NICE Abridged Recommendations for the Management of Migraine

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TA906
TA919

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Evidence and guidance for the initiation of Vydura▼ (rimegepant) for the management of migraine

Rimegepant for preventing migraine [TA906] (published 5th July 2023)
Rimegepant for treating migraine [TA919] (published 18th October 2023)

This document aims to explain the role of rimegepant as an option for the acute treatment of migraine or for the preventive treatment of episodic migraine and thus how it fits into the migraine treatment pathway.

NICE's recommendations are not intended to affect treatment with rimegepant that was started in the NHS before its guidance was published.[1,2] People having treatment outside NICE's recommendations may continue without change to the funding arrangements in place for them before its guidance was published, until they and their NHS clinician consider it appropriate to stop.[1,2]

Vydura is indicated for the:[3]

- Acute treatment of migraine with or without aura in adults
- Preventive treatment of episodic migraine in adults who have at least 4 migraine attacks per month

Rimegepant for treating migraine

NICE recommendation for rimegepant

Rimegepant is recommended as an option for the acute treatment of migraine with or without aura in adults, only if for previous migraines:[1]

- At least 2 triptans were tried and they did not work well enough, or
- Triptans were contraindicated or not tolerated, and nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol were tried but did not work well enough

Clinical treatment of migraine

The aim of acute treatment for migraine is to provide effective and sustained relief of headache and associated symptoms; for example, aura is an associated symptom that a patient expert for NICE considered not to be well managed with existing treatments.[1] Existing acute treatments include oral, nasal and injectable triptans, aspirin, other NSAIDs, and paracetamol, taken either alone or in combination. Antiemetics are also considered, even when there is no nausea or vomiting.[1]

In the clinical management of migraine, people would usually try at least 2 triptans; some clinicians may choose to offer up to 7 triptans (including different formulations), but if there is no response after 2 to 4 triptans then it is unlikely that they will respond to any more triptans.[1] Clinical experts explained that when triptans are ineffective, it may be because they are not being used properly.[1] Clinical experts explained that when triptans are ineffective, not tolerated, contraindicated, or not used properly, there is no further standard treatment, and a person should see a migraine specialist.[1] However, limited numbers of headache centres and long waiting lists result in reduced access to specialists.[1] Rimegepant is now recommended if, for previous migraines, 2 triptans have been ineffective (or triptans are contraindicated or not tolerated and paracetamol and NSAIDs have been tried but do not work well enough).[1]

Clinical trial results for rimegepant (Study 303)

The NICE committee considered clinical trial evidence for acute

Table 1
Inclusion and exclusion criteria for participants in Study 303[4]

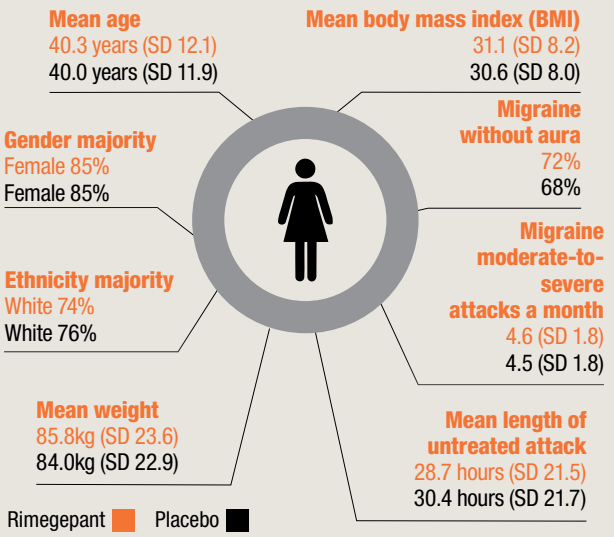
Inclusion criteria	Exclusion criteria
• Adults aged ≥18 years • ≥ 1-year history of migraine with or without aura, according to the criteria of the 3rd Edition of International Classification of Headache Disorders (ICHD) beta version • Onset before 50 years of age • ≥2 but ≤8 migraine attacks/month of moderate-to-severe intensity • <15 days/month with migraine/non-migraine headache within the past 3 months	• Have a medical condition that may interfere with study assessments of efficacy and safety or expose participants to undue risk of a significant AEs • Been treated for drug or alcohol abuse in the past 12 months • Had a history of drug allergy or other allergy that made them unsuitable for participation • Had an electrocardiogram (ECG) or laboratory test findings that raised safety or tolerability concerns

treatment of migraine, which shows that rimegepant is more likely to reduce pain at 2 hours than placebo.[1]

The efficacy, safety, and tolerability of rimegepant orally disintegrating tablet (oral lyophilisate) for the acute treatment of migraine was assessed in a randomised, phase 3, double-blind, placebo-controlled trial at 69 sites in the USA.[4]

Eligible participants (Table 1) were randomly assigned in a 1:1 ratio to either rimegepant or placebo (n=682 and n=693 of whom received study drug, respectively) for treatment of a single migraine attack of moderate or severe pain intensity and provided with an electronic diary.[4]

Figure 1
Baseline characteristics for participants included in Study 303[4]



SD – Standard deviation. BMI – Body mass index.

Rimegepant was statistically significantly more effective than placebo on the co-primary efficacy endpoints of freedom from pain and freedom from the most bothersome symptom (MBS) at 2 hours post dose.[4] Freedom from pain at 2 hours was seen in 21.2% of participants administered rimegepant compared to 10.9% with placebo (10.3% difference, 95% CI 6.5 to 14.2, $P<0.0001$).[4] Freedom from MBS at 2 hours was seen in 35.1% of participants administered rimegepant compared to 26.8% with placebo (8.3% difference, 95% CI 3.4 to 13.2, $P<0.0009$).[4]

Rimegepant was statistically significantly more effective than placebo on 19 out of 21 secondary endpoints, including pain relief post dose at 2 hours (59.3% vs. 43.3%; risk difference 16.1; 95% CI 10.8-21.3) and 60 minutes (36.8% vs. 31.2%; risk difference 5.5; 95% CI 0.5-10.6); ability to function normally post dose at 2 hours (38.1% vs. 25.8%; risk difference 12.3; 95% CI 7.4-17.2) and 60 minutes (22.3% vs. 15.8%; risk difference 6.4; 95% CI 2.3-10.6); sustained pain relief from 2 to 48 hours post dose (42.2% vs. 25.2%; risk difference 16.9; 95% CI 12.0-21.9), and no requirement of rescue medication in the first 24 hours post dose (85.8% vs. 70.8%; risk difference 15.0; 95% CI 10.7-19.3).[4]

Table 2
AE reporting in Study 303[4]

	Rimegepant 75 mg (n=682)[4]	Placebo (n=693)[4]
Participants with AEs	90 (13%)	73 (11%)
AEs reported in ≥1% of participants in either treatment group[4]		
Nausea	11 (2%)	3 (<1%)
Urinary tract infection	10 (1%)	4 (1%)
Dizziness	6 (1%)	7 (1%)
AEs related to treatment	47 (7%)	36 (5%)
Serious AEs	0	0

The most common on-study AEs were nausea, and urinary tract infection (Table 2).[4] No serious AEs were reported in treated participants.[4]

Posology of rimegepant for acute treatment of migraine
For the acute treatment of migraine, the recommended dose is 75 mg, as needed, once daily.[3] The maximum dose per day is 75mg rimegepant.[3]

Prescribing of rimegepant for acute treatment of migraine
NICE do not specifically state whether rimegepant would likely be prescribed in primary or secondary care for the acute treatment of migraine.[1]

Cost-effectiveness analysis of rimegepant for acute treatment of migraine
The cost-effectiveness estimates, after accounting for the committee's preferred assumptions and considering the scenario analyses where alternative populations and assumptions were used, were below or within what NICE normally considers to be an acceptable use of NHS resources.[1]

Rimegepant for preventing episodic migraine

NICE recommendation for rimegepant
Rimegepant is recommended as an option for preventing episodic migraine in adults who have at least 4 and fewer than 15 migraine attacks per month, only if at least 3 preventative treatments have not worked.[2] Rimegepant should be stopped after 12 weeks if the frequency of migraine attacks does not reduce by at least 50%.[2]

If people with the condition and their clinicians consider rimegepant to be 1 of a range of suitable treatments, after discussing the advantages and disadvantages of all the options, use the least expensive. Take account of administration costs, dosage, price per dose and commercial arrangements. [2]

Clinical management of episodic migraine[2]
The aim of preventative treatment is to reduce the frequency, severity or duration of migraine and improve quality of life.[2] A 50% reduction is considered clinically meaningful in episodic migraine. During the consultation on NICE's guidance, it was

noted that there is a high unmet need for new preventive treatment options for episodic migraine, as existing treatments do not work in many patients.[2]

For patients with at least 4 migraine days per month (MMD), there is a range of oral preventative treatments including topiramate, propranolol, and amitriptyline that would usually be tried before moving on to another type of treatment.[2] Therefore, rimegepant can be offered after 3 preventative treatments have not worked.[2]

Other available fourth-line treatments on the NHS are injectable monoclonal antibodies, such as erenumab ▼, fremanezumab▼, galcanezumab▼; rimegepant is an oral treatment, which may be preferable for some patients rather than injectable treatments.[2]

Clinical trial results for rimegepant (Study 305)

The efficacy, safety, and tolerability of rimegepant for the preventive treatment of episodic migraine was assessed by a multicentre, phase 2/3, randomised, double-blind, placebo-controlled trial at 92 sites in the USA.[2,5]

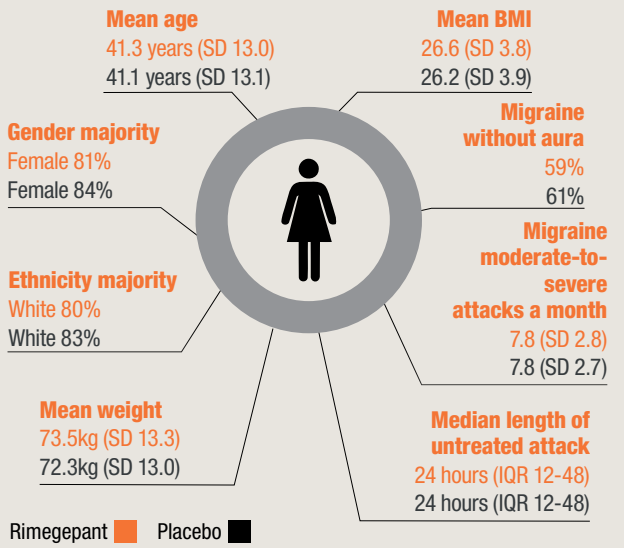
The study comprised 3 phases: a screening phase, which included a 4-week observation period, a 12-week double-blind treatment phase, and a 52-week open-label extension phase.[5] At baseline visit, eligible participants (Table 3) were randomly allocated in a 1:1 ratio to either rimegepant or placebo (n=370 and n=371 of whom received study drug, respectively).[5]

During the 12-week double-blind treatment phase of the study, participants were allowed to take 1 preventive migraine drug, excluding calcitonin gene related peptide (CGRP) receptor antagonists and CGRP monoclonal antibodies, provided that the dose was stable for at least 3 months before the 4-week observation period and did not change during the observation period or the double-blind treatment phase.[5]

The primary efficacy analysis showed that rimegepant demonstrated a statistically significant reduction in mean MMD from baseline during weeks 9 to 12 by 4.3 days (95% CI: -4.8 to -3.9) whilst placebo reduced MMD by 3.5 days (95% CI: -4.0 to -3.0; difference: -0.8 days, *P*=0.0099 (95% CI: -1.5 to -0.2)).[5]

Secondary endpoint results showed that rimegepant was more effective than placebo for the percentage of participants with ≥50% reduction in the mean number of moderate or severe MMD during weeks 9 to 12 (49% vs 41%; 8% difference; 95% CI: 0 to 15; *P*=0.044), and for reduction in mean MMD during weeks 1 to 12 (-3.6 vs -2.7; -0.8 days difference; 95% CI: -1.3 to -0.3; *P*=0.0017).[5]

Figure 2
Baseline characteristics for participants included in Study 305[5]



SD – Standard deviation. BMI – Body mass index. IQR – Interquartile range.

AEs associated with rimegepant were assessed as mostly mild to moderate, with low rates of serious AEs (Table 4).

Posology of rimegepant for episodic migraine

For the preventive treatment of episodic migraine, the recommended dose is 75 mg every other day.[3]

Prescribing of rimegepant for episodic migraine

Feedback from clinical practice reported that General Practitioners (GPs) would likely prefer that people with migraine are referred to them from a neurologist to be prescribed rimegepant as a preventative treatment, instead of treatment being started in primary care.[2]

Due to its proposed position in the treatment pathway, rimegepant is likely to be prescribed by a specialist in secondary care; however, it could also be prescribed in primary care by

Table 3
Inclusion and exclusion criteria for Study 305[5]

Inclusion criteria	Exclusion criteria
• Adults aged ≥18 years • ≥ 1-year history of migraine with or without aura, or chronic migraine, according to the criteria of the ICHD, 3rd Edition • Onset before 50 years of age • ≥4 but ≤18 migraine attacks/month* of moderate-to-severe intensity over a 3-month period before the screening visit and at least 6 migraine days during the 4-week observation period • Normal findings on medical and laboratory assessments	• >18 headache days during the 4-week observation period • History of non-responsiveness to more than 2 types of preventative migraine treatment • A medical condition that would expose undue risk or interfere with the assessment of efficacy or safety • Drug or alcohol abuse treatment in the past 12 months* • History of drug allergy or another allergy that made participation unsuitable • An ECG or laboratory test findings that raised safety or tolerability concerns

*1 month was defined as 4 weeks; 12 months was defined at 48 weeks

Table 4
AE reporting for Study 305[5]

	Rimegepant 75 mg (n=370)[5]	Placebo (n=371)[5]
Participants with AEs	133 (36%)	133 (36%)
AEs reported in at least 2% of participants treated with rimegepant[5]		
Nasopharyngitis	13 (4%)	9 (2%)
Nausea	10 (3%)	3 (1%)
Urinary tract infection	9 (2%)	8 (2%)
Upper respiratory tract infection	8 (2%)	10 (3%)
Participants with mild AEs	92 (25%)	91 (25%)
Participants with moderate AEs	64 (17%)	62 (17%)
AEs related to treatment	40 (11%)	32 (9%)
Serious AEs	3 (1%)	4 (1%)
Serious AEs related to treatment	0	1 (<1%)
AEs leading to discontinuation	7 (2%)	4 (1%)

GPs following Advice and Guidance from a specialist or within a shared care agreement.[2] The Migraine Trust commented that rimegepant provided in primary care could be an excellent opportunity for people with migraine, even if it has to be started in secondary care.[2]

Cost-effectiveness analysis of rimegepant for episodic migraine
The pharmaceutical company base case used a primary care approach, and the External Review Group (ERG) base case used a secondary care approach; the pharmaceutical company and ERG probabilistic base-case incremental cost-effectiveness ratios (ICERs) for rimegepant compared with erenumab, fremanezumab, and galcanezumab showed that rimegepant is less expensive and less effective than 2 of the 3 comparators.[2]

Implementation of rimegepant

Integrated care boards, NHS England, and local authorities have 3 months from publication of the NICE guidance to comply with its recommendations.[1,2] When NICE recommends a treatment 'as an option', the NHS must make sure it is available within this period.[1,2] This means that, if a patient has migraine and the doctor responsible for their care think that rimegepant is the right treatment, it should be available for use, in line with NICE's recommendations.[1,2]

The importance of treating migraine

Migraine attacks may last between 4 and 72 hours, and often can involve disabling throbbing head pain of moderate-to-severe intensity.[1,2] Migraines are frequently accompanied by nausea, vomiting, dizziness, and sensitivity to light, sound and smells.[1,2] Migraine can adversely affect quality of life, affecting people's ability to do their usual activities, including work.[1,2] In fact, comments from the public, carers, and patients with migraine describe migraine as an invisible disability that affects all aspects of life, including work, education, finances, mental health, social activities, and family.[1,2]

Key takeaways

- Rimegepant is recommended as **an option for the acute treatment of migraine with or without aura** in adults, when at least 2 triptans were tried and they did not work well enough, or triptans were contraindicated or not tolerated and NSAIDs and paracetamol were tried but did not work well enough.[1]

NICE do not specifically state whether rimegepant would likely be prescribed in primary or secondary care for the treatment of acute migraine.[1]

- Rimegepant is recommended **as an option for preventing episodic migraine** in adults who have at least 4 and fewer than 15 migraine attacks per month, only if at least 3 preventative treatments have not worked.[2]

Rimegepant may be likely prescribed by a specialist in secondary care or it could also be prescribed in primary care by GPs following Advice and Guidance from a specialist or within a shared care agreement.[2]

References

1. NICE. Rimegepant for treating acute migraine [TA919]. 2023. Available at https://www.nice.org.uk/guidance/ta919. Accessed October 2023.
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3. Vydura (rimegepant) Summary of Product characteristics for Great Britain; Vydura (rimegepant) Summary of Product characteristics for Northern Ireland. 2023.
4. Croop R, Goadsby PJ, Stock DA, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. *Lancet* 2019;394:737-745.
5. Croop R, Lipton RB, Kudrow D, et al. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. *Lancet* 2021;397:51-60.

PRESCRIBING INFORMATION FOR GREAT BRITAIN AND NORTHERN IRELAND

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 of the SmPC for how to report adverse reactions.

VYDURA® ▼(rimegepant) Prescribing Information:
Please refer to the Summary of Product Characteristics (SmPC) before prescribing VYDURA 75 mg oral lyophilisate. **Presentation:** Oral lyophilisates containing 75 mg rimegepant. **Indications:** Acute treatment of migraine with or without aura in adults. Preventive treatment of episodic migraine in adults who have at least 4 migraine attacks per month. **Dosage:** For acute treatment of migraine, the recommended dose is 75 mg rimegepant, as needed, once daily. For prophylaxis of migraine, the recommended dose is 75 mg rimegepant every other day. The maximum dose per day is 75 mg rimegepant. Another dose of rimegepant should be avoided within 48 hours when it is concomitantly administered with moderate inhibitors of CYP3A4 or with strong inhibitors of P-gp (see SmPC section 4.5). VYDURA can be taken with or without meals. The oral lyophilisate should be placed on the tongue or under the tongue. It will disintegrate in the mouth and can be taken without liquid. Patients should be advised to use dry hands when opening the blister and referred to the package leaflet for complete instructions. No dose adjustment is required in patients aged 65 and over as the pharmacokinetics of rimegepant are not affected by age (see SmPC section 5.2). No dose adjustment is required in patients with mild, moderate, or severe renal impairment. Caution should be exercised during frequent use in patients with severe renal impairment. Use of rimegepant in patients with end-stage renal disease (CLcr < 15 ml/min) should be avoided. No dose adjustment is required in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. The use of rimegepant in patients with severe hepatic impairment should be avoided. The safety and efficacy of VYDURA in paediatric patients (< 18 years of age) have not been established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients listed in SmPC section 6.1. **Warnings and Precautions:** Hypersensitivity reactions, including dyspnoea and rash, have occurred in less than 1% of patients treated with rimegepant in clinical studies (see SmPC section 4.8). Hypersensitivity reactions, including serious hypersensitivity, can occur days after administration. If a hypersensitivity reaction occurs, rimegepant should be discontinued and appropriate therapy should be initiated. VYDURA is not recommended in patients with severe hepatic impairment (see SmPC section 4.2), in patients with end-stage renal disease (CLcr < 15 ml/min) (see SmPC section 4.2), for concomitant use with strong inhibitors of CYP3A4 (see SmPC section 4.5) or for concomitant use with strong or moderate inducers of CYP3A4 (see SmPC section 4.5). If overuse is experienced or suspected, medical advice should be obtained, and treatment should be discontinued. The diagnosis of medication overuse headache (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of medicinal products for acute headache. **Drug Interactions:** Rimegepant is a substrate of CYP3A4, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) efflux transporters (see SmPC section 5.2). Concomitant administration of rimegepant with strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, ritonavir) is not recommended (see SmPC section 4.4). Concomitant administration of rimegepant with itraconazole resulted in a significant increase in rimegepant exposure (AUC by 4-fold and C_{max} 1.5-fold). Concomitant administration of rimegepant with medicinal products that moderately inhibit CYP3A4 (e.g., diltiazem, erythromycin, fluconazole) may increase exposure to rimegepant. Concomitant administration of rimegepant with fluconazole resulted in increased exposures of rimegepant (AUC by 1.8-fold) with no relevant effect on C_{max}. Another dose of rimegepant within 48 hours should be avoided when it is concomitantly administered with moderate inhibitors of CYP3A4 (e.g., fluconazole) (see SmPC section 4.2). Concomitant administration of VYDURA with strong CYP3A4 inducers (e.g., phenobarbital, rifampicin, St John's wort (*Hypericum perforatum*)) or moderate CYP3A4 inducers (e.g., bosentan, efavirenz, modafinil) is not recommended (see SmPC section 4.4). The effect of CYP3A4 induction may last for up to 2 weeks after discontinuation of the strong or moderate CYP3A4 inducer. Concomitant administration of rimegepant with rifampicin resulted in a significant decrease (AUC reduced by 80% and C_{max} by 64%) in rimegepant exposure, which may lead to loss of efficacy. Inhibitors of Pgp and BCRP efflux transporters may increase plasma concentrations of rimegepant. Another dose of VYDURA within 48 hours should be avoided when it is concomitantly administered with strong inhibitors of Pgp (e.g., cyclosporine, verapamil, quinidine) (see SmPC section 4.2 and 4.5). Concomitant administration of rimegepant with cyclosporine (a potent Pgp and BCRP inhibitor) or with quinidine (a selective Pgp inhibitor) resulted in a significant increase of similar magnitude in rimegepant exposure (AUC and C_{max} by > 50%, but less than two-fold). **Pregnancy & Lactation**: There are limited data from the use of rimegepant in pregnant women. Animal studies demonstrate that rimegepant is not embryocidal, and no teratogenic potential has been observed at clinically relevant exposures. As a precautionary measure, it is preferable to avoid the use of VYDURA during pregnancy. The relative percentage of a maternal dose estimated to reach the infant is less than 1%. There are no data on the effects on milk production. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for VYDURA and any potential adverse reactions on the breastfed infant from rimegepant or from the underlying maternal condition. **Driving and Operating Machinery:** VYDURA has no or negligible influence on the ability to drive and use machines. **Side Effects:** The most common adverse reaction was nausea for acute treatment (1.2%) and for migraine prophylaxis (1.4%). Most of the reactions were mild or moderate in severity. Hypersensitivity, including dyspnoea and severe rash were uncommon side effects observed in the acute treatment and occurred in less than 1% of patients treated. Hypersensitivity reactions can occur days after administration, and delayed serious hypersensitivity has occurred. **Legal Category**: POM. **Marketing Authorisation Holder Northern Ireland (NI):** Pfizer Europe MA EEIG, Boulevard de la Plaine 17, 1050 Bruxelles, Belgium. **Marketing Authorisation Numbers for NI:** EU/1/22/1645/001, EU/1/22/1645/002 **Marketing Authorisation Holder Great Britain (GB):** Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom **Marketing Authorisation Number for GB**: PLGB 00057/1717 **Local Representative:** Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS, UK. **Package quantities, Basic NHS Price:** VYDURA 75 mg, 2 x 1 oral lyophilisates, £25.80; 8 x 1 oral lyophilisates, £103.20;

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