A new approach to migraines

A review of rimegepant; its merits, synthesis, and pharmacological characteristics

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1 INTRODUCTION

Over the past decade, migraine has become an ever-increasing problem, both for people and for the economy. On a personal level, patients with migraine suffer unbearable pain for days on end, negatively affecting their quality of life and, for some, even to the point of not being able to lead a normal life or work. As a result, migraine results in major economic losses each year (approximately $13 billion in the U.S.)[1].

Much is still unknown about the pathophysiology of migraine. One of the leading theories attributes the pathogenesis of migraine to vasodilation of the cerebral vasculature. According to this theory, migraine can be effectively treated with triptans, which cause vasoconstriction in the cerebral vessels but have numerous adverse effects due to their nonselective constriction of smooth muscle tissue. They are also contraindicated in some patients with pronounced hypertension or heart disease. CGRP antagonists, which include rimegepant, were developed as an improved therapy for migraine attacks. These medications improve patients' quality of life by minimizing the number of adverse effects by not directly causing vasoconstriction[1].

2 THE PATHOPHYSIOLOGY OF MIGRAINES

2.1 Defining migraines

Migraine is a primary or idiopathic headache that cannot be attributed to a local or systemic pathophysiological process. The syndrome manifests as typical recurrent attacks interrupted by pain-free periods. Currently, many types of migraine are known, the most common being migraine without aura and migraine with aura[2,3]. Rimegepant is already approved for the treatment of the above two types of migraine in the U.S. and the EU. Unlike the FDA, the EMA has approved *rimegepant* for the preventive, rather than curative, treatment of patients with at least four migraine attacks per month[4,5].

The typical clinical manifestation of migraine presents primarily as a moderate to severe, pulsating, unilateral (hence the name migraine - Gr. ημικρανία /hēmikranía/, half head), long-lasting (several hours to several days) headache that worsens with physical exertion. Approximately 20% of migraine patients have headache-related transient focal neurological symptoms called auras. These are mainly visual, varying in complexity, ranging from scotomas (in which parts of the visual field are less clear than others) to metamorphopsia (a syndrome in which the shapes of objects in the visual field are distorted). Paresthesia involving half of the affected person's body is also possible since only one hemisphere of the brain is usually affected. Motor auras and disturbances of both speech and consciousness are possible but rare[2].

2.2 Migraine attacks

The exact mechanism by which migraine attacks are triggered is not yet known. Our current understanding of migraine is based on two leading theories: it occurs as a result of both vascular and neurological aspects. Seizures begin with premonitory symptoms (phase 1) and activation

of the hypothalamus, which in turn triggers a cascade of responses. First, the spinal trigeminal nerve (*nucleus trigeminus caudalis* TNC) in the spinal cord is activated, followed by (usually) unilateral activation of the trigeminal ganglia and, through exocytosis, the release of calcitonin gene-related protein (CGRP). Exocytosis is dependent on three soluble SNARE receptors (SNAP25, syntaxin 1, and synaptobrevin), without which it is not possible. Serotype A botulinum toxin cleaves SNAP25, effectively preventing CGRP release and its consequences[6].

The released CGRP causes vasodilation in the brain, with the central meningeal artery being of particular importance in migraine. In addition, it activates the calcitonin receptor-like receptor/receptor activity modulating protein (CLR/RAMP1) on the Aδ nerve. The activated receptor is G protein-coupled and therefore increases adenylate cyclase activity in the Aδ nerves and subsequently increases the intracellular concentration of cAMP, which eventually lowers the activation threshold of the affected nerves. As a result, even minor stimuli can trigger action potentials in the brain, which travel along the Aδ nerve to the TNC and are eventually interpreted as pain in higher parts of the brain[6].

3 PHARMACOLOGICAL ACTION

3.1 Action principle

The action of rimegepant is based on preventing vasodilation and decreasing excitability of Aδ nerves caused by binding of CGRP to the corresponding receptors in Aδ nerves and cerebral vessels. This mechanism of action differs from the current primary treatment of migraine (with triptans), which is based on 5-$HT_{1B/1D}$ receptor agonism, which can have serious adverse effects due to nonselective vasoconstriction of smooth muscle. "*Gepants*" (*rimegepant*-related drugs) bind to the extracellular domain of CLR/RAMP1, preventing binding of CGRP and subsequent activation of the coupled G_S protein and the resulting cascade (described in 2.2)[3,6].

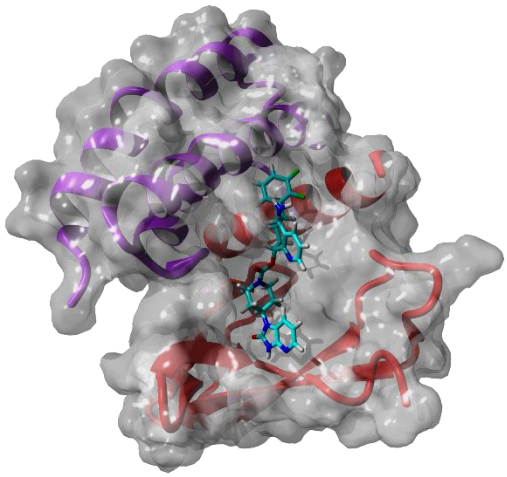
3.2 CGRP receptor binding

The company which developed *rimegepant*, then known as BMS-927711, tested the compound's efficacy in *in vitro* models, however, they did not study how it binds to the CGRP receptor. To date, no high-resolution crystal structure of the complex between *rimegepant* and CLR/RAMP1 has been published, so the exact ligand-receptor interactions are currently unknown. Leung *et al*. used a molecular docking and molecular dynamics simulation approach to investigate the interactions. To reduce the computational cost, they first superimposed the structure of the ECD (from PDB: 3N7R) with the full receptor structure (PDB: 6E3Y). The results showed minimal interactions between the transmembrane domain and the G proteins, allowing them to proceed with docking and dynamics simulations for the lone CLR/RAMP1 complex[7].

The team used Schrödinger Maestro to dock *rimegepant* to the receptor complex and then verified the results using a 1000-nanosecond molecular dynamics simulation between rimegepant and a solvated CLR/RAMP1 complex in water and NaCl. The system was created with an OPLS3e force field using the Desmond System Builder tool. The results show that rimegepant forms important hydrogen bonds between $T112^{ECD}$ (carbonyl and secondary amine group on a dihydroimidazopyridinone skeleton), cation-π interactions (protonated (*S*)-amine), and hydrogen bonds (carbamate group) with $W74^{RAMP1}$, as well as additional interactions with $W84^{RAMP1}$ (not shown in the diagram). *Rimegepant* forms additional π-π bonds with W121 and Y124, and hydrophobic interactions with M43 and W72. The interactions with $W74^{RAMP1}$ are

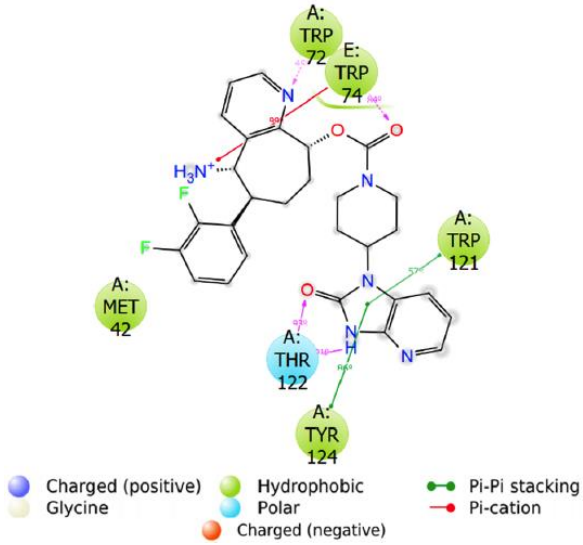
particularly important for selective binding to CLR/RAMP1 because this amino acid residue is not present in other analogs such as CLR/RAMP2 and CLR/RAMP3 (adrenomedullin receptors)[7].

Diagram 1: 3D visualization of rimegepant bound to CLR/RAMP1 complex [modeled after ref.[7]]



Pictured: rimegepant (cyan), RAMP1 (violet), CLR (red) and CLR/RAMP1 complex surface (grey)

Diagram 2: 2D interaction diagram between the ECD of CGRPR and rimegepant[7]

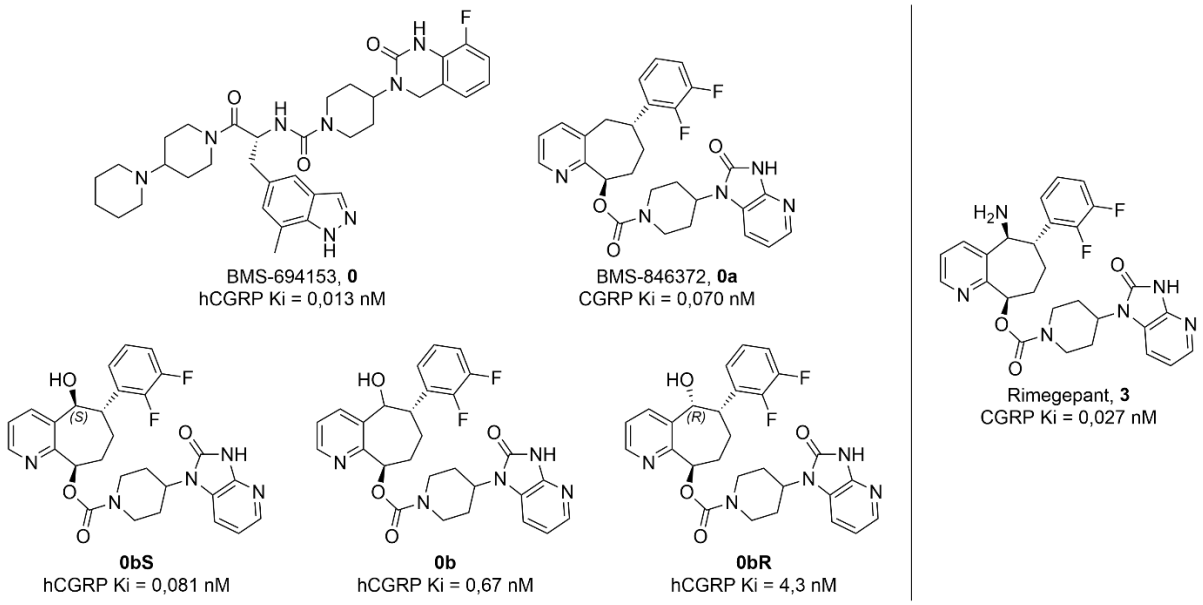


3.3 Adverse effects

In a clinical study of 1186 subjects by Lipton *et al.*, *rimegepant* proved to be an exceptionally safe drug with minimal adverse effects. Nausea (1.8% of users vs. 1.1% in the placebo group) and urologic infections (1.5% of users vs. 1.1% in the placebo group) were reported most frequently. Serious adverse events (back pain) were reported in one patient receiving the drug and two patients receiving the placebo. 2.4% of *rimegepant* users had increased AST or ALT activity, as did 2.2% of the placebo group. Although none of the above adverse effects were statistically significant, any patient may develop hypersensitivity reactions even several days after administration of the drug. In such cases, it is recommended to discontinue treatment [8,9].

4 LEAD COMPOUND OPTIMIZATION

Diagram 3: Design of rimegepant from BMS-694153 [1,10]



Rimegepant development began with compound **0** (BMS-694153), which exhibited a strong affinity (K_i) for the binding site. The compound showed rapid and efficient activity when applied intranasally. While IN use is a potentially attractive route of administration for the treatment of migraine, Luo *et al.* focused primarily on orally active CGRP receptor antagonists and sought to increase the bioavailability of the drug *per os*. In a previous publication[11], Luo *et al*. demonstrated that pyridine was an effective mimetic of the tertiary amide in the structure of CGRP antagonists, and the compound in question retained its efficacy but did not have adequate *per os* bioavailability. The next step was to improve bioavailability by increasing lipophilicity and metabolic stability. Cyclization of the core with the pyridyl segment and replacement of the indazole with a 2,3-difluorophenyl ring resulted in compound **0a** (BMS-846372)[10].

The compound exhibited high bioavailability and potency, but was highly crystalline and consequently poorly water-soluble, limiting its bioavailability and clinical use. Salt formation at the pyridine center (pKa ~ 4) was not possible, because carbamates tend to hydrolyze easily. To increase the hydrophilicity, a polar group was added to the cycloheptapyridine skeleton. First, an alcohol derivative **0b** was synthesized as a racemic mixture (at the –OH group), then the binding affinity for the racemate, **0bS** (*S,S,R*) and **0bR** (*R,S,R*) was investigated. The diastereomer **0bS** (*S,S,R*) exhibited a binding affinity two orders of magnitude higher than **0bR**, so further development focused exclusively on the (*S,S,R*) diastereomer[1].

Finally, to enable salt formation, the team decided to replace the alcohol group with an amine. The resulting compound **3** (*rimegepant*) exhibited an even greater affinity for the binding site compared to the alcohol, presumably due to the additional cation-π binding with $W74^{RAMP1}$. In addition, the new compound exhibited significantly higher bioavailability, resulting in nearly an order of magnitude higher protein-adjusted K_i [1].

Table 1: In vitro hCGRP receptor antagonist data[1,10]

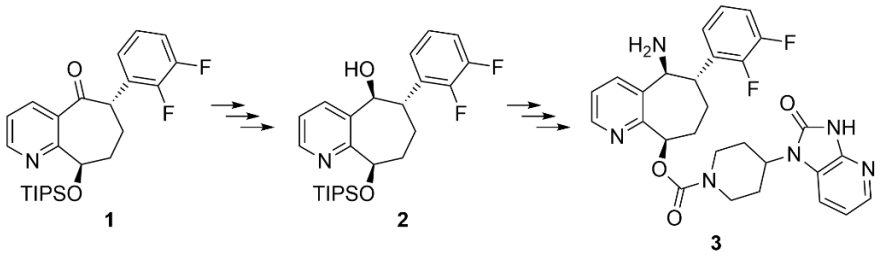
Comp.	hCGRP K_i (nM)	cAMP EC_{50} (nM)	Human f_u	Protein adjusted K_i (nM)[a]	Aq soln (crystalline) (µg/mL)	HMetStab $T_{1/2}$ (min)
0	0,013					
0a	0,070	0,22	2,3	3,0	<2	24
0bR	4,3					
0b	0,67					
0bS	0,081		4,1	2,0	66[b]	70
3	0,027	0,14	6,9	0,39	50	83

Notes: [a]Protein adjusted K_i is defined as K_i/human f_u. [b]Amorphic.

5 SYNTHESIS

5.1 Original process

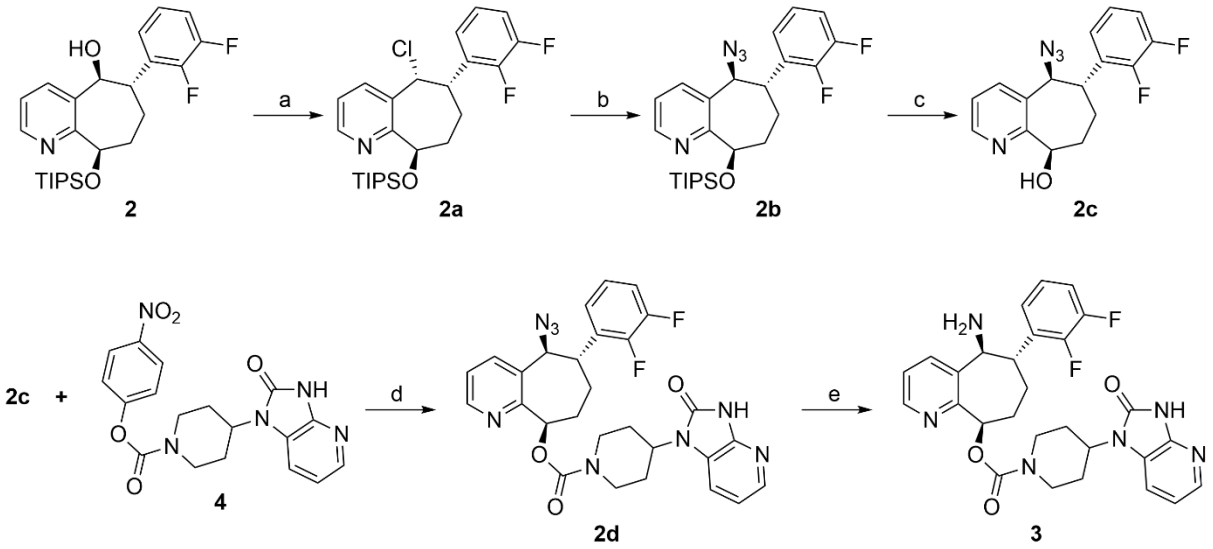
Diagram 4: The main steps in synthesizing rimegepant[1]



In the author's publication (Luo *et al.*), stereoselective synthesis was not the main focus because they worked on a sub-gram scale. An optically pure compound **2** was used as the starting compound for the synthesis, focusing on maintaining the correct configuration on all chiral centers. Compound **2** was obtained by dynamic resolution and diastereoselective reduction of ketone **1** [1].

Leathy *et al*. originally attempted the synthesis using sodium borohydride as the reducing agent, which resulted in a diastereomeric ratio (dr) of 3:1 that was insufficient for further synthesis. Subsequently, reduction was attempted with a more bulky agent, namely lithium tri-(tert-butoxy) aluminum hydride, resulting in a dr of 45:1. Extraction of the alcohol as a salt with HCl gave a dr of 99:1 with a yield of 80%. The diastereoselectivity of the reaction is due to steric hindrance of the *Si* side of the ketone and high torsional forces in the ring system. The tri(isopropyl)silylether (TIPSO) group hinders almost the entire surface of the *Si* side of the cycloheptane ring, making reducing agent attack unlikely. $NaBH_4$ appears to be small enough to attack from both sides, while Li(*t*-BuO)$_3$AlH is large enough to hinder the reaction in sufficient amounts[12].

Diagram 5: Stereospecific synthesis of rimegepant[1]



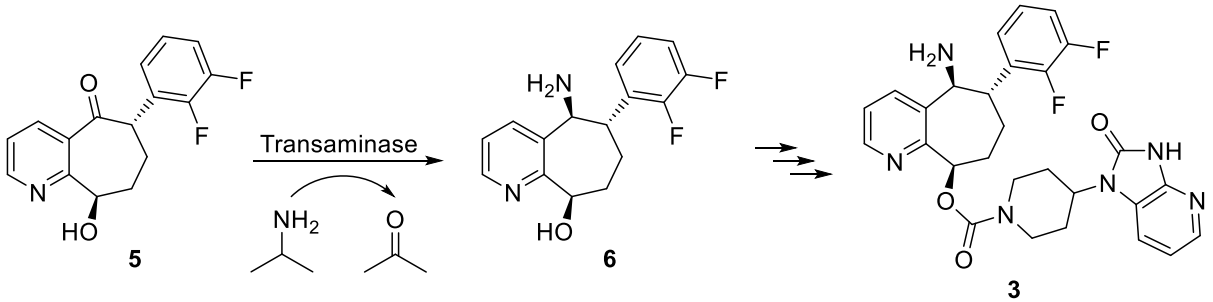
Reagents and conditions: (a) NCS, Ph_3P, THF, rt, 5 h (83%); (b) NaN_3, DMF, 50 °C, 15 h; (c) TBAF, THF, rt, 1.5 h; (d) DMF, NaHMDS, −15 °C to rt, 4 h (73% za 3 korake); (e) PMe_3, THF, H_2O, rt, 5 h (85%).

The next problem in the synthesis of compound **2** was maintaining the correct configuration of C5 in the cycloheptapyridine ring. Luo *et al.* approached the problem with a double inversion[1]. The first chiral inversion with PPh_3 and N-chlorosuccinimide (NCS) via the S_N2 mechanism stereoselectively formed the (R)-chloride **2a** [13]. A second S_N2 substitution of the chlorine with NaN_3 led to further inversion and the formation of the (S)-azide **2b**. After stable formation of the bonding configuration, the TIPSO group was removed and transesterification of the resulting alcohol **2c** with the activated ester **4** was carried out. The transesterification yields compound **2d**, in which the azide must eventually be reduced to an amine to give the *rimegepant* **3**. The reduction was carried out with PMe_3 under reflux for 5 h in THF and H_2O. The authors state that they used an enantiomerically pure alcohol **2** followed by an enantiomerically pure *rimegepant*; however, the enantiomeric excess was not determined[1].

5.2 Improvements

Ma *et al*., in an attempt to improve the original synthesis in terms of green chemistry, efficiency and simplicity, tried to find a new method for the synthesis of *rimegepant*. Biocatalysis using modified transaminases was chosen because it allows milder reaction conditions, as well as higher stereoselectivity, compared to the original method[14].

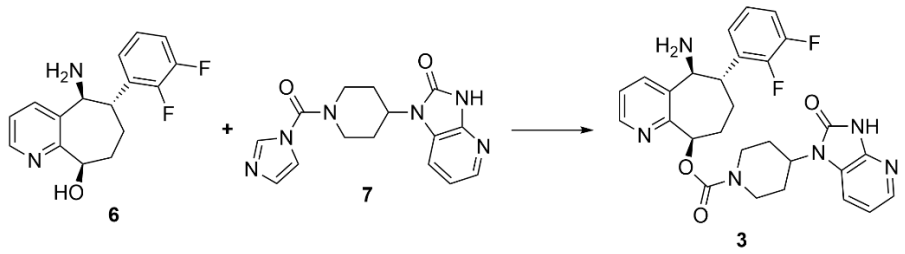
Diagram 6: Transaminase synthesis of rimegepant[14]



A transaminase from *Chromobacterium violaceum* was used as a starting point for the modification to successfully synthesize intermediate **6**. All natural transaminases contain two binding pockets (one large and one small) in their active sites, into which fragments of the substrate are bound. The small pocket binds α-groups (from the carbonyl group); however, it cannot bind fragments larger than a methyl group, making it useless for the synthesis of *gepants*. The enzyme, therefore, had to be mutated to accept substrate **5**. First, an alanine substitution was used to enlarge the binding site of enzyme S6, which showed the strongest activity when screened with a derivative of ketone **6** (without an α-aryl group). The enlargement of the pocket resulted in significantly (even threefold) stronger enzyme activity for the tested substrate; however, due to the unchanged small pocket, there still was no activity with substrate **5**[14].

Surprisingly, the combination of two mutations that by themselves reversed stereoselectivity was the first to show activity, albeit slow, for substrate **5**. L59 proved to be locked in the binding site, while F88 was blocking the entry. Replacement of these groups greatly facilitated substrate entry into the binding site. Further mutations were performed on the flexible loop at the entrance of the substrate tunnel (residues 83-91) and random mutations were performed on the whole enzyme using the error-prone polymerase chain reaction (epPCR). Several iterations finally yielded a mutant enzyme with 19 amino acids altered, allowing 99.9% conversion under optimal conditions with a de from > 99.5% and a yield of 80.5% (after crystallization) at optimal conditions. The results were confirmed in mg, g, and kg scales with nearly identical results. The reaction was carried out in a buffer with a pH of 9.0 and 15% DMSO, as well as i-PrNH$_2$ in excess (20 equivalents). A slight nitrogen gas flow through the solution was used to remove acetone as it could slow down the reaction[14].

*Shema 7: Synthesis of rimegepant from intermediate **6** [15]*



Intermediate **6** can be converted to *rimegepant* in three steps as described in the following experimental procedure: Suspend 1 g of substance **6** in 15 mL of dichloromethane, 5 mL of 20% $NaCO_3$ solution, and 10 mL of H_2O. The two-phase mixture is stirred for 30 min; then the organic phase is separated, and the aqueous layer is discarded. The solvent is then reduced and the mixture azeotropically dried with THF to a final volume of 15 mL. Next, 4 mL of 20% m/m *t*-BuOK in THF is added to the mixture at 20 °C. The reaction mixture is then stirred for 1 h, and the reaction stopped with 5 mL of a 20% NaCl solution and 2.5 mL of a 20% citric acid solution. The organic layer is separated and washed with 15 mL of a 20% NaCl solution, subsequently, the solvent is removed in a rotary evaporator until a viscous oil is obtained. The oil is dissolved, dried over $MgSO_4$, and spun again in a rotary evaporator until an oil is obtained. The compound is finally crystallized from a mixture of EtOH and heptane to give a white crystalline compound **3** (1.14 g; 78.3% yield)[15].

6 PHARMACOKINETICS

6.1 Absorption & distribution

Rimegepant is available in the form of orodispersible tablets for oral administration. For the treatment of acute migraine attacks, the recommended dosage is 75 mg (one tablet) of *rimegepant*, while for prophylaxis, the dosage is 75 mg every two days. The maximum daily dose is 75 mg, but no safety data are currently known for more than 18 doses in a 30-day period[4].

The maximum plasma concentration of the active ingredient was reached 1.5 hours after application, and the absolute bioavailability was 64%. Application with a fat-containing meal delayed TMAX by 1 hour, while CMAX and AUC were reduced by 42-53% and 32-38%, respectively. The volume of distribution at a steady state was determined to be 120 L, while the fraction bound to plasma proteins was 96 % [9,16].

6.2 Metabolism & elimination

The drug is metabolized mainly by CYP3A4 and to a lesser extent by CYP2C9. 77% of the compound is excreted without biotransformation at $t_{1/2}$ = 11 h. Elimination is mainly fecal (78%), while a smaller percentage is excreted in the urine (24%). *Rimegepant* is a substrate for P-gp and BCRP efflux transporters, so ingestion of the drug in combination with P-gp and BCRP inhibitors may result in higher plasma concentrations (a similar effect may occur with inducers). Because *rimegepant* is a CYP3A4 substrate, increased accumulation with grapefruit may occur. Although most of the drug is excreted unmetabolized, it is advisable to avoid inducers and/or inhibitors of P-gp, BCRP, CYP3A4, and CYP2C9 due to a lack of interaction safety studies. Gender, race, age, body weight, and CYP2C9 genotype do not affect the pharmacokinetics of rimegepant[9].

7 CONCLUSION

Rimegepant is an effective new drug for the treatment and prevention of migraine attacks with a much better safety profile than current treatments. It represents a promising advance in the field of treating an increasingly detrimental disease, which represents a burden to not only the lives of individuals in the form of psychosocial stress for the patient as well as their loved ones, but also society and the economy. The compound could also present a starting point for a new class of drugs that could improve the lives of individuals and society as a whole.

8 REFERENCES

(1) Luo, G.; Chen, L.; Conway, C. M.; Denton, R.; Keavy, D.; Signor, L.; Kostich, W.; Lentz, K. A.; Santone, K. S.; Schartman, R.; Browning, M.; Tong, G.; Houston, J. G.; Dubowchik, G. M.; Macor, J. E. Discovery of (5 *S* ,6 *S* ,9 *R*)-5-Amino-6-(2,3-Difluorophenyl)-6,7,8,9-Tetrahydro-5 *H* -Cyclohepta[*b*]Pyridin-9-Yl 4-(2-Oxo-2,3-Dihydro-1 *H* -Imidazo[4,5- *b*]Pyridin-1-Yl)Piperidine-1-Carboxylate (BMS-927711): An Oral Calcitonin Gene-Related Peptide (CGRP) Antagonist in Clinical Trials for Treating Migraine. *J. Med. Chem.* **2012**, *55* (23), 10644–10651. https://doi.org/10.1021/jm3013147.

(2) *Patološka fiziologija: učbenik za študente farmacije*; Pirkmajer, S., Ed.; Medicinska fakulteta, Institut za patolosko fiziologijo: Ljubljana, 2019.

(3) Dubowchik, G. M.; Conway, C. M.; Xin, A. W. Blocking the CGRP Pathway for Acute and Preventive Treatment of Migraine: The Evolution of Success. *J. Med. Chem.* **2020**, *63* (13), 6600–6623. https://doi.org/10.1021/acs.jmedchem.9b01810.

(4) *NURTEC ODT - Rimegepant Sulfate Tablet, Orally Disintegrating [Package Insert]*; Biohaven Pharmaceuticals, Inc: New Haven, CT, 2021.

(5) *CHMP Summary of Positive Opinion for Vydura*; EMA/CHMP/106030/2022; EMA CHMP: Amsterdam, NL, 2022; p 1.

(6) Haanes, K. A.; Edvinsson, L. Pathophysiological Mechanisms in Migraine and the Identification of New Therapeutic Targets. *CNS Drugs* **2019**, *33* (6), 525–537. https://doi.org/10.1007/s40263-019-00630-6.

(7) Leung, L.; Liao, S.; Wu, C. To Probe the Binding Interactions between Two FDA Approved Migraine Drugs (Ubrogepant and Rimegepant) and Calcitonin-Gene Related Peptide Receptor (CGRPR) Using Molecular Dynamics Simulations. *ACS Chem. Neurosci.* **2021**, *12* (14), 2629–2642. https://doi.org/10.1021/acschemneuro.1c00135.

(8) Lipton, R. B.; Croop, R.; Stock, E. G.; Stock, D. A.; Morris, B. A.; Frost, M.; Dubowchik, G. M.; Conway, C. M.; Coric, V.; Goadsby, P. J. Rimegepant, an Oral Calcitonin Gene–Related Peptide Receptor Antagonist, for Migraine. *N Engl J Med* **2019**, *381* (2), 142–149. https://doi.org/10.1056/NEJMoa1811090.

(9) Szkutnik-Fiedler, D. Pharmacokinetics, Pharmacodynamics and Drug–Drug Interactions of New Anti-Migraine Drugs—Lasmiditan, Gepants, and Calcitonin-Gene-Related Peptide (CGRP) Receptor Monoclonal Antibodies. *Pharmaceutics* **2020**, *12* (12), 1180. https://doi.org/10.3390/pharmaceutics12121180.

(10) Luo, G.; Chen, L.; Conway, C. M.; Denton, R.; Keavy, D.; Gulianello, M.; Huang, Y.; Kostich, W.; Lentz, K. A.; Mercer, S. E.; Schartman, R.; Signor, L.; Browning, M.; Macor, J. E.; Dubowchik, G. M. Discovery of BMS-846372, a Potent and Orally Active Human CGRP Receptor Antagonist for the Treatment of Migraine. *ACS Med. Chem. Lett.* **2012**, *3* (4), 337–341. https://doi.org/10.1021/ml300021s.

(11) Luo, G.; Chen, L.; Civiello, R.; Pin, S. S.; Xu, C.; Kostich, W.; Kelley, M.; Conway, C. M.; Macor, J. E.; Dubowchik, G. M. Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists: Pyridine as a Replacement for a Core Amide Group. *Bioorganic & Medicinal Chemistry Letters* **2012**, *22* (8), 2917–2921. https://doi.org/10.1016/j.bmcl.2012.02.065.

(12) Leahy, D. K.; Fan, Y.; Desai, L. V.; Chan, C.; Zhu, J.; Luo, G.; Chen, L.; Hanson, R. L.; Sugiyama, M.; Rosner, T.; Cuniere, N.; Guo, Z.; Hsiao, Y.; Gao, Q. Efficient and Scalable Enantioselective Synthesis of a CGRP Antagonist. *Org. Lett.* **2012**, *14* (18), 4938–4941. https://doi.org/10.1021/ol302262q.

(13) Jaseer, E. A.; Naidu, A. B.; Kumar, S. S.; Rao, R. K.; Thakur, K. G.; Sekar, G. Highly Stereoselective Chlorination of β-Substituted Cyclic Alcohols Using PPh3–NCS: Factors That Control the Stereoselectivity. *Chem. Commun.* **2007**, No. 8, 867–869. https://doi.org/10.1039/B614512D.

(14) Ma, Y.; Jiao, X.; Wang, Z.; Mu, H.; Sun, K.; Li, X.; Zhao, T.; Liu, X.; Zhang, N. Engineering a Transaminase for the Efficient Synthesis of a Key Intermediate for Rimegepant. *Org. Process Res. Dev.* **2022**, acs.oprd.1c00376. https://doi.org/10.1021/acs.oprd.1c00376.

(15) Leahy, D. K.; Fan, Y.; Chan, C.; Desai, L. V.; Patel, S. S.; Sugiyama, M. Process for the Preparation of Cycloheptapyridine Cgrp Receptor Antagonists. WO2012050764A1, April 19, 2012.

(16) Ramasubbu, S. K.; Dakshinamurthy, S.; Palepu, S.; Bandyopadhyay, A.; Rajendran, S. K. Rimegepant: First Novel Oral Calcitonin Gene-Related Peptide Inhibitor for Migraine. *International Journal of Basic & Clinical Pharmacology* **2020**, *9* (5), 829–832. https://doi.org/10.18203/2319-2003.ijbcp20201768.