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Dual Mode of Action of Siponimod in Secondary Progressive Multiple Sclerosis: A Hypothesis Based on the Relevance of Pharmacological Properties

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Abstract Text:

Background: Siponimod, a potent and selective sphingosine 1-phosphate ($S1P_{1,5}$) receptor modulator, is the first oral disease-modifying therapy to reduce disability progression, cognitive decline, and total brain volume loss in broad secondary progressive MS (SPMS) patients. In the EXPAND study, siponimod showed a beneficial effect on myelination via magnetization transfer ratio decrease in normal-appearing brain tissue and cortical gray matter, with a pronounced effect on normal-appearing white matter in the overall SPMS population. New preclinical insights further substantiate the dual mode of action (MoA) of siponimod, demonstrating peripheral and central action targeting both inflammation and neurodegeneration.

Objectives: To propose a working hypothesis of a dual MoA for siponimod based on its specific differential pharmacological profile compared to other S1P modulators.

Methods: Recent preclinical results with siponimod in pharmacokinetic/pharmacodynamic (PK/PD), mechanistic, and disease models were reviewed and placed in perspective.

Results: Preclinical data demonstrate that siponimod triggers $S1P_1$-dependent anti-inflammatory effects on pathogenic lymphocytes and glial cells in the central nervous system (CNS), and $S1P_5$-dependent promyelination effects on oligodendrocytes. Concomitant optimal $S1P_1$- and $S1P_5$-dependent effects are therefore required in both blood and CNS compartments for translation into clinical efficacy. Preclinical data indicate that the $S1P_1$- and $S1P_5$-dependent CNS effects follow non-classical pharmacology (“bell-shaped”), resulting in lowering of efficacy for agonists at supramaximal doses. This suggests an overall particularly complex drug dose-effect relationship. Recent preclinical PK/PD studies show that a CNS/blood drug exposure ratio ($_{CNS/blood}$DER) of ~6 allows siponimod to approach the peak of both $S1P_1$- and $S1P_5$-dependent dose-response curves in the blood and CNS compartments.

Hence, the $_{CNS/blood}$DER might be a key factor impacting therapeutic efficacy of an S1P modulator. Fingolimod-phosphate has a higher $_{CNS/blood}$DER of 20–30, which might differentiate siponimod and fingolimod in terms of $S1P_1$- and $S1P_5$-mediated CNS effects.

Conclusions: Preclinical findings show that siponimod has the differentiated pharmacological characteristics required to elicit an effective dual $S1P_1$/$S1P_5$ MoA in both blood and CNS compartments, which may be of relevance for its clinical efficacy in SPMS. Translational and clinical studies are warranted to further validate this hypothesis.

Title:
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Preferred Presentation Format:
Platform/Oral

Category:
Disease-modifying therapy

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Yes

Category: Disease-modifying therapy

Keywords:
Disease-modifying treatments in MS and Mechanism of action

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