A review of the efficacy and safety of eslicarbazepine acetate in the management of partial-onset seizures

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Abstract: Eslicarbazepine acetate is a once-daily antiepileptic drug (AED) that was approved in 2009 by the European Medicines Agency (EMA) (Zebinix™), and in 2013 by the US Food and Drug Administration (FDA) (Aptiom™) as adjunctive therapy in adults with refractory partial-onset seizures, with or without secondary generalization. It is a third-generation member of the dibenzazepine family of AEDs with distinctive mechanism of action, posology and tolerability profile. The eslicarbazepine acetate development program included an initial phase II study (study BIA 2-093) and three subsequent phase III, multicentre, randomized, double-blinded and placebo-controlled clinical trials (studies BIA-2093-301, BIA-2093-302 and BIA-2093-303). A fourth phase III placebo-controlled trial (study BIA-2093-304) was designed in order to meet specific requirements of the FDA. All performed studies have consistently shown that eslicarbazepine acetate (800 to 1200 mg/day) is effective and well tolerated as adjunctive therapy for adults with partial-onset seizures.

Keywords: antiepileptic drugs, Aptiom™, epilepsy, eslicarbazepine acetate, partial seizures, Zebinix™

Introduction

Despite the large number of antiepileptic drugs (AEDs) available for the treatment of epilepsy, nearly 30% of patients have inadequate seizure control [Kwan and Brodie, 2000]. This justifies the necessity of development of novel antiepileptic treatments, which are both effective and well tolerated as the adverse effects of AEDs have a significant negative effect on the quality of life of patients and may reduce treatment adherence and long-term retention rates [Beghi *et al.* 2012]. The availability of new AEDs with favourable adverse effect profiles and simplification of drug regimens with once-daily therapies could be relevant in increasing adherence, which may improve patient outcomes [Faught, 2012].

Eslicarbazepine acetate (ESL) is a once-daily AED that was approved in 2009 by the European Medicines Agency (EMA) (Zebinix™), and in 2013 by the US Food and Drug Administration (FDA) (Aptiom™) as adjunctive therapy in adults with refractory partial-onset seizures, with or

without secondary generalization. ESL is a third-generation member of the dibenzazepine family of AEDs, a family that also includes carbamazepine (CBZ) and oxcarbazepine (OXC) [Benes *et al.* 1999].

Pharmacology

Like carbamazepine and oxcarbazepine, ESL has the basic chemical structure of a dibenzazepine nucleus with the 5-carboxamide substituent, but is structurally different at the 10,11-position [Benes *et al.* 1999]. This molecular variation results in a different stereoselective metabolism: (1) ESL is not metabolized to carbamazepine-10,11-epoxide (the active metabolite mainly responsible for the adverse effects) nor is it susceptible to the enzyme induction or autoinduction seen with carbamazepine [Hainzl *et al.* 2001]; (2) oxcarbazepine is a prodrug to both enantiomers of the oxcarbazepine monohydroxy derivative, R-licarbazepine and S-licarbazepine (ratio 1:4) whereas ESL is a prodrug of the active compound

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Figure 1. Main metabolic pathway of carbamazepine, oxcarbazepine and eslicarbazepine acetate [Hainzl *et al.* 2001].

S-licarbazepine (ratio 1:20) (Figure 1) [Hainzl *et al.* 2001; Nunes *et al.* 2013]. Although the R-enantiomer of ESL also possesses an anticonvulsant effect, it is to a lesser extent because it undergoes rapid inactivation to the *trans*-diol metabolite [Hainzl *et al.* 2001].

The recommended starting dose of ESL is 400 mg once daily, which should be increased to 800 mg once daily after 1 or 2 weeks. Based on individual response, the dose (as add-on therapy) may be increased to 1200 mg once daily. After oral intake, ESL is extensively metabolised by first-pass hydrolysis to its major active metabolite eslicarbazepine (S-licarbazepine); this hydrolysis accounts for around 95% of the circulating active metabolites [Ben-Menachem *et al.* 2010]. The half-life of ESL is 13–20 hours in epileptic adults. Peak plasma concentrations ($C_{\max}$) are reached at 2–3 hours post-dose, and steady state of plasma concentrations is reached after 4–5 days of once-daily dosing, consistent with a half-life of 20–24 hours [Almeida *et al.* 2004]. Plasma levels of ESL usually remain below the limit of quantification (50 ng/ml) and more than 90% of an oral ESL dose is recovered in urine as eslicarbazepine metabolites [Almeida *et al.* 2008].

ESL is a potent competitive blocker of voltage-gated sodium channels (VGSC), interacting with site 2 of the inactivated state of the channel [Benes *et al.* 1999]. The affinity of ESL for the resting state of the VGSC channel is about 5- to 15-fold lower than that of carbamazepine and oxcarbazepine, leading to an enhanced inhibitory selectivity for neurons that are rapidly firing (typically seen

in epilepsy) over neurons displaying normal activity [Bonifácio *et al.* 2001]. Although the clinical relevance has not yet been demonstrated, current research in animal models suggests a possible protective effect in the pilocarpine mouse model of chronic epilepsy [Pires *et al.* 2014]. When compared with carbamazepine, oxcarbazepine and lacosamide, ESL did not share with carbamazepine and oxcarbazepine the ability to alter fast inactivation of VGSC. Both ESL and lacosamide reduce VGSC availability through enhancement of slow inactivation, although lacosamide demonstrated higher interaction with VGSC in the resting state and with fast inactivation gating [Hebeisen *et al.* 2015]. Furthermore, unlike carbamazepine, oxcarbazepine and R-licarbazepine, S-licarbazepine effectively inhibits high and low affinity $CA_v3.2$ inward currents, which may imply an increased potential protective effect [Brady *et al.* 2011]. In contrast to carbamazepine, S-licarbazepine and R-licarbazepine are lacking the enhancement effects upon sub-maximal gamma-aminobutyric acid (GABA) currents that involves a reduced potential to aggravate absence seizures [Bonifácio *et al.* 2011]. Finally, S-licarbazepine differs from carbamazepine and R-licarbazepine by the lack of inhibitory effects upon KV7.2 outward currents that could entail a reduced capacity of eslicarbazepine to facilitate repetitive firing [Soares-Da-Silva *et al.* 2011]. Recently, Doeser and colleagues reported two relevant findings with ESL. First, using patch-clamp recordings in hippocampal slices from patients with mesial temporal lobe epilepsy who underwent epilepsy surgery and from a rat model of mesial temporal lobe epilepsy, they showed a

Figure 2. Proportion of responders ($\geq 50\%$ reduction in seizure) with eslicarbazepine acetate (ESL) 400, 800 and 1200 mg in the three pivotal phase III studies [Elger *et al.* 2009; Gil-Nagel *et al.* 2009; Ben-Menachem *et al.* 2010]. * $p < 0.05$ versus placebo; ** $p < 0.01$ versus placebo; *** $p < 0.001$ versus placebo.

maintained activity (over carbamazepine) in chronically epileptic tissue. Second, a disease-modifying effect of ESL when the drug was administered early in the course of the epileptogenic process in a mouse model was described. The authors demonstrate that ESL also inhibits Cav3.2 t-type Ca^{2+} channels, which play a central role in the development of epileptogenesis [Doeser *et al.* 2015].

A randomized study in healthy volunteers was performed to evaluate the pharmacokinetics and tolerability of once-daily ESL. Volunteers received either ESL (600 mg on days 1–3 and 1200 mg on days 4–9, once daily) or oxcarbazepine (300 mg on days 1–3 and 600 mg on days 4–9, twice daily). Plasma and cerebrospinal fluid (CSF) sampling was performed following the last dose. Compared with oxcarbazepine, administration of ESL resulted in more S-licarbazepine, less R-licarbazepine, and less oxcarbazepine in CSF and plasma, which explain the tolerability profile of ESL and demonstrating an optimized delivery of eslicarbazepine to the brain (Figure 2) [Nunes *et al.* 2013].

Clinical studies

The ESL development program included an initial phase II study (study BIA-2093-201 [Elger *et al.* 2007]) and three subsequent phase III, multicentre, randomized, double-blind, placebo-controlled clinical trials (BIA-2093-301 [Elger

et al. 2009], BIA-2093-302 [Ben-Menachem *et al.* 2010] and BIA-2093-303 [Gil-Nagel *et al.* 2009]). In these three pivotal phase III trials, adjunctive ESL (both 800 and 1200 mg once daily), significantly reduced seizure frequency *versus* placebo in patients with partial-onset seizures treated with one to three concomitant AEDs. Long-term safety and maintenance of therapeutic effect was demonstrated in 1-year open-label extension studies [Halász *et al.* 2010; Hufnagel *et al.* 2013].

To meet specific requirements of the FDA, a fourth phase III placebo-controlled trial (study BIA-2093-304) was conducted and included a subpopulation of patients from North America [Sperling *et al.* 2015]. Finally, two additional studies that included historical control groups, have been performed to support the potential use of ESL as monotherapy in the US (studies 093-045 [Sperling *et al.* 2015] and 093-046 [Pazdera *et al.* 2014]); study 093-046 included both US (25) and non-US (25) investigational sites, while study 093-045 included only North-American investigational sites (89).

Safety and tolerability

Since the approval of ESL in the EU in 2009, the real-world safety profile of ESL has been evaluated in 18 European countries [Gama *et al.* 2014]. Safety data between 1 October 2009 and 21 October 2013 was collected from different sources

(post-marketing evaluations, literature reports, noninterventional studies and health authorities), and then pooled and analysed. This study showed over a cumulative exposure of 434,468.3 patient-months, 367 serious and 509 nonserious adverse events (AEs) with ESL were reported spontaneously, while 15 serious AEs from post-marketing noninterventional studies were reported. The most common reported terms (only AEs) were hyponatraemia (114), convulsion (48), dizziness (29), fatigue (25), blood sodium decreased (21), vertigo (18) and rash (17) [Gama *et al.* 2014].

A pooled analysis of studies BIA-2093-301, BIA-2093-302 and BIA-2093-304 was performed to assess the tolerability of once-daily ESL as adjunctive therapy for adult patients with refractory partial-onset seizures [Rogin *et al.* 2014]. Overall, 825 patients who received ESL 800 mg ($n = 415$) or 1200 mg ($n = 410$) once daily and 426 patients who received placebo were included in the pooled safety analysis. In these studies, the most commonly reported treatment-emergent AEs were dizziness (19.8% and 28.3% of patients receiving ESL 800 and 1200 mg *versus* 9.4% of patients receiving placebo), somnolence (11.1% and 18.0% *versus* 8.5%, respectively) and headache (12.5% and 14.9% *versus* 9.4%, respectively). For all treatment-related AEs reported, a dose-response relationship was noted, except for blurred vision (5.5% and 4.6% *versus* 1.4%, respectively) and for treatment-related AEs, which lead to study discontinuation (13.5% and 25.4% *versus* 6.6%). Of interest, more patients receiving ESL reported hyponatraemia (17.8% and 21.2% *versus* 6.1%), while allergic reactions were not increased with ESL treatment. In the three pivotal phase III trials, 7.0%, 2.7% and 2.8% of patients receiving ESL 800 and 1200 mg and placebo had a serious AE, respectively [Rogin *et al.* 2014]. No clinically relevant impact on laboratory parameters, vital signs or EKGs were observed with eslicarbazine acetate [Rogin *et al.* 2014].

A second pooled analysis of studies BIA-2093-301, BIA-2093-302 and BIA-2093-304, conducted by Krauss and colleagues [Krauss *et al.* 2014] examined the influence of starting dose and dose titration scheme on TEAEs during treatment with eslicarbazine acetate. During the 2-week titration period of these studies, there was a marked difference between the treatment-emergent AE profile of the ESL 800 mg 'without-titration' group

and the ESL 800 mg 'with-titration' group; the greatest differences were the reported instances of dizziness, somnolence, headache, nausea, vomiting and ataxia, all of which were more common in patients who did not undergo dose titration (the differences being at least 5%). Among groups with a target dose of ESL 800 or 1200 mg, the frequency of treatment-emergent AEs was higher in patients initiated at the 800 mg eslicarbazine acetate dose than patients initiated at the 400 mg eslicarbazine acetate. Furthermore, the incidence of rash was higher among patients maintained on 1200 mg *versus* 800 mg; however, it was not higher among patients initiated at 800 mg *versus* 400 mg [Krauss *et al.* 2014].

A specific commitment of the EMA was to address safety and efficacy of ESL treatment in the elderly. As such, a phase III, multicentre, open-label noncontrolled study (BIA-2093-401) was conducted in 72 patients aged ≥ 65 years who had at least 2 partial-onset seizures during an 8-week baseline period (treated with 1–2 AEDs) [Costa *et al.* 2014]. In this study, patients received 26 weeks of treatment with maintenance ESL 400–1200 mg, which was dosed based on individual response [Costa *et al.* 2014]. Initial results of this study show that the most frequently reported treatment-emergent AEs ($\geq 5\%$ patients) in elderly patients receiving ESL were dizziness, somnolence, fatigue, convulsion and hyponatraemia. The majority of treatment-emergent AEs were mild or moderate in severity and hyponatraemia was reported in 8.3% of the patients included in this study.

Although with the limitation of partially reduced observation periods, several post authorization studies have been conducted in Spain and have evaluated 493 patients receiving ESL [Serrano-Castro *et al.* 2013, Massot *et al.* 2014, Villanueva *et al.* 2014]. These studies have revealed retention rates varying from 72.4% to 88.5% over 3 to 12 months follow up. The most common AEs reported in these studies were dizziness, nausea and somnolence and hyponatraemia was reported in 2.7–6.6% of all patients receiving ESL in these studies.

Efficacy

The efficacy of ESL was demonstrated in the previously discussed phase II trial and the three phase III pivotal studies (Figure 2), with responder rates (defined as a $\geq 50\%$ reduction in seizure

frequency) varying between 34% and 43% (ESL 800 and 1200 mg) and seizure freedom rates varying between 4% and 8% in the main study period [Elger *et al.* 2007, 2009; Gil-Nagel *et al.* 2009; Ben-Menachem *et al.* 2010]. In the 1-year open-label extension studies of the pivotal phase III studies, the responder rates were somewhat higher and ranged between 42% and 53% [Halász *et al.* 2010; Hufnagel *et al.* 2013] with 11–12.5% of patients being seizure free at the end of the extension studies.

In a pooled analysis of studies BIA-2093-301, BIA-2093-302 and BIA-2093-304 the dose-related improvement in standardised seizure frequency observed in individual studies was confirmed [Biton *et al.* 2014]. In the pooled population of 1410 patients, 71.5% of patients were receiving ≥ 2 AEDs and completion rates were 81.9% and 70.6% for eslicarbazepine acetate 800 and 1200 mg, respectively. Overall, the median changes in standardized seizure frequency with ESL 800 and 1200 mg were –31.2% and –33.3%, respectively. The 50% responder rates were 32.3% (ESL 800 mg) and 40.9% (ESL 1200 mg) (Figure 2). Overall, ESL led to dose-related improvements in most efficacy outcomes, the effective dose range being 800–1200 mg once daily [Biton *et al.* 2014].

While ESL is not approved to be used as monotherapy, the results of the studies 093-045 and 093-046 have shown favourable results in this indication [Pazdera *et al.* 2014; Sperling *et al.* 2015]. In these studies, a historical control monotherapy design was adopted using individual patient data from eight previously completed withdrawal to monotherapy studies. ESL was considered effective if the upper limit of the 95% confidence interval was below the lower limit of the prespecified prediction interval of 65.3%, a value determined from the historical controls. In the studies, as the upper limits of the 95% CIs for ESL were both below the prespecified threshold of 65.3%, ESL monotherapy was shown to be superior to historical controls suggesting that it would also be effective as monotherapy in patients with partial onset seizures [Pazdera *et al.* 2014; Sperling *et al.* 2015].

ESL has also demonstrated efficacy as adjunctive to carbamazepine by significantly reducing the standardized seizure frequency from baseline in the pooled population of patient included in the phase III studies [Halász *et al.* 2009]. Also in

mouse models, ESL seems to maintain efficacy in the presence of carbamazepine resistance [Doeser *et al.* 2013].

In elderly patients, the efficacy reported in study BIA-2093-401 showed that ESL decreased the standardized seizure frequency from 2.9 seizures (at baseline) to 1.2 during the maintenance period. The median relative change in standardized seizure frequency was –54.1% [Costa *et al.* 2014].

Moreover, the post-authorization studies have shown a seizure freedom rate ranging from 12.5% (57.5% responder rate) in highly pharmacoresistant patients from Epilepsy Monitoring Units (EMUs) to 25.3% (52.5% responder rate) by outpatients of daily clinical basis [Serrano-Castro *et al.* 2013; Massot *et al.* 2014; Villanueva *et al.* 2014]. In the UK the clinical experience with adjunctive ESL has shown a seizure-free rate of 19.4% (50.2% responder rate at 12 months) [Keogh *et al.* 2014]. In observational studies, switching from oxcarbazepine to ESL was analysed considering tolerability and efficacy. In one study, due to pharmacoresistance, 12 patients were switched from oxcarbazepine to ESL (ratio 1:1). After 5 months of follow up, a significant reduction in seizure frequency ($>50\%$) was observed in 63.4% of these patients with 9% experiencing seizure freedom. AEs were transient in all cases [Massot *et al.* 2014]. In another multicentre study, 48 patients were switched from oxcarbazepine to ESL due to AEs or drug resistance (ratio 1:1). In this study, AEs were resolved in 57.7% of patients and seizure freedom was reached in 16% of patients [Villanueva *et al.* 2014]. As far as we know, there is no published data about the combined use of ESL as an adjunct to oxcarbazepine.

Finally, a phase IV, prospective analysis was performed in six European countries in which ESL was used as first add-on in 109 patients. Here, seizure freedom was reported in 47.8% of patients after an observation period of 6 months [Holtkamp *et al.* 2014].

Discussion

ESL is a third-generation member of the dibenzazepine family of AEDs that offers some important differences to other agents in the dibenzazepine family (carbamazepine and oxcarbazepine). In contrast to carbamazepine, ESL

shows no transformation to carbamazepine-10,11-epoxide leading to a more favourable AE profile [Hainzl *et al.* 2001]. ESL does not alter fast inactivation of VGSC like carbamazepine, but rather appears to modify the kinetics and voltage-dependence of slow inactivation [Hebeisen *et al.* 2015]. In comparison with oxcarbazepine, eslicarbazepine acetate presents an increased proportion of active metabolites allowing a 5-fold higher concentration of S-licarbazepine [Almeida *et al.* 2005]. Also, the administration of eslicarbazepine results in more stable concentration of S-licarbazepine in CSF, which may correlate with a better tolerability profile [Nunes *et al.* 2013]. Other distinction is the simplification of the drug regimen with once-daily administration that has been advocated as a possible way to increase adherence [Faught, 2012].

ESL has been shown to be effective and well tolerated as adjunctive therapy for adults with partial-onset seizures. Overall, the pivotal studies revealed responder rates ranging from 34% to 43% and seizure-freedom rates from 4% to 8% [Elger *et al.* 2009; Gil-Nagel *et al.* 2009; Ben-Menachem *et al.* 2010]. Furthermore, post-authorization studies have shown better seizure-freedom rates ranging from 12.5 to 25.3 (52.5 to 52.7 responder rate) and even higher when eslicarbazepine acetate is used as the first add-on [Serrano-Castro *et al.* 2013; Holtkamp *et al.* 2014; Massot *et al.* 2014; Villanueva *et al.* 2014]. Also, there seems to be a therapeutic margin for combination of ESL with carbamazepine in partial-onset seizures [Halász *et al.* 2009].

In a combined analysis of 4 years of marketing in Europe, it was found that the cumulative safety data of eslicarbazepine were in accordance with extensive experience from the pivotal clinical trial with no new safety issues identified. Based on the available information, the risk-benefit profile of the product remains unchanged and favourable [Gama *et al.* 2014]. The pooled analysis of studies BIA-2093-301, BIA-2093-302 and BIA-2093-304 showed that ESL 800 and 1200 mg once-daily were consistently well tolerated, with a low incidence of serious AEs, when used as adjunctive therapy in adult patients with partial-onset seizures [Rogin *et al.* 2014]. Treatment-emergent AEs, particularly nervous system (diplopia, dizziness, headache, vertigo and somnolence) and gastrointestinal disorders, were higher at higher doses of ESL. However, the incidence of serious treatment-emergent AEs in these studies was low and

were generally predictable, manageable, occurred during the early stages of treatment, and were of mild to moderate intensity. Furthermore, the incidence of hyponatraemia (defined as any report of 'blood sodium decreased' or 'hyponatremia' or any serum sodium value ≤ 135 mmol/l) with ESL treatment were 17.8–21.2% of patients *versus* 6.1% of patients receiving placebo [Rogin *et al.* 2014]. While the incidence of hyponatraemia was higher in this study, the incidence of hyponatraemia reported in the pivotal studies BIA-2093-301; BIA-2093-302 and BIA-2093-303 ranged from 0.6% to 1.3% [Elger *et al.* 2009; Gil-Nagel *et al.* 2009; Ben-Menachem *et al.* 2010], which is lower than the hyponatraemia rates that have been reported with carbamazepine and oxcarbazepine treatment; further investigation into the difference between compounds in the incidence of hyponatraemia is recommended.

The starting dose and dose titration scheme seems to be relevant for the AE profile. Initiation of ESL at a dose of 400 mg led to a favourable AE profile compared with initiation at a dose of 800 mg [Krauss *et al.* 2014]. The AE profile of patients who initiate at 400 mg daily for the first week is similar, regardless of final dose. Risk of rash does not appear to be related to ESL starting dose or to rate of dose escalation. Therefore, frequency of treatment-emergent AEs with ESL may be minimized by use of an appropriate titration scheme [Krauss *et al.* 2014].

Addressing the treatment with ESL in the elderly demonstrated that adjunctive treatment with ESL (400–1200 mg once daily) did not raise unexpected safety concerns and was efficacious [Costa *et al.* 2014]. However, the higher reported frequency of hyponatraemia compared with other studies in adult populations and the fact that few patients were exposed to doses higher than 800 mg/day suggest caution in this age group. With elderly patients it is advisable to begin treatment with low doses and use a slower titration strategy, keeping in mind the possible higher risk of hyponatraemia. Regarding allergic skin reactions, they occur at very low frequency but can eventually be severe. Skin reactions seem to occur especially if it has been demonstrated reactivity prior to the group of dibenzazepines [Massot *et al.* 2014].

While ESL is not approved to use as monotherapy, results of the phase III conversion to monotherapy studies have demonstrate that ESL monotherapy

(1200 or 1600 mg once daily) is more effective than the efficacy of other AEDs seen in other withdrawal to monotherapy studies (i.e. *versus* historical controls) [Pazdera *et al.* 2014; Sperling *et al.* 2015]. ESL monotherapy resulted in low study exit rates, high study completion rates, decreased seizure frequency and responder rates that increased with increasing ESL dose. Also, no new safety issues or trends (compared with the safety profile established in the earlier adjunctive trials) were observed in these studies, and the overall treatment-emergent AE profile was consistent with the known safety profile of ESL.

In summary, despite the lack of studies directly comparing oxcarbazepine or carbamazepine and ESL, the introduction of ESL to the market is an addition to the available pharmacological tools. ESL has a distinct mechanism of action and metabolism with respect to carbamazepine, which promotes better tolerability with high efficiency allowing replacement, or, in some cases, associated treatment. Compared with oxcarbazepine, ESL provides a higher proportion of S-licarbazepine available with a more stable delivery to the brain, which explains a better patient tolerability. Furthermore, hyponatraemia appears to be a less relevant AE with ESL treatment than with oxcarbazepine. In both cases, the once-daily dose constitutes a simplification of the patient's therapeutic scheme and therefore an improvement in their quality of life. Considering the cost-benefit problem, although ESL involves higher costs associated with treatment, it has clear advantages compared with carbamazepine and oxcarbazepine in terms of tolerability, adverse effects and simplification of the treatment regimen. At least in those cases where drug resistance or adverse effects were observed, a change to ESL is adequately justified.

Finally, it must be stated that a limitation of our review is the use of current data published in abstract form only at the time of writing, which have not been peer reviewed. The decision to use these data was made with an aim to use all of the most current information available, and also to include safety reports that are normally not included in published papers.

Conclusion

ESL has been demonstrated to be effective and well tolerated as adjunctive therapy for adults with partial-onset seizures. It offers a distinctive

mechanism of action, posology and tolerability profile when compared with carbamazepine and oxcarbazepine.

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Conflict of interest statement

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