ORIGINAL RESEARCH

Impact of Crisaborole on Sleep Outcomes in Pediatric Patients with Mild-to-Moderate Atopic Dermatitis

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ABSTRACT

Introduction: Using data from three clinical trials, the effect of crisaborole treatment on sleep outcomes for pediatric patients with atopic dermatitis (AD) and their families was examined.

Methods: This analysis comprised patients aged 2 to < 16 years from the double-blind phase 3 CrisADe CORE 1 (NCT02118766) and CORE 2 (NCT02118792) studies, families of patients aged 2 to < 18 years from CORE 1 and CORE 2, and patients aged 3 months to < 2 years from the open-label phase 4 CrisADe CARE 1 study (NCT03356977), all with mild-to-moderate AD who received crisaborole ointment 2% twice daily for 28 days. Sleep outcomes were assessed via the Children's Dermatology Life Quality Index and Dermatitis Family Impact questionnaires in CORE 1 and CORE 2 and the Patient-Oriented Eczema Measure questionnaire in CARE 1.

Results: In CORE 1 and CORE 2, a significantly lower proportion of crisaborole-treated patients than vehicle-treated patients reported sleep disruption at day 29 (48.5% versus 57.7%, $p = 0.001$). The proportion of families whose sleep was affected by their child's AD in the preceding week was also significantly lower in the crisaborole group (35.8% versus 43.1%, $p = 0.02$) at day 29. At day 29 in CARE 1, the proportion of crisaborole-treated patients who experienced ≥ 1 night of disturbed sleep in the previous week decreased by 32.1% from baseline.

Conclusion: These results suggest that crisaborole improves sleep outcomes in pediatric patients with mild-to-moderate AD and their families.

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PLAIN LANGUAGE SUMMARY

Atopic dermatitis (AD), also known as eczema, is a chronic skin disease that causes red or flaky skin patches that can become infected and itch.

Children with AD often experience sleep disturbance, including difficulty falling asleep, restless sleep, waking up more frequently, and daytime drowsiness. Problems with sleep quality negatively impact children with AD, as well as their caregivers. Crisaborole ointment is applied to the skin and has been shown to improve the symptoms of AD in children and adults. This study examined how treatment with crisaborole affected sleep quality for children and their caregivers in three clinical trials. Children in these studies took crisaborole for 28 days. Researchers found that crisaborole treatment improved sleep in children with mild-to-moderate AD and their caregivers. This was determined using four measures. First, a smaller proportion of children who were treated with crisaborole experienced sleep disruption compared with those to whom a vehicle was applied (an ointment with no drug). Second, a smaller proportion of caregivers of children with AD who were treated with crisaborole reported effects on their sleep, compared with children to whom a vehicle was applied. Third, a smaller proportion of children with AD who were treated with crisaborole, as well as their caregivers, had ≥ 1 night per week of disturbed sleep after treatment compared with before treatment. Fourth, the caregivers of children treated with crisaborole reported significantly less exhaustion and tiredness because of the child's AD. These results suggest that treatment with crisaborole improves sleep outcomes in children with mild-to-moderate AD and their caregivers.

Keywords: Atopic dermatitis; Crisaborole; Pediatrics; Sleep

Key Summary Points

Why carry out this study?

Pediatric patients with atopic dermatitis (AD) may experience sleep disturbances, which may lead to daytime fatigue and impaired quality of life for patients and their families.

This post hoc analysis examined how crisaborole ointment 2%, an anti-inflammatory nonsteroidal phosphodiesterase 4 inhibitor, affected sleep outcomes for pediatric patients and their families across the CORE 1, CORE 2, and CARE 1 studies.

What was learned from the study?

After 28 days of twice-daily use, crisaborole treatment resulted in a lower proportion of patients reporting sleep disruption compared with vehicle, a lower proportion of families whose sleep was affected compared with vehicle, and a reduction from baseline in the proportion of patients with ≥ 1 night per week of disturbed sleep.

These results suggest that treatment with crisaborole improves sleep outcomes in pediatric patients with mild-to-moderate AD and their families.

INTRODUCTION

Atopic dermatitis (AD) is associated with a significant psychosocial burden that affects patients, their caregivers, and society [1, 2]. The estimated prevalence of sleep disturbance in US pediatric patients aged 5–17 years with AD is approximately 67% [3]. Sleep disturbances experienced by patients with AD can take many forms, including difficulty in initiating sleep, restless sleep, increased waking, and daytime drowsiness [1, 2, 4]. As the severity of AD increases, so does the magnitude of those negative effects on sleep. AD flares also exacerbate negative impact on sleep [2, 5]. A USA-based survey of more than 90,000 children aged 0–17 years revealed that children who reported having AD within the past year had a higher chance of experiencing impaired sleep, and children with severe AD reported more instances of sleep disruption than children with mild or moderate AD [5, 6]. Similarly, a cohort study of almost 14,000 British children aged

2–16 years found that children with AD, even those with cases of mild or inactive disease, had significantly worse sleep quality relative to children without AD [7].

Problems with sleep quality appear to have a substantial impact on the quality of life (QoL) of patients with AD, even among patients in clinical remission. Children with AD often exhibit behavioral issues that may be linked to sleep disturbances, including negative self-esteem, poor performance in school, and school absenteeism [1, 8–11]. Poor sleep experienced by children with AD has also been linked to increased stress on their families, thereby imposing a psychosocial burden on the family as a whole [1, 2, 12]. A longitudinal study in the UK of almost 12,000 mother–child pairs found that mothers of children with AD experienced more sleep issues than mothers of children without AD, including difficulty falling asleep, insufficient sleep, and daytime exhaustion. Effects on family members' sleep could have negative effects on many aspects of their QoL, for example, performance in the workplace and coping skills at work and home have been observed to significantly decrease after a loss of as little as 1 or 2 h of sleep per night [7].

Crisaborole ointment 2% is a nonsteroidal phosphodiesterase 4 (PDE4) inhibitor, approved in many countries for the treatment of patients aged ≥ 3 months with mild-to-moderate AD [13, 14]. US Food and Drug Administration approval of crisaborole was based on the efficacy and safety demonstrated in two identically designed, randomized, double-blind, vehicle-controlled, 28-day phase 3 studies [CrisADe CORE 1 (NCT02118766) and CrisADe CORE 2 (NCT02118792)] that comprised patients aged ≥ 2 years [15]. In both studies, patients treated with crisaborole experienced a significantly greater reduction in AD severity versus those receiving vehicle [15]. In addition, patients treated with crisaborole achieved a significantly greater improvement in pruritus than vehicle-treated patients [15, 16]. Crisaborole was found to be generally safe and well tolerated [15]. The safety of crisaborole was further investigated in infants with mild-to-moderate AD, aged 3 months to < 2 years, in CrisADe CARE 1 (NCT03356977), a multicenter,

open-label, single-arm, 28-day phase 4 study. In this study, treatment with crisaborole resulted in improvements in AD severity and reductions in "the number of days skin had been itchy" during the previous week. Crisaborole was well tolerated by patients in CARE 1, and the safety profile was similar to that observed in the pivotal phase III studies [17].

The objective of this post hoc analysis was to examine how crisaborole treatment affected sleep outcomes for pediatric patients and their families across the CORE 1, CORE 2, and CARE 1 studies.

METHODS

Patients and Treatment

In CORE 1 and CORE 2, the efficacy and safety of crisaborole were compared with vehicle in patients aged ≥ 2 years with AD per Hanifin and Rajka criteria [18], with mild-to-moderate disease per ISGA, and with percentage of treatable body surface area (%BSA) ≥ 5 (excluding the scalp) [15]. Patients were randomly assigned 2:1 to receive crisaborole ointment 2% or vehicle, with treatment applied twice daily to all AD-affected areas, except the scalp, for 28 days. In CARE 1 (NCT03356977), patients aged 3 months to < 2 years with mild-to-moderate AD and %BSA ≥ 5 (excluding the scalp) were included. Open-label crisaborole was applied twice daily to all AD-affected areas of the body (excluding the scalp) for 28 days, avoiding mucous membranes [17].

Outcomes and Assessments

In CORE 1 and CORE 2, Children's Dermatology Life Quality Index (CDLQI) and Dermatitis Family Impact (DFI) assessments were completed at baseline and day 29. The CDLQI and DFI are questionnaires that assess QoL in pediatric patients with skin disease, and in their families, respectively. Each contains item(s) that assess the effect of AD on sleep. The CDLQI was completed either by the patients or with parental assistance for patients aged < 4 years [19].

The DFI was completed by one caregiver on behalf of the family.

In CORE 1 and CORE 2, sleep outcomes included the responses from patients aged 2 to < 16 years to item 9 of the CDLQI ("Over the last week, how much has your sleep been affected by your skin problem?"). Possible answers were "very much," "quite a lot," "only a little," and "not at all" [20]. The responses from caregivers of patients aged 2 to < 18 years to item 3 of the DFI ("Over the last week, how much effect has your child having eczema had on the sleep of others in the family?") were also analyzed. Possible answers were "very much," "a lot," "a little," and "not at all" [21]. Finally, tiredness and exhaustion were assessed in the families of patients aged 2 to < 18 years via item 7 of the DFI ("Over the last week, how much effect has your child having eczema had on causing tiredness or exhaustion in your child's parents/carers?"). Possible answers were "very much," "a lot," "a little," and "not at all" [21].

In CARE 1, a proxy version of the Patient-Oriented Eczema Measure (POEM) was completed by the parents or guardians of the patient at baseline and at days 8, 15, and 29 [17]. The CDLQI and DFI were not captured in the CARE 1 study [17]. The POEM is a 7-item questionnaire used for monitoring atopic eczema severity, focusing on the illness as experienced by the patient [22]. Each item is measured on a scale of 0–4, with a total score ranging from 0 to 28. Higher scores indicate greater AD symptom impact. In CARE 1, the sleep outcome was represented by responses by parents or guardians of patients to item 2 of the proxy POEM ("Over the last week, on how many nights has your child's sleep been disturbed because of eczema?") [22]. Possible answers were "no days," "1–2 days," "3–4 days," "5–6 days," and "every day" [22].

The institutional review board at each study site approved the study protocol, and written informed consent was provided by parents or legal guardians. The studies were conducted in accordance with the protocol, local legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the International Conference on Harmonisation Guideline for Good Clinical Practice, and the Declaration of Helsinki.

Statistical Analysis

For this post hoc analysis, sleep outcomes were assessed using pooled data from patients aged 2 to < 16 years, and families of patients aged 2 to < 18 years in CORE 1 and CORE 2. p values were derived from a Wilcoxon rank sum test for the comparison of crisaborole versus vehicle. No imputation was performed for missing data; observed cases were used. Analyses were performed using the intention-to-treat population, which consisted of all patients who had been randomly assigned and received study drug. For CARE 1, POEM data were summarized descriptively using the full analysis set of patients, which included any patient receiving ≥ 1 dose of crisaborole.

RESULTS

Baseline Characteristics

A total of 1199 patients (crisaborole 796, vehicle 403) and 1291 families (crisaborole 860, vehicle 431) had CDLQI and DFI sleep data collected, respectively, in CORE 1 and 2. POEM sleep data were collected for 137 infants in CARE 1, all of whom had been treated with crisaborole. The baseline and disease characteristics of CORE 1 and CORE 2 patients aged 2 to < 16 years and patients aged 2 to < 18 years were comparable (Table 1). With regard to demographics, the percentage of white patients in CARE 1 was similar to that in CORE 1 and CORE 2 (∼ 60%), but the overall proportion of female patients was lower (36% versus ∼ 53%) (Table 1). With regard to baseline disease characteristics, patients in CARE 1 had notably higher mean and median %BSAs than patients in CORE 1 and CORE 2 (Table 1). Patients in all three studies had comparable proportions of patients with ISGA scores of 2 (mild) and 3 (moderate) (Table 1).

Table 1 Baseline patient demographics

	CARE 1 patients aged 3 months to < 2 years	CORE 1 and CORE 2 patients aged 2 to < 16 years		CORE 1 and CORE 2 patients aged 2 to < 18 years	
	Crisaborole $n = 137$	Vehicle $n = 412$	Crisaborole $n = 815$	Vehicle $n = 439$	Crisaborole $n = 874$
Age, years					
Mean (SD)	1.1 (0.54)	7.8 (4.0)	7.7 (4.1)	8.4 (4.4)	8.3 (4.5)
Median (min, max)	1.1 (0.3, 1.9)	8.0 (2, 15)	7.0 (2, 15)	8.0 (2, 17)	8.0 (2, 17)
Female, *n* (%)	49 (35.8)	216 (52.4)	433 (53.1)	232 (52.8)	466 (53.3)
White, *n* (%)	84 (61.3)	255 (61.9)	503 (61.7)	273 (62.2)	536 (61.3)
%BSA					
Mean (SD)	28.1 (22.0)	19.1 (17.6)	19.2 (18.7)	18.5 (17.2)	18.9 (18.6)
Median (min, max)	19.0 (5, 94)	12.0 (5, 90)	12.0 (5, 95)	12.0 (5, 90)	12.0 (5, 95)
ISGA, *n* (%)					
Mild (2)	52 (38.0)	154 (37.4)	309 (37.9)	167 (38.0)	333 (38.1)
Moderate (3)	84 (61.3)	258 (62.6)	506 (62.1)	272 (62.0)	541 (61.9)

%BSA percentage treatable body surface area, *ISGA* Investigator's Static Global Assessment, *SD* standard deviation

Sleep Outcomes

To determine the effect of crisaborole treatment on sleep disruption in patients with AD, the distribution of responses from patients aged 2 to < 16 years in CORE 1 and CORE 2 to item 9 of the CDLQI at baseline and day 29 is presented in Fig. 1. At baseline, 72.4% of crisaborole-treated patients and 71.2% of vehicle-treated patients reported that their sleep had been affected by their skin problem in the previous week ($p = 0.192$). At day 29, a significantly lower proportion of crisaborole-treated patients than vehicle-treated patients (48.5% versus 57.7%; $p = 0.001$) reported that their sleep had been affected by their skin problem in the previous week.

To assess the impact of a patient's AD on the sleep of the patient's family, the distribution of responses from families of patients aged 2 to < 18 years in CORE 1 and CORE 2 to item 3 of the DFI at baseline and day 29 is shown in
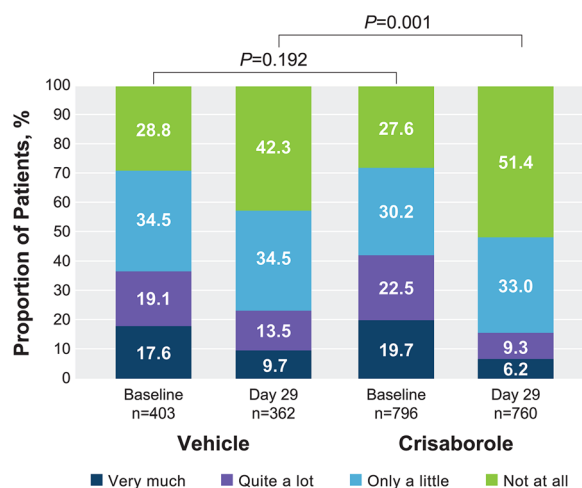

Fig. 1 Responses from pediatric patients (aged 2 to < 16 years) in CORE 1 and CORE 2 to CDLQI sleep item 9: "Over the last week, how much has your sleep been affected by your skin problem?" *p* values were derived from a Wilcoxon rank sum test with factor of treatment group. No missing data were imputed for these calculations. *CDLQI* Children's Dermatology Life Quality Index
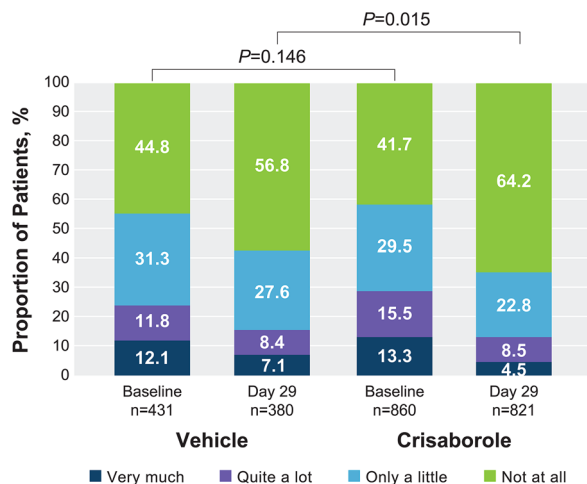
Fig. 2 Responses from families of pediatric patients (aged 2 to < 18 years) in CORE 1 and CORE 2 to DFI sleep item 3: "Over the last week, how much effect has your child having eczema had on the sleep of others in the family?" *p* values derived from a Wilcoxon rank sum test with factor of treatment group. No missing data were imputed for these calculations. *DFI* Dermatitis Family Impact
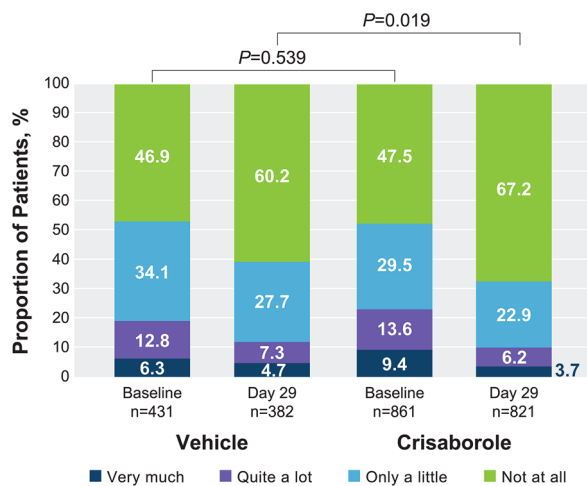

Fig. 3 Responses from families of pediatric patients (aged 2 to < 18 years) in CORE 1 and CORE 2 to DFI sleep item 7: "Over the last week, how much effect has your child having eczema had on causing tiredness or exhaustion in your child's parents/carers?" *p* values derived from a Wilcoxon rank sum test with factor of treatment group. No missing data were imputed for these calculations. *DFI* Dermatitis Family Impact
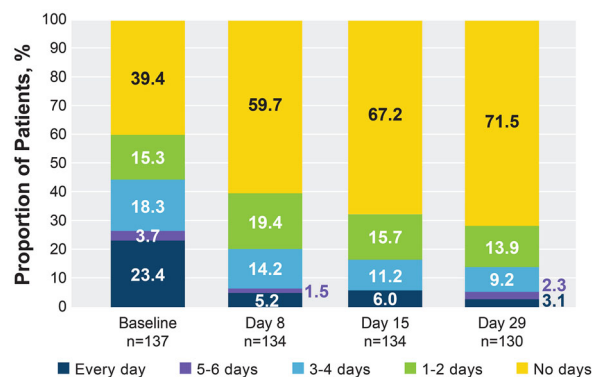
Fig. 4 Responses in CARE 1 to proxy POEM sleep item 2: "Over the last week, on how many nights has your child's sleep been disturbed because of eczema?" The full analysis set of patients included any patient receiving ≥ 1 dose of crisaborole. *POEM* Patient-Oriented Eczema Measure

Fig. 2. At baseline, 58.3% and 55.2% of families of crisaborole- and vehicle-treated patients, respectively, reported that the sleep of other family members had been affected by their child's AD in the previous week ($p = 0.146$). The proportion of families reporting that the sleep of other family members had been affected by their child's AD in the previous week was significantly lower with crisaborole than with vehicle at day 29 (35.8% versus 43.1%, $p = 0.015$).

The DFI also included another measure to capture the sleep impact on families of patients with AD (DFI item 7). The distribution of responses from families of patients aged 2 to < 18 years in CORE 1 and CORE 2 to item 7 of the DFI at baseline and day 29 is presented in Fig. 3. At baseline, 52.5% and 53.2% of families of crisaborole- and vehicle-treated patients, respectively, reported that their child's AD affected the parents or caregivers' feeling tired or exhausted in the previous week ($p = 0.539$). The proportion of families reporting that their child's AD had affected the parents or caregivers' feeling tired or exhausted in the previous week was significantly lower with crisaborole than with vehicle at day 29 (32.8% versus 39.7%, $p = 0.019$).

The distribution of responses from parents or caregivers of crisaborole-treated patients in CARE 1 to the proxy POEM at baseline, day 8, day 15, and day 29 is shown in Fig. 4. At baseline, 60.7% of respondents reported that their child's sleep had been disturbed due to the child's AD one or more nights during the previous week. At days 8, 15, and 29 of crisaborole treatment, that proportion was reduced to 40.3%, 32.9%, and 28.5%, respectively. No sleep-related adverse events were reported in CORE 1, CORE 2, or CARE 1.

DISCUSSION

Despite the documented importance of sleep disruption on the negative QoL impact associated with AD, data on the effects of topical AD treatments on sleep outcomes in this patient population are limited [23–25]. This post hoc analysis examined how crisaborole treatment affected sleep outcomes for pediatric patients and their families across three clinical trials assessing the safety and efficacy of crisaborole in mild-to-moderate AD. At day 29 of CORE 1 and CORE 2, a statistically significant proportion of crisaborole-treated patients aged 2 to < 16 years reported experiencing less sleep disturbance due to their skin problem over the previous week, relative to vehicle-treated patients. Also at day 29, the families of crisaborole-treated patients aged 2 to < 18 years reported statistically significantly less disturbance to the sleep of family members because of their child's eczema, relative to the families of vehicle-treated children. Finally, the families of crisaborole-treated patients aged 2 to < 18 years in CORE 1 and CORE 2 reported statistically significantly less impact on parent or caregiver exhaustion and tiredness because of their child's eczema. At days 8, 15, and 29 of CARE 1, there was an increase in the number of respondents reporting that their child's sleep had not been disturbed by the child's eczema. The increase was observed as early as day 8 of crisaborole treatment. Although crisaborole improved sleep outcomes relative to vehicle in CORE 1 and CORE 2, sleep disturbance was noted in 48.5% of crisaborole-treated patients and about a third

of families at day 29, thereby indicating the persistent impact of AD on sleep.

In addition to sleep improvement, crisaborole has been reported to improve other aspects of QoL. In an analysis by Simpson et al., patients treated with crisaborole in CORE 1 and CORE 2 reported significantly improved QoL compared with vehicle across the domains of pruritus, self-consciousness, and sexual difficulties, as based on the CDLQI (patients aged 2–15 years) and DLQI (patients aged ≥ 16 years) questionnaires [19]. Additionally, most patients reported that AD had had a "moderate effect" on QoL at baseline or worse. By day 29, a numerically greater proportion of crisaborole-treated patients reported that AD had had a "small effect" to "no effect" on QoL than reported by vehicle-treated patients (71.8% versus 65.5%) [19]. These results support the findings of the current analysis in that crisaborole treatment can result in significant QoL improvements relative to vehicle. Also, improvements in pruritus were seen across all timepoints during the CORE 1, CORE 2, and CARE 1 studies [17, 19].

The various manifestations of sleep disruption in patients with AD are still under investigation. Studies have previously found that children with AD display both increased sleep onset latency and waking after sleep, relative to children without AD [26–28]. However, other reports show there is no difference between sleep onset in children with or without AD [29, 30]. Other abnormalities in polysomnography parameters (e.g., sleep efficiency, sleep-stage architecture, arousal, and limb movements) have been noted in children with AD, relative to published normative values [28]. There is a clear need for validated tools that can accurately reflect the impact of AD on sleep in this patient population. Beyond the use of the CDLQI and POEM in future clinical trials with pediatric AD patient populations, newer tools under development, such as the Patient-Reported Outcomes Measurement Information System, may be able to provide higher-quality sleep data in these patients [31].

Because these crisaborole studies were not specifically designed to assess the effects of crisaborole on sleep outcomes, there are

limitations to the analyses. Sleep outcomes were assessed with patient- or proxy-reported measures, and no objective measurements of sleep quality, such as polysomnography or actigraphy, were obtained. There may also be differences in patient and parent, or proxy, recall of AD's sleep impacts. In CORE 1 and CORE 2, the CDLQI was used to evaluate patients aged 2 to < 16 years; however, the questionnaire has been validated only for patients aged > 4 years. Finally, the analyses presented in this manuscript were conducted post hoc, and longer-term studies on sleep outcomes in patients with AD are needed.

CONCLUSION

After twice-daily use for 28 days to treat mild-to-moderate AD in pediatric patients, crisaborole improved sleep outcomes in both the patients and their families. Future trials are warranted to investigate the improvements in sleep associated with PDE4 inhibition in AD.

ACKNOWLEDGEMENTS

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