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FULL-LENGTH ORIGINAL RESEARCH

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Stereotactic Laser Ablation for Mesial Temporal Lobe Epilepsy: A prospective, multicenter, single-arm study

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Abstract

Objective: To describe the development of the Stereotactic Laser Ablation for Temporal Lobe Epilepsy study protocol in the context of current practice. An ideal treatment for drug-resistant epilepsy remains an ongoing area of research. Although there are several options available, each has challenges that not only make deciding on the appropriate treatment not clear-cut but also create difficulties in designing clinical studies to provide evidence in support of the treatment.

Methods: A prospective, single-arm, multicenter study designed to evaluate safety and efficacy of the Visualase™ MRI-Guided Laser Ablation System for the treatment of temporal lobe epilepsy will include up to 150 patients with a primary efficacy endpoint of seizure freedom (defined as Engel Class I) for the first 12 months following the procedure and a primary safety endpoint of incidence of qualifying device-, procedure-, or anesthesia-related adverse events through 12 months following the procedure.

Results: Primary endpoints will be assessed against historical values of safety and efficacy of anterior temporal lobectomy.

Significance: The scientific and payor communities typically demand randomized controlled trials (RCTs) as definitive evidence for safety and efficacy claims. However, in circumstances where the medical device has already been cleared by regulatory authorities and is readily available in the market, an RCT may not be feasible to execute. It is therefore crucial to gain acceptance by both the scientific community and regulators to design a study that will satisfy all concerned.

KEYWORDS

epilepsy, laser ablation, prospective, protocol

1 | INTRODUCTION

Mesial temporal sclerosis (MTS) is a common cause of drug-resistant epilepsy.[1] Anterior temporal lobectomy (ATL) and selective amygdalohippocampectomy have been the most commonly performed operations, but these procedures require a craniotomy and resection or transection of a significant portion of the anterior

temporal lobe.[2] As the pathological substrate mainly resides in mesial temporal limbic structures, particularly the hippocampus, there is increasing interest in more targeted and less invasive methods of surgical treatment. These have the potential for reduced pain and less medical and neurological morbidity because of the lack of a craniotomy, the sparing of anterior temporal neocortex, and the minimized white matter damage. Although radiofrequency ablation and gamma knife radiosurgery have been used as substitutes for ATL, the former has limited effectiveness[3] or involves equipment that is not widely available,[4] and the latter does not appear to reduce morbidity.[3]

In the past few years, stereotactic laser ablation (SLA; also known as laser interstitial thermal therapy) has been employed to treat MTS in place of open procedures, and the initial experience of several groups suggests that this technique is safe and effective[5–9] However, most published reports have been retrospective and lack a standardized approach to patient selection, surgical method, and outcome assessment. Both efficacy and adverse effects require better definition. The medical community and regulatory authorities have expressed a desire for high-level clinical evidence to demonstrate the safety and performance of SLA in treating MTS. Consequently, the Stereotactic Laser Ablation for Temporal Lobe Epilepsy (SLATE) study, a prospective, single-arm, observational, multicenter study, has been designed to provide high-level evidence regarding the safety and efficacy of the Visualase™ System in subjects with mesial temporal lobe epilepsy (MTLE) due to MTS. The study is designed as a prospective observational study with outcomes measured against known effects of ATL.

Much consideration went into the choice of an appropriate and feasible trial design for SLATE, including selection of a control group for a randomized controlled trial (RCT) to control for selection, evaluator-related, and/or patient-related bias. However, expert consultation suggested that there are several challenges to successfully performing an RCT design of SLA hippocampectomy (SLAH) for MTS that would likely be insurmountable: clinical equipoise, enrollment difficulties, and available treatment centers.

Consideration was first given to a continued medical treatment control group. However, in patients with drug-resistant MTLE, surgery has already been shown to be superior to continued medical treatment.[10,11] Therefore, a medically treated control group cannot be used, and surgery must be offered. Next, an open resection control arm was considered. ATL is considered the gold standard for surgically treating MTLE, with seizure-free rates of 59%-73% in controlled trials.[10,11] However, use of this (or any) control arm requires clinical equipoise, by both treating clinicians and patients. Absence of equipoise could limit the number of centers enrolling patients and the number of patients each center can enroll, providing a significant barrier to conducting a suitably powered trial.

Key Points

- Prospective studies on SLA are in high demand
- RCTs are not always a feasible study design when commercially available devices are under investigation
- An appropriately designed single-arm study compared to historical values may provide valuable data for those interested in SLA

Attempts at conducting RCTs in the epilepsy surgery realm have suffered from poor recruitment and early termination. The Early Randomized Surgical Epilepsy Trial (ERSET), funded by the National Institutes of Health (NIH), intended to randomize 200 pharmacoresistant MTLE patients to ATL or continued pharmacotherapy.[12] The study was terminated early, after only 38 patients were enrolled over 2 years despite the participation of 16 centers. Speculation as to why patients did not want to participate in this study centered around either patient reluctance to undergo surgery due to surgical risk and cognitive deficit,[10,13] or unwillingness to continue pharmacotherapy when drugs appeared to be ineffective. Similarly, the Radiosurgery vs Open Surgery for Mesial Temporal Lobe Epilepsy (ROSE) trial, also funded by the NIH, randomized drug-resistant patients to either stereotactic radiosurgery or ATL.[3] The study was planned to have sufficient subjects to achieve >85% power to test the noninferiority hypothesis; however, recruitment was eventually stopped due to slow enrollment and achieved only 41% power for the primary hypothesis. Of those subjects who passed initial screening and were offered participation, 39% did not want to be randomized and declined. The authors of that study speculated that, among other reasons, recruitment lagged due to the perception of lack of clinical equipoise from referring physicians or from the patients themselves.[3] In addition, both therapy arms were available outside of a clinical trial in the ERSET and ROSE trials, so patients could opt for one of the treatments without participating in a study.

The identical situation exists for the SLATE trial in that ATL and SLAH are available without joining a trial. Therefore, patients who might otherwise be interested in enrolling in a study due to the potential merits of SLAH (eg, less invasive, less discomfort) would be less likely to enroll in the study and risk assignment to the control ATL cohort. Other patients who are more interested in a "tried and true" established procedure would be less likely to agree to randomization to the SLAH cohort. Another challenge to an RCT design is the availability

TABLE 1 Key SLATE study inclusion and exclusion criteria for study participation

Inclusion criteria	Exclusion criteria
1. Adult subjects ≥18 y of age and ≤70 y of age at the time of enrollment	1. Subject is currently implanted with a device contraindicating MRI, including deep brain stimulation or responsive neurostimulator
2. History of medically refractory (or intractable) MTLE, defined per the ILAE[1] as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom, as determined by the investigator	2. Subject has progressive brain lesions and/or tumors not associated with epileptic disease state
3. If the subject has a VNS, the subject must have failed to achieve sustained seizure freedom with the VNS implanted for at least 6 mo prior to enrollment	3. Subject has a history of previous intracranial surgery for treatment of epileptic seizures, including intracranial resections, stereotactic radiosurgery, or deep brain stimulation
4. On stable AEDs (and/or stable VNS setting, if applicable) for 30 d prior to the procedure and compliant with medication use, as reported by the subject	4. Subject has persistent (based on medical judgment) extratemporal or predominant contralateral focal interictal spikes or slowing, or generalized interictal spikes on EEG
5. An average of at least 1 complex partial or secondarily generalized seizure compatible with MTLE per month, for a minimum of the last 12 mo prior to enrollment (ie, at least 12 qualifying seizures in the 12 mo prior to enrollment)	5. Subject has seizures with contralateral or extratemporal ictal onset on EEG
6. Subject's seizure symptoms and/or auras are compatible with MTLE	6. Subject's aura and/or ictal behavior suggest an extratemporal focus
7. Based on video-EEG obtained within 24 mo of enrollment, evidence of seizures from one temporal lobe consistent with MTLE; if the video-EEG was obtained >12 mo prior to enrollment, an interictal EEG done within 12 mo of enrollment must show interictal spikes in the same distribution as seen in the previous video-EEG monitoring	7. Subject has evidence on MRI of epileptogenic extratemporal lesions, dual pathology within the temporal lobe, or contralateral hippocampal increased T2 signal changes and/or loss of internal architecture
8. Based on MRI obtained within 24 mo prior to enrollment, evidence consistent with mesial temporal lobe sclerosis (defined as mesial temporal atrophy accompanied either by increased signal on T2-weighted image, indicative of gliosis, or accompanied by loss of internal architecture in the hippocampus); if there is evidence of a change in clinical seizure symptoms/severity or of a brain injury since the MRI, a repeat MRI must be obtained to confirm eligibility	8. If additional testing (eg, PET, SPECT, invasive EEG, or MEG) has been performed, results are discordant with the seizure focus scheduled for ablation
9. Subject is willing and able to remain on stable AEDs (and stable VNS setting, if applicable), as directed by their treating physician, for 12 mo following the procedure	9. As reported by the subject or in the opinion of the investigator, the subject is not compliant with AED medication requirements
10. Subject is able to complete study assessments in English or Spanish language	10. Subject has an IQ < 70, based on the WASI, WASI-II, WAIS-III or WAIS-IV FSIQ, or GAI) performed within 12 mo prior to enrollment, or after enrollment but prior to the procedure
	11. Subject has been diagnosed with dementia or other progressive neurological disease
	12. Subject has an unstable major psychiatric illness, psychogenic nonepileptic seizures, or medical illness that would contraindicate the procedure or affect the neuropsychological assessments
	13. Subject is allergic to gadolinium

Abbreviations: AED, antiepileptic drug; EEG, electroencephalogram; FSIQ, full-scale IQ; GAI, General Ability Index; ILAE, International League Against Epilepsy; IQ, intelligence quotient; MEG, magnetoencephalography; MRI, magnetic resonance imaging; MTLE, mesial temporal lobe epilepsy; PET, positron emission tomography; SLATE, Stereotactic Laser Ablation for Temporal Lobe Epilepsy; SPECT, single photon emission computed tomography; VNS, vagus nerve stimulator; WAIS, Wechsler Adult Intelligence Scale; WASI, Wechsler Abbreviated Scale of Intelligence.

of eligible treatment centers. Relatively few epilepsy centers had significant experience with the Visualase™ system. A randomized design dictates that a study investigator would need to be expert in both the SLA system and the control treatment, limiting the number of sites that could participate. This same limitation of eligible centers was cited as a factor in the ROSE trial enrollment woes.[3] A nonrandomized approach might also be considered if patients were thought to be good candidates for either procedure, comparing outcomes after ATL and SLAH; however, such a nonrandomized approach, with potential for

inherent biases, could not be considered valid for comparing the two procedures. In addition, it is possible that an attempt at a nonrandomized comparison would lack sufficient statistical power.

Therefore, an alternative design to an RCT was considered necessary to generate high-level clinical evidence. Comparing outcomes to established literature was deemed the best feasible option. Attiah et al published a decision analysis to calculate the seizure freedom rate and late mortality/morbidity rate that SLAH would need to achieve to provide quality of life improvements equivalent to ATL.[14] The meta-analysis included records of >25 000 cases of ATL and the available dataset for laser ablation from a recent retrospective multicenter study. The results of the analysis revealed that equivalence would be demonstrated if SLAH achieved 43% Engel Class I outcomes and no more than 40% late morbidity/mortality. These figures allow for the confidence intervals (CIs) that surround reported outcomes after ATL. Therefore, the SLATE study compares safety and efficacy outcomes of SLAH to the threshold determined by Attiah et al.[14] Discussion with key opinion leaders in neurology and neurosurgery with major input from two authors of this paper (M.R.S., R.E.G.) resulted in the final SLATE design, detailed below.

2 | MATERIALS AND METHODS

2.1 | Study population

Key inclusion and exclusion criteria for participation are provided in Table 1. Criteria were designed to enroll adult patients with medically intractable MTLE (per the International League Against Epilepsy definition[15]: failure of two tolerated and appropriately chosen antiepilepsy drug schedules) with confirmed radiological evidence of MTS (without other lesions) and electrophysiological evidence consistent with unilateral MTLE. Patients whose clinical history, examination, or laboratory investigations suggested nonmesial temporal lobe onset (eg, nonhippocampal lesion in the imaging, symptoms referable to a nonmesial temporal source such as a visual aura, or extratemporal or posterior temporal interictal spikes or seizures) were excluded.

Surgical decisions were made by a local multidisciplinary team, and all were approved by central reviewers. Patients were offered either SLA or ATL and made the final decision.

2.2 | Study objectives and design

The SLATE study (NCT02844465) is a prospective, single-arm, multicenter Investigational Device Exemption (IDE) study to evaluate the safety and efficacy of the Visualase™ system for necrotization or coagulation of epileptogenic foci in patients with intractable MTLE.

The procedure has been described in detail elsewhere.[7,16] Briefly, the subject is prepared for intraoperative navigation. At the surgeon's discretion, general anesthesia may be induced. Navigation planning is performed to identify the precise entry point on the skull as well as to define the target and safest trajectory through the brain. A minimally invasive twist drill craniotomy is made, and the dura is opened. The laser anchor bolt is secured into the skull at the correct trajectory. The laser applicator probe is advanced to target mesial temporal lobe structures (chiefly hippocampus and amygdala). The subject is transferred to the magnetic resonance imaging (MRI) suite, where an MRI scan is performed to confirm correct laser probe positioning. Alternatively, the entire procedure may be performed in the MRI suite using an MRI-compatible platform. Selected MRI images are transferred to the workstation, and safety set points are identified on the images to prevent overheating of adjacent tissues. The ablation parameters (power and duration) are determined by the surgeon. After a test laser ablation is successfully completed, the MRI-guided laser ablation is performed at a wattage to achieve cell death, while the surgeon monitors the real-time thermal maps with MRI. The laser application probe may need to be repositioned several times and the laser ablation repeated. A final MRI is acquired to confirm the ablation zone. Follow-up visits are scheduled for 14 days and 3, 6, and 12 months after the procedure, where clinical, laboratory, neuro-ophthalmological, neuropsychological, and radiological assessments are performed (Table 2). Subjects who fail to achieve Engel Class I seizure freedom or whose procedure could not be completed as intended prior to discharge are eligible to undergo retreatment.

2.3 | Study endpoints

The primary efficacy endpoint is seizure freedom with or without auras (defined as Engel Class I) for the first 12 months following the procedure. The primary safety endpoint is the incidence of qualifying device-, procedure-, or anesthesia-related adverse events (AEs) through 12 months following the procedure. The relevant AEs were those proposed by Attiah et al[14] and included death, heminopsia, quadrantanopsia, infection, stroke/hemiparesis, aphasia, intracranial hemorrhage, diplopia, memory impairment, and cerebrospinal fluid leak. AEs were assessed and registered by the treating physicians, independent of the sponsor. Multiple secondary endpoints are also being assessed, including, but not limited to, seizure freedom for subjects re-treated with SLA and cognitive and quality of life outcomes.

TABLE 2 Schedule of key assessments

Assessment	14 d	3 mo	6 mo	12 mo
Primary—seizure assessment	X	X	X	X
Primary—AEs	X	X	X	X
Health care services utilization	X	X	X	X
Cognitive/ neuropsychological			X	X
Boston Naming Test				
Rey AVL, COWA				
WAIS, WASI, WMS-IV				
Emory Semantic Fluency Tasks				
Emory Famous Faces				
Naming/Recognition				
QOL			X	X
QOLIE-31				
SF-36				
Beck Depression/Anxiety				
Driving/employment/ school status				
Neuro-ophthalmological		X[a]	X[a]	X[a]
Acuity				
Fields and extraocular movement				
MRI			X	

Abbreviations: AE, adverse event; AVL, Auditory Verbal Learning Test; COWA, Controlled Oral Word Association Test; MRI, magnetic resonance imaging; QOL, quality of life; QOLIE-31, Quality of Life in Epilepsy Inventory-31; SF-36, 36-item Short-Form Health Survey; WAIS, Wechsler Adult Intelligence Scale; WASI, Wechsler Abbreviated Scale of Intelligence; WMS, Wechsler Memory Scale.

[a]Any subject who has an abnormal neuro-ophthalmologic finding at any follow-up visit is required to have neuro-ophthalmologic examinations at subsequent study follow-up visits.

2.4 | Sample size

Up to 25 sites located within the USA are participating. Sites are accredited Level 4 National Association of Epilepsy Centers and had previously obtained the SLA systems through commercial processes. The first patient was enrolled and underwent the procedure in December 2016. The study is projected to enroll up to 215 subjects to achieve a minimum of 150 subjects undergoing SLA.

2.5 | Data analysis

The analysis of the primary efficacy endpoint of the 12-month seizure-free rate will include a point estimate and exact 95% CI of the rate to determine whether the lower bound of the CI for seizure freedom at 12 months following the procedure (πV) will be >43%.[14,17] For the primary safety endpoint, an exact 95% CI will be calculated to determine whether the upper bound of the CI for qualified AEs is <40%.[14] Although constrained by certain analytic factors and limited to the available data for laser ablation, this analysis provides the best current estimate for a success or performance threshold of laser ablation to match the well-documented long-term effectiveness of ATL.

Several secondary neuropsychological and life quality endpoints will also be evaluated. Included among the tested secondary analyses are the within-subject change prior to and 12 months following the procedure on the Boston Naming Test, Rey Auditory Verbal Learning Test 5-Trial, Quality of Life in Epilepsy-31, and 36-item Short-Form Health Survey (mental and physical components). In addition, a number of non–hypothesis-driven ancillary data analyses will be performed, including, but not limited to, the relationship of cognitive and mood assessment relative to language dominance and association of ablated tissue volume and outcomes. Neuro-ophthalmological assessments will be conducted assessing visual fields, optical coherence tomography, and eye movement.

2.6 | Study organization

The study is sponsored by Medtronic Navigation, Inc and is conducted in accordance with all laws and regulations governing medical research. All subjects provide informed consent and have their qualification for the procedure confirmed by a central review committee. The central committee reviews patient histories, MRI images, electroencephalographic recordings, and additional testing (if performed), and members are compensated for their time. All patient AEs will be prospectively captured during the course of the study. A data safety monitoring committee, consisting of external reviewers otherwise not involved with the study at centers not participating in the study and independent of the sponsor, is responsible for the review and monitoring of study safety data at regular intervals. Clinical investigators are qualified practitioners and experienced in the diagnosis and treatment of epilepsy.

3 | DISCUSSION

Per Walicke et al,[18] certain characteristics of RCTs should be replicated in observational studies to achieve reliable results. These include:

- Prospective specification of outcomes and analytic methods without resort to the actual outcome data, even if they are already available
- Prospective estimation of sample size

- Outcome measures that are clearly defined and captured in the study data
- The ability to measure and record all of the important covariates that influence treatment assignment
- Completeness of the dataset for outcomes, that is, limiting missing data

The SLATE study design addresses four of the five characteristics; the fifth, completeness of the dataset, will not be known until the study concludes, and efforts are being made during the trial to obtain all required data. It is anticipated that the SLATE study should provide the high-level evidence required to comprehensively assess efficacy and adverse effects of SLA for MTLE. Furthermore, because of the specific neurocognitive and visual acuity assessments, the SLATE study may provide critical information on secondary outcomes that is not yet fully elucidated with other treatment options.

Too often, surgical procedures are introduced without a truly comprehensive, unbiased assessment of their effects. In contrast, this study will provide valid data that can be used to guide clinical decisions. The trial also employs a standard approach to treatment and assessment, and it is hoped that these will be broadly applied if the procedure achieves widespread use. In planning and conducting the study, neurosurgeons have had multiple opportunities to meet and share information regarding surgical technique, and this is likely to be disseminated and lead to improved clinical practice. This study design may also be used in the future to assess other treatments, both medical and surgical, for a variety of conditions.

The outcome of the SLATE trial is expected to impact clinical care in several ways. First, it is an IDE trial under a premarket application. If both the primary efficacy endpoint, indicating noninferiority of SLAH compared to ATL, and primary safety endpoints are met, it is expected that US Food and Drug Administration (FDA) approval of the use of SLA for MTLE with MTS as an indication will be achieved, which we hope will increase accessibility to this procedure. This may also impact clinical care; given noninferiority, that is, similarity to ATL, patients and physicians may opt for either treatment, and the reduced perioperative discomfort and minimal period of disability after SLAH may lead to patient preference for that procedure.

The impact on clinical care may be less predictable if the primary efficacy and/or safety endpoints are not both achieved. First, failure to obtain FDA approval for the specific epilepsy indication will not mean that SLA cannot be used for MTLE/MTS (and other) indications, because its use is and will remain covered by the present 510k clearances. However, clinical judgment may be called upon to interpret the findings to determine best clinical care for patients. If the lower bound of the seizure-free efficacy CI does not exceed 43% (ie, not achieving the primary efficacy endpoint), this would indicate no difference of SLAH compared to ATL. Even in the setting of late morbidity/mortality not exceeding 40% (ie, achieving the primary safety endpoint), the results of Attiah et al would suggest that patients would not readily adopt the procedure. However, additional ablation or an ATL can be performed after SLAH failure.[5,19–21] The efficacy of repeat ablation will be assessed as a secondary endpoint and achieving this endpoint even in the setting of failure to achieve the primary efficacy endpoint may influence patient and clinician decision-making. If neither the primary efficacy nor secondary (repeat ablation) efficacy endpoints are achieved, assuming safety is <40%, patients may still be inclined to opt for the less invasive procedure. However, persistence of uncontrolled seizures is associated with continued excess in morbidity and mortality after surgery in contrast to the seizure-free state,[22] so preference for a less effective, although less painful procedure may lead to worse outcomes. Physicians will need to discuss these considerations with patients so that the most appropriate choice is made. Finally, failure to achieve the primary safety endpoint (ie, <40% late morbidity/mortality) suggests that patients will be less inclined to select SLAH over ATL, especially if the primary and secondary efficacy endpoints are not attained. Clinical judgement in discussing options with patients will need to be exercised in weighing the pros and cons of SLAH versus ATL in individual cases.

The study has a number of limitations. First, the efficacy and AEs in treating MTLE are determined by the surgical approach chosen by the investigators. Extensive investigator workshops to discuss different strategies to ablate the mesial temporal structures have and will continue to be part of the SLATE trial. Nevertheless, surgical variability might yield different results across patients, surgeons, and centers. Retrospective analyses relating outcome to ablation size and location[16,23,24] will continue to guide how surgical targeting evolves, and the analysis of the ablation/outcome relationship will be a critical part of the SLATE trial as well. Second, the conclusions from this trial will pertain solely to the treatment of MTLE with MTS by SLA. The efficacy and AEs of SLA when treating other causes of MTLE (eg, lesional, such as epileptogenic tumors, or nonlesional MRI cases), or other causes of epilepsy in other locations, including hypothalamic hamartomas, cavernous hemangioma, cortical dysplasias, periventricular nodular heterotopias, and other small lesions, will require further study.

In conclusion, it is hoped that the SLATE trial will provide sufficient information to better inform physicians and patients about treatment options for MTLE with MTS. The present gap in knowledge should be closed, and we anticipate that improved medical knowledge will lead to better medical care.

CONFLICT OF INTEREST

M.R.S. has received research support from Medtronic, SK Life Science, Cavion, Xenon, Takeda, Eisai, Neurelis, Engage Therapeutics, and UCB Pharma; has consulted for Medtronic

and NeurologyLive; and has been a speaker for Eisai. R.E.G. serves as a consultant to Medtronic and receives compensation for these services. Medtronic develops products related to the research described in this paper. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict of interest policies. R.E.G. also has received research support from Medtronic, Neuropace, Boston Scientific, and MRI Interventions, and has served as a consultant for Neuropace, Boston Scientific, Abbott, Zimmer Biomet, Monteris, Voyager Therapeutics, SanBio, and Neuralstem. G.E.A. is an employee of Medtronic, sponsor of the SLATE study. G.M.M. has served as a paid consultant for Koh Young. V.S. has received research support from Medtronic and Neuropace. V.S. was the Indiana University site principal investigator (PI) for the NIH ERSET trial, NIH ROSE trial, responsive neurostimulation (RNS, Neuro-Pace trial) pivotal trial and RNS long-term follow-up, and the SANTE trial, and is the Indiana University site PI for the Medtronic SLATE trial. I have no conflicts of interests. J.G. is an employee of Medtronic, Sponsor of the SLATE study. 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.

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