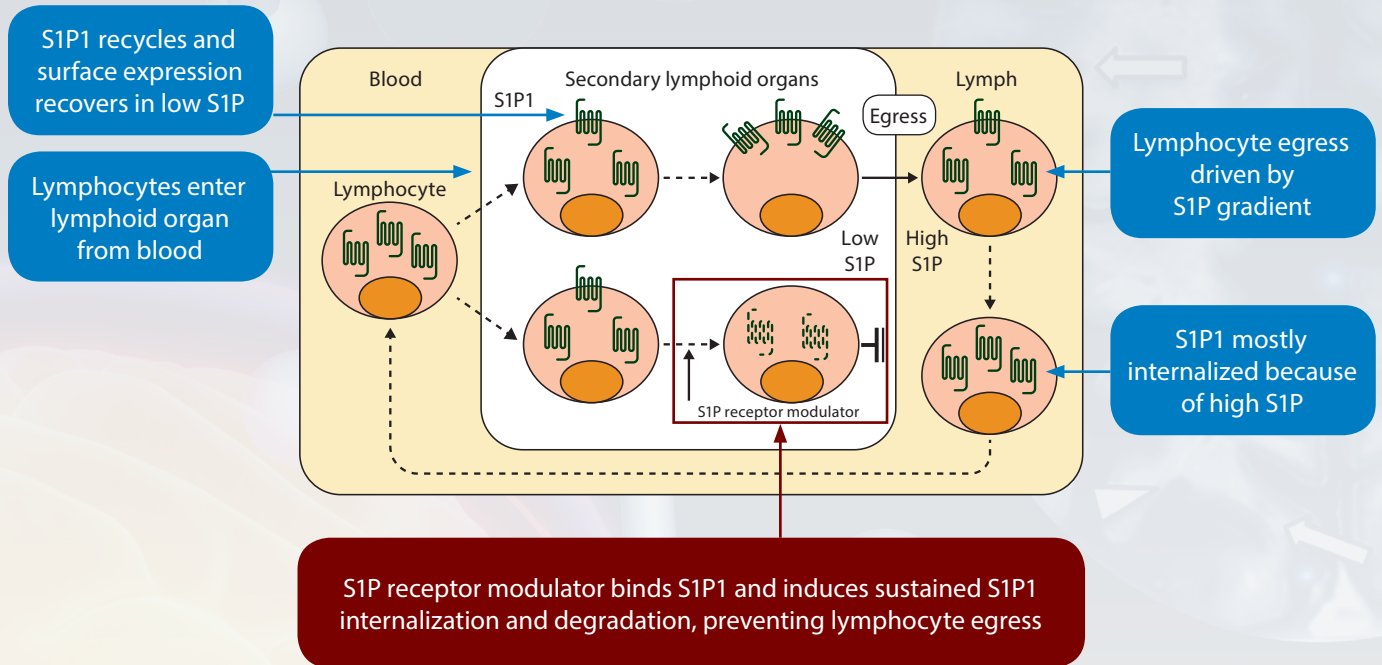


## S1P Receptor Modulators Improve MS by Isolating Lymphocytes



## S1P Receptor Specificity of Approved and Emerging S1P Receptor Modulators

| Available/<br>Investigational S1P<br>Receptor Modulators |                        | S1P1 | S1P2 | S1P3 | S1P4 | S1P5 |
|----------------------------------------------------------|------------------------|------|------|------|------|------|
| Approved                                                 | Fingolimod             | ✓    | ✗    | ✓    | ✓    | ✓    |
|                                                          | Siponimod              | ✓    | ✗    | ✗    | ✗    | ✓    |
|                                                          | Ozanimod               | ✓    | ✗    | ✗    | ✗    | ✓    |
| Emerging                                                 | Ponesimod <sup>a</sup> | ✓    | ✗    | ✗    | ✗    | ✗    |

<sup>a</sup> Investigational agent.

# Mechanisms of Action for S1P Receptor Modulators<sup>1-7</sup>

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[PeerView.com/VTT40](https://www.peerview.com/VTT40)

## S1P Receptor Subtype

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

|                                 | S1P1                                                                                | S1P2                                                                                                                        | S1P3                                                                                                | S1P4                                          | S1P5                                                        |
|---------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|-----------------------------------------------|-------------------------------------------------------------|
| <b>CNS</b>                      | Neurons (function, migration), astrocytes (activation), microglia, oligodendrocytes | Neurons, astrocytes, microglia, oligodendrocytes                                                                            | Neurons (function, migration), astrocytes (activation), microglia, oligodendrocytes                 |                                               | Oligodendrocytes (function), astrocytes, microglia, neurons |
| <b>Cardiovascular</b>           | Heart: HR slowing<br>Smooth muscle: vascular tone                                   | Smooth muscle: vascular tone                                                                                                | Heart: slowed conduction<br>Smooth muscle: vascular tone                                            |                                               |                                                             |
| <b>Endothelium</b>              | Permeability                                                                        | Permeability                                                                                                                | Permeability                                                                                        |                                               |                                                             |
| <b>Immune system</b>            | Lymphocytes: trafficking                                                            |                                                                                                                             |                                                                                                     | Lymphoid tissues, dendritic cells, mast cells | NK cells (S1P5 > S1P1 in blood NKs)                         |
| <b>Potential adverse events</b> | 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) |                                               |                                                             |

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

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

## Practical Aspects of Use: Monitoring and Titration

### Assessments

- All agents: CBC, cardiac evaluation, liver function, medications, vaccinations
- Ophthalmic assessment: all agents (for ozanimod, only in patients with certain conditions<sup>e</sup>)
- CYP2C9 genotype: siponimod

### Titration<sup>d</sup>

Siponimod, ozanimod  
(per prescribing information)

### First-Dose Monitoring<sup>d</sup>

Siponimod  
(patients with certain conditions<sup>f</sup>),  
fingolimod

<sup>a</sup> Increased by 50% in patients with moderate to severe heart disease. <sup>b</sup> Major ozanimod active metabolite. <sup>c</sup> Ninety percent recovery to baseline lymphocyte count within 3 months. <sup>d</sup> Also on reinitiation following treatment interruption. <sup>e</sup> For ozanimod, requirement for pre-initiation assessment is specific to patients with a history of uveitis or macular edema. <sup>f</sup> 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<sub>c</sub> 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

Fingolimod

Siponimod

Ozanimod

Transaminase  
increase

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

Headache, HTN

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

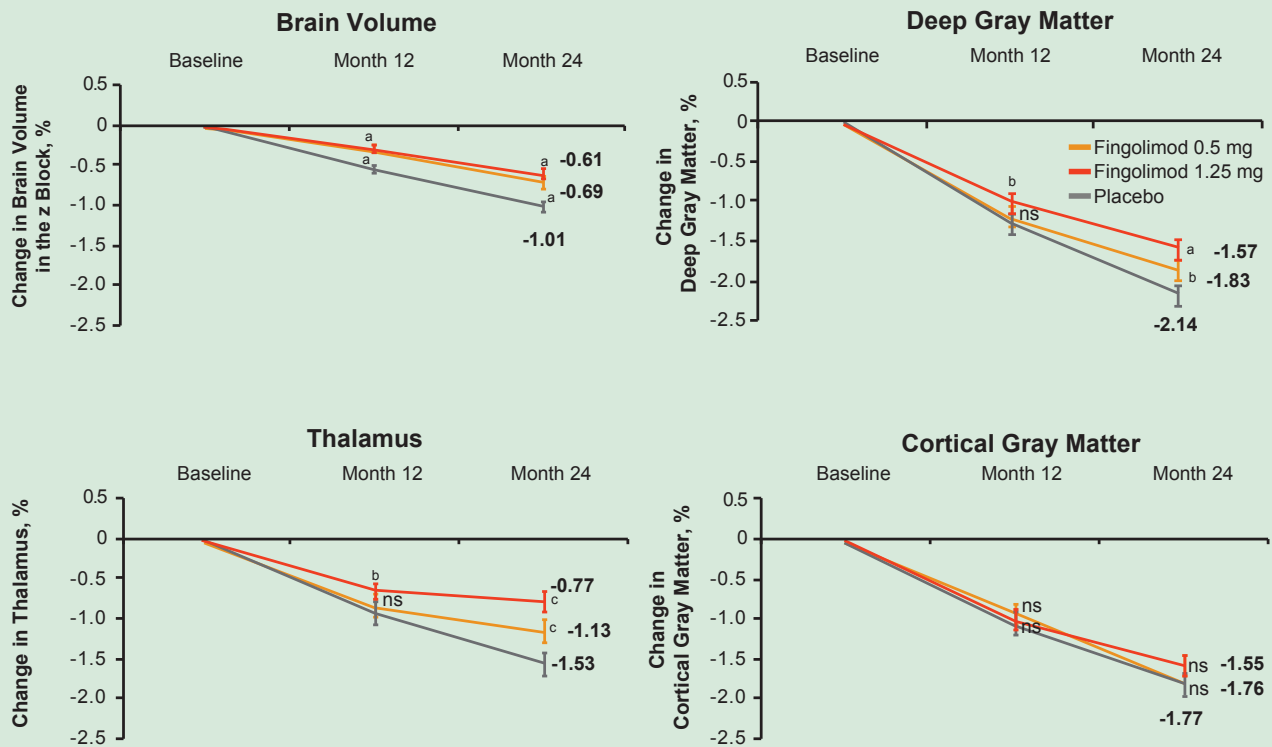
# Imaging Outcomes of S1P Receptor Modulators in Patients With MS<sup>1-8</sup>

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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 $\beta$ -1a 30 mcg (12 mo) | Siponimod 2 mg/d vs placebo | Ozanimod 0.5 mg/d vs IFN $\beta$ -1a | Ozanimod 1.0 mg/d vs IFN $\beta$ -1a | Ozanimod 0.5 mg/d vs IFN $\beta$ -1a | Ozanimod 1.0 mg/d vs IFN $\beta$ -1a |
| NEL              | ↓ 74%<br>( $P < .001$ )                | ↓ 74%<br>( $P < .0001$ )               | ↓ 35%<br>( $P < .001$ )                               | ↓ 81%<br>( $P < .0001$ )    | ↓ 25%<br>( $P = .0032$ )             | ↓ 48%<br>( $P < .0001$ )             | ↓ 34%<br>( $P = .0001$ )             | ↓ 42%<br>( $P < .0001$ )             |
| GEL              | ↓ 82%<br>( $P < .0001$ )               | ↓ 67%<br>( $P < .0001$ )               | ↓ 55%<br>( $P < .001$ )                               | ↓ 86%<br>( $P < .0001$ )    | ↓ 34%<br>( $P = .0182$ )             | ↓ 63%<br>( $P < .0001$ )             | ↓ 47%<br>( $P = .0030$ )             | ↓ 53%<br>( $P = .0006$ )             |

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

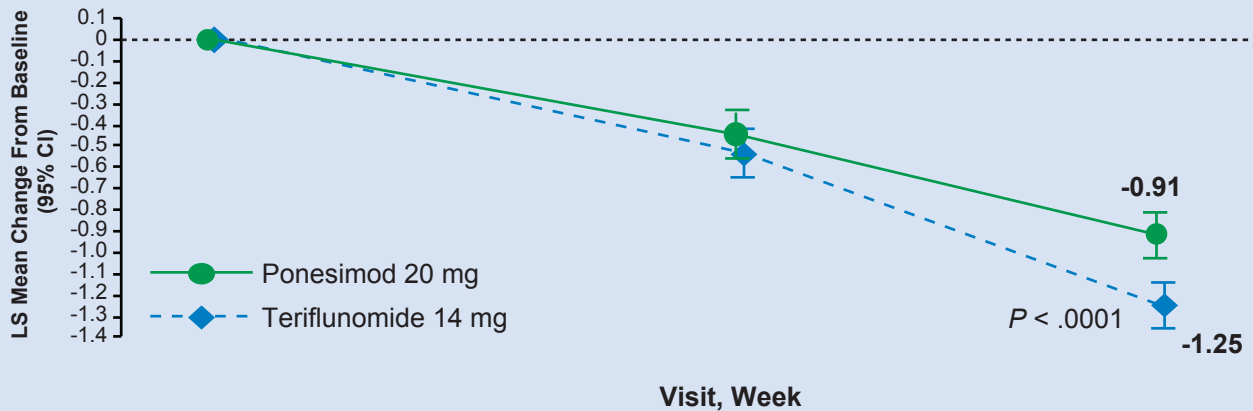


<sup>a</sup>  $P < .001$ . <sup>b</sup>  $P < .05$ . <sup>c</sup>  $P < .01$ .

# Imaging Outcomes of S1P Receptor Modulators in Patients With MS<sup>1-8</sup>

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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

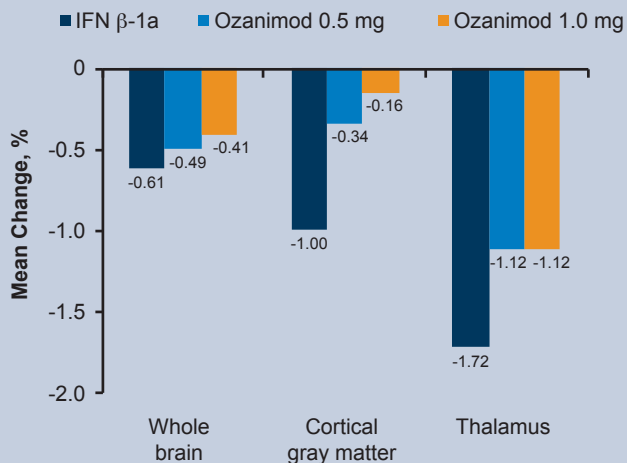
376

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 $\beta$ -1a: Phase 3 Clinical Trials

### Brain Volume Changes (12 Months)



### Brain Volume Changes (24 Months)

