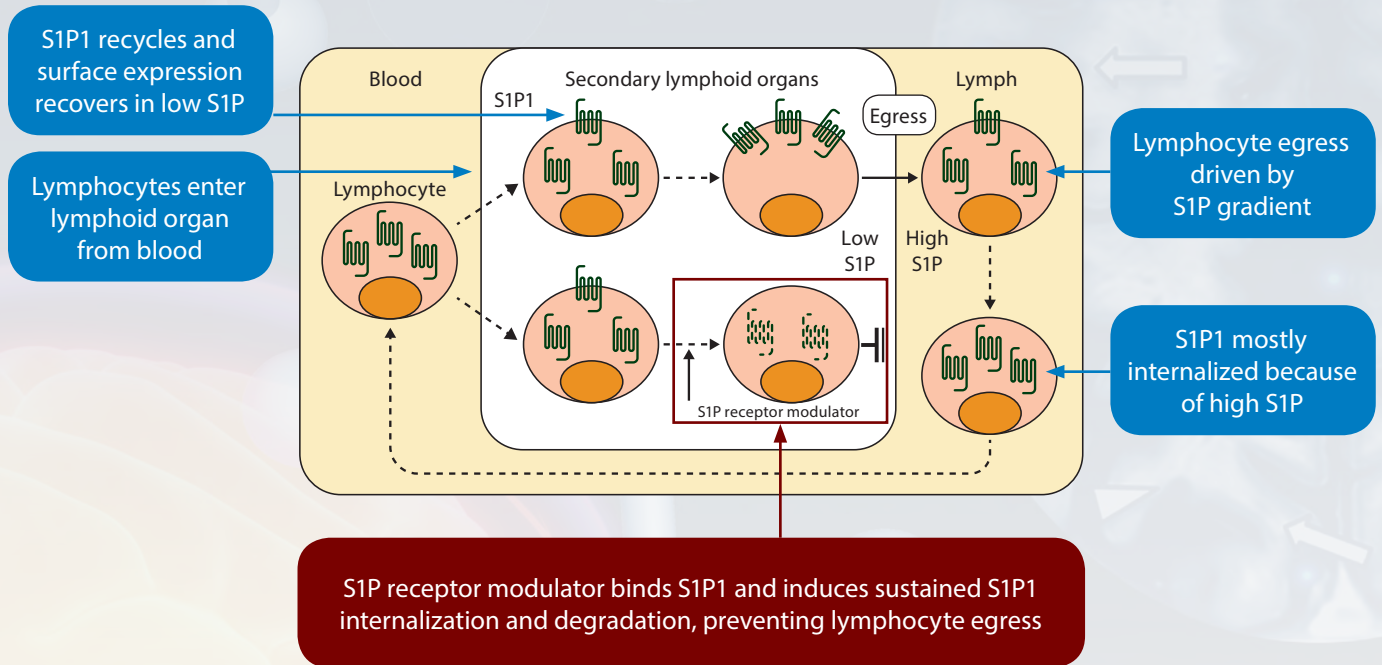


Mechanisms of Action for S1P Receptor Modulators¹⁻⁷

Full abbreviations, accreditation, and disclosure information available at
[PeerView.com/MS20-Live](https://www.peerview.com/MS20-Live)

S1P Receptor Modulators Improve MS by Isolating Lymphocytes



S1P Receptor Specificity of Approved and Emerging S1P Receptor Modulators

Available/ Investigational S1P Receptor Modulators		S1P1	S1P2	S1P3	S1P4	S1P5
Approved	Fingolimod	✓	✗	✓	✓	✓
	Siponimod	✓	✗	✗	✗	✓
	Ozanimod	✓	✗	✗	✗	✓
Emerging	Ponesimod ^a	✓	✗	✗	✗	✗

^a Investigational agent.

Mechanisms of Action for S1P Receptor Modulators¹⁻⁷

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S1P Receptor Subtype

Localization and Function of S1P Receptors in the Context of MS Care

	S1P1	S1P2	S1P3	S1P4	S1P5
CNS	Neurons (function, migration), astrocytes (activation), microglia, oligodendrocytes	Neurons, astrocytes, microglia, oligodendrocytes	Neurons (function, migration), astrocytes (activation), microglia, oligodendrocytes		Oligodendrocytes (function), astrocytes, microglia, neurons
Cardiovascular	Heart: HR slowing Smooth muscle: vascular tone	Smooth muscle: vascular tone	Heart: slowed conduction Smooth muscle: vascular tone		
Endothelium	Permeability	Permeability	Permeability		
Immune system	Lymphocytes: trafficking			Lymphoid tissues, dendritic cells, mast cells	NK cells (S1P5 > S1P1 in blood NKs)
Potential adverse events	Activation may contribute to macular edema, decreased retinal cell death	Activation may contribute to HTN, pathological retinal angiogenesis (rodents), profibrotic responses (cultured fibroblasts)	Activation may contribute to second-degree heart block, profibrotic response (cultured fibroblasts)		



Practical Clinical Considerations With the Use of S1P Receptor Modulator in Patients With MS¹⁻⁴

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Pharmacokinetics/Pharmacodynamics of S1P Receptor Modulators: Implications for Clinical Care

S1P Receptor Modulators	T _{1/2} Elimination	Median Recovery Time to Normal Lymphocyte Count
Fingolimod	6-9 d ^a	1-2 months
Siponimod	30 h	10 days, but up to 3-4 weeks for some patients
Ozanimod CC112273 ^b	21 h 11 d	30 days ^c
Ponesimod (investigational)	21-33 h	4 days

Practical Aspects of Use: Monitoring and Titration

Assessments

CBC, cardiac evaluation, liver function, medications, vaccinations, ophthalmic assessment^e, CYP2C9 genotype (siponimod)

Titration^d

Siponimod, ozanimod
(per prescribing information)

First-Dose Monitoring^d

Siponimod
(patients with certain conditions^f),
fingolimod

^a Increased by 50% in patients with moderate to severe heart disease. ^b Major ozanimod active metabolite. ^c Ninety percent recovery to baseline lymphocyte count within 3 months. ^d Also on reinitiation following treatment interruption. ^e For ozanimod, requirement for pre-initiation assessment is specific to patients with a history of uveitis or macular edema. ^f Sinus bradycardia, Mobitz type I AV block, history of MI or HF.

Contraindications Other Than Hypersensitivity

Fingolimod, siponimod, ozanimod

- Recent (last 6 months): MI, unstable angina, TIA, decompensated HF with hospitalization, class III/IV HF
- History (fingolimod) or presence (siponimod, ozanimod) of Mobitz type 2 second- or third-degree AV block or sick sinus syndrome, unless patient has a pacemaker

Fingolimod

- BL QT_c interval ≥500 msec
- Arrhythmias needing treatment with class Ia or class III antiarrhythmic agents

Ozanimod

- Severe untreated sleep apnea
- Concomitant MAOI use

Common Adverse Reactions

All

Transaminase
increase

Fingolimod

Headache, diarrhea,
cough, influenza,
sinusitis, pain (back,
abdominal, extremity)

Siponimod

Headache, HTN

Ozanimod

Infection (upper
respiratory, urinary
tract), orthostatic
hypotension,
back pain, HTN

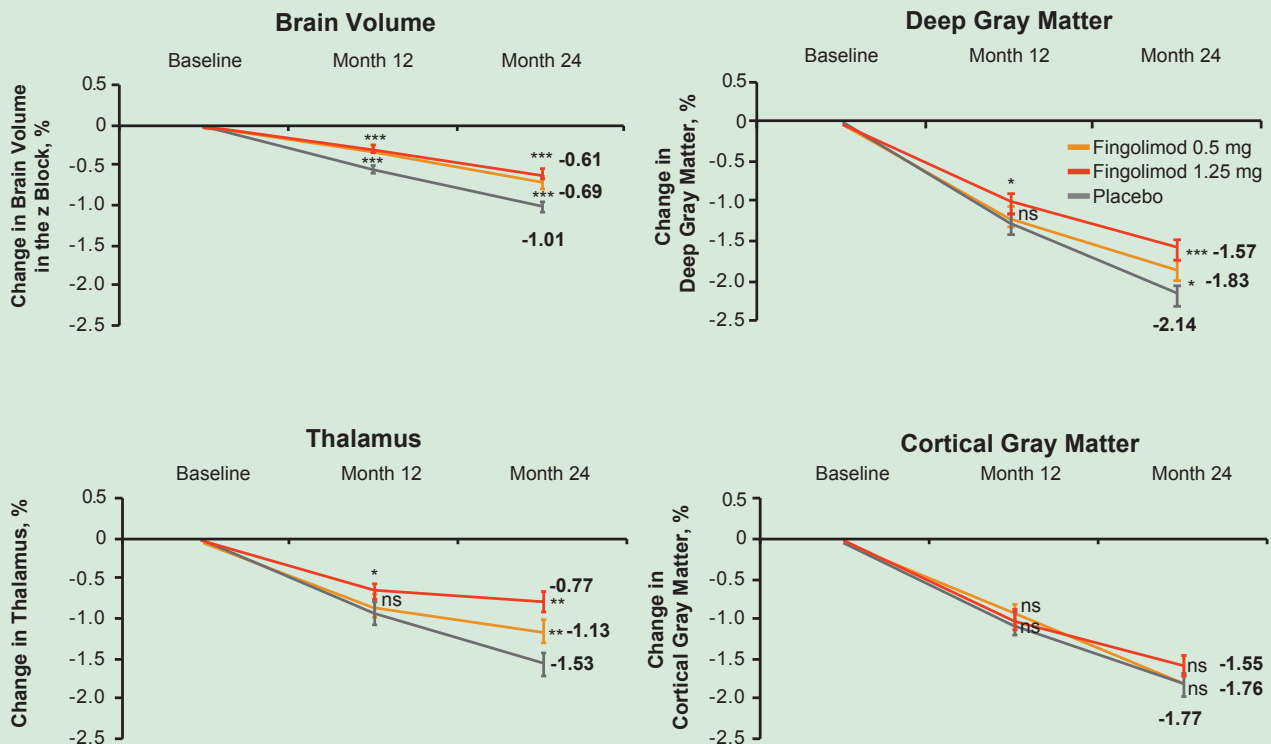
Imaging Outcomes of S1P Receptor Modulators in Patients With MS¹⁻⁸

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Efficacy of Fingolimod, Siponimod, and Ozanimod: Phase 3 Trials

Trial	FREEDOMS I	FREEDOMS II	TRANSFORMS	EXPAND	SUNBEAM	RADIANCE Part B		
Treatment Groups	Fingolimod 0.5 mg/d vs placebo (24 mo)	Fingolimod 0.5 mg/d vs placebo (24 mo)	Fingolimod 0.5 mg/d vs IFN β -1a 30 mcg (12 mo)	Siponimod 2 mg/d vs placebo	Ozanimod 0.5 mg/d	Ozanimod 1.0 mg/d	Ozanimod 0.5 mg/d	Ozanimod 1.0 mg/d
NEL	↓ 74% ($P < .001$)	↓ 74% ($P < .0001$)	↓ 35% ($P < .001$)	↓ 81% ($P < .0001$)	↓ 25% ($P = .0032$)	↓ 48% ($P < .0001$)	↓ 34% ($P = .0001$)	↓ 42% ($P < .0001$)
GEL	↓ 82% ($P < .0001$)	↓ 67% ($P < .0001$)	↓ 55% ($P < .001$)	↓ 86% ($P < .0001$)	↓ 34% ($P = .0182$)	↓ 63% ($P < .0001$)	↓ 47% ($P = .0030$)	↓ 53% ($P = .0006$)

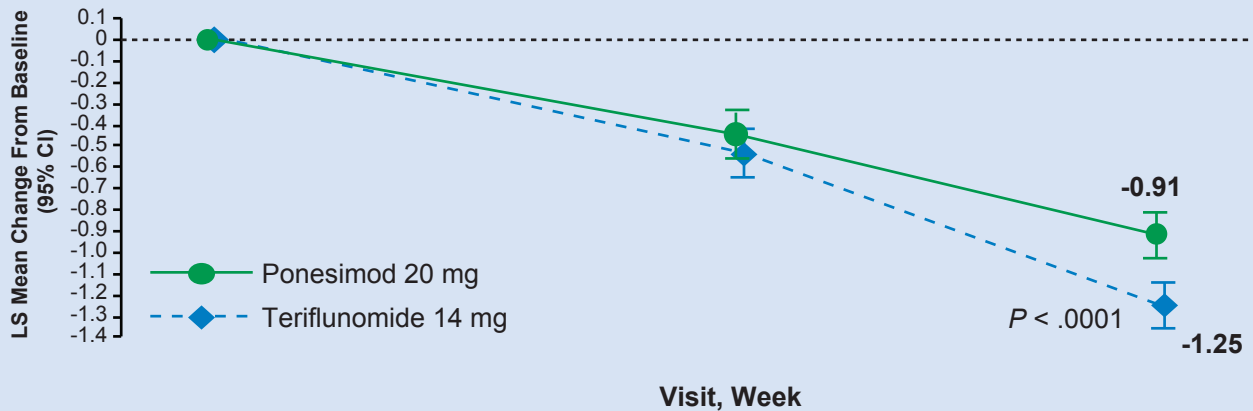
Less Brain Volume Loss With Fingolimod: Pooled Data from Phase 3 Trials



Imaging Outcomes of S1P Receptor Modulators in Patients With MS¹⁻⁸

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Less Brain Volume Loss With Ponesimod Versus Teriflunomide: Phase 3 Clinical Trial



No. of patients

Ponesimod 20 mg (N = 567)

Teriflunomide 14 mg (N = 566)

403

403

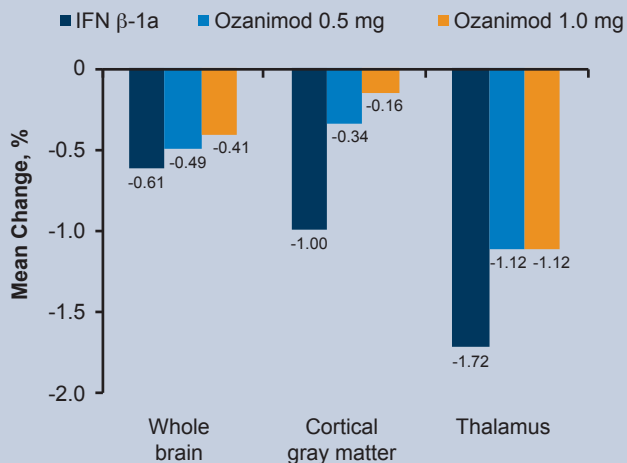
376

368

Similar changes have been reported for siponimod vs placebo in SPMS
(-0.71% vs -0.84% at 24 weeks; $P < .05$)

Less Brain Volume Loss With Ozanimod Versus IFN β -1a: Phase 3 Clinical Trials

Brain Volume Changes (12 Months)



Brain Volume Changes (24 Months)

