A Report on Comparative Safety and Efficacy of Ponesimod in the treatment of Multiple Sclerosis (MS)

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Introduction

MS is traditionally considered to be an inflammatory autoimmune disease of the central nervous system (CNS) which is mediated by an aberrant lymphocyte attack directed against CNS elements. Although the auto-antigen has not yet been discovered, it is assumed that the auto-reactive immune response in MS patients is directed against a distinct component (or various components) of the myelin sheath ultimately leading to formation of inflammatory CNS lesions[1, 2]. The inflammatory attacks do not just destroy the myelin sheath (i.e., demyelination) but as well affect the integrity of neuronal structures such as axons, dendrites, synapses or even entire nerve cells[3,4]. Given its indisputable inflammatory character, neurodegeneration in MS is commonly considered to be a direct consequence of inflammatory attacks. Following this concept, recruited peripheral immune cells release inflammatory mediators leading to neuronal damage. However, some authors believe that inflammation and neurodegeneration are two separate aspects of MS, especially during the progressive disease stage[5, 6].

Sphingosine 1-phosphate (S1P) is a bioactive sphingolipid that regulates a variety of physiological processes including lymphocyte recirculation and cardiac function. There are five known members of the sphingosine-1-phosphate (S1P) receptors (S1P1, S1P2, S1P3, S1P4, S1P5)[7]. These receptors are differentially expressed on various cell types, including lymphocytes[8,9], cardiomyocytes and brain cells[10,11]. S1P1, S1P2, and S1P3 receptors are all present in the heart[11] and S1P1, S1P3 and S1P5 are expressed in atrocytes and oligodendrocytes[12-14].

Fingolimod, the first oral disease-modifying therapeutic agent to be approved for the treatment of MS by USFDA, is a pro-drug which is rapidly converted in vivo into the active S-Fingolimod-phosphate (FTY720-P) which is a potent agonist on S1P1, S1P3, S1P4 and S1P5 receptors. Since S1P-receptors are ubiquitinated and subsequently degraded when exposed to Fingolimod[15].

In general, Fingolimod has a favorable benefit-risk profile[16]. However, a critical challenge of Fingolimod therapy still remains in the initiation phases due to the risk of cardiac events. The first dose of Fingolimod is associated with a decrease in heart rate and slowing of atrioventricular conduction[17-19]. The discovery of the S1P3 receptor mediating bradycardia in mice[20] prompted the search for S1P-receptor modulators devoid of S1P3 signaling. This effort led to the discovery of Siponimod (also called BAF312), which is a selective modulator of S1P1 and S1P5 receptors. Siponimod was furthermore designed to have a relatively short elimination half-life that provides a rapid recovery of blood lymphocyte counts on stopping treatment, but would allow once-daily oral dosing[21].

Dimethyl fumarate (DMF) was approved by the US Food and Drug Administration and European Medicines Agency during March 2013 for relapsing forms of MS. Though recently approved for relapsing forms of MS, DMF use for psoriasis dates back to 1990s and has widely published favorable efficacy and safety data in the literature[22]. DMF is one of the first-line agents for treatment of new-onset RRMS with intermediate disease activity[23]. Due to ease of administration, favorable efficacy and adverse effect profile, DMF was one of the most prescribed oral medication post approval[24].

The exact mechanism of action of DMF has not yet been fully elucidated. Most studies conducted so far propose that the therapeutic benefits of DMF are primarily through immunomodulatory and antioxidative mechanisms[25].

Janssen, a subsidiary of Johnson & Johnson, presented positive top-line results from the Phase III OPTIMUM study for their research drug Ponesimod, a selective, rapidly reversible, orally active, $S1P_1R$ modulator for the treatment of Multiple Sclerosis (MS). The study evaluated the efficacy and safety of Ponesimod compared to Aubagio (Teriflunomide) in adults with relapsing multiple sclerosis (RMS). Ponesimod is also under development for the treatment of relapsing-remitting multiple sclerosis (RRMS) and secondary progressive multiple sclerosis (SPMS) [26].

Ponesimod is a Sphingosine 1-Phosphate receptor modulator, developed by Janssen Pharmaceuticals and approved by USFDA in March, 2021 for treating Relapsing forms of Multiple Sclerosis, to include Clinically Isolated Syndrome, Relapsing-Remitting Disease and Active Secondary Progressive Disease[27].

Pharmacokinetic data[26-30]

Innovator	Janssen Pharmaceuticals (US – 2021)
Brand Name	PONVORY
Patents & Exclusivities	US/EU/IND/CN/JP/KR: 16/11/2024; NCE: 18/03/2026 (INH-IPM/Orange Book)
Regulatory Approval	USFDA - 2021
Dose & Dosage form	Tablets – 2mg, 3mg, 4mg, 5mg, 6mg, 7mg, 8mg, 9mg, 10mg, 20mg - OD
Approved Indications	Indicated to treat Relapsing forms of Multiple Sclerosis, to include Clinically Isolated Syndrome, Relapsing-Remitting Disease and Active Secondary Progressive Disease
Indications under trial	No Development Reported: Graft-versus-host disease
Time to peak	2-4 hours
Protein Binding	>99%
Metabolism	Hepatic; UGT1A1, UGT2B7
Elimination T½	33 hours
Excretion	Feces (Major), Urine

Comparison of Safety[27, 30-36]

Parameter	Ponesimod	Ozanimod	Teriflunomide	Dimethyl Fumarate	Fingolimod	Siponimod
			Headache – 19%,		Bradycardia –	Bradycardia

Adverse Effects	URTI – 37%; Hepatic enzyme elevation – 23%; Hypertension – 10%; UTI – 6%; Dyspnea, Dizziness – 5%; Cough, Pain in extremity – 4%; Somnolence – 3%; Pyrexia, Raised CRP, Hypercholesterolemia, Vertigo – 2%	URTI – 26%, Hepatic enzyme elevation – 10%, Orthostatic Hypotension – 4%, Hypertension – 4%, UTI – 4%, Back pain – 4%, Upper abdominal pain – 2%	Diarrhea – 18%, ALT rise – 14%, Alopecia – 13%, Influenza – 12%, Paresthesia – 10%, URTI – 9%, Sinusitis – 6%, Hypertension, Cystitis, Viral Gastroenteritis, Oral Herpes, Neutropenia, Anxiety, musculoskeletal pain – 4%, Blurred vision, Sciatica, Carpal Tunnel Syndrome, Pruritus, Acne, – 3%	Flushing – 40%, Abdominal pain – 18%, Diarrhea – 14%, Nausea – 12%, Vomiting – 9%, Pruritus, Rash – 8%, Albumin in urine – 6%, Dyspepsia, Erythema – 5%, Lymphopenia – 2%	4%, Hypertension – 6%, Peripheral Edema – 0.4%, Headache – 25%, Dizziness – 7%, Influenza Infection – 13%, Herpes Infection – 9%, Bronchitis – 8%, Sinusitis – 7%, Gastroenteritis – 5%, Tinea Infections – 4%, Diarrhea – 12%	– 6%, Hypertension – 13%, Peripheral Edema – 8%, Headache – 15%, Dizziness – 7%, Herpes Viral Infection – 4.6%, Bronchitis, Sinusitis, Tinea Infections – 2.9%, Diarrhea – 6%
Precautions	Dosage adjustment is not required in patients with renal impairment, Whereas it is required in	Use is not recommended in patients with hepatic impairment. No Dosage adjustment is needed in	No dosage adjustment is needed in patients with any degree of renal impairment and mild-moderate hepatic impairment. Black	No dosage adjustment is recommended in patients with any degree of hepatic or renal impairment.	No dosage adjustment is needed in patients with any degree of renal impairment and mild-	No dosage adjustment is needed in patients with any degree of renal or hepatic impairment.

	individuals with mild hepatic impairment.	patients with renal impairment.	box warning for hepatotoxicity and risk of teratogenicity		moderate hepatic impairment.	

Comparison of Efficacy[27, 30-36]

Parameter	Ponesimod	Ozanimod	Teriflunomide	Dimethyl Fumarate	Fingolimod	Siponimod
Annualized relapse rate	0.202	0.18	0.36	0.17	0.18	0.071
Relative reduction in relapse	30.5%	48%	31%	53%	-	55%
Percentage of patients without relapse	70.7%	78%	56.5%	73%	70%	-
MRI - Mean (median) number of new or newly enlarging T2 lesions over 24 months	1.40	1.47	-	2.6	2.5	-

Conclusions

- Ponesimod is a Sphingosine 1-Phosphate receptor modulator, developed by Janssen Pharmaceuticals and approved by USFDA in March, 2021 for treating Relapsing forms of Multiple Sclerosis, to include Clinically Isolated Syndrome, Relapsing-Remitting Disease and Active Secondary Progressive Disease.

- As per the innovator, Ponesimod exhibited a superior efficacy compared to Teriflunomide. However, when we compare the results stated as per the respective individual trials of other agents, the efficacy of Ponesimod in reduction of relapse rate is similar to that of Fingolimod and Dimethyl Fumarate.
- Safety wise, cardiotoxicity is a concern with all the sphingosine-1-phosphate (S1P) receptor modulators (Fingolimod, Siponimod and Ponesimod). Teriflunomide carries a black box warning; also it has reported many other adverse effects. Hence Dimethyl Fumarate (DMF) remains a comparatively safer option. Also, DMF is a safer choice in patients with hepatic or renal impairment.
- All in all, the safety vs. efficacy of Ponesimod, Fingolimod, Ozanimod and Dimethyl Fumarate (DMF) were more favorable over the others.

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