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

Marc Bigaud, **Thomas Hach**, **Frank Dahlke** and **Daniela Piani-Meier** are employees of Novartis

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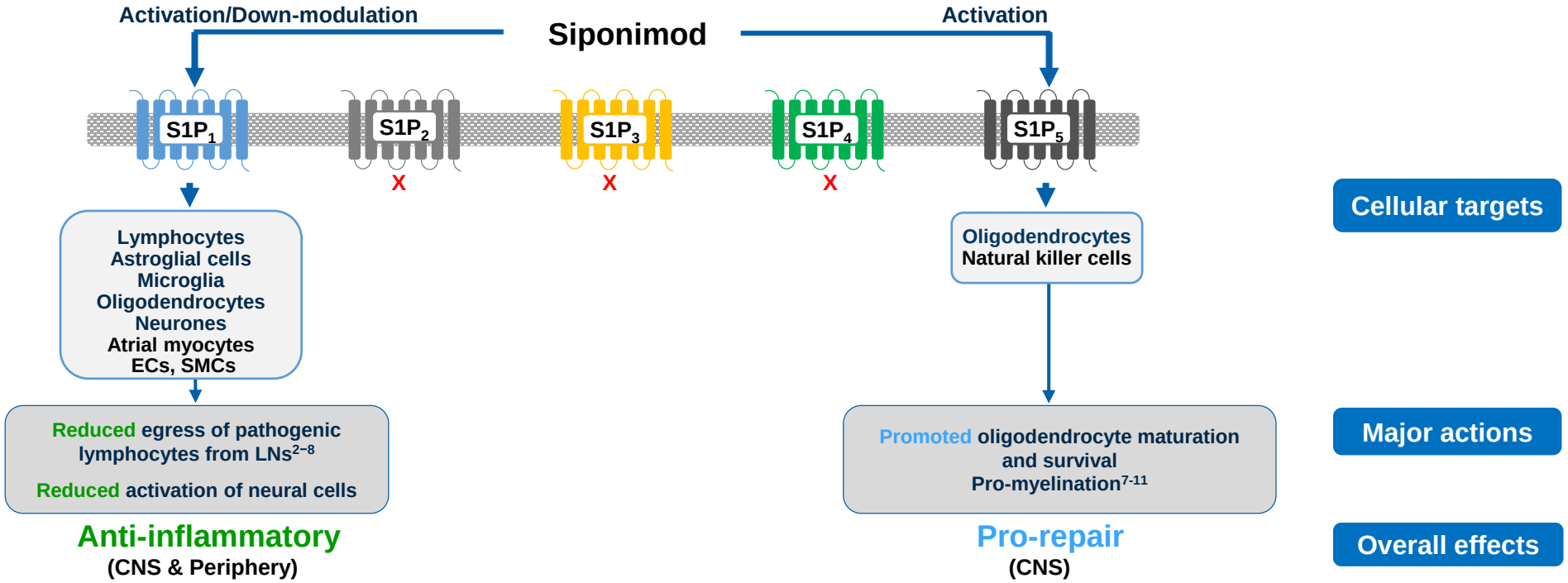
Dual mode of action of siponimod

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

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

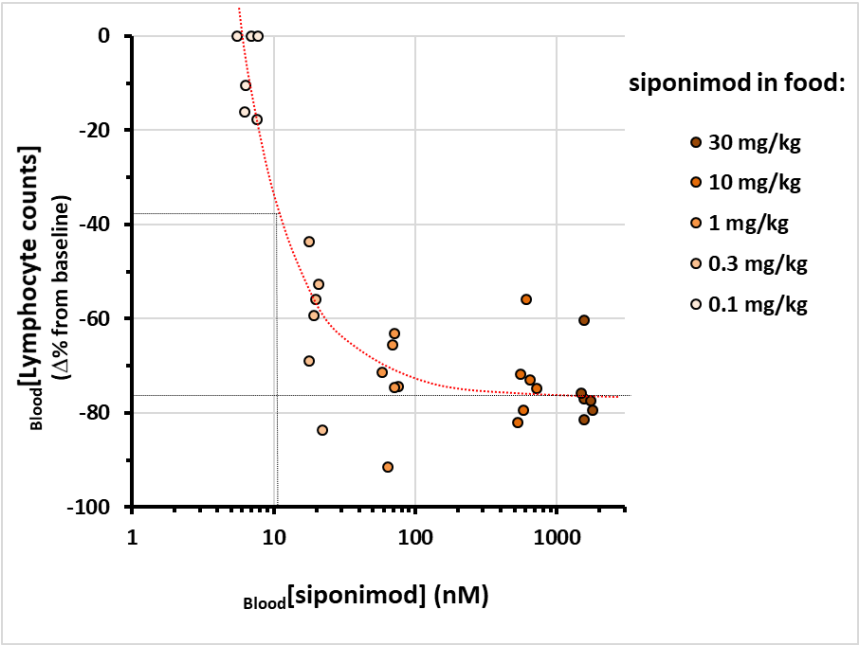
1. Larochelle C, et al. *Trends Neurosci*. 2016;39:325–339; 2. Chun J and Hartung HP. *Clin Neuropharmacol.* 2010;33:91–101; 3. Mandala S, et al. *Science*. 2002;296:346–9; 4. Gergely P, et al. *Br J Pharmacol.* 2012;167:1035–47; 5. Matloubian M, et al. *Nature*. 2004;427:355–60; 6. Brinkmann V. *Pharmacol Ther.* 2007;115:84–105; 7. Mizugishi K, et al. *Mol Cell Biol*. 2005; 25:11113–21; 8. Rosen H, et al. *Nat Rev Immunol.* 2005;5:560–70; 9. Kimura A, et al. *Stem Cells*. 2007;25:115–24; 10. Jaillard C, et al. *J Neurosci.* 2005;25:1459–69. 11. Dusaban et *J Neuroinflamm.* 2017; 14:111al.

Anti-inflammatory effects of siponimod

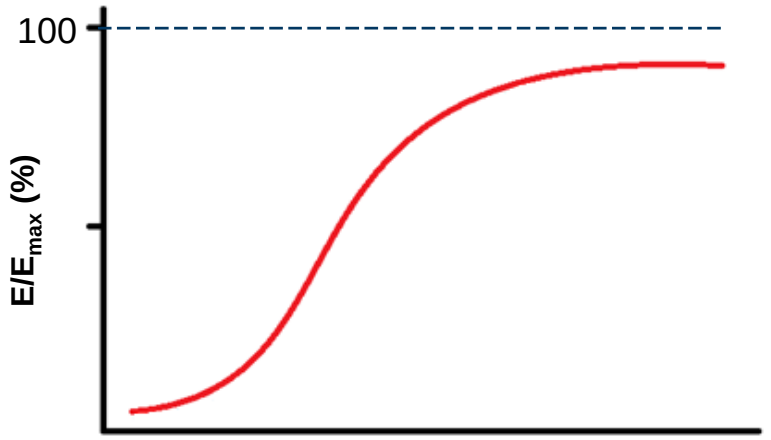
$S1P_1$-dependent inhibition of lymphocyte egress from lymph nodes

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

Mouse



Classical Pharmacological model



$S1P_1$-dependent effects in blood
Functional antagonism = Steady E_{max}
(Receptor down-modulation)

- **Agonist-induced $S1P_1$ down-modulation on lymphocytes follows classical dose-related pharmacology (steady E_{max})**
- **Agonist-induced $S1P_1$ down-modulation also seen in astrocytes[2]**

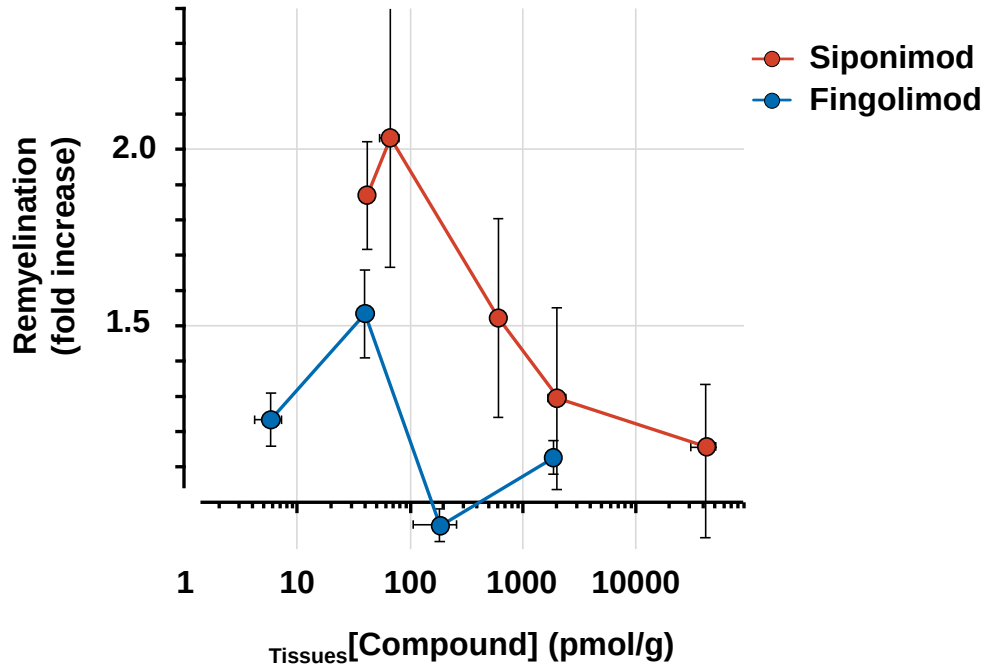
PD, pharmacodynamic; S1P, sphingosine 1-phosphate

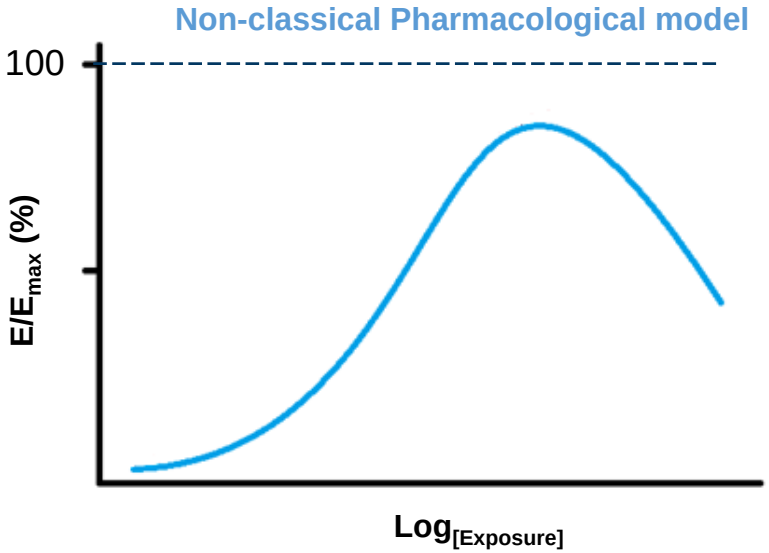
1. Bigaud M, et al. Presented at *ECTRIMS*. 2019; P622. 2 Ben Yacoub et al. Presented at ECTRIMS 2020, P0357

Pro-repair effects of siponimod

$S1P_5$-dependent pro-remyelination effects

CNS: Dose-dependent increase in remyelination following toxin-induced demyelination *in vivo*
(mechanistic model in tadpoles[1,2])





$S1P_5$-dependent effects in CNS
Bell-shaped dose-response curve = Receptor signaling with desensitization at supra-maximal doses

- **Pro-remyelination effects of siponimod and fingolimod are $S1P_5$-dependent[1, 2] and follow non-classical pharmacology (bell-shaped)**
- **Compatible with agonist-induced $S1P_5$ signaling[3]**

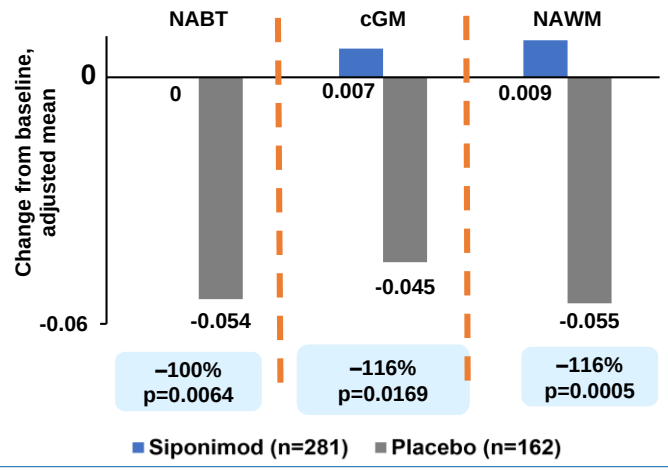
CNS, central nervous system; S1P, sphingosine 1-phosphate

1. Mannioui A, et al. *Multi Scler J*. 2018; 24:1421–1432; 2. Martin E, et al. Presented at *ECTRIMS*. 2019; P1376; 3. Bigaud et al. Presented at *ECTRIMS* 2018, EP1617.

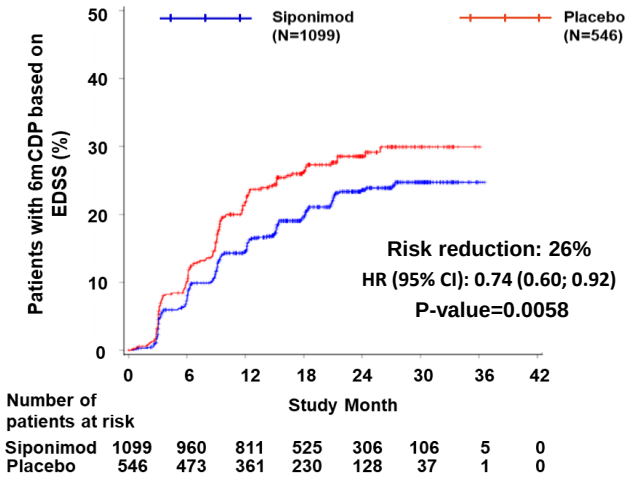
Effects of siponimod in SPMS patients

MRI and clinical measures from the EXPAND trial

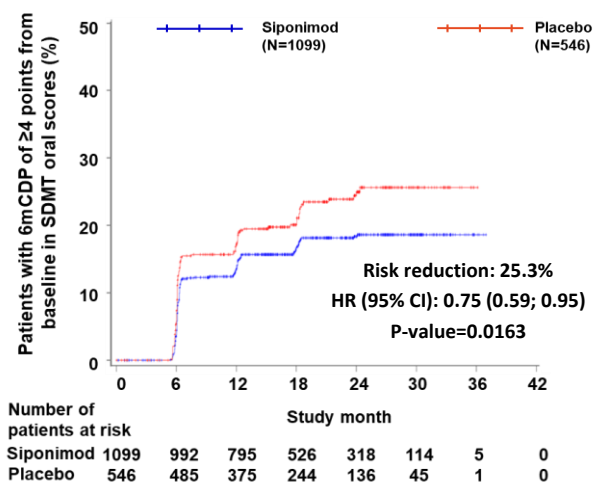
Effect of siponimod on changes in median nMTR in NABT, cGM and NAWM in overall SPMS population (PPS)[1]



Time to 6 month confirmed progression on the EDSS versus placebo[2]



Time to 6 month confirmed worsening on the SDMT versus placebo[2]



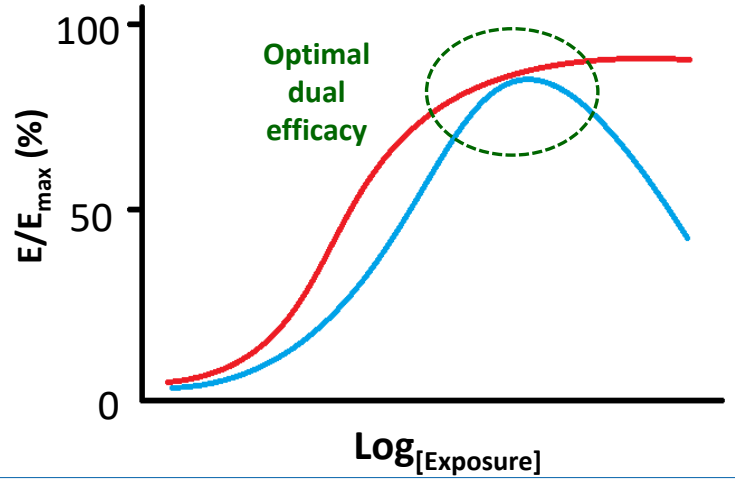
- **In the EXPAND Ph III study in SPMS patients, siponimod significantly reduced the risk for confirmed disability progression and decline in cognitive processing speed[2]**
- **Also observed were positive effects in reducing gray matter atrophy and MTR changes in normal appearing brain tissue, cortical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

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

1. Arnold DL. et al. Presented at *EAN*. 2020; EPR1147; 2. Kappos L, et al. Presented at *EAN*. 2019; EPR2075.

Working hypothesis about the dual MoA of siponimod

Concomitant efficacy of siponimod in blood and CNS compartments[1]



Immunomodulatory/anti-inflammatory
Blood - S1P$_1$ functional antagonism
Dose-dependent signaling and down-modulation

Pro-remyelination CNS effects
CNS - S1P$_5$ agonism
Dose-dependent signaling with desensitization

	S1P$_1$-dependent anti-inflammatory effects	S1P$_5$-dependent Pro-remyelination effects
Siponimod CNS/blood ratio: ~ 4–6	+++	+++
Fingolimod CNS/blood ratio: >20	+++	+

- **Dual MoA requires optimal (+++) exposure in both CNS and blood compartments to achieve efficacy through:**
  - S1P$_1$-dependent anti-inflammatory effects on blood lymphocytes
  - S1P$_5$-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**

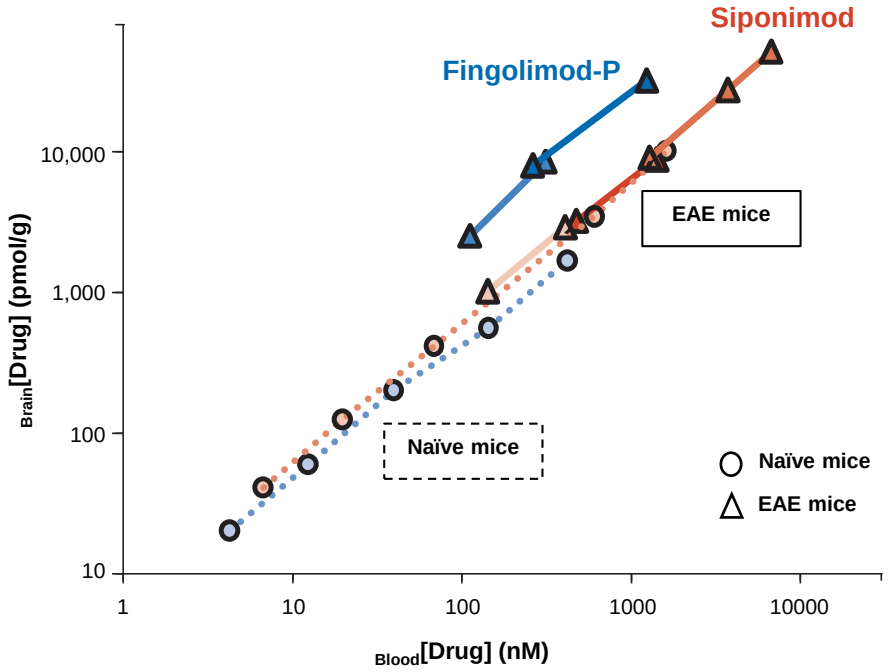
CNS, central nervous system; MoA, mechanism of action; S1P, sphingosine 1-phosphate

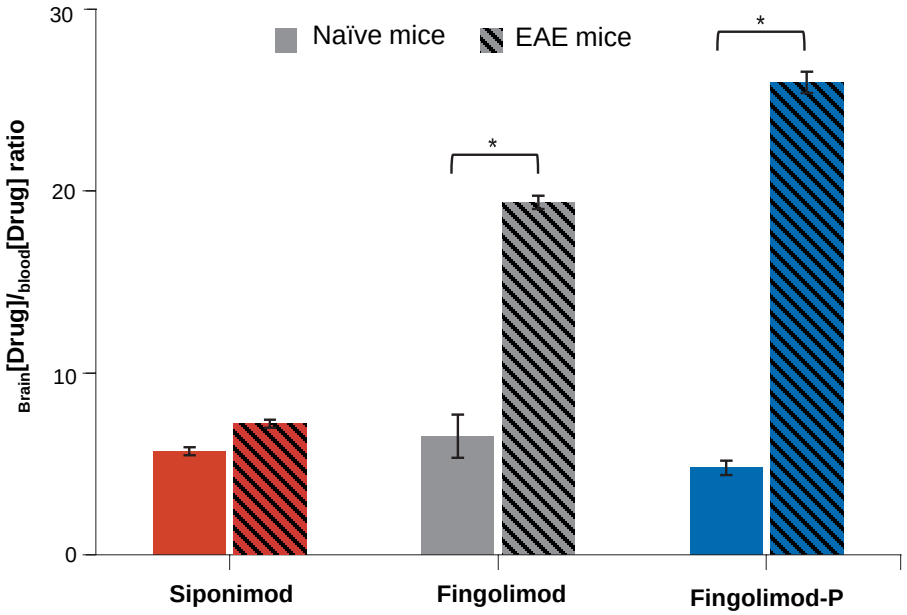
1. Bigaud M, et al. Presented at *AAN*. 2020; P12.1-006.

CNS/blood Drug Exposure Ratios (DER)

Siponimod versus fingolimod

CNS/blood drug exposure ratios of siponimod, fingolimod and fingolimod-P in naïve versus EAE mice[1,2]





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

*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

1. Bigaud M, et al. Poster presentation P622 at ECTRIMS 2019. 2. Bigaud M, et al. Presented at *AAN*. 2020; P12.1-006.

Conclusions

Understanding MoA helps in differentiating siponimod from fingolimod

- **Preclinical findings show that siponimod may have the specific target selectivity ($S1P_{1,5}$) 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