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STUDY PROTOCOL

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# Study protocol of short versus long-term levetiracetam in brain tumors (LIBRA): a phase 3 randomized controlled trial

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## Abstract

**Background** Seizures are common in patients with brain tumors, impacting daily life and healthcare burden. In contemporary neuro-oncology practice, levetiracetam is the most commonly prescribed anti-seizure medication (ASM). Although the practice is widely variable, levetiracetam is usually used for 2–3 years following surgery to prevent further seizures. However, the incidence of seizures post antitumoral treatment is relatively low, and the duration of use is not well defined. To address this knowledge gap, the current randomized controlled non-inferiority trial will be conducted comparing a shorter regimen of levetiracetam with the standard long-term schedule.

**Methods and analysis** Patients with newly diagnosed primary brain tumors (brain metastasis excluded) in the supratentorial compartment with a prior history of seizure will be eligible for the study. Adults (> 18 years), within 1 year from surgery, and controlled on levetiracetam monotherapy for 6 months will be randomized in a 1:1 ratio to either standard arm (long course: additional 2 years levetiracetam) or experimental arm (short course: tapered of levetiracetam and stopped). Stratification factors include tumor location, seizure type, histology, grade, and adjuvant therapy. The primary endpoint is 2-year seizure-free survival (SFS); secondary endpoints include seizure impact, quality of life, progression-free survival (PFS), and overall survival (OS). Assuming a 2-year SFS rate of 80%, a total of 431 patients (167 events) will be needed to prove the non-inferiority of the experimental arm (non-inferiority margin of 8%, $\alpha = 0.05$, power = 80%). Considering an attrition rate of 40% (25% accounting for death and 15% lost to follow-up), the final sample size is 604.

**Discussion** The trial will provide level 1 evidence on the optimal duration of ASM use in primary brain tumors with a history of seizures. If short-term ASM use is non-inferior, it will reduce drug utilization, lower neurotoxicity, improve quality of life, and optimize resource usage.

**Ethics and dissemination** The trial has been approved by the Institutional Ethics Committee of Tata Memorial Centre, Mumbai.

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**Registration** Registered with CTRI/2024/06/069498, Clinicaltrials.gov: NCT06442748.
**Keywords** Seizures, Levetiracetam, Brain tumor, Antiepileptics, Glioma

## Introduction

Seizures are frequently observed in the clinical course of patients with brain tumors, including the presenting complaint in 15–30% of patients [1–3]. Seizures may develop during treatment (including the immediate postoperative period) and follow-up [4, 5]. The International League Against Epilepsy (ILAE) clinically defines an epileptic seizure as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain [6]. The ILAE recognizes tumor-related epilepsies (TRE) as a specific category [7], which include focal awareness seizures (simple partial seizure), focal impaired awareness seizures (complex partial seizures), focal to bilateral tonic-clonic seizures (Secondary Generalized Tonic-Clonic Seizures GTCS), and GTCS [4]. The incidence of seizures in brain tumors varies based on the type of tumor, ranging around 85% in low-grade glioma, 69% in anaplastic glioma, 49% in glioblastoma, and more than >80% in glioneural tumors [8, 9]. Seizures can occur due to several factors, such as tumor location, tumor burden, the growth rate of the tumor, and altered internal milieu in the peritumoral environment [8]. Tumors located in the frontal lobe, temporal lobe, and eloquent areas of the brain are more frequently linked with seizures [10]. Lower-grade tumors are more likely to have seizure incidence as compared to high-grade tumors, which are rapidly growing tumors [11]. Alteration in the neurotransmitter homeostasis, such as the increased release of glutamate from glioma cells, contributes to the glutamatergic cellular pathway, resulting in increased excitability at the synaptic region in the glioma microenvironment [12, 13]. This is commonly observed in Isocitrate dehydrogenase (IDH) mutant tumors, which have increased production of D-2-Hydroxyglutarate, a glutamate receptor agonist, either as a direct effect [14–16],, or by activation of altered pathways and metabolites [17, 18]. In non-glial tumors, information on the mechanism of epileptogenesis is limited; the association of peritumoral edema is commonly related to the incidence of preoperative seizures, specifically in meningiomas [19].

The use of anti-seizure medication (ASM) is a common practice in patients with brain tumors and is commonly used as a primary or secondary prophylaxis. The choice of antiseizure medications has changed over the years. Previous generation antiseizure medications such as carbamazepine, phenytoin, and valproic acid are commonly avoided in the first-line setting due to their significant drug interactions and unfavorable toxicity profile [20]. Second-generation antiseizure medication such as levetiracetam is usually preferred in brain tumor-related epilepsy. In a recent European Association of Neuro-Oncology (EANO) survey, levetiracetam was the preferred ASM in 90% of the respondents [21]. The drug is usually well tolerated, has no known drug interactions, and has a favorable toxicity profile [22]. Levetiracetam binds to synaptic vesicle glycoprotein SV2A, which interferes with the release of neurotransmitters from the synaptic vesicle. The drug has shown seizure control rates of over 40–96% in brain tumor patients depending upon factors like tumor histology, location, etc [23, 24]. The drug is considered safe and efficacious while switching over from phenytoin [25], not contraindicated in liver impairment, and is relatively safe in pregnancy [23, 26, 27]. Notably, it is hypothesized that levetiracetam may also contribute to antineoplastic roles by inhibiting epileptogenesis and increasing the activity of chemotherapeutic agents in brain tumors [28]. However, a pooled analysis of four randomized clinical trials analyzing 1869 patients demonstrated no survival benefit with the use of ASMs (valproic acid or levetiracetam), which provides strong evidence to discard the survival benefit with these medications [29].

In patients who have undergone antitumoral treatment, the incidence of seizures is relatively low (15–20%), with an uncertain benefit for ASMS in reducing the incidence of new seizures [8, 30]. In congruence with the majority of contemporary neuro-oncology practice, levetiracetam is prescribed in our canter for a duration of 2–3 years following surgery (or at least 2 years from the last seizure episode). The duration of ASMs in preventing seizures is not clearly defined and is routinely extrapolated from non-oncological causes of epilepsy. To address this knowledge gap, we propose a randomized controlled non-inferiority trial comparing a shorter regimen of levetiracetam with the standard long-term schedule.

## Study methodology

### Study design/ population

This is an open-label, prospective, non-inferiority, interventional, phase 3 randomized controlled trial. Patients will be screened from the neuro-oncology clinic at Tata Memorial Centre, Mumbai. Patients with a prior history of seizures with a diagnosis of histologically proven supratentorial brain tumor and no history of seizures on levetiracetam monotherapy for at least six months will be considered eligible for the study. Patients with extracranial malignancies with brain metastasis will be excluded. Patients will be assessed for the eligibility criteria below before inclusion in the study. Informed consent will be

obtained before study inclusion. Patients will be randomized in one of the two arms (standard arm or experimental arm) in a 1:1 ratio. Randomization will be done via computerized software using a permuted block design. The trial has been approved by the Institutional Ethics Committee of Tata Memorial Centre, Mumbai. The trial has been registered with the Clinical Trial Registry of India (CTRI/2024/06/069498) and Clinicaltrials.gov (study identifier NCT06442748). The trial will be periodically monitored as per the guidelines by the Tata Memorial Centre Data Monitoring Committee.

#### *Inclusion criteria*

1. Age ≥ 18years.
2. History of seizure.
3. Histological diagnosis of primary brain tumor.
4. Supratentorial location of the primary tumor.
5. Controlled on levetiracetam monotherapy (no seizure relapse) for 6 months.
6. Index surgery (first surgery) within 1 year.
7. Karnofsky Performance Scale (KPS) ≥ 50.

#### *Exclusion criteria*

1. Karnofsky Performance Score (KPS) < 50.
2. No history of seizure.
3. Unclear history of seizure episodes in the past.
4. Use of antiepileptics other than levetiracetam in the previous 6 months.
5. No histological diagnosis.
6. Progressive disease.
7. Brain metastasis.
8. Altered mental status with deficits in understanding or inability to consent to the study.

### Study intervention

After meeting study eligibility, written consent forms will be obtained from all the patients. Patients will be randomized in a 1:1 ratio accounting for the following stratification factors. The following stratification factors will be considered.

1. Seizure type: Focal seizure versus Generalized Tonic-Clonic Seizure versus both.
2. Location: Involvement of temporal lobe by tumor or edema (yes versus no).
3. Histology: Diffuse glioma versus meningioma versus others.
4. Tumor grade: Grade 4 versus others.
5. Adjuvant therapy (radiation/ chemotherapy): yes versus no.

In the standard arm, patients will continue the same dose and schedule of levetiracetam (typically prescribed in the range of 1000–3000 mg/ day in 2–3 divided doses) for a duration of 2 years. In the experimental arm, levetiracetam will be tapered by 250–500 mg weekly. No additional follow-ups will be required for study purposes, and follow-ups will be done every 3–6 months as per standard practice for the tumor histology. Neuroimaging will be done 6–12 monthly as per routine clinical practice. A drug diary and seizure diary will be maintained in both arms. The quality-of-life assessment will be done every six months. Study investigators will review the drug and seizure diary during each follow-up visit. The tentative workflow of the study methodology is illustrated in Fig. 1. Patients will continue to receive standard treatment, including adjuvant therapy as standard practice.

The study endpoints have been summarized in Table 1. The date of seizure after study accrual will be considered an event for the primary endpoint, with the date of randomization considered the baseline. Radiological evidence of disease progression will be regarded as an event for progression-free survival, and the date of death from any cause will be considered an event for overall survival. In case in either arm, the patient develops a seizure episode after stopping levetiracetam will be restarted on levetiracetam monotherapy. If a patient develops a seizure episode while on levetiracetam monotherapy, further add-on ASM will be considered as per standard practice by the responsible physician. Any indeterminate events that raise suspicion for seizures will be reviewed independently by at least two study investigators, and if there is a concern, they will be labeled as an event with the purpose of not underestimating the relapse of seizures. Any complications arising from previous treatments (e.g., radionecrosis) or recurrent disease during the study period will be managed according to standard institutional practice without any influence of the study. Patients with seizure relapse in patients in the experimental arm requiring additional expenses for medical management will be compensated. The data related to the study will be collected and stored in secured places with the principal investigator.

### Sample size calculation

Assuming a 2-year seizure-free survival rate of 80% in the standard arm, the sample size was estimated using a non-inferiority log-rank test. A total of 431 patients (total of 167 events) will be needed to prove the non-inferiority of the experimental arm (non-inferiority margin of 8%, $\alpha = 0.05$, power = 80%; HR:1.47). Considering an attrition rate of 40%, with 25% to account for death and 15% lost to follow-up, the final sample size will be 604. We anticipate 150–200 patients to be accrued annually, and with a

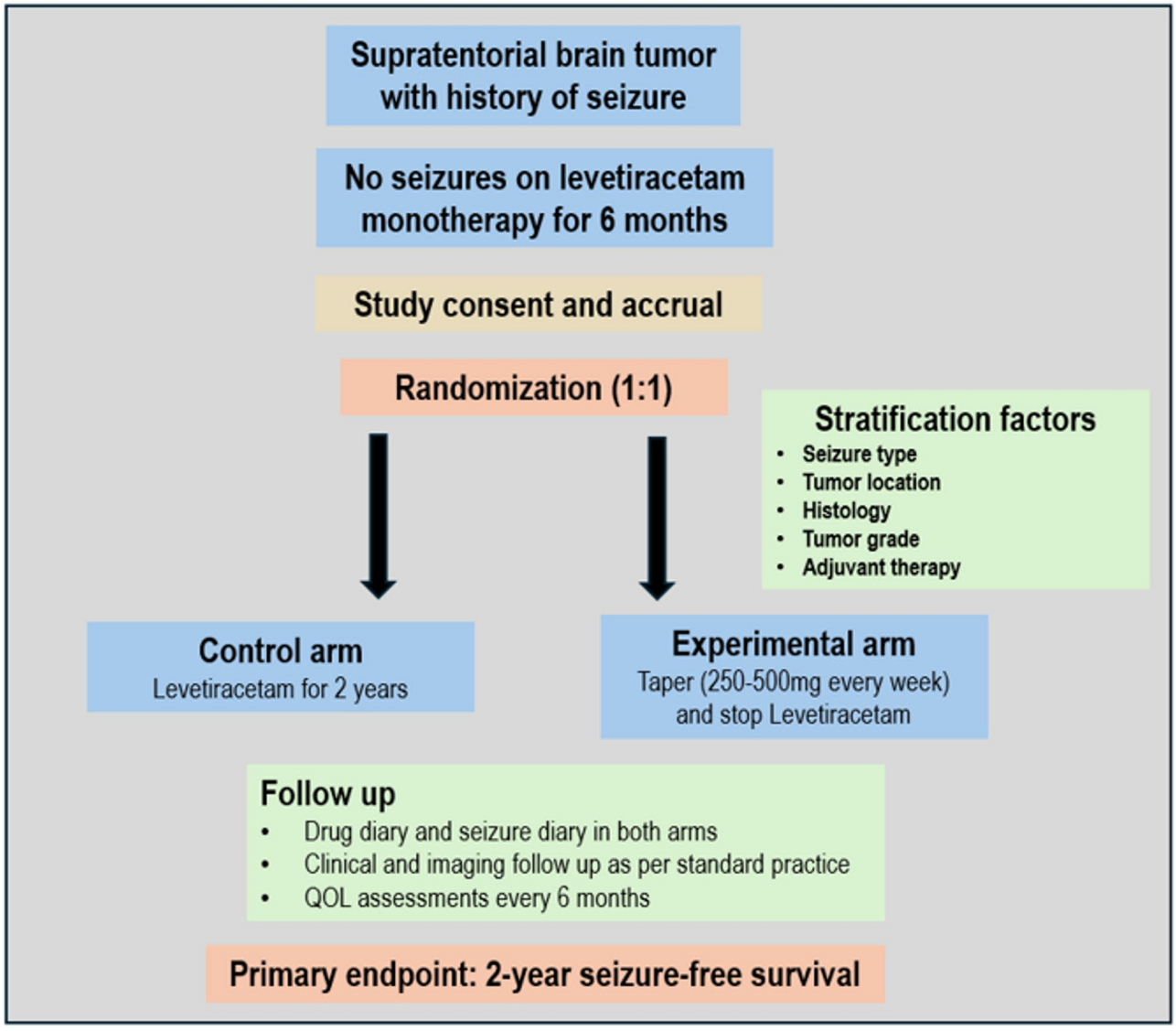


**Fig. 1** Workflow of the study

**Table 1** Objectives and endpoints of the study

| **Study Objective** | **To assess seizure-free survival in patients with brain tumors with a history of seizures** |
|---|---|
| **Study Endpoints** | |
| **Primary Endpoint** | 2-year seizure-free survival calculated from the time of randomization. |
| **Secondary Endpoint** | 1. Cumulative incidence of seizures impacting awareness in both study arms<br>2. Two-year seizure-free survival in each stratum.<br>3.Quality of life assessment<br>4.Cost-benefit analysis<br>5.Progression-free survival<br>6.Overall survival<br>7.Post hoc analysis per histological category for seizure control |

follow-up of 2 years after the accrual of the last patient, the total study duration is expected to be seven years.

#### Interim analysis

An interim analysis will be done for safety after 25% events ($n = 42$) with stopping the trial if there is a higher incidence of seizures in the experimental arm with a $p$-value of $< 0.01$.

#### Statistical analysis

Seizure-free survival will be calculated using the Kaplan-Meier method, and differences between the two study arms will be compared using the log-rank test. The date of randomization will be considered as the baseline for survival analysis, the date of seizure will be considered as the event, and a $p$-value of 0.05 (one-sided) will be

considered for statistical analysis. Patients lost to follow-up or dead (in either arm) will be censored for the assessment of seizure-free survival. To conclude non-inferiority, the upper bound of the 90% CI of the hazard ratio resulting from the comparison between the two arms should be less than this prespecified margin of 1.47. All time-to-event outcomes will be calculated using the Kaplan-Meier product-limit method. Secondary analysis will be done for the seizure-free survival, accounting for death as a competing risk. Separate analysis will be performed to compare the seizure incidence for patients with or without gross total excision across the two arms. End-of-life seizures will be analyzed as a separate exploratory endpoint. Univariate and multivariate analyses will be done using the log-rank test and Cox regression, respectively. Toxicity will be documented using Common Toxicity Criteria for Adverse Events (CTCAE) v 5.0 and compared between the groups using the Chi-square test or Fischer exact test as appropriate. Quality of life will be documented using the European Organization for Research and Treatment of Cancer (EORTC) C30 and BN 20 questionnaires. QOL outcomes will be analyzed using longitudinal, repeated measure analyses with mixed effects models with time and treatment interaction, unstructured covariance, and patient-level random effects. The results arising from the study will be disseminated in scientific conferences and publications.

## Discussion

Seizure events can have debilitating effects on individuals. It can impair daily activities, including quality of life, increase the need for healthcare visits, and is associated with neurological morbidity. The chances of seizures recurring after antitumoral treatment are relatively low and will depend on factors such as the extent of resection, tumor location, histological features, and tumor regrowth. Antiepileptics are routinely prescribed in standard neuro-oncology practice for 2–3 years to prevent further seizure episodes. Levetiracetam is the commonly preferred ASM among neuro-oncologists, with 90% of respondents reporting its use as the first choice in a survey conducted by EANO [21]. In our center, levetiracetam is the preferred monotherapy for management and antiseizure prophylaxis. The efficacy of levetiracetam in reducing seizures is demonstrated at doses of 1000 mg, 2000 mg, or 3000 mg/day in two to three divided doses [31]. Levetiracetam has reliable safety but is associated with its own set of toxicity profiles [31]. Generalized fatigue and irritability are commonly seen in patients using levetiracetam. Rare side effects include mood disturbances and suicidal tendencies. The current study will randomize patients based on the eligibility criteria into two arms. In the experimental arm, levetiracetam will be tapered by 250-500 mg every week and then stopped. In the standard arm, patients would be continued on levetiracetam for another 2 years.

The practice regarding the use of ASMs in patients with brain tumors is variable, particularly concerning the duration of use of ASMs. In patients without a history of seizures, the use of ASM as prophylaxis is less commonly practiced, with 29% of respondents in the EANO survey reporting the use of ASM in seizure-naïve patients [21]. The Society for Neuro-Oncology (SNO) and EANO recommended against the use of ASMs in patients without a prior history of seizures (level A evidence) [32]. There is a concern about an increased risk of seizures in the postoperative period. The question was addressed by a randomized controlled trial that included 81 patients, and patients without seizure history and undergoing surgery were randomized to 1 week or 6 weeks of levetiracetam prophylaxis [33]. The rates of seizure development were low in both arms (1 in each arm), demonstrating the lack of role of ASM prophylaxis in the postoperative period. The SPRING trial, a phase 3 randomized controlled trial, studied the role of using levetiracetam prophylaxis for 1 year in patients with glioma undergoing surgery and seizure-naïve was closed prematurely due to poor accrual [34]. Though underpowered, the study reported similar seizure-free survival rates in the observation and the prophylaxis group. Another randomized multicentre RCT (STOP 'EM) is evaluating the role of 2 weeks of levetiracetam prophylaxis in patients with meningioma undergoing surgery without a history of seizures [35].

In patients with a history of seizures, ASM use is considered an essential part of integral management along with appropriate antitumoral therapy, including surgery, radiotherapy, and systemic therapy. With the start of tumor-directed treatment, the chance of seizure relapse is considered to be low, with tumoral activity considered to play a significant role in epileptogenesis [2]. According to the EANO survey, 93% of the respondents considered reducing the number of ASMs or reducing the ASM dose. While around 79% routinely considered a complete withdrawal of ASM after completion of antitumor treatment [21]. The EANO survey was primarily focused on the prescription preferences of antiepileptic drugs; the duration of ASM use was not investigated. It is important to note the duration of antitumor treatment may be highly variable according to the histology or tumor grade. In our study, we have accounted for the variation by incorporating stratification factors such as tumor grade, histology, and use of adjuvant therapy after surgery, which is believed to have significant effects on the subsequent risk of seizure relapse. Another critical determinant of seizure control is the involvement of temporal lobe, which is associated with relatively poor seizure control, which is another stratification factor in this study. As mentioned earlier, there is no clear consensus regarding the

optimal duration of ASM use after the last seizure episode. In general, many clinicians extrapolate the practice of ASM use from non-oncological conditions of seizure. In a retrospective study of 109 patients with glioma, the risk of seizure recurrence post antitumor treatment was reported in 47%, 31%, and 44% in the short-term (≥ 3–12 months), medium term (12–24 months) and long term (≥ 24 months) respectively [36]. A prospective study had undertaken a shared decision-making process regarding the withdrawal of ASM in patients with low-grade and anaplastic gliomas after being seizure-free for 2 years [37]. After ASM withdrawal, 26% of patients had relapses of seizure during follow-up, of which 58% of patients had progressive disease. Therefore, recurrence of disease can lead to seizure relapses, which will be clinically relevant in patients with aggressive histology like glioblastoma. After the study is completed, we will perform a secondary analysis to analyze the relationship between seizure relapses and disease recurrence, which will also provide further insights into whether ASM needs to be continued in any selected group of patients.

To the best of our knowledge, the LIBRA study is the only phase 3 randomized controlled trial investigating the optimal duration of ASM usage. This will generate level 1 evidence guiding contemporary neuro-oncology practice. Also, secondary endpoints of the study will answer critical clinical questions, including cost-benefit analysis and the impact of long-term use of levetiracetam on quality of life. Interestingly, some interest is laid in the antitumor activity of ASMs, with conflicting results from different studies [32]. With a large number of patients to be accrued in the current study (604), we expect to get some insights regarding the effect of levetiracetam on disease control.

## Conclusion

The LIBRA study is a phase 3 randomized controlled trial investigating the role of optimal duration of ASM use in patients with supratentorial brain tumors with a history of seizures. Patients controlled on levetiracetam monotherapy for 6 months will be randomized to either the standard arm (another 2 years of levetiracetam) or the experimental arm (tapered and stopped). The primary endpoint of the study is 2-year seizure-free survival. The study through secondary endpoints would also provide information regarding the impact of ASMs on quality of life and survival outcomes.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14305-7.

Supplementary Material 1

Supplementary Material 2

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**Author contributions**
A.D and T.G devleoped the study concept and design. Statistical analysis done by S.K, A.D and T.G. Study conduct and data collection by all authors. The manuscript was written by A.D and S.M and reviewed and edited by all authors. Funding acquisition and project administration by A.D.

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**Data availability**
No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
The study is being conducted in accordance with ICMR (2017) "National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines, Good Clinical Practice and the principles of the Declaration of Helsinki. The study, including all the study-related documents, has obtained approval from the Ethics Committee prior to the enrolment of participants. The trial has been registered with Clinical Trial Registry of India (CTRI/2024/06/069498) and Clinicaltrials.gov (study identifier NCT06442748).

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

**Conflict of interest**
All the study investigators declare no conflict of interest in the conduct or outcome of the study.

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