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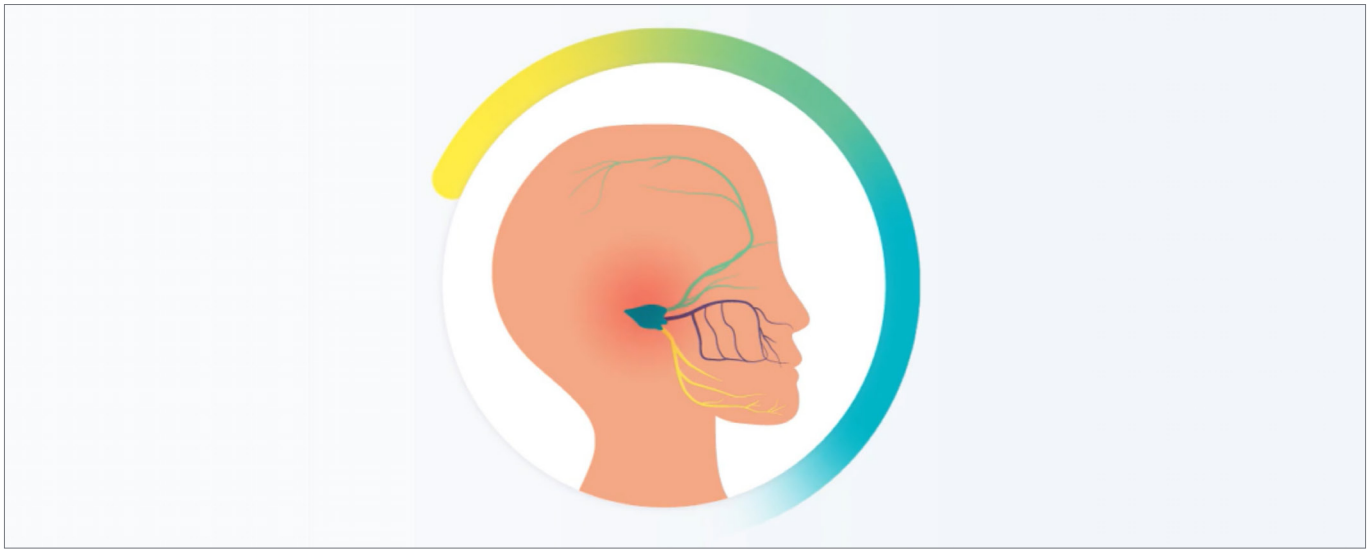
MIGRAINE THERAPY: TARGETING CALCITONIN GENE RELATED PEPTIDE (CGRP)

Vydura® ▼(rimegepant) prescribing information and adverse event reporting can be found at the bottom of this article.



Migraine and the role of CGRP

Migraine is a long-term neurovascular condition that affects over 1 billion people worldwide, most commonly women younger than 50 years of age.[1,2] It is a leading global cause of disability, with estimates indicating that migraine accounted for >40 million years lived with disability (YLDs) in 2019 (88.2% of all YLDs due to headache disorders of any type).[2] In the UK, it is estimated that around 10 million people aged between 15 and 69 suffer from migraines, leading to around three million migraine-related sick days every year and costing the UK National Health Service an estimated £150 million per year on treating migraine alone.[3]

Current evidence indicates that migraines are linked to dysfunction of the trigeminal nerve system in the brain, more specifically, excessive release of calcitonin gene related peptide (CGRP).[4,5] As a pain signalling neuropeptide and potent vasodilator, it is thought that CGRP plays a causal role in the pathophysiology of migraine by inducing pain via exaggerated CGRP signalling through trigeminal sensory afferents and the spinal trigeminal nucleus.[4–6] It is this dysfunctional signalling that is now thought to be a factor that gives rise to the characteristic and debilitating symptoms of the condition, such as prolonged headache (4–72 hours), throbbing pain, light sensitivity, sound sensitivity and nausea.[4,7] As such, CGRP represents a viable therapeutic target for migraine, with treatments aimed at selectively blocking the action of CGRP.[6]

Vydura®▼ (rimegepant) is a small molecule CGRP receptor antagonist that selectively binds to the CGRP receptor with high affinity.[8] Based on supporting evidence from randomised clinical studies, including those that will be discussed in this article,[9,10] Vydura is indicated for the acute treatment of migraine (with or without aura) in adults, or for the preventive treatment of episodic migraine in adults who have at least four migraine attacks per month.[8]

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Rimegepant for the acute treatment of migraine

The efficacy and safety of oral rimegepant for the acute treatment of migraine was assessed in a multicentre, phase 3, randomised, double-blind, placebo-controlled trial (Study 303; NCT03461757) conducted across 69 sites in the USA between February and August 2018.[9]

Patients eligible for the study were ≥18 years of age, had at least a 1-year history of migraine according to 3rd edition International Classification of Headache Disorders (ICHD-3) criteria (with or without aura; onset before the age of 50), suffered 2–8 migraine attacks/month of moderate-to-severe intensity, and experienced <15 headache days/month (of any type, not just migraine) during the 3 months prior to the study. Patients were excluded if they had a history or current evidence of any medical (or other) condition that could cause safety concerns or interfere with study analysis (including alcohol or drug abuse and relevant drug allergies), or had electrocardiogram (ECG) or laboratory test findings that raised safety or tolerability concerns. Patients were permitted to take preventive migraine medication during the study, as long as it had been at a stable dose for at least 3 months prior to the study.[9]

Eligible patients were randomised 1:1 to receive either a single dose of oral rimegepant 75 mg (n=669) or placebo (n=682) for the treatment of a migraine attack of moderate-to-severe intensity occurring within 45 days of randomisation.[9] The study was conducted using the orally disintegrating tablet formulation of rimegepant 75 mg; the formulation of rimegepant used within the UK is oral lyophilisate 75 mg.[8] Patients completed an electronic diary assessment of pain and most bothersome symptoms, including photophobia, phonophobia, and nausea, at migraine onset, at 2 hours post-dose and at other time points, in line with the endpoints studied.[9] Patients were only permitted to use non-steroidal anti-inflammatory drugs, paracetamol, anti-emetics or baclofen after 2 hours post-dose.[9] The co-primary endpoints were freedom from pain at 2 hours post-dose and freedom from most bothersome symptom at 2 hours post-dose. Freedom from pain was defined as a reduction in headache severity from moderate-to-severe at baseline to no pain.[9] Secondary endpoints included: pain relief at 2 hours post-dose; ability to function normally at 2 hours post-dose; sustained pain relief at 2–24 hours; and sustained freedom from most bothersome symptom at 2–24 hours.[9] There were 21 secondary endpoints in total, which were subject to a hierarchical gate-keeping procedure.[9] Pain relief was defined as a reduction in moderate-to-severe migraine pain to mild or no pain.[9]

Patient baseline characteristics were well balanced between treatment groups and are summarised in **Table 1.**[9] Overall, the mean age of patients was 40.2 years, the mean age at migraine onset was 21.0 years, patients experienced a mean of 4.6 moderate-to-severe migraines per month, most patients were women (85%), and most patients experienced migraine without aura (70%).[9]

Table 1. Patient baseline demographics and characteristics (Study 303; NCT03461757).[9]

	Rimegepant (n=669)	Placebo (n=682)	Total (n=1351)
Age, years (SD)	40.3 (12.1)	40.0 (11.9)	40.2 (12.0)
Sex			
Female	568 (85%)	579 (85%)	1147 (85%)
Male	101 (15%)	103 (15%)	204 (15%)
Primary migraine type			
Migraine without aura	480 (72%)	462 (68%)	942 (70%)
Migraine with aura	189 (28%)	220 (32%)	409 (30%)
Age at disease onset, years (SD)	20.9 (10.2)	21.1 (10.2)	21.0 (10.2)
Duration of untreated attacks, hours, (SD)	28.7 (21.5)	30.4 (21.7)	29.5 (21.6)
Moderate-to-severe attacks per month (SD)	4.6 (1.8)	4.5 (1.8)	4.6 (1.8)

SD, standard deviation.
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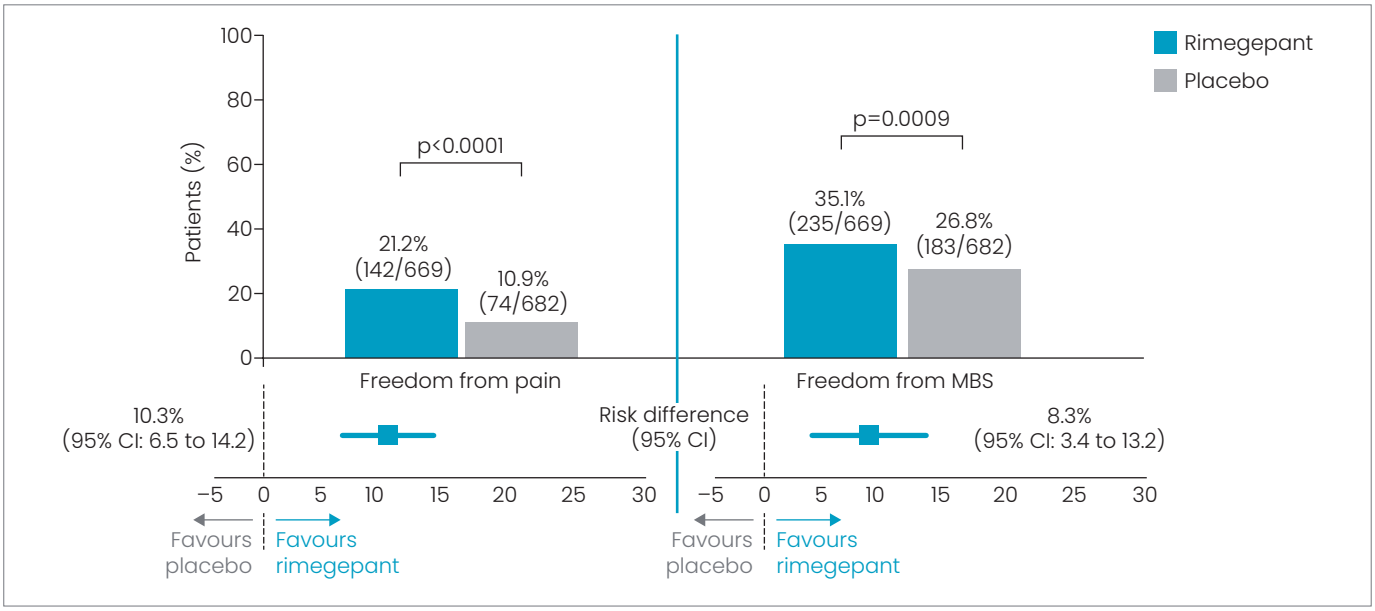
Figure 1. Rimegepant was statistically significantly more effective than placebo on the co-primary efficacy endpoints of freedom from headache pain and most bothersome symptom* at 2 hours post-dose (modified ITT population [N=1,351],† Study 303; NCT03461757).[9]



*CI, confidence interval; ITT, intention-to-treat; MBS, most bothersome symptom.**
**Freedom from pain was defined as a reduction in headache severity from moderate-to-severe at baseline to no pain, and most bothersome symptoms included photophobia, phonophobia, and nausea; †Defined as all patients who were randomised to treatment, experienced a migraine of moderate-to-severe intensity, took a dose of study medication, and had at least one subsequent efficacy assessment.*
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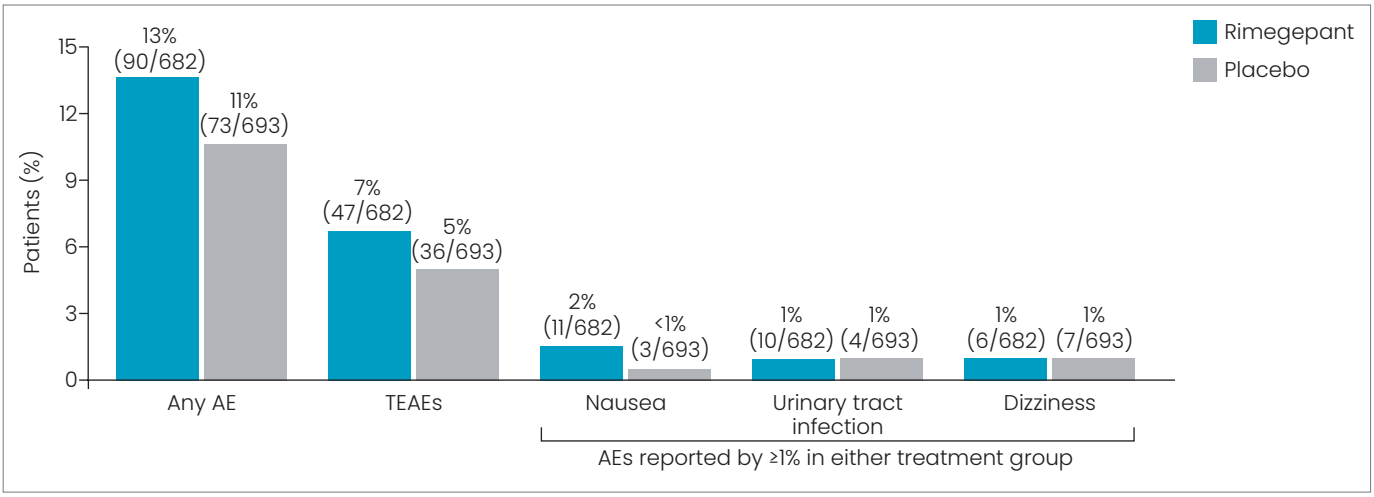
Efficacy analyses showed that rimegepant was statistically significantly more effective than placebo on the co-primary efficacy endpoints of freedom from headache pain and most bothersome symptom at 2 hours post-dose (21.2% vs 10.9%; risk difference 10.3%; 95% confidence interval [CI]: 6.5 to 14.2; p<0.0001 and 35.1% vs 26.8%; risk difference 8.3%; 95% CI: 3.4 to 13.2; p=0.0009, respectively; **Figure 1**).[9] The secondary endpoint results also showed that (i) rimegepant works to relieve pain following a migraine attack vs placebo (proportion of patients with pain relief at 2 hours post-dose: 59.3% vs 43.3%; risk difference 16.1%; ; 95% CI: 10.8 to 21.3; p<0.0001) and (ii) rimegepant works to improve ability to function normally following a migraine attack vs placebo (proportion of patients able to function normally at 2 hours post-dose: 38.1% vs 25.8%; risk difference 12.3% 95% CI: 7.4 to 17.2; p<0.0001).[9]

Overall, rimegepant was generally well tolerated in clinical trials with 13% and 11% of patients reporting adverse events (AEs) after receiving a single dose of rimegepant and placebo, respectively.[9] The most common AEs (for rimegepant vs placebo, respectively) were nausea (2% vs <1%), urinary tract infection (1% vs 1%), and dizziness (1% vs 1%; **Figure 2**); no serious AEs were reported in either treatment group.[9]

In conclusion, the results of this study show that in adults experiencing an acute migraine of moderate-to-severe intensity, a single oral dose of rimegepant 75 mg was statistically significantly more effective than placebo on the co-primary efficacy endpoints of freedom from pain and most bothersome symptom at 2 hours post-dose.[9] Rimegepant was also generally well tolerated in clinical trials.[9]

Figure 2. Summary of adverse events with rimegepant and placebo (Study 303; NCT03461757; safety data analysis population [N=1,375]*).[9]



AE, adverse event; TEAE, treatment-emergent adverse event.
**Defined as all patients randomised to treatment who received a single dose of study medication.*
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Rimegepant for the preventive treatment of migraine

The efficacy and safety of oral rimegepant for the preventative treatment of migraine was assessed in a multicentre, phase 2/3, randomised, double-blind, placebo-controlled trial (Study 305; NCT03732638) conducted across 92 sites in the USA between November 2018 and August 2019.[10]

Patients eligible for the study were ≥18 years of age, had at least a 1-year history of migraine according to ICHD-3 criteria (with or without aura; onset before the age of 50), had suffered 4–18 migraine attacks/month of moderate-to-severe intensity during the 3 months prior to the study, and had ≥6 migraine days during the 4 week lead-in observation period.[10] Patients were excluded if they experienced ≥18 headache days during this period (of any type, not just migraine), had previously received more than two different categories of preventive migraine treatment without success, or had a history or current evidence of any medical condition that could cause safety concerns or interfere with study analysis (including alcohol or drug abuse and relevant drug allergies), or had ECG or laboratory test findings that raised safety or tolerability concerns.[10]

After the initial 4-week lead-in observation period, patients were randomised 1:1 to receive either oral rimegepant 75 mg (tablet formulation, n=370; the formulation of rimegepant used within the UK is oral lyophilisate 75 mg[8]), or placebo (n=371), every other day (QOD) for 12 weeks.[10] During this time, patients recorded the frequency and severity of their migraines using an electronic diary, and were permitted to take rescue medication such as triptans, nonsteroidal anti-inflammatory drugs, and paracetamol.[10] Rimegepant was not permitted as a rescue medication.[10] The primary endpoint was change from the 4-week observation period (baseline) in the mean number of migraine days (MMD) per month in the last 4 weeks of the double-blind treatment phase (weeks 9–12). Secondary endpoints included: the number of patients achieving at least a 50% reduction from baseline in mean number of moderate-to-severe MMD during weeks 9–12; and change from baseline in mean MMD across weeks 1–12.[10]

Patient baseline characteristics were well balanced between treatment groups and are summarised in **Table 2**. In brief, the mean age of patients was 41.2 years, the median age at migraine onset was 18 years, the mean number of migraine days/month during the observation period was 10.1, and most patients were women (83%), did not have a history of chronic migraine (77%), and experienced migraine without aura (60%).[10]

Table 2. Patient baseline demographics and characteristics (Study 305; NCT03732638).[10]

	Rimegepant (n=370)	Placebo (n=371)	Total (n=741)
Age, years	41.3 (13.0)	41.1 (13.1)	41.2 (13.1)
Sex			
Female	300 (81%)	313 (84%)	613 (83%)
Male	70 (19%)	58 (16%)	128 (17%)
Age at disease onset, years	18 (14–28)	18 (13–28)	18 (13–28)
Duration of untreated attacks, hours	23 (12–48)	24 (12–48)	24 (12–48)
Moderate or severe attacks per month, n	7.8 (2.8)	7.8 (2.7)	7.8 (2.7)
History of chronic migraine			
Yes	78 (21%)	95 (26%)	173 (23%)
No	292 (79%)	276 (74%)	568 (77%)
Primary migraine type			
Migraine without aura	220 (59%)	226 (61%)	446 (60%)
Migraine with aura	150 (41%)	145 (39%)	295 (40%)
Migraine days per month in the 4-week observation period, days	10.3 (3.2)	9.9 (3.0)	10.1 (3.1)

Data presented are mean (standard deviation), n (%), or median (interquartile range).
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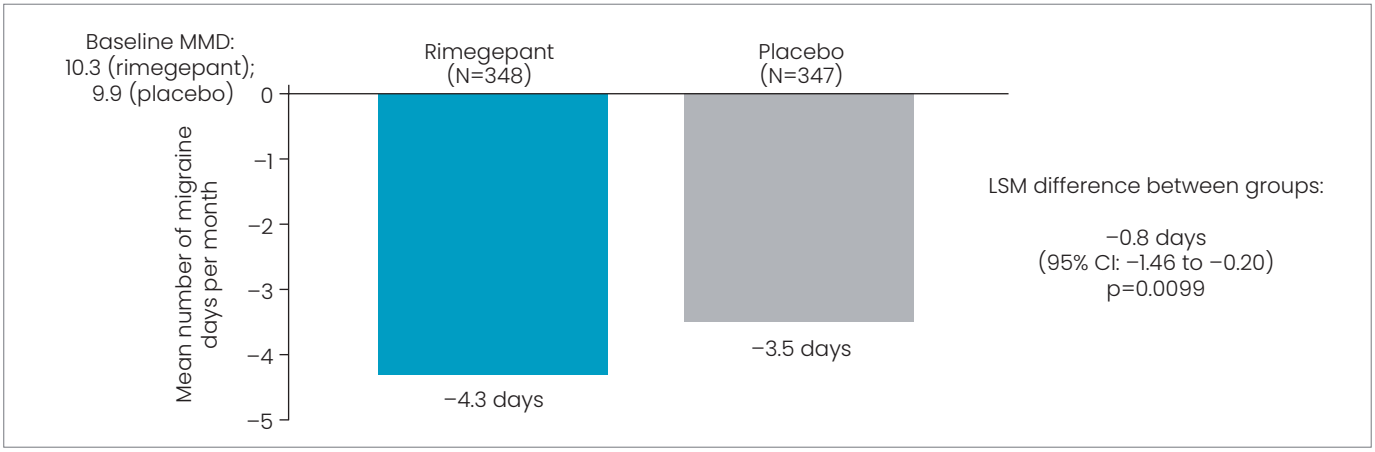
Figure 3. Rimegepant can prevent episodic migraines by reducing MMD from baseline (4-week observation period) during weeks 9–12 vs placebo (Study 305; NCT03732638; efficacy analysis population [N=695]*).[10]



CI, confidence interval; LSM, least squares mean; MMD, monthly migraine days.
**The efficacy analysis population consisted of all patients who received at least one dose of study medication and had ≥14 days of data from both the observation period and one 4-week period during treatment; efficacy data were analysed using a generalised linear mixed-effects model with treatment group, preventive migraine medication use at randomisation, study month, and month-by-treatment-group interaction as fixed effects, and participant as a random effect.*
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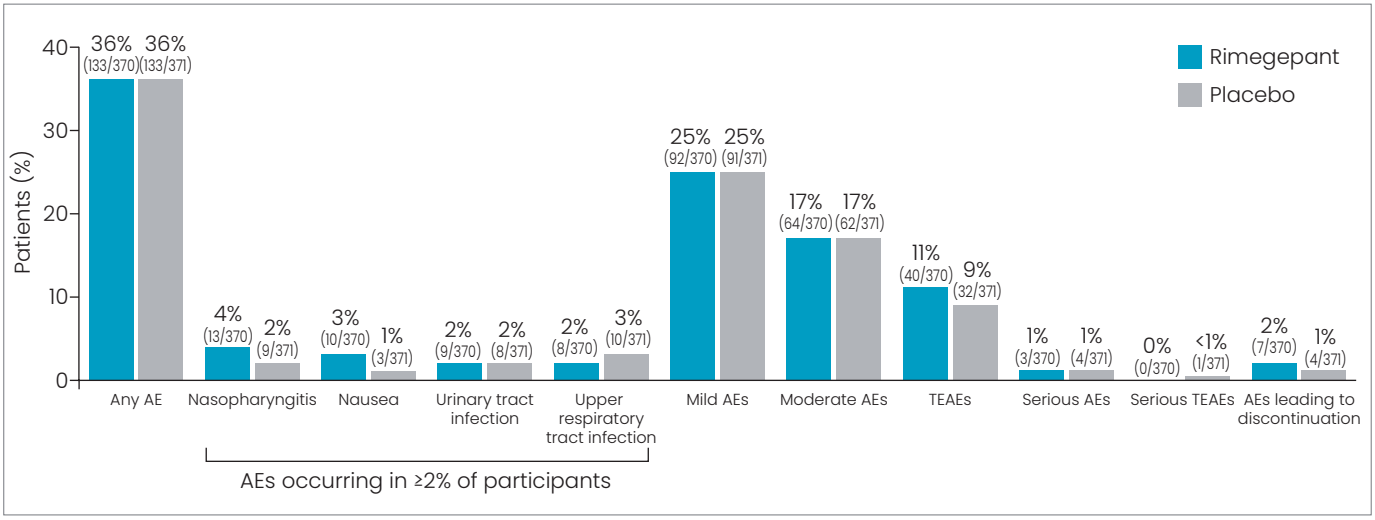
Efficacy analyses showed that rimegepant can prevent episodic migraines by reducing MMD from baseline during weeks 9–12 vs placebo (primary endpoint; **Figure 3**; difference: −0.8 days; 95% CI: -1.46 to -0.20; p=0.0099).[10] Secondary endpoint results included a reduction in mean MMD starting at Week 1 and continuing to Week 12 for rimegepant vs placebo (difference -0.8 days; 95% CI: -1.3 to -0.3; p=0.0017), and more patients taking rimegepant had a ≥50% reduction from baseline in the mean number of moderate or severe MMD during weeks 9–12 vs placebo (49.1% vs 41.5%; 7.6% difference; 95% CI: 0 to 15; p=0.044).[10]

Figure 4. Summary of adverse events with rimegepant and placebo (Study 305; NCT03732638; safety data analysis population [N=741]*).[10]



AE, adverse event; TEAE, treatment emergent adverse event.
**The safety analysis population consisted of all patients who were randomised to treatment and received at least one dose of study medication.*
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Overall, rimegepant was generally well tolerated in clinical trials with 36% of patients reporting AEs in both groups, most common being nasopharyngitis (4% vs 2% [rimegepant vs placebo]), nausea (3% vs 1%), urinary tract infection (2% vs 2%), and upper respiratory tract infection (2% vs 3%; **Figure 4**).[10] Serious AEs were infrequent, occurring in 1% of patients in both groups, the rates of discontinuation due to AEs were also low in both groups (2% vs 1%), and no patients died during the study.[10]

In conclusion, the results of this study show that rimegepant 75 mg every other day (QOD) can help prevent episodic migraines in adults who have at least four migraine attacks/month, by reducing the frequency of MMD compared with placebo.[10] Rimegepant 75 mg QOD was generally well tolerated in clinical trials.[10]

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PRESCRIBING INFORMATION

▼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 P gp 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 P gp (e.g., cyclosporine, verapamil, quinidine) (see SmPC section 4.2 and 4.5). Concomitant administration of rimegepant with cyclosporine (a potent P gp and BCRP inhibitor) or with quinidine (a selective P gp 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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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Pfizer Medical Information on 01304 616161.