Dual mode of action of siponimod in secondary progressive multiple sclerosis: A hypothesis based on the relevance of pharmacological properties

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Disclosures

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Dual mode of action of siponimod
Selective for S1P$_1$ and S1P$_5$ receptors

As MS evolves, peripherally driven inflammation declines while central inflammation and neurodegeneration become more prominent$^1$

**Objective**
To propose a working hypothesis of a dual MoA for siponimod in SPMS, based on latest preclinical and clinical observations, and explore differences to fingolimod MoA

**Cellular targets**
- Lymphocytes
- Astroglial cells
- Microglia
- Oligodendrocytes
- Neurones
- Atrial myocytes
- ECs, SMCs

**Major actions**
- Activation/Down-modulation
- Activation

**Overall effects**
- Anti-inflammatory (CNS & Periphery)
- Pro-repair (CNS)

- Reduced egress of pathogenic lymphocytes from LNs$^{2-8}$
- Reduced activation of neural cells
- Promoted oligodendrocyte maturation and survival
- Pro-myelination$^7$-$^{11}$

**Major effects**
- Oligodendrocytes
- Natural killer cells

**Anti-inflammation**
- As MS evolves, peripherally driven inflammation declines while central inflammation and neurodegeneration become more prominent$^1$

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CNS, central nervous system; COX, cyclooxygenase; ECs, endothelial cells; LNs, lymph nodes; MoA, mechanism of action; S1P, sphingosine 1-phosphate; SMCs, smooth muscle cells; SPMS, secondary progressive multiple sclerosis

Anti-inflammatory effects of siponimod

S1P₁-dependent inhibition of lymphocyte egress from lymph nodes

Periphery: Dose-dependent reduction of circulating lymphocyte counts (PD readout, as in humans)¹

Mouse

- Agonist-induced S1P₁ down-modulation on lymphocytes follows classical dose-related pharmacology (steady $E_{max}$)
- Agonist-induced S1P₁ down-modulation also seen in astrocytes²

PD, pharmacodynamic; S1P, sphingosine 1-phosphate
² Ben Yacoub et al. Presented at ECTRIMS 2020, P0357
Pro-repair effects of siponimod

S1P<sub>5</sub>-dependent pro-remyelination effects

- Pro-remyelination effects of siponimod and fingolimod are S1P<sub>5</sub>-dependent<sup>1,2</sup> and follow non-classical pharmacology (bell-shaped).
- Compatible with agonist-induced S1P<sub>5</sub> signaling<sup>3</sup>

CNS: Dose-dependent increase in remyelination following toxin-induced demyelination in vivo (mechanistic model in tadpoles<sup>1,2</sup>)

![Graph showing dose-dependent remyelination](image)

- Siponimod
- Fingolimod

Non-classical Pharmacological model

Bell-shaped dose-response curve = Receptor signaling with desensitization at supra-maximal doses

CNS, central nervous system; S1P, sphingosine 1-phosphate

Effects of siponimod in SPMS patients

MRI and clinical measures from the EXPAND trial

- In the EXPAND Ph III study in SPMS patients, siponimod significantly reduced the risk for confirmed disability progression and decline in cognitive processing speed\(^2\).
- Also observed were positive effects in reducing gray matter atrophy and MTR changes in normal appearing brain tissue, cortical gray matter and normal appearing white matter\(^1\).
- Beneficial effects on MTR are compatible with preclinical observations on pro-remyelination effects\(^1\).

**Effect of siponimod on changes in median nMTR in NABT, cGM and NAWM in overall SPMS population (PPS)**\(^1\)

**Time to 6 month confirmed progression on the EDSS versus placebo**\(^2\)

**Time to 6 month confirmed worsening on the SDMT versus placebo**\(^2\)

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cGM, cortical gray matter; CNS, central nervous system; EDSS, Expanded Disability Status Scale; MTR, magnetization transfer ratio; nMTR, normalized magnetization transfer ratio; NABT, normal appearing brain tissue; NAWM, normal appearing white matter; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis.
Working hypothesis about the dual MoA of siponimod

Concomitant efficacy of siponimod in blood and CNS compartments

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<thead>
<tr>
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<th>S1P₁-dependent anti-inflammatory effects</th>
<th>S1P₅-dependent Pro-remyelination effects</th>
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<tr>
<td><strong>Immunomodulatory/anti-inflammatory</strong> Blood - S1P₁ functional antagonism</td>
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<td>Dose-dependent signaling and down-modulation</td>
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<td><strong>Siponimod</strong> CNS/blood ratio: ~ 4–6</td>
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<td><strong>Fingolimod</strong> CNS/blood ratio: &gt;20</td>
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- **Dual MoA requires optimal (+++)** exposure in both CNS and blood compartments to achieve efficacy through:
  - S1P₁-dependent anti-inflammatory effects on blood lymphocytes
  - S1P₅-dependent pro-repair effects
- **Any treatments achieving adequate drug exposure in blood but too low/high drug exposure in CNS would show good anti-inflammatory efficacy but no or reduced pro-repair effects in the CNS**
- **CNS/blood drug exposure ratio seen as key for expression of dual MoA**

CNS, central nervous system; MoA, mechanism of action; S1P, sphingosine 1-phosphate
**CNS/blood Drug Exposure Ratios (DER)**

*Sipimod versus fingolimod*

- Sipimod shows similar CNS penetration in naïve and EAE mice (CNS/blood ratio: ~ 4–6)
- Fingolimod demonstrates CNS uptake similar to sipimod in naïve mice but 3–4 fold higher CNS penetration in EAE mice (CNS/blood ratio: >20)

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* *p<0.05. CNS, central nervous system; DER, drug exposure ratio; EAE, experimental autoimmune encephalomyelitis; fingolimod-P, fingolimod-phosphate; PK, pharmacokinetic, S1P, sphingosine 1-phosphate
Conclusions

*Understanding MoA helps in differentiating siponimod from fingolimod*

- Preclinical findings show that siponimod may have the specific target selectivity (S1P<sub>1,5</sub>) and CNS/blood drug exposure ratio for a favorable expression of its dual MoA (peripheral/central anti-inflammatory and central pro-repair)

- PET/MRI studies in SPMS patients versus controls including PK/PD readouts would further contribute to corroborate this hypothesis

Thank you

CNS, central nervous system; MoA, mechanism of action; MRI, magnetic resonance imaging; PD, pharmacodynamic; PET, positron emission tomography; PK, pharmacokinetic; S1P, sphingosine-1 phosphate; SPMS, secondary progressive multiple sclerosis