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A Review on Ozanimod Drug used in Multiple Sclerosis and Ulcerative Colitis

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ABSTRACT

ZEPOSIA® Ozanimod is the first S1PR modulator to receive approval in the United States and the European Union (EU). This oral treatment is administered once daily for both induction and maintenance therapy. In clinical trials (Touchstone and True North), Ozanimod demonstrated the ability to induce and maintain clinical remission in adult patients with moderate to severe colitis who had not responded well to conventional therapy or biologic treatment. The studies showed that Ozanimod was generally well-tolerated, with only mild and temporary adverse reactions. The recent Touchstone and True North data, including the open-label extension, align with the findings of the main studies in terms of therapeutic effectiveness and tolerability. No new safety concerns have emerged. While further data will provide more insights into the use of ozanimod, it expands the treatment options available for adults with moderate to severe colitis.

Key Words - Ozanimod, Ulcerative colitis, Multiple Sclerosis, spingosin-1-phosphate receptor modulator, chronic pain

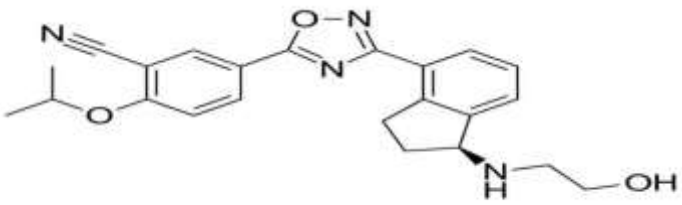
Introduction-

Ozanimod, also known as ZEPOSIA, is an S1PR modulator that gained approval from the FDA in March 2020 for the treatment of RRMS, SPMS, and CIS. ZEPOSIA is the sole S1PR drug currently sanctioned in the United States by the FDA. Unlike other medications in its category, there is no requirement for genetic testing or monitoring post initial dosing. ZEPOSIA

is an oral S1PR drug that targets peripheral lymphocytes in circulation within the gastrointestinal tract.Multiple sclerosis (MS) is a prevalent and debilitating neurological condition globally. It is characterized by chronic inflammation leading to widespread neurodegeneration and the development of demyelinating plaques in the central nervous system. Approximately 2.5 million individuals worldwide are affected by MS, with most individuals experiencing symptoms between the ages of 20 and 40. Women are more commonly affected than men, with a prevalence ratio of nearly 3:1. The exact cause of MS remains unknown, but it is believed to develop in genetically predisposed individuals exposed to environmental and immune triggers. Various environmental and lifestyle factors, such as Vitamin D deficiency, limited sun exposure, Epstein–Barr virus, smoking, and obesity, have been implicated in the onset of MS. Sphingosine-1-phosphate receptors (S1PR) play a critical role in cellular processes like migration, proliferation, and differentiation. These receptors encompass multiple subtypes (S1PR1 to S1PR5), each contributing to distinct functions..

S1PR1, expressed by immune cells, plays a crucial role in regulating lymphocyte movement and preventing their migration to sites of inflammation by impeding their exit from lymph nodes. Ozanimod, a sphingosine-1-phosphate (S1P) modulator, effectively blocks the trafficking of lymphocytes from lymph nodes to the bloodstream. This medication has been granted approval by the US Food and Drug Administration (FDA) for treating relapsing multiple sclerosis and has recently been authorized for managing moderate to severe ulcerative colitis (UC). Multiple sclerosis (MS) is an inflammatory condition impacting the central nervous system, with a global prevalence of nearly 3 million individuals.

STRUCTURE



Ozanimod also called Zeposia

IUPAC Name 5-[3-[(1*S*)-1-(2-hydroxyethylamino)-2,3-dihydro-1*H*-inden-4-yl]-1,2,4-oxadia. zol-5-yl]-2-propan-2-yloxybenzonitrile

Molecular Weigh Average: 404.47

Monoisotopic: 404.184840649

Chemical Formul -. $C_{23}H_{24}N_4O_3$

Boiling Poin - 648.3±65.0

Melting Point -. 134-137

PHARMACOKINETIC STUDY

immersion and distribution

Ozanimod, an oral drug, is absorbed in the gastrointestinal tract and reaches its peak attention(Cmax) of0.244 ng/ mL within 6 to 8 hours after administration. The volume of distribution of Ozanimod ranges from 73 to 101 L/ kg. When taken on an empty stomach, the median Tmax for single boluses is between8.0 to12.0 hours, and for multiple boluses, it's8.0 hours. Clinical trials have demonstrated a cure-commensurable increase in Cmax and the area under the tube- attention- time wind(AUC). The input of food doesn't affect the exposure of Ozanimod and its active metabolites. thus, the drug can be taken without food. Co-administration with a high- fat mess doesn't significantly impact the rate and extent of immersion. still, it's important to avoid consuming foods high in tyramine(further than 150 mg) while taking Ozanimod, as it may increase perceptivity to tyramine and potentially lead to severe hypertension.

Volume of distribution

The average apparent volume of distribution for Ozanimod is 5590L.

Tube protein binding

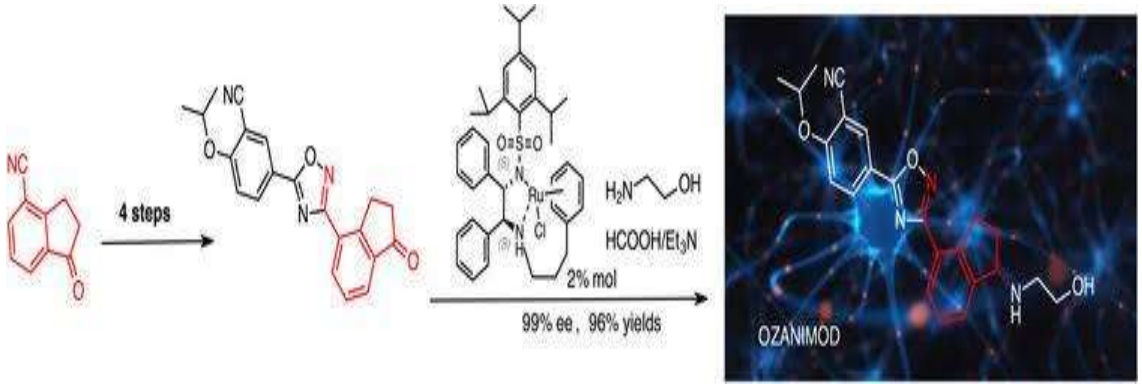
The probabilities of tube protein binding for Ozanimod, CC112273, and CC1084037 are98.2,99.8, and99.3, independently.

Oral Tmax

The time it takes for Ozanimod to reach its peak tube attention(Tmax) orally is roughly 6 to 8 hours. The Tmax for the primary active metabolite RP112273 varies, with median values ranging from 6 to 10 hours.

METABOLISM

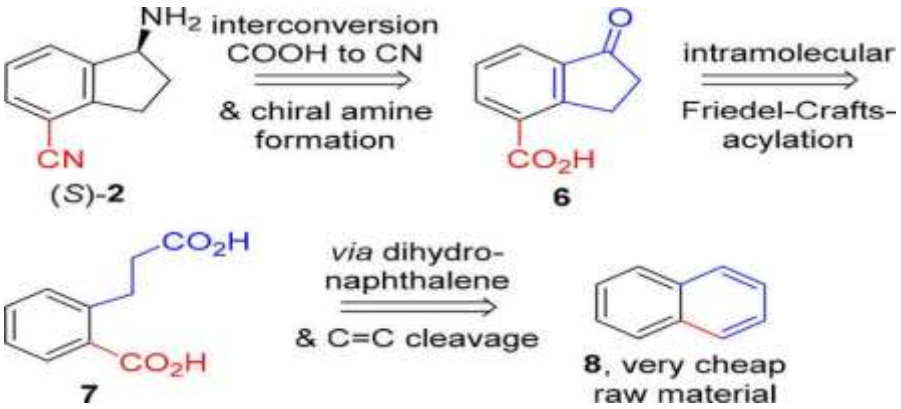
Ozanimod is primarily metabolized by the liver's cytochrome P4502C8(CYP2C8) system, with some involvement from CYP3A4, to produce its active metabolite. The elimination of Ozanimod doesn't primarily do through the feathers. The situations of Ozanimod and its active metabolites may be told by the coadministration of CYP2C8 impediments or corrupters . Ozanimod undergoes metabolism through colorful pathways, performing in the conformation of multiple circulating metabolites, similar as CC112273 and CC1084037, which partake analogous characteristics with Ozanimod. still,



METABOLIC PATHWAY

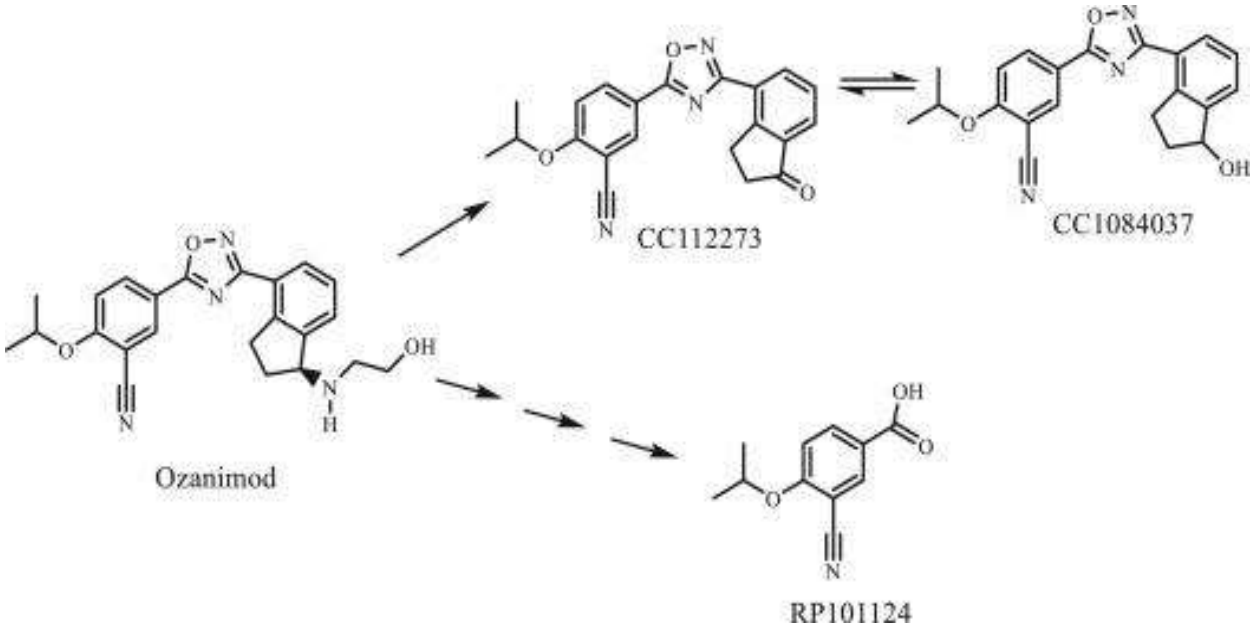
Ozanimod is extensively metabolized in humans, leading to the production of over 13 metabolites found in plasma, urine, and feces. These metabolites consist of CC112273 (also known as RP112273), CC1084037 (also known as RP100798), RP101988, RP101075, RP112289, RP101442, and an inactive metabolite named RP101124. Both Ozanimod and its active metabolites demonstrate similar activity and selectivity towards S1P1 and S1P5 receptors. Following repeated administration of Ozanimod to healthy subjects, around 6% of the total active drug exposure in circulation is attributed

to Ozanimod itself, while CC112273 and CC1084037 contribute to approximately 73% and 15% of the exposure, respectively. The metabolism of Ozanimod involves various enzyme systems.



Inducer/Inhibitor

Ozanimod, together with its primary metabolites CC112273 and CC1084037, does not demonstrate any inhibitory properties on CYPs 1A2, 2B6, 2C19, 2C8, 2C9, 2D6, and 3A. Additionally, it does not elicit any effects on CYPs 1A2, 2B6, and 3A.



ELIMINATION

Ozanimod is eliminated through the urinary tract, with an average excretion of 0.03% to 0.06% for a single oral dose. In a 7-day treatment plan, the excretion rate ranges from 0.04% to 0.09%, while in a 28-day regimen, it falls between 0.03% and 0.06%. The renal clearance of Ozanimod varies, with a single dose ranging from 0.116 to 0.287 L/h, a 7-day dosing regimen from 0.189 to 0.435 L/h, and a 28-day regimen from 0.229 to 0.291 L/h. It is worth noting that renal clearance does not have a significant impact on the excretion of Ozanimod.

1^0 excretion

After the administration of a single oral dose of [14C]- ozanimod HCl, the total radioactivity retrieved was found to be 63%. Specifically, 26% of the radioactivity was recovered from urine, while 37% was recovered from feces. The reduced retrieval of the entire radioactivity can be attributed to the prolonged half-life of the total radioactivity, which lasts for approximately 99 hours.

Half life

1. Ozanimod has a half-life (t½) of around 20 hours, while RP112273 and CC1084037 have a half-life of approximately 280 hours.

PHARMACODYNAMIC STUDY

Ozanimod functions as a potent modulator of S1PR, specifically targeting S1PR1 and S1PR5, with a strong binding affinity [26]. In laboratory experiments, its primary active metabolites (CC112273 and CC1084037) have exhibited similar levels of activity and selectivity for these two receptors [24,25]. It is worth noting that Ozanimod has minimal to no impact on S1PR2, S1PR3, and S1PR4 [26]. While Ozanimod may temporarily decrease heart rate, it does not prolong the QTc interval or cause any clinically significant bradycardia [24,25].

Ozanimod demonstrates selectivity for S1PR1 over S1PR5, acting as an agonist for both receptors. Its interaction with S1PR leads to the internalization of the receptor and subsequent degradation through the ubiquitin-proteasome pathway. This prevents the reinstallation of the receptor in the cellular membrane, resulting in the inhibition of lymphocyte egress from lymph nodes. Consequently, there is a decrease in the absolute lymphocyte count (ALC). The reduction in ALC is dependent on the dosage, reaching a plateau effect at a dose of 1 mg/d. Ozanimod specifically affects certain subtypes of lymphocytes, particularly CD4+ CCR7+ and CD8+ CCR7+ T cells. Other S1P modulators have also demonstrated this selectivity for lymphocyte subsets, indicating a class-wide ability to target the immunopathologic pathway of multiple sclerosis (MS) while maintaining protective immunity. Previous studies have shown that the effects of ozanimod are rapidly reversible, with ALC returning to normal within 48-72 hours after discontinuation of the drug.

In addition to its impact on circulating lymphocytes, ozanimod has also been suggested to possess a neuroprotective effect. This hypothesis is based on a study where ozanimod demonstrated beneficial effects on mice with experimental autoimmune encephalomyelitis (EAE), even when the ALC was within the normal range.

THERAPEUTIC EFFICACY

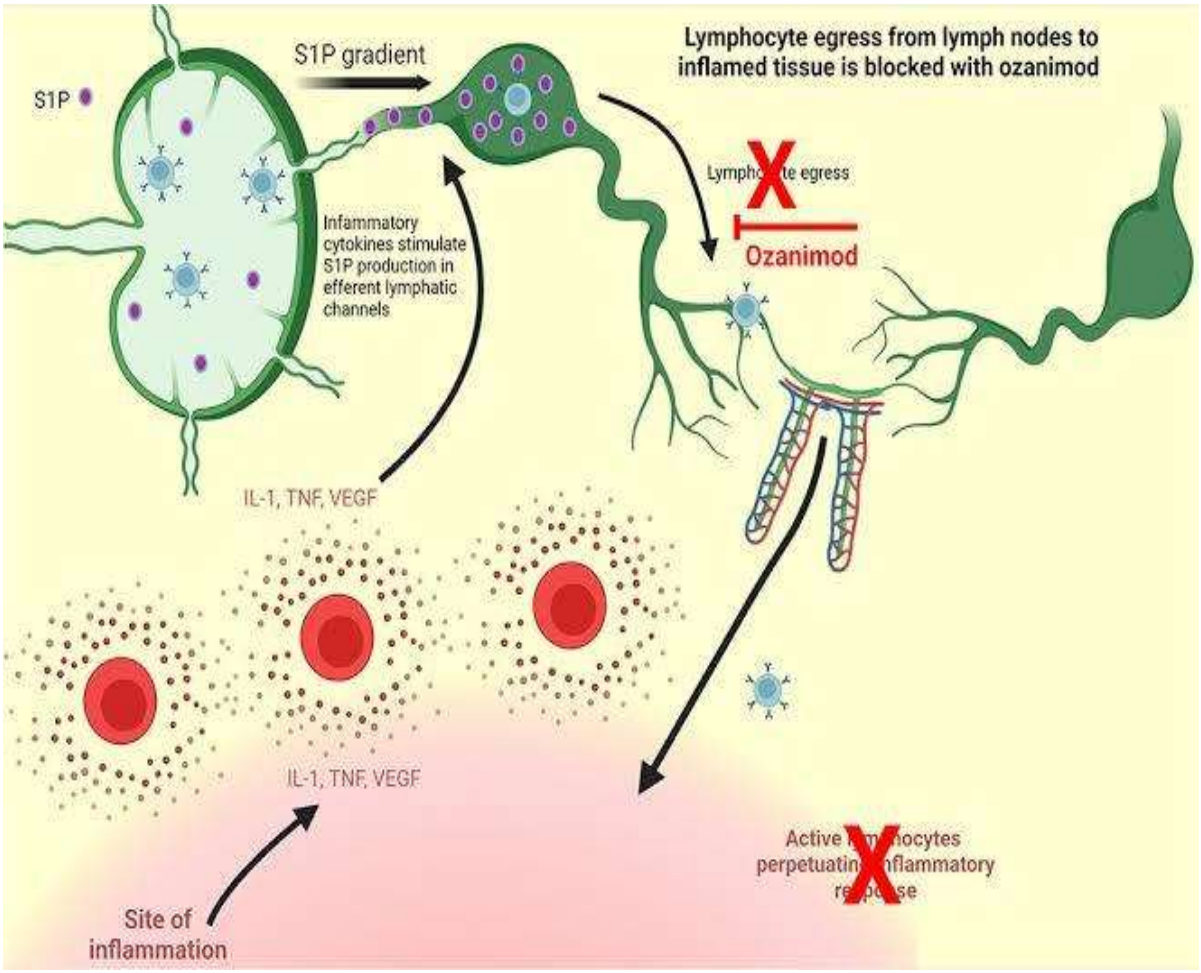
The efficacy of ozanimod in adults with moderately to severely active ulcerative colitis was assessed in two randomized, double-blind, placebo-controlled trials conducted across multiple countries. These trials include the 52-week pivotal phase 3 True North clinical trial, which involved 1012 participants, and the 32-week phase 2 Touchstone trial, which included 197 participants. Both trials consisted of an induction phase and a maintenance phase, followed by the opportunity for patients to participate in the open-label extension (OLE) of the respective trials. This section primarily focuses on the pivotal True North trial, while also incorporating additional insights from the Touchstone trial. The trial design for True North has been thoroughly described.

Table 1. Clinical Efficacy and Safety.

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Tran J. et al. (2017) [112]	Phase 1 single-center, randomized, double-blind, placebo-controlled study comparing single-ascending doses of ozanimod 0.3, 1, 2, or 3 mg; 7-day multiple ascending-doses of ozanimod 0.3, 1, or 2 mg; 28-day multiple ascending-doses of ozanimod of 0.3, 1, or 1.5 mg; a dose-escalation protocol up to ozanimod 2 mg; and placebo in 88 healthy subjects.	A dose-dependent negative chronotropic effect occurred on day 1 with ozanimod. This effect was mitigated in the dose-escalation cohort.	The dose escalation protocol appears to be a safer approach to dosing and has been carried forward into subsequent clinical trials.
Tran J. et al. (2018) [114]	Phase 1 single-center, randomized, double-blind, placebo-controlled, positive-controlled, parallel-group thorough QT/QTc study comparing ozanimod 0.25, 0.5, 1, and 2 mg to placebo in healthy subjects.	One ozanimod-treated subject and one placebo-treated subject had a QTcF > 450 ms; no subjects had a QTcF > 480 ms. There were no clinically significant effects on the PR or QRS intervals. The incidence of adverse effects was similar between ozanimod-treated and placebo-treated groups.	Ozanimod does not prolong the QTc interval at therapeutic or supratherapeutic doses. There were no safety issues discovered during this study.
Cohen J. et al. (2016) [115]	Phase 2 multi-center, randomized, double-blind, placebo-controlled clinical trial (RADIANCE) comparing ozanimod 0.5 and 1 mg with placebo in subjects with relapsing multiple sclerosis over 24 weeks.	The mean cumulative number of gadolinium-enhancing lesions on MRI was reduced with both doses of ozanimod: 1.5 with ozanimod 0.5 mg and 1.5 with ozanimod 1 mg versus 11.1 with placebo. The most common TEAEs were nasopharyngitis and headache. There were no serious infectious or cardiac adverse events and no cases of macular edema.	Ozanimod was effective in reducing MRI lesion activity and was well tolerated in participants with RRMS.
Cohen J. et al. (2019) [99]	Dose-blinded 2-year extension of the RADIANCE phase 2 study; participants previously assigned ozanimod continued at the same dose and participants previously assigned placebo were randomized to ozanimod 0.5 or 1 mg.	The number of gadolinium-enhancing lesions and new or enlarging T2 lesions were low in all treatment groups throughout the study period. The TEAEs reported in this study were consistent with those seen during the 24-week RADIANCE phase 2 study. There were no clinically significant cardiac TEAEs. There were four cases of increased ALT that led to study discontinuation; all recovered after drug cessation.	Ozanimod demonstrated continued efficacy in participants previously assigned ozanimod and reached similar efficacy in participants who were previously assigned placebo. Ozanimod continued to be well tolerated with no safety issues discovered. The incidence of TEAEs did not appear to increase over time and was similar between the two doses.

MECHANISM OF ACTION

Ozanimod, in addition to its active metabolites S1P1 and S1P5, functions as agonists. It results in the retention of lymphocytes in lymphoid tissues and a decrease in the number of lymphocytes in the peripheral blood, which is dependent on the dosage. The therapeutic benefits of ozanimod in multiple sclerosis (MS) may be attributed to the reduction in lymphocyte migration into the central nervous system. Ozanimod, also known as Zeposia, is an immunomodulatory medication prescribed for clinically isolated syndrome, relapsing-remitting, and secondary progressive forms of MS. This oral medication alters the progression of the disease by selectively influencing the activity of sphingosine-1-phosphate receptor-1 (S1P1) and receptor-5 (S1P5).



DOSSAGE AND ADMINISTRATION

Oral ozanimod has been granted approval for the treatment of adults with moderately to severely active ulcerative colitis in the United States [25]. In the European Union, it is approved for adults with moderately to severely active ulcerative colitis who have not responded well to, or cannot tolerate, conventional therapy or a biologic [24]. The recommended initial dose of ozanimod is 0.23 mg once daily with a 7-day titration period, followed by a maintenance dosage of 0.92 mg once daily. Patients have the option to take the capsules with or without food [24,25]. Prior to and during ozanimod treatment, patients should undergo evaluation of complete blood count, cardiac and liver function, vaccination history, as well as review of current or past medications [24,25].

Dose proportion

The dose proportionality of ozanimod and CC112273 increased as the dose range escalated from 0.5 mg to 1 mg.

CONTRAINDICATIONS

.Individuals with immunodeficiency, severe liver impairment, or a history or presence of second-degree atrioventricular block Type II, third-degree atrioventricular block, or sick sinus syndrome should not use Ozanimod, unless they have a functioning pacemaker [24,25]. While taking Ozanimod, there is a temporary reduction in the number of lymphocytes in the peripheral blood. However, it is crucial to avoid consuming foods that contain a significant amount of tyramine (more than 150 mg) as it can heighten sensitivity to tyramine and potentially result in the development of severe hypertension [34].

Tolerability

Ozanimod displayed favorable tolerability in cases with relatively to oppressively active ulcerative colitis in phase 2 and 3 clinical trials. In the True North study, after 52 weeks, adverse events were observed in around 40 and 49 of cases entering ozanimod during the induction and conservation phases, independently, as opposed to 38 and 37 of those on a placebo. Pooled data from the induction phases of the True North and Touchstone studies indicated that the most frequent adverse events linked to ozanimod0.92 mg(with an prevalence of ≥ 2 and ≥ 1 advanced than placebo) were upper respiratory infection(5 vs 4 in the separate groups), increased liver test(5 vs 0), headache(4 vs 3), pyrexia and nausea(3 vs 2 each), and arthralgia(3 vs

1). Throughout the True North conservation phase, adverse events in cases entering ozanimod with an prevalence of ≥ 4 and ≥ 1 advanced than placebo were increased liver test(11 vs 2) and headache(5 vs< 1).

In both the induction and conservation phases of the True North study, roughly 5 of ozanimod donors encountered serious adverse events(SAEs). This is in discrepancy to 3 and 8 of placebo donors in the separate phases. Regarding SAEs related to treatment, four cases(0.5) endured them during the induction phase, while none passed during conservation. On the other hand, two placebo donors(0.9) educated SAEs during induction, and one(0.4) during conservation. The specific SAEs weren'tdetailed.During the conservation phase, one case from each group(ozanimod and placebo) reported hypertensive extremity as a SAE. nonetheless, neither of them discontinued treatment as a result. In terms of treatment termination due to adverse events,3.5 and1.3 of ozanimod donors discontinued during the induction and conservation phases, independently.

CURRENT STATUS OF OZANIMOD IN ULCERATIVE COLITIS

The main goal of managing ulcerative colitis in adults is to achieve a sustained response and prolonged periods of remission without relying on steroid treatment [36]. Current guidelines propose the use of oral corticosteroids (such as prednisolone) to induce remission in cases of moderately to severely active ulcerative colitis, particularly for patients who did not respond well to sulfasalazine or aminosalicylate therapy [37]. However, the long-term use of systemic corticosteroids is not advised for maintaining remission due to significant safety concerns [38]. Alongside corticosteroids, anti-TNF agents (such as infiximab, adalimumab, and golimumab), vedolizumab, tofacitinib, or ustekinumab are also recommended for inducing remission and can be continued as maintenance therapy if the patient responds well to the initial treatment [38,39]. It is important to acknowledge that the effectiveness of these biologics may decrease over time [40].

Source: Celgene Earnings Releases

SAFETY

No significant variations were noted among the groups in the most frequently reported adverse events during the trial (Table 2). A single patient in the 0.5-mg ozanimod group, who exhibited preexisting bradycardia (heart rate of 50 beats per minute and a PR interval of 198 msec before starting ozanimod treatment), experienced first-degree atrioventricular block and sinus bradycardia on day 8 (heart rate, 46 beats per minute; PR interval, 201 msec [upper limit of the normal range, 200 msec]); this incident was asymptomatic and temporary, resolving without any intervention. Subsequently, the patient discontinued treatment. Additionally, four patients administered ozanimod (one patient receiving 0.5 mg and three receiving 1 mg) displayed an elevation in alanine aminotransferase levels exceeding 3 times the upper limit of the normal range during treatment. Furthermore, squamous-cell carcinoma of the skin emerged in a patient who received 1 mg of ozanimod; this individual had previously undergone mercaptopurine treatment for over 2 years.

Exposure	Ozanimod 0.5 mg N=979	Ozanimod 1 mg n=965
≥ 6 months	939 (95.9%)	932 (96.6%)
≥ 12 months	820 (83.8%)	818 (84.8%)
≥ 18 months	407 (41.6%)	416 (43.1%)
≥ 24 months	291 (29.7%)	299 (31.0%)

Applications

1.Multiple sclerosis

Zeposia is indicated for the treatment of active relapsing remitting multiple sclerosis (RRMS) in adult patients, based on clinical or imaging features.

2. Ulcerative colitis

Zeposia has been authorized for the treatment of adult individuals suffering from moderately to severely active ulcerative colitis (UC) who have shown inadequate response, loss of response, or adverse reactions to conventional therapies or biologic drugs.

Conclusion

Our understanding of the pathophysiology of multiple sclerosis and its clinical consequences has greatly increased over time. The management of this condition has become more complex as a result of the numerous pharmacological treatments now accessible to healthcare providers.

Acknowledgement

I am deeply grateful and sincerely appreciate the invaluable guidance, motivation, and direction provided by my esteemed mentor, Miss Moon, throughout my project. Furthermore, I would like to extend my gratitude to the professors of the Pharmaceutical Chemistry department for their unwavering support, innovative ideas, encouragement, and assistance.

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