Brand Name[1]: Nurtec ODT

Generic Name[1]: Rimegepant

Manufacturer[1]: Biohaven Pharmaceutical Holding Company Ltd.

Drug Class[2,3,4]: Oral calcitonin gene-related peptide (CGRP) receptor antagonist; antimigraine, central feverous system agent

Uses[1,2,3,4]:

Labeled: Acute treatment of migraine with or without aura in adults

Unlabeled: None

Mechanism of Action[1,2,3,4,5]: Nurtec is a calcitonin gene related peptide receptor antagonist, however, the exact mechanism in which its clinical effects are exerted is currently unknown. CGRP, involved in pain modulation, is located in the trigeminovascular system which is an anatomical site involved in migraine pathophysiology. CGRP has higher concentrations during acute migraine attacks and may even be chronically elevated in patients who suffer from chronic migraines.

Pharmacokinetics[2,3,4]:

Absorption: Absolute oral bioavailability is approximately 64%; Tmax is delayed 1 hour when taken following a high fat mean and Cmax is reduced 42% - 53%.

Distribution: Plasma protein binding is approximately 96%, and the steady state volume of distribution is 120 L.

Metabolism: Enzymatic inhibitor of CYP3A4, OATP1B1, OAT3, OATP1B3, OCT2, and MATE1; it is also a substrate of CYP3A4, CYP2C9, P-gp, and BCRP. Metabolized primarily through CYP3A4 and CYP2C9.

Elimination: The half-life is approximately 11 hours. The excretion occurs through the urine with 51% of unchanged drug, and through the feces with 42% unchanged drug.

Efficacy[6,7,8]:

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(10200):737-745. doi:10.1016/S0140-6736(19)31606-X

Study Design: Randomized Phase 3 Double Blind Placebo Controlled Trial

Description of Study: The objective of the study was to show efficacy, safety, and tolerability of the novel oral disintegrating tablet formulation of Rimegepant compared to placebo when treating acute migraines.

> **Methods**: Patients who were aged 18 and older with a history of migraine, with or without aura, of at least 1 year were recruited to one of the 69 study centers in the United States. Patients were either given rimegepant 75 mg or placebo. Additional inclusion criteria included patients who had initial migraine onset before the age of 50, at least 2 but not more than 8 migraines of moderate or severe intensity per month, and fewer than 15 days per month with migraine or nonmigraine headache within the past 3 months. 1466 patients were randomly assigned, with 682 receiving rimegrapant, and 693 receiving placebo. Patients tracked their migraine pain and current symptoms with an electronic diary. Patients treated a single migraine in the study period.
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> **Results**: The primary endpoints were freedom from pain and freedom from the most bothersome symptoms associated with migraines (phonophobia, photophobia, or nausea) at 2 hours after the dose. Of the randomized patients, 1375 experienced a qualifying migraine and took the study medication, on the primary outcomes, rimegepant was superior to placebo for freedom from pain (21 % vs 11%; $p<0.0001$) and freedom from the most bothersome symptom (35% vs 27%; $p = 0.0009$). Secondary outcomes included pain relief and ability to function normally at 60 minutes post dose, freedom from pain and freedom from the most bothersome symptom at 90 minutes post dose, rescue medication use within 24 hours, and sustained freedom from pain and pain relief within 24 to 48 hours. Rimegepant was superior to placebo in all instances except on 2-hour freedom from nausea. The most common adverse events were nausea (11 [2%] of 682 patients vs 3 [<1%] pf 693 patients), and urinary tract infection (10 [1%] of 682 patients vs 4 [1%] of 693 patients]. No serious adverse events were reported.

Limitation: limitations included not having an active comparator and use of placebo, as well as using a single attack study design which can limit the assessment of the consistency of the treatment. The study was funded by the manufacturer of Rimegepant which could introduce bias.

Conclusions: Rimegepant was significantly more effective compared to placebo when treating a single acute migraine of moderate or severe intensity; and tolerability was similar to placebo. CGRP receptor antagonists are a large study area in the treatment for migraines and this provides encouraging results from a novel compound that uses a dosage form that has rapid onset of therapeutic action. These results show the potential for early and sustained therapeutic action in the treatment of acute migraine.

Lipton R. B., Croop R., Stock E. G., Stock D. A., Morris B. A., Frost M., et al. (2019). Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. N. Engl. J. Med. 381 (2), 142–149. 10.1056/NEJMoa1811090

Study Design: Randomized Phase 3 Double Blind Placebo Controlled Trial

Description of Study: The purpose of this study was to assess efficacy and safety, specifically of freedom from pain and freedom from the most bothersome symptom identified by the patient comparing Rimegepant and placebo two hours after administration

Methods: Patients over the age of 18 had migraines with or without aura, had a history of 1 year with migraines, onset before the age of 50, had 2 to 8 migraines of moderate to severe intensity per mouth, and had any other headache less than 15 days per month during the previous 3 months. People either received 75 mg of Rimegepant or placebo and were instructed to take the medication when they experienced a single migraine of moderate or severe intensity. They recorded their current pain and symptoms in an electronic diary which they updated for 48 hours. 1186 patients were randomized from 49 centers in the United States, and 538 patients completed the trial with Rimegepant, while 542 patients completed the trial with placebo.

Results: In the Rimegepant group, 19.6% of patients were pain free after 2 hours of taking the medication, compared to the placebo group which had 12.0% of patients pain free after 2 hours. Rimegepant had 37.6% of patients free from their most bothersome symptoms 2 hours after the dose, compared to 25.2% in the placebo group. For secondary endpoints, 37.4% of Rimegepant patients experienced freedom from photophobia at 2 hours after a dose, compared to 22.3% of placebo group ($p<0.0001$) and freedom from phonophobia was 36.7% in the Rimegepant group vs 26.8% in the placebo group ($p=0.004$). The difference in patients who experienced freedom from nausea 2 hours after the dose was not significant. Nausea was the most common adverse event occurring 1.8% in the Rimegepant group and 1.1% in the placebo group; and urinary tract infections occurred in 1.5% of the Rimegepant group and 1.1% in the placebo group. Liver function tests showed that the levels were above the normal range in 2.4% of patients in the Rimegepant group, and 2.2% in the placebo group; but none of the levels were more than three times the upper limit of normal.

Limitation: This trial did not use an active comparator drug, and the treatment was only for one migraine attack, and while no cardiac adverse events were seen the trial population did not have patients with cardiovascular disease.

Conclusions: Rimpegepant when given as a single dose of 75 mg was superior in treating acute migraines compared to placebo; it helped patients meet endpoints such as freedom from pain and freedom from the most bothersome symptom 2 hours after taking the medication. The occurrence of adverse events was low and were reported as nausea and urinary tract infections. The trial helped add to the other literature showing that oral CGRP inhibitors result in higher percentages of patients who were pain free and free from their most bothersome symptom after an acute migraine attack.

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(10268):51-60. doi:10.1016/S0140-6736(20)32544-7

Study Design: Phase 2/3 Randomized Double Blind Placebo Controlled Trial

Description of Study: The purpose of this study was to compare the safety, tolerability, and efficacy of Rimegepant when taken every other day with placebo for prevention of migraines.

Methods: Patients were enrolled from 92 study centers in the United States, and there were three phases to the trial, a screening phase which lasted 4 weeks as an observation phase, 12 weeks where double blinded treatments were given, and an additional 52-week open label extension phase. Patients were over the age of 18, had a 1-year history of

migraine with or without aura, or chronic migraines, migraine development before the age of 50, and have had at least 4 but no more than 18 attacks per month, with at least 6 migraines occurring in the 4-week observation period. Patients maintained an electronic diary to document the occurrence ad severity of migraines and a paper diary to record the use of other migraine drugs and menstrual cycle information. During the 12-week double blind phase where Rimegepant was dosed 75 mg every other day. Patients were then assessed for entry into the open label extension phase which is not assessed within this manuscript. 747 patients were randomized, with 316 patients in the Rimegepant group and 310 patients in the placebo group who completed the trial. The study population had a mean age of 41.2, 83% were women, and 82% were white.

Results: The primary endpoint looked at the change in the mean number of migraines days per month in the last 4 weeks of the double-blind treatment phase compared to the first 4-week observation period. Secondary endpoints examined the achievement of a 50% reduction in the mean number of moderate to severe migraine days, change in the mean number of migraines days per month, mean number of rescue medication days per month. The mean number of tablets used per month was 13.8 for Rimegepant and 13.9 for placebo. Rimegepant was superior to placebo in the primary endpoints with the difference in migraines days per month during week 9 – 12 being a reduction of 4.3 days for Rimegepant and 3.5 days with placebo. Rimegepant was also more effective than placebo with at least a 505 reduction in mean number of migraine days per month (49% in Rimegepant patients compared to 41% in placebo (p=0.044)). There was no statistically significant difference with the mean days of reduce medications per month. Patients in the Rimegepant group were also equally likely to have an adverse event as individuals in the placebo group with 36% of individuals in each group reporting and event such as nasopharyngitis, nausea, urinary tract infection, and upper respiratory tract infection.

Limitation: Limitations included short study duration and a relatively small sample size, no use of active comparators, as well as excluding patients with more than 18 migraines per month.

Conclusions: The study showed efficacy with a reduction in the mean number of total migraine days per months as well as an early onset of preventative effects during the first 4 weeks of treatment. Compared to placebo, Rimegepant also showed benefit in reducing headache days by 50%. Rimegepant also had similar safety compared to placebo. Additional studies are needed to compare Rimegepant to other current prophylactic treatments of migraine to assess comparative efficacy.

Contraindications[1,2,3,4]: Hypersensitivity to Rimegepant or any component of the formulation. Hypersensitivity reactions can include dyspnea, rash, and delayed serious reaction. If hypersensitivity reactions due occur, discontinue the medication.

Precautions[2,3]:

Renal function impairment: use is not recommended in patients with end stage liver disease; CrCl <15 mL/minute; and safety has not been studied when used in patients on dialysis.

Hepatic function impairment: use is not recommended in patients with severe hepatic impairment; avoid in Child-Pugh C; plasma concentrations are significantly higher in haptic failure patients.

Adverse effects[1,2,3,4]:

Occurring 1 – 10%: Gastrointestinal and nausea

Occurring <1%: Dermatologic skin rash and dyspnea

Drug interactions[1,2,3,4]: avoid concomitant use with strong inhibitors of CYP3A4, strong or moderate inducers of CYP3A, and inhibitors of P-gp or BCRP.

Avoid Combination: Abametapir, BCRP/ABCG2 Inhibitors, Conivaptan, CYP3A4 moderate inducers, CYP3A4 strong inducers, CYP3A4 strong inhibitors, Fusidic Acid (systemic), Idelalisb, Lasmidaitan, P-gP/ABCB1 inhibitors, and Voxilaprevir.

Monitor Therapy: Clofazimine, Deferasirox, Eradfitinib, Fosaprepitant, Ivosidenib, Larotrectinib, Palbociclib, Sarilumab, Siltuximab, Tafamidis, and Tocilizumab

Consider Therapy Modification: CYP3A4 moderate inhibitors and Stripipentol

Dosing/Administration[1,2,3,4]:

Usual dose: 75 mg taken orally placed on or under the tongue as needed; maximum dose of 75 mg in a 24-hour period. The treatment of over 15 migraines in one month has not been established.

Geriatric dose: Same as the typical adult dose.

Pediatric dose: Safety and efficacy have not been established.

Renal impairment: CrCl > 15 mL/min has no dosage adjustment needed; patients with CrCl <15 mL/min or are on dialysis avoid use.

Hepatic impairment: Mild to moderate hepatic impairment (Child -Pugh A or B) has no dosage adjustment needed; patients with severe impairment (Child-Pugh C) should avoid use.

Use in special circumstances[2,3,9]:

Pregnancy consideration: adverse events have been observed in animal reproduction studies, but at doses which also caused maternal toxicity. There are other agents which are preferred in pregnant women for the treatment of acute migraine. Decreased fetal body weight and increased fetal variations occurred at doses 300mg/kg/day in pregnant rats, well above the recommended human dose 75 mg/day.

Breast feeding considerations: it is currently unknown if the medication passes through breast milk, and individual treatment decisions must be considered when considering the mother's clinical need for the medication and any potential adverse effects on the breast fed infant.

Conclusion: Nurtec is a new CGRP receptor inhibitor which has been recently (2020) approved for the use of abortive therapy in the treatment of acute migraines in patients with or without aura. Nurtec is to be taken orally and has a novel oral disintegrating tablet which aids in absorption time and ease of administration. The adverse events have been limited with nausea being the most commonly reported, and some urinary tract infections have been seen during the clinical trials. More severe side effects can include hypersensitivity reactions, and elevated liver function tests (never reaching above 3 times the upper limit of normal), but the prevalence rates were extremely low. Safety has not been studied in patients who need to take Nurtec more than 15 days per month. Patients who have taken Nurtec have experienced reduced migraine days and lessening of their most bothersome symptom 2 hours after taking a dose and has shown to be effective up to 48 hours after a dose. Nurtec is currently only approved in adults, and the data on the safety in pregnancy and breast feeding is limited, however there are other preferred agents in pregnancy. Cost may be an issue as Nurtec is significantly more expensive than other approved migraine abortive medications. However, Nurtec does have a patient savings program where patients with eligible commercial insurance can pay as little as $0 out of pocket with a copay card for a prescription of 8 tablets a month. Ultimately, more studies assessing Nurtec's efficacy with currently available migraine abortive medications are needed to determine it's place in therapy, but Nurtec may be an option in patients who have failed or are not otherwise able to use current migraine abortive medications.

Citations:

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