirolimus treatment. Sirolimus trough levels were measured by high-performance liquid chromatography–mass spectrometry/mass spectrometry chromatography at the Erasmus MC pharmacy. Laboratory control values were measured by the Erasmus MC Department of Clinical Chemistry, including renal function (urea and creatinine), liver enzymes (aspartate transaminase, alanine transaminase, γ-glutamyltransferase), blood cell counts, total cholesterol, and triglycerides.

All data from all study visits and assessments were checked by at least 2 investigators.

The data safety monitoring board (DSMB) consisted of a pediatrician, pediatric neurologist, and statistician. The DSMB was provided with biannual progress reports and was notified in case of a serious adverse event, and could stop or adapt the trial in case of safety concerns.

Figure 1 Flow diagram of study participants

Patients assessed for eligibility
(N=139)

Patients not eligible (n=97):
• No epilepsy or not enough seizures (52)
• Age not appropriate (43)
• Severe CNS damage (1)
• Dutch language not sufficient (1)

Patients eligible
(n=42)

Patients declined (n=19):
• Burden to child (8)
• Afraid of adverse events (6)
• Other reason (5)

Randomly assigned
(n=23)

Assigned to early intervention
(n=12)

Assigned to late intervention
(n=11)

Lost to follow-up due to adverse event,
enough data to include in analyses
(n=1)

Lost to follow-up
(n=0)

Analyzed
(n=12)

Analyzed
(n=11)

Adverse events were monitored throughout the trial, and were classified according to the WHO adverse reaction terminology and graded according to the National Cancer Institute common terminology criteria for adverse events.[22]

Classification of evidence. Our primary research question was whether sirolimus treatment could reduce seizure frequency in children with TSC and intractable epilepsy. This interventional study provides class III evidence that 6 months of sirolimus treatment does not seem to reduce seizure frequency in children with TSC and intractable epilepsy (41% decrease, $p = 0.11$). As our sample size is small, a beneficial effect is not ruled out, especially in children who reach the target trough level.

Statistical analysis. Data from all randomized participants (intention-to-treat) were used to analyze primary outcome, neuropsychological outcomes, spike index, and delta amplitude. A linear mixed-effects model was applied. For seizure frequency, data were log-transformed to obtain a normal distribution, and 0.5 was added to remove zero values. A multivariable model including the variables sirolimus treatment, month during the study (baseline, sixth month of first period, sixth month of second period), and randomization group was applied. The same model was used in the per protocol group of 14 children who reached the predefined effective trough levels in the sixth month of the sirolimus period.

A χ^2 test was used to compare number of responders in the sirolimus and standard-care periods, to determine change in seizure severity, and to analyze changes in presence of electrodecrements, generalization of epileptiform discharges, occipital rhythm, and location of spikes.

Cutoff level for significance was set at 0.05 (2-sided) for all tests. Interim analyses were not performed, and corrections for multiple testing were not made.

All data were analyzed using IBM (Armonk, NY) SPSS Statistics version 21 and the R 3.1.3 statistical package.

RESULTS **Study population.** Between September 7, 2011, and December 4, 2013, 23 patients were

Table 1 Baseline characteristics

	Early sirolimus (n = 12)	Late sirolimus (n = 11)
Age at inclusion, y	5.5 (1.8-10.9)	5.1 (2.2-10.1)
Male	8 (67)	3 (27)
Mutation TSC1/TSC2/NMI	1/10/1 (8/83/8)	3/8/0 (27/73/0)
History of infantile spasms	8 (67)	6 (55)
Age at first seizure, mo	3 (0-14)	6 (0-83)
Seizure frequency in baseline months	48 (2-402)	35 (17-85)
No. AEDs tried in total	4.5 (2-11)	5 (2-9)
No. AEDs at baseline	2 (1-4)	3 (1-4)
BSID cognitive scale at baseline	9 (3-74)	18 (0.7-76)

Abbreviations: AED = antiepileptic drug; BSID-III = Bayley Scales of Infant and Toddler Development, third edition, developmental level in months; NMI = no mutation identified. Data are median (range) or n (%).

randomly assigned to receive add-on sirolimus treatment immediately (n = 12) or after 6 months (n = 11). With consent of the local ethics committee, the DSMB, and the sponsor (Dutch Epilepsy Foundation), we decided to stop inclusion at 23 patients without an interim analysis. This yielded 80% power to show a significant effect. One patient was lost to follow-up (figure 1). Baseline demographics and disease characteristics were well balanced between the randomized groups (table 1).

Treatment. Mean daily sirolimus dose in the last month of sirolimus was 3.65 mg and ranged from 0.9 to 8.0 mg. Eighteen children had interruptions of sirolimus treatment due to adverse events (median 2 events, median duration 7 days). Sirolimus was used on 82% of all days in the sirolimus period. AED treatment was adjusted during sirolimus in 3

children and during standard care in 8 children (χ^2 2.987, p = 0.17).

Primary outcome. Median seizure frequency at baseline was 35 seizures per month (interquartile range [IQR] 20–65), 25 (IQR 7–47) after the sirolimus period, and 32 (IQR 9–62) after the control period. In the intention-to-treat analysis, we found that during sirolimus treatment, patients had 41% less seizures than during standard care (95% confidence interval [CI] −69% to +14%; p = 0.11). Seizure frequency change from baseline per patient is shown in figure 2, A and B, for sirolimus and standard care, respectively. Per protocol analysis, including the 14 patients who reached the target trough level of ≥5 ng/mL during the last month of the sirolimus period, showed a mean seizure frequency reduction of 61% (95% CI −86% to +6%; p = 0.06). Inspection of individual seizure frequency curves did not reveal evidence for a carryover effect.

Secondary outcomes. Nine children responded during the sirolimus period (≥50% seizure frequency reduction), of whom 3 became seizure-free, while 6 children responded during the standard care period, of whom 1 became seizure-free (NS). Secondarily generalized seizures were present in 6 patients (26%), and their frequency was not affected by sirolimus treatment. No status epilepticus was recorded during the trial.

EEG analysis showed a median spike index of 50% at baseline, 40% after sirolimus treatment, and 40% after standard care (p = 0.86). No change was found between sirolimus and standard care in presence of hypsarrhythmia or encephalopathy, occurrence of multifocal spikes, electrodecrements, generalization of epileptiform abnormalities, or the occurrence of an occipital rhythm.

No significant differences in cognitive or motor development, behavioral problems, adaptive behavior, or sensory processing were identified between sirolimus and standard care (table 2). Data from the social responsiveness scale could not be analyzed, as many participants were too severely intellectually disabled.

Adverse events. Adverse events were consistent with the safety profile of sirolimus (table 3). All patients reported at least one adverse event, most commonly upper respiratory tract infections, gastrointestinal problems, and acne-like skin lesions. Aphthous ulcers were observed only during the sirolimus period. Serious adverse events occurred in 5 patients. During sirolimus treatment, 3 individuals required hospitalization due to pneumonia, 1 following otitis media. Two patients were hospitalized during the standard care period, 1 for a tonsillectomy and 1 for refusing food intake.

Sirolimus trough levels in the last month of the sirolimus period ranged from 2.3 to 14.2 ng/mL. Reduction of sirolimus dose due to adverse events

Figure 2   Seizure frequency change from baseline
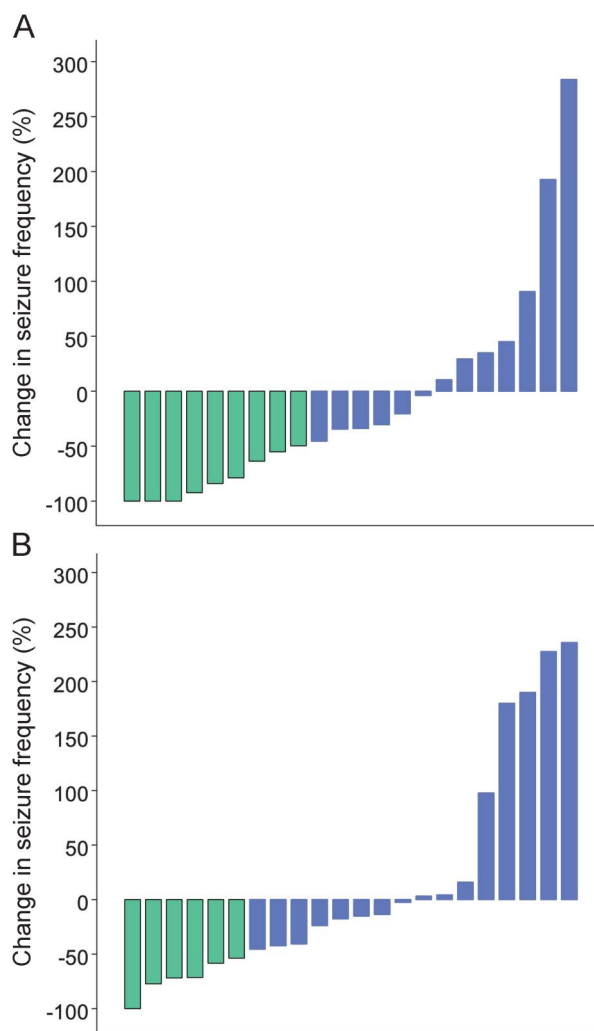
Decrease in seizure frequency is depicted by negative change, increase in seizure frequency is depicted by positive change. Every bar is 1 child. Green bars represent children with a decrease of ≥50%. (A) Seizure frequency in the last month of the sirolimus period relative to baseline seizure frequency. (B) Seizure frequency in the last month of the standard care period relative to baseline seizure frequency.

Table 2   Effect of sirolimus on secondary outcomes

	Treatment effect (95% confidence interval)	p Value
Cognitive development (BSID-III, n = 21; WPPSI-III full-scale IQ, n = 2)	1.46 (−0.49 to 3.40)[a]	0.15
Fine motor development (BSID-III, n = 21)	1.18 (−0.52 to 2.88)[a]	0.18
Gross motor development (BSID-III, n = 21)	−0.42 (−1.73 to 0.90)[a]	0.54
Adaptive behavior (Vineland, n = 22)	0.44 (−1.21 to 2.09)[a]	0.60
Sensory processing (SP-NL, n = 21)	1.91 (−3.91 to 7.73)[a]	0.53
Total problem score (CBCL, n = 22)	−2.29 (−9.18 to 4.60)[b]	0.52
Internalizing problem score (CBCL, n = 22)	−0.77 (−3.58 to 2.05)[b]	0.60
Externalizing problem score (CBCL, n = 22)	−0.50 (−3.29 to 2.30)[b]	0.73

Abbreviations: BSID-III = Bayley Scales of Infant Development; CBCL = Child Behavior Checklist; SSP = Short Sensory Profile; WPPSI-III-NL = Wechsler Preschool and Primary Scale of Intelligence Dutch version.
BSID-III and Vineland depict developmental months; SP-NL and CBCL depict raw scores.
Data are missing for BSID-III fine and gross motor scale because the developmental level of 2 children was tested using WPPSI-III-NL. Data are missing for other questionnaires due to incomplete answers to essential items on the checklist.
[a] Higher is better.
[b] Lower is better.

was required in 12 children. Five children discontinued sirolimus due to adverse events. These included aphthous ulcers in 2 children, pneumonia requiring hospitalization, upper respiratory tract infection, and increased seizure frequency. Excluding the increased seizure frequency, all adverse events subsided after sirolimus was discontinued.

Clinically relevant laboratory results requiring follow-up occurred in 5 children (table 3). Three children had elevated cholesterol levels within the first month of starting sirolimus that normalized after dietary advice. None of the laboratory results led to discontinuation of sirolimus treatment.

DISCUSSION We report a randomized controlled trial of mTORC1 inhibitor sirolimus for treatment of intractable epilepsy in 23 children with TSC. We did not observe a significant therapeutic benefit of sirolimus on seizure frequency in the intention-to-treat analysis (41% decrease in seizures due to sirolimus; 95% CI −69% to +14%; p = 0.11). All children reported adverse events, for which sirolimus treatment was discontinued in 5. Due to these adverse events, not all children reached the predefined target trough level. Per protocol analysis of children who did reach the target trough level showed a seizure frequency decrease of 61% (95% CI −86% to +6%; p = 0.06).

The rationale of our study is based on the knowledge that mTORC1 inhibition directly targets the molecular mechanism underlying the pathophysiology in TSC-related epilepsy.[12] This would make mTORC1 inhibitors fundamentally different from current insufficient treatment with traditional AEDs

aimed at seizure suppression. Mouse models have convincingly shown that mTORC1 inhibition can prevent and reverse epileptogenesis in TSC and epilepsies.[11,12,23,24] Several case series and an uncontrolled study have suggested a clinically relevant benefit in groups of patients with TSC treated with sirolimus or everolimus. These are summarized in table e-1. Notably, when we specifically look at effects obtained during the treatment period, these published findings are very similar to our own findings, both with respect to seizure reduction as well as the number of responders. However, this effect is not statistically significant compared to a control period. Three children in our study became seizure-free on sirolimus treatment, which might indicate that sirolimus could be beneficial for some children. We did not find a different response rate when comparing children with a *TSC1* or *TSC2* mutation, children with or without infantile spasms, or a correlation with the number of months the child had seizures before trial start.

The decrease in seizures during standard care may reflect spontaneous fluctuations of seizure frequency, and the tendency of individuals to participate in a trial when seizure frequency is high and regression to the mean is likely. Uncontrolled studies may overestimate the treatment effect, leading to an underestimation of the number of participants needed in a trial to achieve sufficient power.

Moreover, despite our efforts to keep patients on the same AED regimen during the entire study, several changes to AEDs were necessary, particularly during the 6-month standard care period. This may have further contributed to the observed decrease in seizure frequency in the standard care period, possibly resulting in underestimation of the effect of sirolimus.

We did not observe a beneficial effect of sirolimus treatment on cognition and behavior. Most children in our study were severely intellectually disabled, which may complicate detection of an effect of sirolimus on cognitive and motor development. Improved seizure control is likely to be beneficial for cognition and behavior, but preclinical studies have also shown a therapeutic benefit of mTORC1 inhibitors on neuronal plasticity and cognitive and behavioral outcomes in the absence of seizures.[5,25] Future trials could address the value of mTORC1 inhibitors in treating TSC-associated cognitive and behavioral problems.

We were able to include 23 of the intended target of 30 participants, mainly because parents were reluctant to give their child an experimental drug and to minimize changes in treatment during the standard care period. The decision to stop inclusion at 23 participants was made after consulting with the DSMB. We considered extending the study

Table 3	All adverse events during the sirolimus and standard care period				
		Sirolimus period		Standard care period	
		All grades	Grade 3	All grades	Grade 3
Upper respiratory tract infection		20 (87)	0	19 (83)	1 (4)
Gastrointestinal		19 (83)	0	13 (57)	0
Acne-like skin lesions		17 (74)	0	8 (35)	0
Other infection		12 (52)	0	7 (30)	0
Aphthous ulcers		7 (30)	0	0	0
Fever		6 (26)	0	0	0
Injury due to accident		4 (17)	0	3 (13)	0
Fatigue		3 (13)	0	4 (17)	0
Behavioral change		3 (13)	0	0	0
Eczema		3 (13)	0	1 (4)	0
Pneumonia		3 (13)	3 (13)	0	0
Otitis media		2 (9)	1 (4)	2 (9)	0
Hemorrhagic disorders		2 (9)	0	2 (9)	0
Edema		2 (9)	0	0	0
Anorexia		1 (4)	0	1 (4)	1 (4)
Hair loss		1 (4)	0	0	0
Headache		1 (4)	0	0	0
Muscle pain		1 (4)	0	0	0
Polyuria		1 (4)	0	0	0
Red eye		1 (4)	0	0	0
Muscle weakness		0	0	1 (4)	0
Laboratory					
Cholesterol >6.5 mmol/L		3 (13)	0	0	0
Triglycerides >3.0 mmol/L		1 (4)	0	0	0
Alanine transaminase >100 units/L		2 (9)	0	0	0
Urea >8.0 mmol/L		0	0	1 (4)	0

Data are n (%) of children.

period further; however, the prospect of recruiting another 7 children within a reasonable time window was unrealistic. Although a larger study could have statistical power to show a significant effect, these results give an indication of the potential effect size and may help physicians in guiding parents and patients. Combined with other and future studies, possibly in a meta-analysis, our data could help position the role of mTORC1 inhibition in TSC-related epilepsy.

The choice of a crossover design was based on its large power to show an effect in a relatively small number of patients with a rare disease, as all participants function as their own control. Our trial did not include placebo treatment, and was not masked. We chose this trial design, together with the TSC parents association and parents of young children with TSC-related epilepsy, as having the least burden.

The sirolimus treatment period was 6 months, which is longer than most clinical trials for AEDs in intractable epilepsy.[26] A treatment period of 6 months is sufficient to investigate a clinically relevant effect of sirolimus on seizure frequency, especially in patients with frequent seizures. Continuing a therapy aimed at seizure reduction for more than 6 months without evidence of efficacy does not seem advisable. A longer treatment period would also necessitate an undesirably long control period.

We only selected patients with intractable epilepsy and high seizure frequency, which may limit the applicability of our results to the general TSC population. We aimed to keep children on blood trough levels of 5–10 ng/mL. Due to adverse events, only 14 children reached this target trough level in the last month of sirolimus treatment. A possible benefit of sirolimus might be present in children who are kept

on the target trough level of sirolimus or even higher levels, as the per protocol analysis of this group showed a larger decrease in seizure frequency. However, all children in our study had adverse events, for which 5 children discontinued sirolimus treatment. These adverse events may limit clinical use of sirolimus. Our study is unsuitable for detecting rare adverse events, although the adverse events profile of sirolimus is well-known from other indications.

We were unable to show a significant effect of sirolimus on seizure reduction in children with TSC and intractable epilepsy. A beneficial effect is not ruled out, however, and further studies are needed to assess the value of mTORC1 inhibitors in the treatment of TSC-related epilepsy.

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