Title

Ponesimod to treat multiple sclerosis

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Keywords

Ponesimod; ACT-128800; Sphingosine 1-phosphate receptor (S1PR) modulators; Treatment of Autoimmune Diseases; Multiple Sclerosis

Running title

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Summary

Ponesimod (ACT-128800) is a directly bioavailable, rapidly reversible sphingosine 1-phosphate receptor modulator, highly selective for the subtype 1 ($S1PR_1$). It acts by blocking the egress of lymphocytes from the lymphoid organs, thus limiting the entry of autoreactive cells into the central nervous system (CNS).

Unlike fingolimod, ponesimod does not require monitoring of the first dose, thanks to a 15-day up-titration regimen, which markedly reduces the incidence of cardiodynamic effects related to the initiation of therapy.

Results from the OPTIMUM phase 3 trial demonstrated the superiority of ponesimod over teriflunomide on disease activity markers, without unexpected safety concerns. Furthermore, the drug is eliminated within 1 week of discontinuation, allowing for the reversibility of its effects.

Ponesimod was recently approved in both US and EU for the treatment of relapsing forms of multiple sclerosis (MS). This review summarizes the pharmacological characteristics of ponesimod and the main studies that led to its approval.

Background

Multiple sclerosis is a chronic disease with likely autoimmune pathogenesis, characterized by inflammation and demyelination of the central nervous system, associated with a variable degree of neuroaxonal damage and atrophy (1–3).

It represents the main cause of non-traumatic neurological disability in young adults, with a prevalence of 142/100,000 cases in Europe (4). The age of onset is between 20 and 40 years with a peak of incidence around 30 years, however the disease can also present in children or adolescents (3-5%) and in people over the age of 50 (4-9%)(5). The frequency of MS is higher in women than in men; globally, the female to male ratio is 2.2:1 and can be as high as 4:1 in some countries (4).

It is still debated whether the initial pathophysiological event is the inflammation itself, or this is secondary to the action of a yet-unknown infectious agent or intrinsic event of the CNS (6). Nonetheless, most MS investigators believe that the primary pathogenic event is represented by the entry of self-reactive immune cells into the CNS (mainly T and B lymphocytes), attacking components of the myelin sheath, thus perpetrating inflammatory damage.

The course of multiple sclerosis relies on the interaction between two phenomena: relapses and progression. In many patients, these phenomena overlap for most of the duration of the disease, while in other cases the prevalence of one or the other is more marked.

Over the past thirty years, extraordinary advances have been made in the treatment of MS, once considered a disease with an inexorable course (7). Disease modifying therapies (DMTs) tend to be MS-specific and aim to reduce the frequency, severity and duration of relapses, as well as prevent disability caused by disease progression (9). Up until 20 years ago, the only DMTs approved were interferon and glatiramer acetate, while fingolimod, the first oral drug, was approved only 11 years ago.

The sphingosine-1-phosphate receptor (S1PR) modulator fingolimod (FTY-720), acts by sequestering lymphocytes in the lymph nodes, thereby reducing the entry of autoreactive cells into the CNS. After demonstrating superiority over placebo and interferon in preventing relapses, it was the first oral drug to be approved for use in MS (8,9).

In more recent years, the role of sphingosine 1-phosphate (S1P) in the immune, cardiovascular and central nervous systems has been better understood. It is expressed on the lymphocyte surface and acts as a

signalling molecule that can bind to five different G protein-coupled receptors, $S1PR_{1-5}$ (10). Due to the expression of these receptors in multiple organs and systems, S1PR has been implicated in several immune-mediated diseases, including MS. Therefore, multiple S1PR-directed therapies have been developed, each with a different selectivity profile for each receptor subtype. In order to reduce the potential risk of atrioventricular conduction blocks and bradycardia, the new S1P modulators were designed not to interact with the $S1PR_3$ subtype and to more selectively target subtype 1 (11). Among drugs with similar mechanism of action, siponimod (BAF312) was the first DMT to obtain approval for the treatment of secondary progressive MS (12). It was followed by ozanimod (RPC1063) for use in relapsing MS and, on March 19, 2021, by ponesimod (ACT128800) (13,14). Other S1PR modulators in various stages of development are ceralifimod (ONO-4641), GSK2018682 and amiselimod (MT-1303) (15–17). A summary of the main characteristics of all approved S1PR modulators is presented in table 1.

This review will focus on the pharmacology and on the recent clinical trials that have evaluated the efficacy and safety of ponesimod for the treatment of multiple sclerosis.

Preclinical Pharmacology

Ponesimod [ACT-128800 or 5-(3-chloro-4-(2,3-dihydroxy-propoxy) benzylidene)-2-propylimino-3-o-tolyl-thiazolidin-4-one] is a highly selective modulator for S1PR1, rapidly active and directly bioavailable, because it does not require phosphorylation (Figure 1). It acts as a functional antagonist: after binding with $S1PR_1$, it causes the temporary activation of this G-protein coupled receptor, followed by its internalization and degradation. This mechanism ultimately leads to the blocking of lymphocyte egress from the lymph nodes. The selection of this compound occurred after extensive research led to the discovery of a class of agonists for S1P receptors, derived from the 2-imino-thiazolidin-4-one scaffold (18).

The affinity of ponesimod is 4.4 times higher for $S1PR_1$ and 150-fold lower towards $S1PR_3$, compared to their natural ligand, resulting in about 650 times greater selectivity for $S1PR_1$ compared to S1P (19). In animal studies, oral administration of ponesimod showed a dose-dependent reduction in lymphocyte count, completely reversible in 48 hours after discontinuation. Ponesimod immediately demonstrated efficacy in preventing the clinical manifestations of inflammatory cutaneous and joint diseases in murine animal models

(20). Subsequently, ponesimod was studied alone or in combination therapy together with dimethyl fumarate (DMF) in mouse and rat experimental autoimmune encephalitis (EAE) models and it showed significant efficacy on clinical scores, with a synergistic effect when associated with DMF (21).

Pharmacokinetics and Metabolism

From the first in-human study on the administration of ascending doses of ponesimod, it is possible to detect salient data on its pharmacokinetics (PK). In fasting conditions, ponesimod was absorbed in 2-4 hours, while it took 5 hours for the drug to be completely absorbed after a high-fat meal. Peak plasma concentrations were directly proportional to the administered dose and were slightly higher in non-fasting subjects. Elimination of the drug took about 30 hours, regardless of the dose (22).

In a subsequent study on healthy human subjects, ponesimod confirmed its dose-proportional PK. The time to maximum concentration varied between 2.5 and 4 hours, with a moderate accumulation (2.3-fold), while the elimination half-life was just over 30 hours. The time to reach steady-state was 5 days, and even at this point the median tmax ranged 2.5-4 hours. In this study, the elimination of the drug occurred in 21-33 hours (23).

The metabolism of ponesimod generates two main compounds: M12 (ACT-204426) and M13 (ACT-338375) (24). M12 and M13 can undergo further metabolic transformations, but are pharmacologically inactive. While these metabolites do not seem to contribute to the efficacy of the drug, they could be relevant for its safety, especially in subjects with hepatic impairment. It has been noted that in subjects with hepatic insufficiency, the exposure to ponesimod increases up to 3 times, while the exposure to its metabolites is up to 9 times greater. Body weight also represents a variable that alters the volume of distribution of the drug, leading to 10% greater or lesser exposures for subjects 60 or 90 kg, respectively, when compared to a standard 75 kg subject (25).

Unlike siponimod, ponesimod metabolism is independent of the cytochrome P450 system, therefore genotyping is not required (26).

The elimination of the drug occurs for the most part through the faeces (57.3-79.6%), where a small proportion of non-metabolized ponesimod can also be found. It is eliminated to a lesser extent via the urine

(10.3-18.4%) as a metabolized compound and a less significant amount is also found in the exhaled air (24). Gender studies have noted that absorption may be higher in females than in males. The comparison between ethnic groups showed a slightly higher exposure in the Japanese than in Caucasians. In both cases, however, the efficacy in reducing lymphocyte counts, as well as the metabolism of the drug, did not differ between subjects, making a dose adjustment unnecessary (27).

Safety

The first S1PR modulator to be approved, fingolimod, showed the risks of modulating all sphingosine-1-phosphate receptors. The risk-benefit profile of fingolimod has been shown by all clinical trials, as well as by post-marketing studies and real-world evidence. Nonetheless, fingolimod therapy is complicated by a higher incidence of cardiovascular alterations. Notably, symptomatic bradycardia occurs in 0.6% of patients, typically 4-5 hours after the first dose, with a mean maximum heart rate (HR) reduction of 8 bpm. In 0.2% of cases, a Mobitz type 1 second degree atrio-ventricular block appears. Furthermore, the interaction with $S1PR_3$, $S1PR_4$ and $S1PR_5$ might be responsible for the onset of hypertension, prolongation of the QT interval, macular edema, pulmonary and hepatic toxicity (11).

In the first study on ponesimod in healthy human subjects, the incidence and severity of adverse events (AEs) were proportional to the dose administered. The most frequent AEs at the highest dose of 75 mg were fatigue, dyspnea, dizziness, headache and bradycardia. HR reduction was also dose dependent and significantly more frequent than placebo only for doses ≥8 mg (22).

Subsequent phase I trials confirmed the safety considerations on ponesimod that emerged after the first study. In particular, it was noted that while lung-related events (dyspnea, decreased pulmonary function) appeared several days after the initiation of therapy before stabilizing, other AEs, including those related to cardiac function, were much more frequent during the first day of dosing. Also in these studies, the significant increase in heart and lung alterations occurred for doses > 10 mg. However, all AEs subsided after drug discontinuation (23,26).

$S1P_3$ receptors were initially thought to be solely responsible for reducing HR. After evidence emerged regarding the cardiodynamic effects of selective $S1P_1$ modulators, an additional mechanism was hypothesized (22,28). The agonism of $S1P_1$ and $S1P_3$ receptors on the myocyte surface causes HR reduction

via stimulation of the inwardly rectifying $G_{\alpha i}$-protein-regulated potassium channel (GIRK/IK.ACh) (29). Once activated, S1P receptors are internalized, leading to the desensitization of this system in the cardiomyocytes and to the normalization of heart rate and rhythm, which is maintained by repeated administrations of the drug (30). After safety concerns regarding heart function emerged, a new up-titration protocol was investigated, with the aim of mitigating the effects of ponesimod on cardiac rhythm and conduction. In a double-blind, placebo-controlled, randomized, 2-way crossover study, patients received multiple doses of ponesimod with different titration escalation regimens, or matching placebo. The study showed that an incremental dose of ponesimod from 2 to 20 mg in 9 steps over a period of 14 days markedly reduced the incidence of cardiodynamic effects related to the initiation of therapy (31).

In the first phase II study, different doses of ponesimod (10, 20 and 40 mg) were compared with placebo. All patients took the initial dosage of 10 mg and then could switch, depending on the randomization, to 20 mg after one week and to 40 mg after another week. The percentage of patients with at least one adverse event during the study was similar between the various ponesimod groups and placebo. All cardiovascular AEs occurred on day 1 after administration of ponesimod at the 10 mg dose, while no significant effects were noted after up-titration. Dyspnea and peripheral edema occurred mostly in the group receiving ponesimod 40 mg, while 3 cases of macular edema were reported, all in the 20 mg group and within the first 3 months of starting treatment. Other AEs reported more frequently in the ponesimod groups were anxiety, dizziness, insomnia, increased alanine aminotransferase (ALT) and influenza (32).

Patients who participated in the phase II study rolled over into its extension, in which they were all treated with ponesimod 20 mg. After a median exposure of more than 8 years, between core and extension studies, the drug confirmed its substantial safety. No SAEs with an incidence greater than 1% were reported and the most common adverse events were nasopharyngitis (30%), headache (24%) and upper respiratory tract infection (21%) (33).

The phase III trial (OPTIMUM study) compared ponesimod to teriflunomide. In this study, the proportion of patients who experienced at least one AE was similar between the 2 groups, although the events leading to treatment discontinuation were more frequent in the ponesimod group (8.7%) compared to teriflunomide (6.0%). The most common AEs in the ponesimod group were an increased ALT level (19.5%), nasopharyngitis (19.3%), headache (11.5%) and upper respiratory tract infection (10.6%) (14).

As for the cardiodynamic AEs, only 2.1% of patients experienced first-dose HR and rhythm alterations, thanks to the 14-day up-titration regimen applied. Furthermore, no first-day cardiac AEs were considered serious, or led to treatment discontinuation. During follow-up, no major cardiac adverse events were reported for patients on ponesimod (34).

Furthermore, in the OPTIMUM study, basal cell carcinoma was detected in 0.4% of patients on ponesimod treatment, compared to 0.2% of patients on teriflunomide (34).

Another limitation of S1PR modulators is the risk of rebound after cessation of therapy for any reason. Rebound refers to an increase in disease activity that is disproportionate to the pre-treatment period (35). In this regard, patients who had completed the OPTIMUM phase 3 study or who had discontinued treatment prematurely were included in a safety study. The analysis conducted on 1124 patients showed that there is no increased early post-treatment relapse activity in patients treated with ponesimod, suggesting that it can be used with more confidence in those patients who may need therapy interruptions, for example due to pregnancy planning (36). An overview of the safety considerations for ponesimod is presented in table 2.

Finally, rodent studies have shown that elevated ponesimod exposures are teratogenic. For this reason, both in clinical studies and in commercial use, ponesimod is contraindicated for women of childbearing age who do not use effective contraceptive methods and for those who are pregnant (37).

Clinical Studies

In a study on human healthy volunteers, oral administration of ponesimod was associated with dose-dependent reductions in total lymphocyte count (70.3% with the maximum dose of 75 mg) (22). The decrease was even more pronounced on T lymphocytes, which decreased by 67-89% from baseline with the maximum dose (38). Among lymphocyte subsets, the most altered ones were T-helper (CD4 +) and T-cytotoxic (CD3 + CD8 +) cells, with a less pronounced effect also on B cells (CD20 +). Natural killer cells (CD3 - 16 +) and regulatory lymphocytes were not altered. A further phase I trial confirmed the sustained reduction effect on T lymphocytes, with a major alteration of CD4 + and T-cytotoxic lymphocytes. NK cells and CD8 + memory T-effector cells were not significantly reduced after the administration of ponesimod, allowing for the preservation of defenses against viral agents (39). In humans, the dose-dependent decrease in total lymphocyte count was reversible within 7 days after therapy discontinuation.

In another dose ascending study in healthy human subjects, sinus bradycardia and AV block were noted on the first days of ponesimod administration. This prompted the design of an up-titration program, which was able to reduce the onset of cardiovascular effects related to initiation of therapy (23).

The clinical efficacy of ponesimod in the treatment of MS was studied in 2 phase II clinical trials and 3 phase 3 clinical trials (table 3).

In the first, dose-finding, phase 2 study (AC-058B201, NCT01006265), 464 patients were randomized in a 1: 1: 1: 1 ratio to receive placebo or ponesimod 10, 20 or 40 mg (32). Patients randomized to higher doses of ponesimod followed an up-titration scheme with dose escalation on days 8 and 15. Visits and MRI scans were performed at baseline and every 4 weeks for 24 weeks. The primary endpoint of this study was the cumulative number of new brain T1 Gadolinium (Gd) positive MRI lesions from weeks 12 to 24. MRI scans performed during weeks 4 and 8 were excluded from the analysis, taking into account the already known delayed anti-inflammatory effect of S1PR modulators. At week 24, ponesimod was able to significantly reduce the onset of new brain lesions by 43% (10 mg dose), 83% (20 mg dose), 77% (40 mg dose), compared to placebo. The number of new combined unique active lesions (CUALs, the sum of all new T1 Gd + lesions and new or enlarging T2 lesions) was reduced by 42% (10 mg), 80% (20 mg) and 73% (40 mg), compared to placebo. The number of adverse events did not differ significantly between groups, although more patients in the ponesimod 40 mg group discontinued the study due to adverse events, mainly respiratory (dyspnea, reduced forced expiratory volume in one second, FEV1). Based on the reduced tolerability, with no added clinical or pharmacodynamic benefit, the 40 mg dose was withdrawn at the end of the study and not considered for subsequent trials.

Patients who had completed the core study were offered enrollment in the extension of the phase II trial (NCT01093326), in which all 353 participants were treated with ponesimod (33). In an early part of the study, patients were still given the three different doses of ponesimod. At the end of treatment period 1 (TP1), the 40 mg dose was discontinued, while at the end of TP2 the 20 mg dose was confirmed to be more effective and with similar safety compared to the 10 mg dose. Thus, the 20 mg dose was chosen as the standard and was administered to all patients in an open label TP3, which is still ongoing. The results of an analysis performed after a median 8.02-year exposure to the 20 mg dose, considering both the core study and the extension phase, showed that the annualized relapse rate in patients treated with ponesimod was 0.154,

while 64.1% patients were still free of relapses and only 20.4% had confirmed disability accumulation. Ponesimod showed a sustained effect from an imaging standpoint, too. The mean number of Gd+ T1 lesions per patient per scan was 0.448, and after nearly 9 years the 47.9% of patients were free of new/enlarging T2 lesions.

Based on the efficacy demonstrated in the phase 2 studies, ponesimod was compared with another DMT already approved for multiple sclerosis, teriflunomide, in a randomized, double-blind, superiority phase III trial. The OPTIMUM trial (AC-058B301, NCT02425644) was the first phase 3 study to compare two oral treatments for relapsing multiple sclerosis (14). 1133 patients were randomized to either ponesimod 20 mg or teriflunomide 14 mg and were followed-up for 108 weeks. Only patients with a relapsing course (RMS or active secondary progressive MS) and recent clinical or MRI activity were enrolled. The baseline characteristics were equally distributed across the two groups. In particular, the patients had a mean age of 37 years, with more than 7 years of disease history and a mean EDSS of 2.6. Moreover, 35% of patients in both groups were considered to have highly active disease. As for the primary outcome, mean ARR in the ponesimod group was reduced by 30.5% (0.202 versus 0.290 for teriflunomide). Regarding imaging endpoints, ponesimod demonstrated superiority over teriflunomide in reducing the appearance of new brain lesions by 44% (1.405 vs 3.164 per year) and reducing brain volume loss by 0.34% (−0.91% vs −1.25%). No significant difference was found between the two treatments on the accumulation of disability, instead a preventive effect on fatigue worsening was noted in the ponesimod arm. In this trial, the impact of fatigue was measured with a new scale, developed by Janssen in line with FDA guidance. Fatigue symptoms and impacts questionnaire in relapsing multiple sclerosis (FSIQ-RMS) is a comprehensive measure of fatigue-related symptoms and their impact on patients with RMS. In the ponesimod group, the mean FSIQ-RMS score at week 108 remained stable compared to baseline. In contrast, in the teriflunomide group, the mean score gradually increased from baseline through week 108. A significant difference in mean FSIQ-RMS scores favoring ponesimod 20 mg over teriflunomide 14 mg was present from Week 60 and was maintained until the end of the study. Importantly, this effect on fatigue symptoms did not depend on EDA / NEDA status (40).

Therefore, ponesimod was shown to be more effective than a well-established first-line DMT on inflammation markers, but its benefits may also extend to tissue damage reduction, although the study was underpowered to detect a significant clinical effect on disability accumulation.

Out of the 944 patients who completed core study AC-058B301, 877 agreed to continue in the long-term open-label extension of the trial (OPTIMUM-LT, NCT03232073) (41). Patients who received teriflunomide in the OPTIMUM study have undergone the accelerated elimination procedure before starting ponesimod with the established 15-day up-titration regimen. The aim of the study is to investigate the long-term safety and tolerability of ponesimod, as well as its sustained efficacy on the disease activity and, possibly, on disability progression. Currently, the study is ongoing and preliminary results regarding the various exploratory outcomes have not yet been published.

Based on the positive results from studies on EAE models, another phase III trial (POINT, NCT02907177) was started in 2017, in order to compare the efficacy and safety of ponesimod versus placebo in patients with active relapsing MS already treated with DMF (21,42). The study aimed to include 600 patients, to randomize 300 of them to combination therapy and 300 to DMF plus placebo. Unfortunately, only 136 patients were recruited in 3 years, therefore the study was judged futile and terminated by the sponsor on March 26, 2020. Due to the small sample size, neither differences in the efficacy endpoints nor the safety profile of ponesimod as an add-on therapy to DMF could be detected.

Drug Interactions

In vitro studies have shown that none of the main enzyme systems are responsible for the metabolization of ponesimod (cytochrome P450s, UDP-glucuronosyltransferase flavin mono-oxygenases, aldehyde oxidase, xanthine oxidase, alcohol dehydrogenases, aldehyde dehydrogenases). Therefore, it is highly unlikely that subjects receiving ponesimod will experience increased or decreased exposure to most of their concomitant medications (43).

Effective contraception is indicated in all women of childbearing potential during treatment with ponesimod. In this regards, one study demonstrated that there is no pharmacokinetic interaction between ponesimod and an oral hormonal contraceptive containing 1 mg of norethisterone/norethindrone and 35 mcg of ethinyl

estradiol. Interactions with medications containing other progestins have not been studied, but concomitant use of ponesimod is not expected to decrease the effectiveness of hormonal contraceptives (37).

It is necessary to be careful about the concomitant use of ponesimod with beta-blockers, due to the pharmacodynamic interaction on heart rate. A clinical trial (NCT03882255) investigated the cardiac effects of the first dose of ponesimod in subjects receiving propranolol (80 mg once daily). Compared to ponesimod alone, the combination with propranolol resulted in a decrease of 12.4 bpm in the mean hourly HR after the first dose of ponesimod (2 mg). At the first dose after up-titration (20 mg), concomitant administration of propranolol resulted in a 7.4 bpm HR reduction (44).

Preclinical data indicate that the immune response to non-live vaccines during treatment with ponesimod and for up to 1 week after discontinuation may be reduced, although this effect may not be clinically relevant in humans (37). Currently, a vaccination sub-study is ongoing as part of the phase II trial AC-058B202 extension. As for live attenuated vaccines, if they are required, ponesimod treatment should be paused from 1 week prior to 4 weeks after vaccination.

Finally, ponesimod has not been studied in combination with antineoplastic or immunomodulatory therapies, but an additive effect on the immune system is very likely. Therefore, it is necessary to use caution in the concomitant use of these drugs.

Indications

On March 18, 2021, ponesimod (marketed under the name Ponvory) was approved by the Food and Drug Administration (FDA) for the treatment of relapsing forms of MS, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in US adults (45).

On May 19, 2021, the European Medicines Agency (EMA), through the Committee for Medicinal Products for Human Use (CHMP), granted ponesimod the marketing authorization valid throughout the European Union for the same indication (46).

Treatment begins on day 1 with a 2 mg tablet taken orally once a day, and the dose increase proceeds according to the 15-day up-titration scheme (table 4). After completion of dose titration, the recommended maintenance dose of ponesimod is one 20 mg tablet taken orally once a day, regardless of fed state. Re-

initiation of therapy with the same up-titration regimen is indicated every time the patient misses four or more consecutive doses.

Unlike fingolimod, ponesimod does not require first-dose observation with ECG monitoring. However, since the initiation of treatment may lead to a reduction in the HR, a 4-hour monitoring after the first administration is recommended in patients with sinus bradycardia, first grade or Mobitz I second grade atrio-ventricular block, heart failure or myocardial infarction occurred more than 6 months before treatment initiation.

Vaccination against varicella-zoster virus is also recommended, so patients must provide documentation of a complete vaccination course that took place at least 4 weeks before starting treatment. Ponesimod should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease. In addition, during the follow-up, patients should undergo dermatological and ophthalmological examinations due to the increased risk of skin malignancies and macular edema (0.9% and 0.7% risk in the clinical trial experience, respectively) and must be warned against unprotected sun exposure.

Conclusion

Ponesimod is a highly selective $S1PR_1$ modulator with a similar efficacy profile to the already known fingolimod. Unlike the latter, however, ponesimod has a PK and pharmacodynamic profile that make it safer for the patient and more easily manageable for the neurologists (table 1). Patients do not need to undergo first dose monitoring, except for selected cases. Moreover, unlike siponimod, its metabolism is not dependent on major cytochrome systems, so genotyping is not required and all patients are prescribed the same dose.

The half-life of ponesimod is about 33 hours, much shorter than fingolimod, allowing for a more rapid reversibility of its effects in case of need. Besides, after discontinuation, lymphocytes return to normal levels in just 7 days, while with fingolimod this process takes about 6 weeks.

Unlike siponimod, which is only approved for active secondary progressive forms of MS, ponesimod is also approved for relapsing forms of the disease, including clinically isolated syndromes, reflecting the fact that it is a well manageable drug even in initial forms of the disease.

Ponesimod shares many features with ozanimod, though ozanimod is less specific for the S1P1 receptor. Furthermore, mean lymphocyte count reduction is 55% with ozanimod, versus the 60-70% shown by ponesimod. Studies have shown that the effectiveness of these treatments is proportional to the reduction in lymphocyte count, reaching a plateau for levels 60–70% lower than baseline (32,47).

Currently, there are no data available on the comparison between various S1PR modulators. However, ponesimod is the only one to have demonstrated superiority over another oral drug in a phase 3 trial and is more easily manageable than drugs of the same class.

Disclosures

No funding has been received for the conduct of this study.

AI has nothing to disclose. CP received consulting and lecture fees from Sanofi-Aventis, Biogen Idec, Bayer Schering, Merck Serono, and Novartis. He also received research funding from Novartis, Sanofi-Aventis, Merck Serono, and Bayer Schering.

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Figura 1: chemical structure of ponesimod

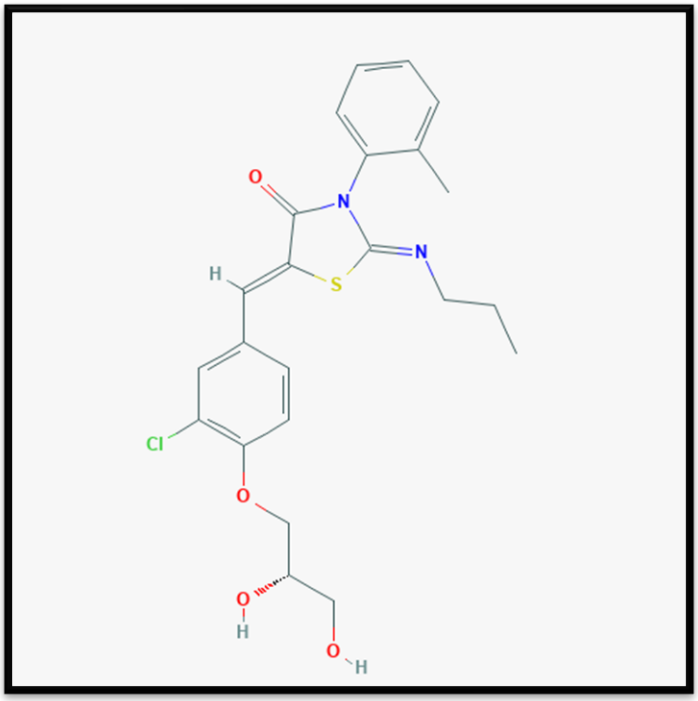

Table 1: summary of the main characteristics of approved S1PR modulators

Drug	Ponesimod	Fingolimod	Siponimod	Ozanimod
Receptor selectivity	$S1PR_1$	$S1PR_1$ $S1PR_3$ $S1PR_4$ $S1PR_5$	$S1PR_1$ $S1PR_5$	$S1PR_1$ $S1PR_5$
Genotypying needed	No	No	Yes (CYP2C9)	No
Elimination half-life	33 hours	6-9 days	30 hours	21 hours
Mean lymphocyte count reduction	60-70%	70-80%	70-80%	55%
Lymphocyte count reversibility after discontinuation	7 days	6 weeks	Within 10 days	2-3 days
Dose titration	14 days	None	5 days	7 days
Oral maintenance dose	20 mg once daily	0.5 mg once daily (0.25 mg once daily for children with body weight < 40 kg)	2 mg once daily (1 mg once daily for patients with a CYP2C9*2*3 or *1*3 genotype)	0.92 mg once daily
First-dose monitoring	4 hours for patients with a history of cardiac conditions	6 hours for all patients	6 hours for patients with a history of cardiac conditions	6 hours for patients with a history of cardiac conditions
Indication	Adults with relapsing forms of MS, including clinically isolated syndrome, RRMS and active SPMS	Adults and children ≥10 years old with highly active RRMS	Adults with SPMS with active disease	Adults with relapsing forms of MS, including clinically isolated syndrome, RRMS and active SPMS

Table 2: contraindications and safety profile of ponesimod 20 mg

Contraindications	▪ Hypersensitivity to the active substance or excipients ▪ Immunodeficiency ▪ Active malignancies ▪ Severe active infections or active chronic infections ▪ Pregnancy or women of childbearing age without contraception ▪ Patients who in the previous 6 months experienced MI, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalisation or NYHA Class III/IV heart failure ▪ Presence of Mobitz Type II 2nd-degree AV block, 3rd-degree AV block or sick sinus syndrome, unless patient has pacemaker ▪ Moderate or severe hepatic impairment (Child–Pugh Class B or C)
Main AEs during phase II and III trials	▪ Nasopharyngytis (9.6-19.3%) ▪ Increased ALT level (6-19%) ▪ Headache (11.5-13.2%) ▪ Hypertension (10%) ▪ Upper respiratory tract infections (8-10.6%) ▪ Fatigue (8%)
Bradyarrhythmia	Mean decrease in HR on day 1 of dosing (2 mg) was 6 bpm. The decrease begins after 1 hour and reaches its nadir in 2-4 hours. After day 1 of titration, the decrease in HR is less pronounced and no further post-dose decreases in HR are observed after day 3.
Risk of infections	Mean lymphocyte count reduction with ponesimod is 30-40% of baseline values, increasing the risk of infections. Absolute lymphocyte counts of $<0.2\times10^9$/L should lead to interruption of therapy until the level reaches $>0.8\times10^9$/L, when re-initiation of ponesimod can be considered.
Liver injury	Increased transaminases level is common. Ponesimod should be discontinued if significant liver injury is confirmed.
Macular edema	In clinical trial experience the rate of macular edema was 0.7% and most cases occurred during the first 6 months of treatment. Patients with a history of uveitis or with diabetes mellitus are at increased risk of macular oedema during therapy with S1PR modulators.
Respiratory effects	Dose-dependent reductions in forced expiratory volume in 1 second (FEV1) and reductions in diffusing capcity for carbon monoxide (DLCO) were observed in ponesimod-treated patients, mostly occurring in the first month after treatment initiation. Respiratory symptoms associated with ponesimod treatment can be reversed with administration of a short-acting β2 agonist.
Hypertension	Mean, reversible, increase in blood pressure is < 3 mmHg.
Cutaneous neoplasms	0.9% risk in clinical trial experience. Patients should be warned against unprotected sun exposure or concomitant phototherapy.
Teratogenicity	Based on animal studies, ponesimod may cause fetal harm. Women of childbearing potential should use effective contraception to avoid pregnancy during and for 1 week after stopping ponesimod treatment.
Return of disease activity after ponesimod discontinuation	No increased early post-treatment relapse activity has been observed after ponesimod. Anyway, patients should be monitored for a severe exacerbation or return of high disease activity upon ponesimod discontinuation.

Table 3: clinical trials on ponesimod for multiple sclerosis.

Trial	Phase	Status	Drugs	Subjects	Endpoints	Key results (if available)
AC-058B201 (NCT01006265, EudraCT2008-006786-92)	Phase II: randomized, double blind, placebo controlled, dose-finding study	Completed	▪ Ponesimod ▪ Placebo	▪ Ponesimod 10 mg (108 pts) ▪ Ponesimod 20 mg (116 pts) ▪ Ponesimod 40 mg (119 pts) ▪ Placebo (121 pts)	**Primary endpoint:** ▪ Cumulative number of new T1 Gd+ lesions on MRI from week 12 to week 24 **Key secondary endpoints:** ▪ Mean ARR ▪ Number of new or enlarging non-enhancing lesions from week 12 to week 24	**Primary endpoint:** ▪ New T1 Gd+ lesions lower in all ponesimod groups (3.5, 1.1, 1.4) vs placebo (6.2) **Key secondary endpoints:** ▪ Mean ARR reduced by 52% in the ponesimod 40 mg group ▪ Number of new or enlarging non-enhancing lesions reduced by 42%, 80%, 73% vs placebo.
Extension of AC-058B201 (NCT01093326, EudraCT2009-011470-15)	Phase II: Randomized, double blind, parallel-group study	Ongoing	▪ Ponesimod	353 pts randomized to: ▪ Ponesimod 10 mg ▪ Ponesimod 20 mg ▪ Ponesimod 40 mg All patients received the 20 mg dose during the open-label phase	**Exploratory endpoints:** ▪ ARR at EOS (660 weeks) ▪ Time to first confirmed relapse ▪ Time to 24 weeks CDA up to EOS	**Primary endpoints:** ▪ ARR is 0.154 ▪ 64.1% of patients are free of confirmed relapses after 8 years
POINT (NCT02907177, EudraCT2012-000541-12)	Phase III: randomized, double blind, parallel-group, add-on, superiority study	Terminated (slow recruitment rate)	▪ Ponesimod Plus DMF ▪ Placebo Plus DMF	▪ Ponesimod Plus DMF (86 pts) ▪ Placebo Plus DMF (86 pts) [Estimated: 600 pts]	**Primary endpoint:** ▪ ARR at EOS (167 weeks) **Key secondary endpoints:** ▪ Time to 12-week CDA ▪ Time to first confirmed relapse ▪ Mean number of CUAL per post-baseline scan ▪ Change in FSIQ-RMS ▪ Brain volume percent change from baseline	The insufficient sample size did not allow to detect the differences for the main efficacy endpoints

OPTIMUM (NCT02425644, EudraCT2012-000540-10)	Phase III: randomized, double-blind, parallel group, active-controlled, superiority study	Completed	▪ Ponesimod ▪ Teriflunomide	▪ Ponesimod (567 pts) ▪ Teriflunomide (566 pts)	**Primary endpoint:** ▪ ARR **Key secondary endpoints:** ▪ Changes in FSIQ-RMS at week 108 ▪ Number of CUAL per year on MRI ▪ Time to 12 and 24-week confirmed disability accumulation	**Primary endpoint:** ▪ 30.5% reduction in ARR (0.202 vs 0.290) **Key secondary endpoints**: ▪ Mean difference in FSIQ-RMS: -3.57 (-0.01 vs 3.56) ▪ 56% risk reduction of CUAL per year ▪ No significant results for time to disability accumulation
OPTIMUM-LT (NCT03232073, EudraCT2016-004719-10)	Phase III: single-group, open-label study	Ongoing	▪ Ponesimod	▪ Ponesimod (877 pts)	**23 exploratory endpoints**	

[ARR: annualized relapse rate; CDA: confirmed disability accumulation; CUAL: combined unique active lesions; DMF: dimethyl fumarate; EDSS: expanded disability status scale; EOS: end of study; EOT: end of treatment, FSIQ-RMS: fatigue symptoms and impacts questionnaire-relapsing multiple sclerosis; MRI: magnetic resonance imaging; NEDA: no evidence of disease activity]

Table 4: starting dose up-titration regimen of ponesimod

Titration day	Daily dose
Days 1, 2	2 mg
Days 3, 4	3 mg
Days 5, 6	4 mg
Day 7	5 mg
Day 8	6 mg
Day 9	7 mg
Day 10	8 mg
Day 11	9 mg
Days 12, 13, 14	10 mg
Day 15	20 mg (maintenance dose)