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REVIEW ARTICLE

Sphingosine 1-Phosphate Receptor Modulators for Multiple Sclerosis

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Abstract
Fingolimod (Gilenya) received regulatory approval from the US FDA in 2010 as the first-in-class sphingosine 1-phosphate (S1P) receptor (S1PR) modulator and was the first oral disease-modifying therapy (DMT) used for the treatment of the relapsing forms of multiple sclerosis (MS). Development of this new class of therapeutic compounds has continued to be a pharmacological goal of high interest in clinical trials for treatment of various autoimmune disorders, including MS. S1P is a physiologic signaling molecule that acts as a ligand for a group of cell surface receptors. S1PRs are expressed on various body tissues and regulate diverse physiological and pathological cellular responses involved in innate and adaptive immune, cardiovascular, and neurological functions. Subtype 1 of the S1PR ($S1PR_1$) is expressed on the cell surface of lymphocytes, which are well known for their major role in MS pathogenesis and play an important regulatory role in the egress of lymphocytes from lymphoid organs to the lymphatic circulation. Thus, $S1PR_1$-directed pharmacological interventions aim to modulate its role in immune cell trafficking through sequestration of autoreactive lymphocytes in the lymphoid organs to reduce their recirculation and subsequent infiltration into the central nervous system. Indeed, receptor subtype selectivity for $S1PR_1$ is theoretically favored to minimize safety concerns related to interaction with other S1PR subtypes. Improved understanding of fingolimod's mechanism of action has provided strategies for the development of the more selective second-generation S1PR modulators. This selectivity serves to reduce the most important safety concern regarding cardiac-related side effects, such as bradycardia, which requires prolonged first-dose monitoring. It has led to the generation of smaller molecules with shorter half-lives, improved onset of action with no requirement for phosphorylation for activation, and preserved efficacy. The shorter half-lives of the second-generation agents allow for more rapid reversal of their pharmacological effects following treatment discontinuation. This may be beneficial in addressing further treatment-related complications in case of adverse events, managing serious or opportunistic infections such as progressive multifocal leukoencephalopathy, and eliminating the drug in pregnancies. In March 2019, a breakthrough in MS treatment was achieved with the FDA approval for the second S1PR modulator, siponimod (Mayzent), for both active secondary progressive MS and relapsing–remitting MS. This was the first oral DMT specifically approved for active forms of secondary progressive MS. Furthermore, ozanimod received FDA approval in March 2020 for treatment of relapsing forms of MS, followed by subsequent approvals from Health Canada and the European Commission. Other second-generation selective S1PR modulators that have been tested for MS, with statistically significant data from phase II and phase III clinical studies, include ponesimod (ACT-128800), ceralifimod (ONO-4641), and amiselimod (MT-1303). This review covers the available data about the mechanisms of action, pharmacodynamics and kinetics, efficacy, safety, and tolerability of the various S1PR modulators for patients with relapsing–remitting, secondary progressive, and, for fingolimod, primary progressive MS.

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1 Mechanism of Action of Sphingosine 1-Phosphate Receptor Modulators

Sphingosine 1-phosphate (S1P) is a bioactive soluble lysophospholipid signaling molecule generated through physiologic metabolism of the cell membrane sphingolipid through phosphorylation of sphingosine by sphingosine kinase 1 or 2 (SphK1, SphK2) [1]. Under normal homeostatic conditions, erythrocytes and endothelial cells are considered the major sources of S1P in the plasma, whereas mast cells and platelets contribute to exaggerated local

Key Points

The newer generation of sphingosine 1-phosphate receptor (S1PR) modulators demonstrate efficacy in the treatment of multiple sclerosis.

The selectivity of the newer-generation S1PR modulators allows for better tolerability and safety profiles than fingolimod but maintained efficacy.

The longer-term safety profiles of these newer-generation S1PR modulators have yet to be determined.

production of S1P during inflammatory and prothrombotic conditions [2–4].

Within plasma, S1P is bound to high-density lipoproteins and other plasma proteins, which provides a stable reservoir for S1P [5, 6]. S1P is critically involved in the embryonic development of the cardiovascular system and the central nervous system (CNS). It has a dual action as an extracellular first messenger and an intracellular second messenger. Extracellularly, S1P acts as a ligand for a family of specific high-affinity G protein-coupled lipid cell surface receptors (S1PR), which regulate cytoskeletal re-arrangements of cell membrane essential for endothelial and vascular smooth muscle cell migration, vascular smooth muscle tone and vascular permeability, endothelial barrier integrity, cardiac conductivity, and immune cell trafficking. Intracellularly, S1P strongly influences cell survival through regulation of cell growth, proliferation, and suppression of apoptosis [7]. In the CNS, S1PRs are expressed on neurons, oligodendrocytes, astrocytes, and microglial cells [8]. Preclinical data suggest that S1PRs have important roles in many physiologic functions within the CNS, including regulation of neuronal progenitor cell migration toward areas of damage, oligodendrocyte function and survival, modulation of myelination following injury, astrocyte migration and communication with other CNS cells, and regulation of microglial numbers and activation [9, 10].

Five subtypes of S1PRs have been identified ($S1PR_1$, $S1PR_2$, $S1PR_3$, $S1PR_4$, and $S1PR_5$), which differ in their tissue expression and physiological response of their activation. S1PR modulators also differ in their receptor subtype selectivity. Fingolimod is a nonselective S1PR modulator that acts on four of the five S1PR subtypes ($S1PR_1$, $S1PR_3$, $S1PR_4$, and $S1PR_5$), whereas ozanimod and ponesimod are known for their potent selectivity for $S1PR_1$ with activity at $S1PR_5$. Siponimod, ceralifimod, and amiselimod are also selective $S1PR_1$ and $S1PR_5$ modulators.

$S1PR_1$ and $S1PR_3$ present ubiquitously in many tissues, including in the cardiovascular system, immune system, and CNS [11]. $S1PR_1$ is predominantly expressed on lymphocytes and provides the exit signal for lymphocytes that traffic through lymphoid organs (C–C chemokine receptor type 7 [CCR7]-positive lymphocytes) through interaction with S1P. CCR7 is a cell surface receptor expressed on naïve T cells, central memory T (TCM) cells, and B cells. For lymphocytes to egress from lymphoid organs to the lymphatic circulation, an efferent S1P concentration gradient is required, which is established by a relatively high S1P concentration in the blood and lymph compared with a typically low concentration in the lymphoid organs. Under normal physiological conditions, lymphocytes upregulate their $S1PR_1$ expression within lymphoid organs. Binding of S1P to $S1PR_1$ on lymphocytes promotes the initial receptor activation with subsequent internalization of the bound product, which down-modulates $S1PR_1$ expression. This alters the lymphocyte response to the efferent S1P chemotactic gradient, resulting in transient retention of lymphocytes within lymphoid organs, which serves as the major gateway for lymphocyte activation. Following lymphocyte activation and clonal expansion, $S1PR_1$ is re-expressed on the cell surface, allowing for lymphocyte egress to the lymphatic circulation in response to the efferent S1P concentration gradient through overcoming the retention signal mediated by $S1PR_1$ and CCR7 [12–14]. Indeed, agonism of $S1PR_1$ is responsible for the autoreactivity seen in several autoimmune disorders, including multiple sclerosis (MS) [15] (Table 1).

S1PR modulators are high-affinity agonists of S1PRs. They are designed to be structural analogs of the endogenous S1P and therefore modulate the physiologic interaction between S1P and $S1PR_1$. They exert their immunomodulatory effect through indirect (functional) antagonism of the $S1PR_1$ signaling pathway. Agonistic binding of an S1PR modulator to $S1PR_1$ on lymphocytes induces rapid and sustained receptor internalization and desensitization. This causes any newly formed S1PR to remain in an inactive state inside the cell until S1PR modulation is removed, which alters the cell surface signaling required for lymphocyte trafficking. This results in selective retention of CCR7-positive lymphocytes in lymphoid organs, preventing their trafficking to sites where they contribute to immune-mediated pathology. Since effector memory T cells (TEMs) do not traffic through peripheral lymphoid organs, they circulate in the periphery to perform their immediate effector functions important for immunosurveillance [16–18]. TCMs represent more than 90% of the T cell pool in the cerebrospinal fluid of patients with MS and are thought to differentiate locally into terminal effectors upon re-stimulation within the CNS. The majority of proinflammatory T-helper 17 cells reside in the TCM cell pool [19].

Both $S1PR_1$ and $S1PR_3$ are cell surface receptors on cardiac myocytes and endothelial and vascular smooth muscle cells. However, $S1PR_1$ is also strongly expressed on atrial,

septal, and ventricular myocytes and cardiac vessel endothelial cells and plays a more dominant role in the regulation of atrial myocyte function and heart rate [20, 21]. Initial binding of S1PR modulators to $S1PR_1$ and $S1PR_3$ on cardiac myocytes activates G protein-coupled inwardly rectifying potassium channels, which leads to potassium efflux, resulting in hyperpolarization, reduced cell membrane excitability, and subsequent transient slowing in cardiac conduction prior to receptor internalization and desensitization [22, 23]. Agonism of $S1PR_3$ is responsible for the Mobitz I second-degree atrioventricular (AV) block seen with S1PR modulators. The increases in mean blood pressure effect observed with modulatory agents is a result of activation of $S1PR_1$ on arterial smooth muscle cells, which increases nitric oxide production, resulting in vasodilation and intracellular calcium increase. This leads to smooth muscle contraction that initially offsets the nitric oxide-induced vasodilation. Following $S1PR_1$ internalization, receptor binding shifts toward $S1PR_3$, making it the overriding force of arterial smooth muscle contraction [24–26].

In the setting of the blood–retinal barrier, agonism of $S1PR_3$ reduces the tight junction of retinal capillary endothelial cells. This results in breakdown of the inner blood–retinal barrier, which leads to retention of proteins and subsequent accumulation of fluids within the interstitial spaces of the central retina. This fluid accumulation causes deformation in the retinal architecture and presents clinically as macular edema [27].

$S1PR_2$ is expressed in the CNS. It plays essential roles in the mediation of neuronal excitability and ensures proper functioning of the auditory and vestibular systems but has no role in immune function. $S1PR_4$ is specifically expressed at low levels on lymphocytes in lymphoid tissues and regulates lymphoid tissue expression. $S1PR_5$ is primarily expressed in the white matter tracts of the CNS and oligodendrocytes and plays regulatory roles in their function and migration [28, 29].

In addition to the effects of S1PR modulators on immune function in MS, they readily cross the blood–brain barrier and have neuroprotective effects through direct interaction with S1PRs on neural cells. This might help in promoting neural cell survival, decreasing demyelination, stimulating remyelination, and restoring the integrity of the blood–brain barrier [29, 30]. S1PR modulation allows for the translocation of cadherins and catenins, which allows for the maintenance of adhesion between endothelial cells of the blood–brain barrier, thereby reinforcing it [31–33].

In secondary progressive MS (SPMS), recent preclinical data suggest a major role for the innate immune response of the CNS in chronic inflammation through the pathogenic activity of microglia, astrocytes, and proinflammatory monocytes recruited in the CNS. This promotes demyelination and axonal loss without major contributions from the adaptive immune system. Astrocytes play a central role in neurodegeneration through expression of neurotoxic molecules, proinflammatory cytokines, and chemokines, which induce and amplify the neurodegenerative activities of microglia and proinflammatory monocytes. Thus, attenuation of astrogliosis and microgliosis may suppress neurodegeneration-promoting mechanisms in SPMS. Data on the effects of S1PR modulation in SPMS are limited but do suggest a potential effect of S1PR modulation on the local CNS innate immune response through downregulation of the pathogenic activities of astrocytes and microglia. The effects of S1PR modulation on chronic CNS innate immune responses and their relevance to disease progression in MS are still unknown [34].

2 Fingolimod (FTY720, Gilenya)

Fingolimod is a chemically modified structural analog of endogenous sphingosine that was first described in 1994. It is derived from myriocin, which is a fungal metabolite of Isaria sinclairii, a fungus that infects a range of insect host species [35, 36]. In humans, myriocin exerts immunosuppressive activity through its action on serine palmitoyl transferase (SPT), which inhibits T-cell activation and proliferation, cytokine production, memory T-cell formation, and antibody production [37, 38]. Unlike myriocin, fingolimod has no activity against SPT. Thus, fingolimod does not impair humoral immunity against viral infections and so is considered an immunomodulatory rather than immunosuppressant agent [39]. In vivo, fingolimod undergoes reversible stereoselective phosphorylation by the endogenous SphK2 to its pharmacologically active metabolite: fingolimod phosphate (fingolimod-P) [40]. Fingolimod-P is a high-affinity, nonselective, reversible S1PR agonist. Since fingolimod is lipophilic, it readily crosses the blood–brain barrier and is phosphorylated within the CNS. Preclinical data suggest it has neuroprotective and reparative effects within the CNS, independent of its immune cell trafficking activity, through interaction with S1PRs on neural cells [41, 42]. In models of experimental autoimmune encephalitis, modulation of the S1PR by fingolimod led to reduced $S1P_1$ in astrocytes and therefore reduced the amount of demyelination, axon loss, and astrogliosis [43]. The blocking of the $S1PR_1$ receptors also helps facilitate the maturation of oligodendrocytes, which helps promote remyelination [44].

2.1 Pharmacokinetics

Fingolimod has a high oral bioavailability of 93%. It is absorbed efficiently after oral administration, independent of food intake, and has a time to maximum plasma concentration (t_{max}) of 12–16 h. It reaches steady-state plasma

Table 1 Pharmacological profile, phase III trials, and approval status for the various S1PR modulators

S1PR antagonist	S1PRs affected	Half-life	Maximal decrease in lymphocyte counts from BL	Time to recovery of BL lymphocyte counts	Associated phase II/III trials	Approval status for subtype of MS
Fingolimod	$S1P_1$, $S1P_3$, $S1P_4$, $S1P_5$	6–9 days	Up to 73% reduction	4–8 weeks	FREEDOMS, FREEDOMS II TRANSFORMS, PARADIGM	RRMS
Siponimod	$S1P_1$, $S1P_5$	22–38 h	Up to 70% reduction	7–10 days[a]	EXPAND	RRMS and SPMS
Ozanimod	$S1P_1$, $S1P_5$	19–22 h	Up to 68% reduction	30 days–3 months[b]	RADIANCE SUNBEAM	RRMS
Ponesimod	$S1P_1$ mostly, with some activity at $S1P_5$	32 h	Up to 70%	7 days	OPTIMUM[c] POINT[d]	Awaiting approval for RRMS
Ceralifimod	$S1P_1$, $S1P_5$	82–89 h	40–65% reduction	14 days	No phase III trial; DreaMS (phase II study)	Further development discontinued
Amiselimod	$S1P_1$, $S1P_5$	380–420 h	60–66% reduction	Up to 7 weeks	No phase III trial; MOMENTUM (phase II study)	Further development discontinued

BL baseline, *MS* multiple sclerosis, *RRMS* relapsing–remitting MS, *SPMS* secondary progressive MS, *S1P* sphingosine 1-phosphate, *S1PR* S1P receptor

[a]In 90% of patients, the lymphocyte count recovered to BL levels within this timeframe, but time to recovery can take 3–4 weeks for some patients

[b]90% of patients recover their BL lymphocyte counts within 3 months because of the longer half-life of ozanimod's metabolite CC112273

[c]The OPTIMUM trial has been submitted for publication

[d]The POINT trial was discontinued due to low recruitment

concentration after 1–2 months of regular daily dosing. Fingolimod and its active metabolite bind extensively to plasma proteins (99.7%). The free form of fingolimod is found in high concentrations in the erythrocytes (86%), whereas fingolimod-P is found in low concentrations (< 17%). Within the first week of oral administration, fingolimod reduces the number of peripherally circulating lymphocytes by 20–30% from baseline, reaching a maximum reduction of around 73% after the first month [45–47]. Fingolimod has a long half-life of 6–9 days; however, the mean lymphocyte count starts to rise within days of treatment discontinuation and returns to normal limits within 4–8 weeks. Fingolimod is largely cleared through metabolism by cytochrome P450 (CYP)-4F2. About 81% of the dose is slowly excreted in the urine as inactive metabolites, with minimal concentrations excreted unchanged in the stool [47, 48].

2.2 Efficacy Data: Relapsing–Remitting Multiple Sclerosis (MS)

Between 2006 and 2007, two large, multicenter, randomized, double-blind, phase III studies (the 24-month FREEDOMS [FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis] and the 12-month TRANSFORMS [Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing–Remitting Multiple Sclerosis]) enrolled patients with active relapsing–remitting MS (RRMS), an Expanded Disability Status Scale (EDSS) score of < 6, and age 18–55 years to evaluate the efficacy and safety of fingolimod in the treatment of RRMS. In FREEDOMS, 1272 patients were randomized to once-daily doses of fingolimod 0.5 or 1.25 mg or placebo for 24 months. A total of 1033 patients completed the study. At 24 months, both doses of fingolimod met the primary endpoint, with a statistically significant reduction in the annualized relapse rate (ARR) compared with placebo (54 and 60% for 0.5 and 1.25 mg, respectively). Both doses reduced the risk of disability progression (17.7 and 16.6% for 0.5 and 1.25 mg, respectively, versus 24.1% for placebo). All magnetic resonance imaging (MRI)-related endpoints favored fingolimod. Interestingly, there was significant preservation of brain volume loss in those receiving fingolimod 0.5 mg compared with placebo (− 0.84 vs. − 1.31%) [49].

In the FREEDOMS patient subgroup analysis, it was noted that—at the 6- and 12-month mark—patients receiving fingolimod appeared to exhibit accelerated brain volume loss. This was thought to be secondary to a "pseudoatrophy" effect due to the reduction in inflammatory edema [50]. EDSS scores remained stable or improved slightly in both fingolimod groups [49]. In TRANSFORMS, 1292

patients were randomized to the same doses of fingolimod as in FREEDOMS versus a weekly intramuscular dose of interferon (IFN)-β1a (Avonex 30 μg) for 12 months; 1153 patients completed the study. Both fingolimod doses demonstrated superiority to Avonex in reducing the ARR (52 and 38% for 0.5 and 1.25 mg, respectively). The proportion of patients who were relapse free and time to confirmed relapse was greater in both fingolimod groups. The MRI-related endpoints also favored fingolimod. Significant differences in time to confirmed disability progression (CDP) were observed [51].

The 24-month, randomized, double-blind FREEDOMS II trial was the third phase III clinical study for fingolimod and was carried out mainly in the USA between 2006 and 2009. In this trial, 1083 patients were randomized to the same doses of fingolimod as in the core study versus placebo. In 2009, all patients assigned to fingolimod 1.25 mg were switched to 0.5 mg in a blinded manner based on a recommendation from the data and safety monitoring board; however, they were analyzed as receiving 1.25 mg in the primary outcome analysis. The study reconfirmed the results obtained from the core study for reduction in ARR and MRI-related endpoints [52].

Extension of the pivotal studies confirmed sustained efficacy of fingolimod in the long term. In the FREEDOMS extension study, the ARR reduced in the continuous-fingolimod group (48 and 54% for 0.5 and 1.25 mg, respectively) versus placebo. The ARR also improved in the groups switched from placebo to either of the fingolimod doses, mainly in the group switched to 0.5 mg. The percentage of patients in the continuous-fingolimod group who received 0.5 mg and remained relapse free was 59% compared with 37% in the switched groups. The 3-month CDP improved more in the continuous-fingolimod groups than in the switched groups. The brain volume loss was less in the continuous-fingolimod groups and also improved in the switched groups [53, 54]. In the TRANSFORMS extension study, the ARR reduced by 0.17 for 0.5 mg in the continuous-fingolimod group compared with 0.27 in patients who switched from Avonex to either of the fingolimod doses. The ARR improved by 50% in the switched group. The brain volume loss was lower (− 1.01%) in the continuous-fingolimod group than in the switched group (− 0.96%) [55, 56].

Given the efficacy of fingolimod in FREEDOMS and TRANSFORMS, fingolimod 0.5 mg received regulatory approval from the US FDA in September 2010 under the brand name Gilenya as the first orally administered disease-modifying therapy (DMT) for treatment of relapsing forms of MS. In 2011, fingolimod was approved by Health Canada and the European Medicines Agency (EMA). Fingolimod is a first-line treatment in the USA, Canada, and many other countries, whereas its approval in Europe is as a second-line treatment preserved for highly active disease in which at least one DMT failed to suppress disease activity or for severe and rapidly worsening disease [57].

A 10-year open-label, single-arm extension study (LONGTERMS) evaluated the long-term efficacy, safety, and tolerability of fingolimod in 3168 patients who had previously participated in phase II, III, and IIIb studies. Results showed sustained efficacy of fingolimod in the long term, as expressed by clinical and MRI outcomes, with no new safety concerns [58, 59]. A retrospective analysis of pooled FREEDOMS/FREEDOMS II data for patients aged < 30 years showed statistically significant data for consistent disease control with fingolimod in young adults, with greater long-term benefit with early initiation of fingolimod therapy.

2.3 Efficacy in Progressive MS

Between 2008 and 2011, a multicenter, randomized, double-blind, parallel-group, placebo-controlled phase III study (INFORMS) enrolled 970 patients aged 25–65 years with primary progressive MS (PPMS) and a disease duration of 2–10 years to evaluate the efficacy and safety of fingolimod in PPMS. Patients were randomized to a once-daily oral dose of fingolimod 0.5 mg versus placebo for at least 36 months and a maximum of 5 years. The study assessed time to 3-month CDP using a novel composite endpoint based on change from baseline EDSS, Timed 25-Foot Walk (T25FW) test, or nine-hole peg test. The study was completed in December 2014 but failed to demonstrate any benefit from fingolimod versus placebo, with 69% of patients in both groups having CDP at 3 months. However, the safety results were generally consistent with those in studies of patients with RRMS [60].

2.4 Efficacy in Pediatric MS

Between 2013 and 2016, a flexible-duration (up to 24 months), multicenter, randomized, double-blind, active-controlled, parallel-group, phase III study (PARADIGMS) enrolled 215 pediatric patients (aged 10 to < 18 years) with active RRMS and an EDSS score < 6 to evaluate the efficacy and safety of fingolimod compared with IFN-β1a (Avonex). Patients were randomized to receive once-daily fingolimod 0.25 or 0.5 mg, dependent on the body weight, or weekly IFN-β1a (Avonex 30 μg) intramuscularly. Prior therapy with IFN-β, glatiramer acetate, or dimethyl fumarate was permitted. A total of 188 patients completed the study; 63.3% of these patients had not previously received treatment with a DMT. At up to 24 months, fingolimod met the primary endpoint with a statistically significant reduction in the ARR of 81.9% compared with Avonex. The proportion of patients who remained relapse free was 85.7% for fingolimod and 38.8% for Avonex. The relative difference in the annualized rate of new or newly enlarged T2 lesions was significantly

lower with fingolimod (52.6%). The relative reduction of the mean number of Gad-enhancing (GdE) lesions was 66%. The annualized rate of brain volume loss was also significantly reduced with fingolimod compared with Avonex (-0.48 vs. -0.8) [61].

In May 2018, the FDA expanded the approval of fingolimod for the treatment of relapsing forms of MS in children and adolescents aged 10 to < 18 years. As such, it was the first and only DMT specifically approved for use in pediatric MS [62]. In November 2018, the European Commission also approved fingolimod for use in the same age group.

2.5 Safety and Tolerability Data

The safety and tolerability profile of fingolimod has been demonstrated in a phase II study, three phase III studies, a long-term follow-up study, and in post-marketing observational studies. Several adverse effects were noted, which are thought to be mediated through the interaction of fingolimod and $S1PR_1$ and off-target interactions with other S1PR subtypes.

Recent data from the LONGTERMS extension study showed that the most common adverse effects of fingolimod were viral upper respiratory infection (17.3%), headache (13.3%), hypertension (11.0%), and lymphopenia (10.7%), which tended to occur less frequently with continuous treatment [59]. Fluctuating annual frequencies for urinary tract infection (1.7–4.9%) and basal cell carcinoma (0.1–1.1%) were also observed. Other reported adverse effects included fever, chills, back pain, leukopenia, herpes infections, bronchitis, gastroenteritis, nausea, vomiting, diarrhea, liver enzyme elevation, cough, wheeze, dyspnea, numbness, tingling, seizure, blurred vision, macular edema, localized skin cancer (basal cell carcinoma and melanoma), breast cancer, and lymphoma. In the pediatric population, adverse events reported in the PARADIGMS trial were similar to those seen in the adult population; however, a higher rate of seizures was reported with fingolimod than with Avonex (5.6 vs. 0.9%). The most common adverse events in the pediatric population were headaches, upper respiratory tract infections, leukopenia, and influenza, whereas no opportunistic infections, cancers, or death were reported during the clinical trial period [61].

First-dose cardiovascular events, including bradycardia and first- and second-degree AV block were frequently observed in clinical trials but were usually transient and self-limiting. Following the first-dose administration of fingolimod, a transient reduction in heart rate usually occurs, with a mean maximum reduction of 8 bpm. The maximum heart rate-lowering effect of fingolimod usually occurs within 6 h of the first dose, reaching nadir at 4–5 h post dose. However, analysis of changes in heart rate confirmed a biphasic effect of fingolimod in some patients, with an initial decrease within the first 6 h and a second decrease as late as 12–20 h post dose. Pooled data analysis of the three phase III trials showed that only 0.6% of patients developed symptomatic bradycardia. The incidence of first-degree AV block was 4.7%, whereas the incidence of second-degree AV block (Mobitz I) was lower at 0.2% [63]. In a large cohort of 906 Italian patients with RRMS enrolled in an open-label, single-arm study to assess the safety and tolerability of the first dose of fingolimod, 95.3% of patients did not experience any cardiovascular adverse events. However, self-limiting adverse events were reported in 18 (2%) patients, including bradycardia (1.3%) and first- and second-degree AV block (0.3%), none of which required any intervention [64]. Although no cases of symptomatic bradycardia occurred beyond 24 h of the first-dose administration in clinical trials, a published case report described symptomatic bradycardia after 39 h of a single dose of fingolimod in a 30-year-old patient with MS with vagotonia, which required atropine and took a week to resolve [65]. Another case report described more serious cardiovascular events with fingolimod: asystole for 7.5 s occurred 21 h after the first dose in a 20-year-old patient receiving risperidone [66]. In November 2011, the marketing authorization holder reported the first case of sudden unexpected death within 24 h of the first dose of fingolimod in a patient with extensive brainstem lesions who was receiving amlodipine and metoprolol [67, 68]. Another case of sudden unexpected death was also reported in the 5th month of fingolimod treatment in a 48-year-old patient; autopsy results suggested ventricular arrhythmia as the leading cause of death, although whether fingolimod contributed to the arrhythmia was unclear [69]. Thus, a strict first-dose monitoring protocol was instituted for close observation of vital signs and electrocardiograms. The first dose of fingolimod should be administered in a setting where symptomatic bradycardia can be managed. Upon first-dose administration, hourly checks of heart rate and blood pressure and electrocardiographic monitoring (either predose and 6 h post-dose, according to the FDA, or continuously, according to the EMA) is recommended, with extended on-site monitoring when required. Repeat first-dose monitoring is also required after discontinuation of fingolimod for more than 2 weeks and upon switching from 0.25 to 0.5 mg in pediatric patients.

In the clinical trials, the overall incidence of infections with fingolimod was low and similar to that with IFN-β1a and placebo. However, a relatively higher incidence of infection was reported for herpes viruses with CNS latency, especially herpes simplex virus (HSV) and varicella zoster virus (VZV). Two incidences of fatal CNS herpes infections were reported in the TRANSFORMS trial in the group receiving 1.25 mg. The incidence of infections seems to be unrelated to lymphocyte count, with no significant increase in infection risk, even in patients whose lymphocyte counts decreased below 200 cells/μL [70]. Data suggested subclinical VZV

reactivation with fingolimod, demonstrated through detection of VZV polymerase chain reaction (PCR) in the saliva [71]. In the post-marketing setting, the incidence of VZV infection was comparable with the clinical trial data and remained stable with long-term exposure. On the other hand, many cases of CNS herpes infections have been reported, mostly HSV, with some cases of VZV infections. Although some patients experienced disability or died, most recovered [72]. Given the overall low risk of HSV infections, particularly serious infections, routine prophylaxis with acyclovir is not recommended; however, establishing the patient's VZV immune status and administering VZV vaccine in seronegative patients at least 1 month before initiating fingolimod is recommended [73]. Since fingolimod reduces the immune response to vaccinations, completion of all immunizations, if possible, is recommended prior to initiation of fingolimod therapy in pediatric patients. Similar safety monitoring for infections is applied in pediatric patients, but 2 months of monitoring for infection is recommended after discontinuation of treatment in pediatric patients.

Progressive multifocal leukoencephalopathy (PML) results from reactivation of latent infection with the John Cunningham virus (JCV). Natalizumab carries the highest global incidence of PML, with 4.2 cases per 1000 treated patients [74]. Although the risk of PML has been commonly linked to natalizumab therapy, many cases of PML have been reported in association with fingolimod treatment. In 2012, the manufacturing company reported the first case of PML with fingolimod in a patient switched from natalizumab to fingolimod because they had positive JCV antibodies, noting that PML was likely linked to previous exposure to natalizumab [75]. Subsequently, many cases of PML with fingolimod therapy in relation to previous treatment with natalizumab have been reported. However, in 2015, two cases of PML were reported with fingolimod in the absence of prior exposure to natalizumab or other immunosuppressive drugs [76]. As of May 2018, a total of 19 cases of PML have been reported with fingolimod unrelated to previous treatment with natalizumab. Analysis of the marketing authorization holder's safety database for 15 PML cases that could be attributed to fingolimod therapy alone (data lock point 31 August 2017) showed that three cases were fatal; however, the estimated risk of PML with fingolimod in the absence of prior natalizumab treatment remains low (0.069 per 1000 patients), with an estimated incidence rate of 3.12 cases per 100,000 patient-years. The risk of PML was clearly age and treatment duration dependent: 13 of the 15 patients were aged > 45 years at time of diagnosis, and 14 of them had been receiving fingolimod for more than 24 months. Although lymphopenia has been inconsistently reported as a risk factor for PML, none of the 14 patients for whom absolute lymphocyte counts were available exhibited sustained grade 4 lymphopenia (≤ 200 cells/μL) [77]. Indeed, no precise estimates or stratification tools have been identified for PML risk with fingolimod. Given the low risk of PML, screening for JCV antibodies is not routine; however, if the lymphocyte count falls below 200 cells/μL, fingolimod treatment should be interrupted until lymphocyte counts recover. MRI is a sensitive screening tool to detect early radiographic manifestations of PML in asymptomatic patients since radiographic evidence of PML precedes its associated neurologic deficits. If PML is suspected, fingolimod should be immediately discontinued and appropriate investigations for PML-suggestive lesions on MRI scans and ultrasensitive PCR assay for JCV-DNA in cerebrospinal fluid initiated [78].

Asymptomatic elevations of hepatic enzymes, mostly alanine aminotransaminase (ALT), have been reported in the clinical trials. The majority of elevations occurred within 6–9 months of treatment initiation. Threefold or higher elevations in ALT were reported in 8.5% of patients, whereas more than fivefold elevations were seen in only 1.9% of patients; however, ALT levels usually normalized after 2 months of treatment discontinuation [48].

Macular edema results from accumulation of fluid within the central retina, which usually manifests as metamorphopsia, blurred vision, and painless decreases in visual acuity. It has been reported in 0.4% of patients receiving fingolimod in the clinical trials, and patients were mostly asymptomatic; however, this low incidence might be confounded by the inclusion and exclusion criteria. Most macular edema cases occurred in the first 3–4 months of treatment initiation, although late-onset macular edema has been reported as late as 12 months after treatment initiation [79]. It usually improved or resolved with or without treatment after discontinuation of fingolimod; however, some patients had residual visual impairment even after resolution of the macular edema. A history of uveitis or diabetes mellitus increases the risk for macular edema; however, an ophthalmic evaluation for macular edema with optical coherence tomography is required in all patients prior to treatment and 3–4 months post treatment initiation, with regular evaluation for high-risk patients [80].

Cases of localized skin cancers (basal cell carcinoma, melanoma, and Kaposi's sarcoma), breast cancers, and lymphoma have been reported in patients treated with fingolimod in clinical trials and in the post-marketing setting [48]. Medical evaluation of the skin is recommended before initiation of treatment and at least yearly during treatment. For suspicious skin lesions existing before treatment initiation, regular monitoring during treatment is recommended.

Fingolimod is pregnancy category C. It should be used with adequate contraception and should be stopped at least 2 months prior to conception to allow for washout. Pooled data from phase II, III, and IV trials reported 66 cases of in utero exposure to fingolimod at the time of conception or

within 6 weeks before conception. Of those cases, there were 24 elective abortions, nine spontaneous abortions, 28 live births, and four pregnancies were ongoing. Two infants were born with malformations (acrania and unilateral posteromedial bowing of the tibia). Three of the elective abortion cases were due to tetralogy of Fallot, failure of fetal development, and spontaneous intrauterine death [81].

Following discontinuation of fingolimod, an ideal washout period of 2 months is required for lymphocyte counts to return to baseline levels. However, many reports have emerged over the last few years describing rebound effects 2–24 weeks following treatment discontinuation, with severe clinical and radiographic exacerbation of MS activity surpassing pretreatment activity. Most patients experienced the rebound effect in the first 12 weeks after treatment discontinuation. This might be due to changes in peripheral lymphocyte phenotypes in a way that promotes disease activity. Indeed, the disability caused by rebound activity was more severe than typical MS relapses. However, no predictive features for potential risk of rebound effect have been identified; hence, close monitoring for evidence of disease exacerbation is required following fingolimod withdrawal [82].

3 Siponimod (BAF312, Mayzent)

Siponimod is the second S1PR modulator to enter clinical trials for the treatment of MS. It is a novel alkoxyamine derivative discovered through de novo design using fingolimod as the chemical starting point to develop a more selective $S1PR_1$ modulator [83]. It is an orally active, high-affinity selective $S1PR_1$ and $S1PR_5$ agonist. Unlike fingolimod, it does not require phosphorylation for activation, but its immune cell trafficking activity is similar to that of fingolimod. Preclinical data suggested a neuroprotective effect of siponimod within the CNS through direct interaction with $S1PR_1$ and $S1PR_5$ on astrocytes and microglia, which reduced the resident immune cell activation. Interestingly, siponimod reduced the release of interleukin (IL)-6 and RANTES (regulated on activation, normal T cell expressed and secreted) from activated microglia. Both IL-6 and RANTES have a role in T-cell recruitment and regulation, so a reduction in these proinflammatory cytokines and chemokines by siponimod leads to reduced lymphocyte infiltration to the CNS. Siponimod also prevented and recovered synaptic gamma aminobutyric acid (GABA)-ergic interneuron loss, which is thought to be a contributor to neurodegeneration. The interneuron survival is thought to be due to the reduced local inflammatory reaction. This was seen in models of experimental autoimmune encephalitis treated with siponimod [84, 85]. The recovery of GABA transmission has been seen with siponimod modulation, whereas fingolimod has been shown to correct glutamatergic transmission alterations in models of experimental autoimmune encephalitis. Other studies have suggested that siponimod might promote remyelination through interaction with $S1PR_5$ on oligodendrocyte precursor cells [86].

3.1 Pharmacokinetics

The absolute oral bioavailability of siponimod is around 84%. It is extensively absorbed following oral administration ($\geq$ 70%), but food intake may delay absorption without affecting its systemic exposure. Therefore, siponimod may be taken without consideration of meals. Siponimod reaches t_{max} in 3–8 h following oral administration. Upon treatment initiation, an uptitration regimen is used to reach the therapeutic dose of 2 mg after 6 days. However, an additional 4 days of dosing are required to reach steady-state plasma concentrations. Like fingolimod, siponimod binds extensively to plasma proteins (> 99.9%), although the fraction of siponimod found in plasma was 68%. Siponimod induces an immediate dose-dependent reduction in the peripheral lymphocyte count of 20–30% from baseline within 4–6 h of the first-dose administration. Furthermore, the lymphocyte count continues to decrease with continued dosing, reaching up to 70% reduction within 1 week. Siponimod has a short half-life of 22–38 h. It undergoes extensive metabolism (79.3% via CYP2C9) and is subsequently excreted in the stool. Thus, it is contraindicated in patients homozygous for CYP2C9*3 (CYP2C9*3/*3 genotype). In 90% of patients, lymphocyte counts recovered to normal baseline levels within 7–10 days of treatment discontinuation; however, residual lymphocyte-lowering effects of siponimod might persist for up to 3–4 weeks after the last dose. The pharmacokinetic properties of siponimod facilitate treatment initiation and improve its safety profile [87, 88].

3.2 Efficacy Data

Between 2009 and 2010, a 6-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group, adaptive dose-ranging, phase II trial, BOLD (BAF312 on MRI lesion given once daily) was undertaken. BOLD enrolled 188 patients aged 18–55 years with active RRMS and an EDSS score < 5.5 to evaluate the dose response of siponimod versus placebo on percentage reduction in monthly number of combined unique active lesions (CUAL = new or enlarging T2 lesions and GdE lesions) at 3 months. Patients were randomized into two cohorts. In cohort 1, patients were randomized to receive once-daily siponimod 0.5, 2, or 10 mg versus placebo in a 1:1:1:1 ratio for 6 months. Based on the results of the interim analysis of cohort 1 at 3 months, 109 patients in cohort 2 were randomized to receive siponimod 0.25 or 1.25 mg versus placebo in a 4:4:1 ratio for 3 months. At 3 months, all siponimod

doses met the primary endpoint, with statistically significant dose-dependent reductions in CUAL (35, 50, 66, 72, and 82% for 0.25, 0.5, 1.25, 2, and 10 mg, respectively) compared with placebo. The ARR was also reduced with the 2 and 10 mg doses (0.2 and 0.3, respectively) [88]. A 24-month, randomized, dose-blinded extension of the BOLD trial assessed the efficacy and safety of siponimod in 252 patients in which the 2 mg dose appeared to be the most appropriate for future trials, especially if uptitrated to mitigate its cardiac effects; no new safety signals were observed [89, 90].

The EXPAND (EXploring the efficacy and safety of siponimod in patients with secondary progressive multiple sclerosis) trial was completed between 2013 and 2015. This was a large 60-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group phase III study. The EXPAND trial enrolled 1651 patients aged 18–60 years with SPMS and an EDSS score of 3.0–6.5 to investigate the efficacy and safety of siponimod versus placebo in SPMS. It is the largest phase III study of a DMT in SPMS to date. Patients who had documented EDSS progression in the 2 years before entering the study and experienced at least one relapse within those 2 years with no evidence of relapse in the 3 months before randomization were considered active. However, 64% of the study population had not relapsed in the 2 years before enrolment. At baseline, the mean time since first MS symptoms was 16.8 years, whereas the mean time since conversion to SPMS was 3.8 years. More than 50% of the study population in EXPAND had a median EDSS score of 6, with 56% of patients relying on a walking aid. Only about 20% of patients had inflammatory activity depicted by the presence of GdE lesions. Patients were randomized to receive once-daily siponimod 2 mg or placebo in a 2:1 ratio for up to 3 years or until the occurrence of a prespecified number of CDP. A total of 1327 patients completed the study. Siponimod met the primary endpoint, with 21% relative risk reduction in time to 3-month CDP in patients with active disease compared with placebo (CDP was defined as a 1-point increase in EDSS score if the baseline score was 3.0–5.0 or as a 0.5-point increase in EDSS if the baseline score was 5.5–6.5). It also reduced the risk of 6-month CDP by 26%. This makes siponimod the first potential DMT to delay disability progression in typical SPMS, including patients with a high level of disability. Siponimod also limited the change in T2 lesion volume from baseline over 12 and 24 months by 79.1% compared with placebo, whereas the rate of brain volume loss was reduced by 23%. More patients were free from GdE lesions (89%) and from new or enlarging T2 lesions (57%). The relative reduction in ARR was 55%. Subgroup analyses suggested that the most beneficial effect of siponimod was in younger patients with more inflammatory disease activity. However, no significant differences were observed in the T25FW test and the 12-item Multiple Sclerosis Walking Scale for the overall study population [91].

In March 2019, given the positive data from EXPAND, siponimod received regulatory approval from the FDA under the brand name Mayzent across the relapsing spectrum of MS in adults to include RRMS, active SPMS, and those with the first clinical episode of neurologic symptoms, known as clinically isolated syndrome, making siponimod the first oral treatment specifically approved for treatment of SPMS. Mayzent was approved in the European Union in January 2020 and in Canada on 3 March 2020 [92–94].

3.3 Safety and Tolerability Data

The safety profile of siponimod in clinical studies was overall consistent with the known effects of S1PR modulators. In the BOLD trial, 5% of patients experienced second-degree AV block. One case of nonfatal myocardial infarction was reported 45 days after the last dose of siponimod 10 mg in a patient who smoked. One patient developed herpes zoster meningitis. A case of basal cell carcinoma was reported in the siponimod 0.5 mg group. One case of death was reported with siponimod 1.25 mg in a patient who had vascular risk factors and died 27 days after treatment discontinuation. Otherwise, the overall frequencies of infections, malignancies, and death were not increased with siponimod [89]. In EXPAND, the most common adverse events were hypertension (10%), increased liver transaminases (1% for ALT elevations and < 1% for aspartate transaminase elevations), lymphopenia (1%), bradycardia at treatment initiation (4%), macular edema (2%), and varicella zoster reactivation (2%). Convulsions, which occurred in 2% of those receiving siponimod, occurred more frequently with siponimod than with placebo [91].

Bradycardia occurred in 4.4% of those receiving siponimod and was generally asymptomatic, resolving within 24 h without intervention. A 5-day uptitration scheme starting with 0.25 mg on day 1 to the maintenance dose of 2 mg was used to mitigate the heart rate-lowering effects of siponimod at treatment initiation with no requirement for monitoring in a health facility upon treatment initiation except for individuals with preexisting heart conditions. Dose re-titration is required if siponimod treatment is interrupted for ≥ 4 consecutive days. Following the first dose of siponimod, the heart rate starts to decrease within 1 h, with the maximum decline occurring during the first 3–4 h, representing the highest daily post-dose decrease in heart rate. However, a less pronounced decline in heart rate was observed with subsequent uptitration up to day 6. After day 6, heart rate started to increase and reached baseline within 10 days of treatment initiation [95].

Siponimod is contraindicated in patients homozygous for CYP2C9*3 (CYP2C9*3/*3 genotype). The recommended

maintenance dose in patients with CYP2C9*1/*3 and *2/*3 genotype is 1 mg daily with an initial uptitration period of 4 days. Before siponimod is initiated, the following actions are recommended: complete blood count, electrocardiogram, and ophthalmic evaluation, and establish the patient's CYP2C9 genotype and VZV antibody status, with vaccination of antibody-negative patients 4 weeks before treatment initiation [95].

4 Ozanimod (RPC1063)

Ozanimod is an orally active S1PR modulator with a specific and potent selectivity for $S1PR_1$ and $S1PR_5$. Like siponimod, it does not require phosphorylation for activation; however, metabolism studies in animals have identified three pharmacologically active metabolites of ozanimod that have similar S1PR selectivity and potency to ozanimod in vitro [96]. CC112273 is the major active metabolite of ozanimod, responsible for about 90% of ozanimod's efficacy and safety profile observed in late-stage testing. Preclinical data suggested that ozanimod diminished inflammatory markers in experimental allergic encephalitis and effectively crosses the blood–brain barrier [97].

4.1 Pharmacokinetics

Ozanimod is a small molecule with high oral bioavailability; however, it has delayed absorption, with a high volume of distribution, leading to lower peak plasma concentration and less systemic exposure, which reduces the first-dose effects on heart rate observed with other S1PR modulators. Following oral administration of the first dose, ozanimod induces immediate dose-dependent reduction in the peripheral lymphocyte count, reaching up to 68% from baseline. The t_{max} of ozanimod is 6–8 h. The short mean half-life of ozanimod and its active metabolites (19–22 h) should theoretically allow for rapid recovery of lymphocyte counts (within 2–3 days) following treatment discontinuation, but CC112273 has a longer half-life (10–13 days) so has a longer elimination time of up to 2–3 months. The median time for lymphocytes to return to the normal range was 30 days after treatment discontinuation, although 90% of patients returned to their baseline counts in 3 months [96].

4.2 Efficacy Data

Between 2012 and 2014, a multicenter, randomized, double-blind, parallel-group, combined phase II/III study, the RADIANCE trial, enrolled patients aged 18–55 years with active RRMS and an EDSS score < 5.5 to evaluate the efficacy and safety of ozanimod in relapsing MS. The phase II, part A, of the trial was a 24-week, placebo-controlled study in which 258 patients were randomized to receive once-daily ozanimod 0.5 or 1 mg versus placebo in a 1:1:1 ratio to evaluate efficacy, safety, and tolerability. Both doses of ozanimod met the primary endpoint, with 86% reduction in the cumulative number of GdE lesions from weeks 12–24 compared with placebo. Secondary endpoints also favored ozanimod, with a significant reduction in the total number of GdE lesions at week 24 (91 and 94% for 0.5 and 1 mg, respectively) versus placebo. The cumulative number of new or enlarging T2 lesions from weeks 12 to 24 was reduced by 84 and 91% for 0.5 and 1 mg, respectively [98]. The ARR was also reduced by 31 and 53%, respectively [99].

Between 2013 and 2016, a 2-year, dose-blinded extension of part A of the trial demonstrated sustained efficacy of both ozanimod doses with greater efficacy observed for the 1 mg dose on both clinical disease and MRI measures. No unexpected safety signals were observed [98].

Based on the preliminary results of the phase II part of the trial, a 24-month phase III (part B) trial was initiated to compare the two doses of ozanimod with IFN-β1a (Avonex). A total of 1313 patients with RRMS, progressive-relapsing MS, or SPMS were randomized to receive once-daily ozanimod 0.5 or 1 mg or a weekly intramuscular dose of IFN-β1a (Avonex 30 μg) in a 1:1:1 ratio. Both doses of ozanimod met the primary endpoint, with a significant reduction in ARR of 21 and 38% for 0.5 and 1 mg, respectively, compared with Avonex. The number of new or enlarging T2 lesions was also significantly reduced with ozanimod, with 34 and 42% reductions for 0.5 and 1 mg, respectively, compared with Avonex. The number of GdE lesions significantly reduced with ozanimod 0.5 mg (47%) and 1 mg (53%) [100].

A second 12-month, multicenter, randomized, double-blind, double-dummy, parallel-group, active comparator phase III study, the SUNBEAM trial, enrolled 1346 patients with RRMS to evaluate the efficacy and safety of two doses of ozanimod against IFN-β1a (Avonex). Patients were randomized to receive once-daily ozanimod 0.5 or 1 mg or a weekly intramuscular dose of IFN-β1a (Avonex 30 μg). Both doses met the primary endpoint, with an ARR of 0.17 for ozanimod 1 mg, 0.22 for ozanimod 0.5 mg, and 0.28 for IFN-β1a. This was a statistically significant reduction in the ARR of 31 and 48% for 0.5 and 1 mg, respectively, compared with Avonex. The number of new or enlarging T2 lesions at month 12 was also significantly reduced with ozanimod (25 and 48% for 0.5 and 1 mg, respectively), and the number of GdE lesions was reduced by 34 and 63% for 0.5 and 1 mg, respectively [101].

4.3 Safety and Tolerability Data

Compared with all other S1PR modulators, ozanimod showed a favorable safety profile, and the majority of reported adverse events were mild. The overall incidence

of serious adverse events was low. There were no reports of serious opportunistic infections, macular edema, clinically significant abnormalities in pulmonary function tests, or malignancy. However, in the phase II (part A) RADIANCE trial, three serious adverse events were reported with the 0.5 mg dose: optic neuritis, somatoform autonomic dysfunction, and uterine cervical squamous metaplasia. Other serious events reported in the extension period included a case of acute myocardial infarction in a patient with hypertension and a history of lupus, one case of hepatitis, and moderate pancytopenia that resolved without treatment discontinuation. The first-dose effect on cardiac conduction was minimal, with no reports of clinically significant cardiac conduction abnormalities. The maximum reduction in heart rate following the first dose was 2 bpm in the first 6 h in the combined ozanimod group [98]. The greatest mean reduction in baseline heart rate took place at hour 5 on day 1 and was a decrease of 1.2 bpm from baseline [102]. A dose uptitration regimen is used to mitigate the heart rate-lowering effects at treatment initiation, with a starting dose of 0.23 mg daily for days 1–4, followed by 0.46 mg for days 5–7, then 0.92 mg daily from day 8 and thereafter. Other adverse events included nasopharyngitis, headache, increased transaminases, influenza-like illness, hypertension, urinary tract infection, herpes zoster infection, and transient lymphopenia below 200 cells/μL [98].

Ozanimod is contraindicated in patients who have had a myocardial infarction, unstable angina, stroke, or transient ischemic attack and those with severe untreated sleep apnea, heart failure, or a resting heart rate < 55 bpm at baseline [102].

Given the positive data from RADIANCE and SUNBEAM, the manufacturing company, Celgene, applied to the FDA for approval of ozanimod for the treatment of relapsing forms of MS in adults. Although the new drug application was initially rejected by the FDA in February 2018 on the grounds of insufficient nonclinical and clinical pharmacology data, both the FDA and the EMA accepted the re-submitted applications for regulatory review for the key drug in June 2019 [103]. On 26 March 2020, the FDA approved ozanimod for adults with RRMS, clinical isolated syndrome, and SPMS [104]. Ozanimod has been approved in Canada and the European Union for treatment of RRMS [105, 106].

5 Ponesimod (ACT-128800)

Ponesimod is an orally active, selective S1PR modulator with a potent selectivity for $S1PR_1$ and some activity at $S1PR_5$. It induces a rapid reduction in the number of circulating lymphocytes, with predominant reduction of naïve T cells and helper T cells compared with memory and cytotoxic T cells with partial sparing of regulatory T cells. Like other S1PR modulators, preclinical data suggested that ponesimod penetrates the CNS and may have direct neuroprotective effects. Treatment with ponesimod after the onset of experimental autoimmune encephalomyelitis increased the survival of the animals [107].

5.1 Pharmacokinetics

Ponesimod is absorbed rapidly after oral administration independent of food intake, with a t_{max} of 2.5–4 h. A steady-state plasma concentration of ponesimod was established with continuous dosing. Ponesimod induces rapid dose-dependent reduction in the total lymphocyte count, with a maximum reduction of around 70% from baseline within 7–14 days of the first-dose administration. However, most reduction occurs by day 8 of treatment. The short half-life of ponesimod (32 h) allows for rapid normalization of lymphocyte count within 1 week of treatment discontinuation [108].

5.2 Efficacy Data

A 24-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled, phase IIb dose-finding trial enrolled 464 patients with RRMS to evaluate the efficacy and safety of three doses of ponesimod as treatment for RRMS. Patients were randomized to receive either 10, 20, or 40 mg of ponesimod daily or placebo for 24 weeks. From week 12 to 24, there was a significant reduction in the cumulative number of new GdE lesions for all ponesimod doses compared with placebo (43, 83, and 77% for 10, 20, and 40 mg doses, respectively). The ARR reduction and time to first confirmed relapse was only significant for the 40 mg dose (52 and 58%, respectively). The 20 and 40 mg doses showed significant reductions in CUAL (GdE and new or enlarging T2 lesions) but not in new or enlarging T2 lesions. All ponesimod doses showed preservation of brain volume from baseline compared with placebo [109].

A 5-year, phase II extension of the core study confirmed the initial study results with a maintained long-term efficacy on clinical and MRI outcomes. All patients received ponesimod at week 24, and patients in the placebo group were re-randomized to ponesimod 10, 20, or 40 mg in a 1:1:1 ratio. A total of 326 patients received at least 48 weeks of study treatment. At week 48, the ARR in the continuous-ponesimod group was 0.22, 0.23, and 0.15 for the 10, 20, and 40 mg doses, respectively. In the switched group, the ARR reduced from 0.52 at week 24 to 0.25 at week 48. The mean total number of GdE lesions at baseline was 2.8, 2.7, and 2.1 for the 10, 20, and 40 mg doses of ponesimod, respectively, and 1.6 in the switched group. A sustained reduction was observed in the mean total number of GdE lesions of 0.8, 0.2, and 0.2 for the ponesimod doses versus 0.2 in the switched group at week 72 [107]. Interim analysis

of the extension study showed that ponesimod 20 mg had better clinical and MRI outcomes than the 10 mg dose and a similar safety profile [110, 111].

Two large, multicenter, randomized, double-blind, parallel-group, active-controlled, superiority, phase III studies (OPTIMUM [Oral Ponesimod Versus Teriflunomide In Relapsing Multiple Sclerosis] and POINT [Ponesimod and Tecfidera]) evaluated the efficacy and safety of ponesimod in treatment for relapsing MS. In OPTIMUM, 1133 patients were randomized to receive once-daily ponesimod 20 mg or once-daily teriflunomide 14 mg for 108 weeks. The primary endpoint was the ARR, whereas secondary endpoints included time to 12-week confirmed disability accumulation, time to first confirmed relapse, cumulative number of CUAL, percent change in brain volume, and change in fatigue-related symptoms from baseline to week 108 [112–114].

On 25 July 2019, the manufacturing company, Janssen, reported positive top-line results from OPTIMUM and announced that ponesimod met its primary endpoint and most of the secondary endpoints. The trial data were presented at the 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis in September 2019. In relation to the primary efficacy endpoint of OPTIMUM, data showed that ponesimod 20 mg reduced the ARR up to the end of study by 30.5% compared with teriflunomide. The mean ARR was 0.202 for ponesimod and 0.290 for teriflunomide. Change in fatigue-related symptoms from baseline to week 108 was lower in the ponesimod group according to the Fatigue Symptom and Impact Questionnaire—Relapsing MS. A mean difference of 3.57 for the ponesimod 20 mg group versus the teriflunomide 14 mg group was shown. The number of CUALs up to week 108 was lower for ponesimod than for teriflunomide, with a 56% reduction between the two. The confirmed disability accumulations at 12 and 24 weeks were 17 and 16% lower for ponesimod, although this was not statistically significant [112]. The OPTIMUM trial was the foundation of ponesimod's submission for regulatory approval for treatment for relapsing forms of MS. The company filed regulatory submissions on 19 March 2020 [115].

POINT was an add-on phase III study evaluating the added benefit of ponesimod versus placebo in patients taking dimethyl fumarate for at least 6 months. The study intended to recruit 600 participants who were to be randomized to receive once-daily ponesimod 20 mg or placebo. The primary endpoint was the change in ARR between the two groups. The study was also to measure time to confirmed disability accumulation, time to first relapse, and mean number of CUAL. However, this study was terminated in March 2020 because of low recruitment rates [114].

5.3 Safety and Tolerability Data

Ponesimod has a favorable safety profile and was generally well tolerated at doses of 10 and 20 mg. Reported adverse events were mainly related to first-dose bradycardia and AV block. The heart rate reduction occurs earlier with ponesimod than with fingolimod and reaches its maximum 2–3 h after the first dose, with normalization at around 6 h post-dose. An optimized uptitration dosing regimen was introduced for mitigation of the first-dose effect on heart rate. A dose-dependent effect on pulmonary function was observed mainly at 40 mg, the onset of which usually occurred within the first month of treatment. However, forced expiratory volume in 1 s returned to baseline values within 10 days of treatment discontinuation. The proportion of patients with one or more infection-associated adverse events was similar in all groups. Herpetic infections occurred in 4.8% of patients in both the ponesimod 20 mg treatment group and the teriflunomide treatment group of the OPTIMUM study [116]. Other frequently reported adverse events with ponesimod in the phase II and OPTIMUM trials included abdominal pain, dizziness, night sweats, dyspnea, and chest discomfort. In the phase II study, reported adverse events included anxiety, dizziness, dyspnea, increased ALT, influenza, insomnia, peripheral edema, and macular edema, whereas the most common in the extension study were nasopharyngitis, headache, dyspnea, and upper respiratory tract infection. Two cases of malignancy were reported during clinical studies: one case of breast cancer in the ponesimod 10 mg group and another case of cervical carcinoma in the placebo group [110–114, 116]. In the OPTIMUM study, five cases of skin malignancies were reported in the ponesimod 20 mg group. Two patients had basal cell carcinomas, another two underwent excisions of preexisting benign lesions, and one patient had malignant melanoma. The most common adverse events of special interest in the OPTIMUM study were hepatobiliary disorders and liver enzyme abnormalities, which occurred in 0.5% of patients in the ponesimod group. ALT increases that were 3 times the upper limit of normal were transient in the ponesimod group, whereas ALT increases > 8 times the upper limit of normal occurred in a higher proportion of patients in the teriflunomide group. After hepatobiliary abnormalities, hypertension and pulmonary events were the next most common adverse events of special interest. In the group receiving ponesimod 20 mg, 1.1, 4.8, and 1.4% of patients reported macular edema, herpetic infection, and seizures, respectively, and 2.1% of patients experienced an effect on heart rate and rhythm and hypotension on day 1. The rates of macular edema and herpetic infection in the teriflunomide group were both 0.2%, the risk of herpetic infection was also 4.8%, and 0.4% of patients reported an effect on heart rate and rhythm on day 1 [113, 116].

6 Ceralifimod (ONO-4641)

Ceralifimod is an orally active selective $S1PR_1$ and $S1PR_5$ modulator. It has an immune cell trafficking effect similar to that of other S1PR modulators. Preclinical data showed that ceralifimod prevented relapses of relapsing–remitting experimental autoimmune encephalomyelitis in a nonobese diabetic mouse model [117]. Although a phase II clinical trial of ceralifimod resulted in successful data, the clinical development of ceralifimod in MS was discontinued by the developing company in June 2014 because of the significant changes in market circumstances of treatment for MS.

6.1 Pharmacokinetics

Ceralifimod is absorbed rapidly after oral administration, with a t_{max} of 4.2–6.2 h. It induced a dose-dependent reduction in the total lymphocyte count of 40–65% from baseline. The half-life of ceralifimod is 82–89 h, allowing for normalization of lymphocyte count within 2 weeks of treatment discontinuation [118, 119].

6.2 Efficacy Data

In 2010, a 26-week, multicenter, randomized, double-blind, placebo-controlled, phase II study (DreaMS [Drug Research and Evaluation in Multiple Sclerosis]) enrolled 407 patients with active RRMS with an EDSS score < 6 aged 18–55 years to evaluate the efficacy and safety of ceralifimod versus placebo over a 26-week period. Patients were randomized to receive once-daily doses of ceralifimod 0.05, 0.1, or 0.15 mg or placebo in a 1:1:1:1 ratio. In December 2011, a total of 360 patients had completed the study [120]. Ceralifimod met its primary endpoint with significant reductions in the total number of GdE lesions of 82, 92, and 77% for the 0.05, 0.1, and 0.15 mg doses, respectively, versus placebo [121]. Although the dose-blinded extension of DreaMS was prematurely terminated due to market changes, the interim analysis of the extension at 26 weeks confirmed the core study findings with sustained efficacy [122, 123].

6.3 Safety Data

Data about the safety of ceralifimod are limited, but the risk profile appeared similar to those of other S1PR modulators, including first-dose bradycardia, liver enzyme elevations, and lymphopenia.

7 Amiselimod (MT-1303)

Amiselimod is a potent selective $S1PR_1$ and $S1PR_5$ modulator with an immune cell trafficking effect similar to that of the other S1PR modulators. Despite positive data from a phase II trial, the development plan for amiselimod was discontinued in October 2016 by the developing company, Biogen, for strategic reasons.

7.1 Pharmacokinetics

Unlike other the second-generation agents, amiselimod requires phosphorylation by the endogenous SphK2 to its active metabolite: amiselimod phosphate (amiselimod-P). The t_{max} of amiselimod is similar to that of fingolimod, at 12–16 h. It induced a 60–66% reduction in lymphocyte counts from baseline. Amiselimod-P may be distributed in the heart tissue at lower levels than fingolimod-P [124, 125]. Unlike other new S1PR modulators, amiselimod has a long half-life of approximately 380–420 h, resulting in a delay of up to 7 weeks after treatment discontinuation for lymphocyte count recovery.

7.2 Efficacy Data

In 2013, a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-finding, phase II study (MOMENTUM) enrolled 415 patients aged 18–60 years with active RRMS and an EDSS score < 6 to evaluate the efficacy and safety of amiselimod versus placebo. Patients were randomized to receive once-daily amiselimod 0.1, 0.2, or 0.4 mg or placebo in a 1:1:1:1 ratio for 24 weeks. By October 2014, a total of 367 patients had completed the study. The 0.2 and 0.4 mg doses of amiselimod met the primary endpoint with significant dose-dependent reductions in total number of GdE lesions of 61 and 77%, respectively, compared with placebo at week 24, whereas patients receiving 0.1 mg and those receiving placebo had a similar number of GdE lesions. Both doses also reduced the ARR, although the reduction observed with 0.4 mg was more significant [125]. In a 72-week dose-blinded extension of the phase II study, patients receiving amiselimod in the core study continued at the same dose, whereas those receiving placebo were re-randomized to amiselimod 0.1, 0.2, or 0.4 mg for another 72 weeks. However, most patients receiving 0.1 mg were re-randomized again to 0.2 or 0.4 mg once the core study results became available. For up to 2 years, amiselimod showed long-term sustained efficacy with no new safety concerns [126].

7.3 Safety Data

Amiselimod has high potency with minimal adverse events. No serious adverse events were reported in any of the amiselimod doses with no cases of serious infections, macular edema, or malignancy. Indeed, amiselimod has a favorable cardiac safety profile with no significant effects on heart rate. Only one case of second-degree AV block was reported in the 0.1 mg group, and one case of nonsustained ventricular tachycardia was reported in the 0.2 mg group. Lymphopenia and mild elevation in liver enzymes were observed. The most common adverse events reported with amiselimod were headache and nasopharyngitis [125].

8 Conclusion

The introduction of S1PR modulators has transformed the treatment landscape for patients with MS because of their ability to retain autoreactive lymphocytes and possibly neuroprotective effects through interaction with the S1PR on neuronal cells. The second-generation agents have demonstrated superior pharmacodynamics and pharmacokinetics, offering a convenient alternative to fingolimod with improved safety and tolerability profiles. More long-term data are needed to determine the risk of rebound after treatment discontinuation and illuminate whether the shorter half-lives affect the period in which people may be at risk for rebound. Finally, whether PML is a risk with these newer treatments and the degree of that risk has yet to be determined. Although more long-term safety data for the new S1PR modulators are needed, some of the newer S1PR modulators have already been approved. Siponimod is the first oral therapy to be approved for treatment of SPMS, and ozanimod has been approved as a first-line agent in Canada and the USA, offering a higher-efficacy oral agent as an option for first-line therapy. It is likely that more agents will be approved for the treatment of MS in the near future.

Declarations

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