EPR1152

Siponimod in the Central Nervous System: Translational Evidence on its Penetration and Distribution

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Disclosures

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Background and Objective

- Siponimod, a potent, oral, selective sphingosine 1-phosphate (S1P) receptor subtype 1 and 5 ($S1P_{1,5}$) modulator, is the first DMT proven to reduce disability progression, cognitive decline, and total brain volume loss versus placebo in a broad range of SPMS patients[1]
- The mechanism of action of siponimod is believed to involve, at low nM range, both $S1P_1$-dependent anti-inflammatory effects on pathogenic lymphocytes and glial cells in the central nervous system (CNS) as well as $S1P_5$–dependent pro-remyelination effects on oligodendrocytes

Objective:

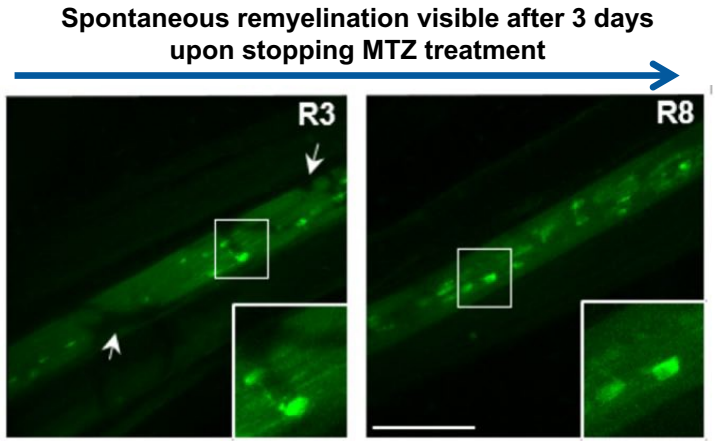
- To establish the CNS penetration and action of siponimod by consolidation of translational evidence
- Siponimod penetration and distribution in the CNS was explored in Xenopus tadpoles, rodents, NHPs and SPMS patients from the EXPAND Phase 3 study

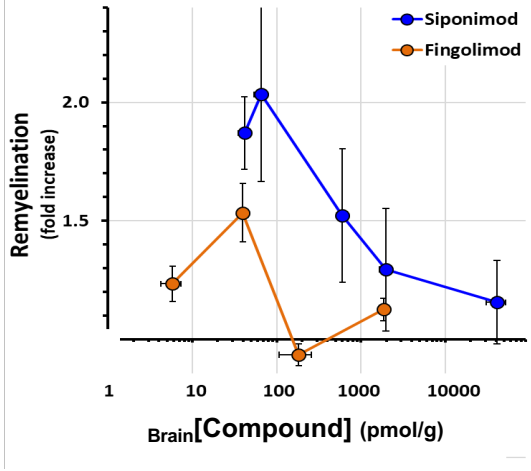
CNS, central nervous system, DMT, disease modifying therapy; NHP, non-human primates; SPMS, secondary progressive multiple sclerosis

1. Kappos L, et al. Lancet. 2018;39:1263–1273

Xenopus Tadpoles: Siponimod Penetrates the CNS and shows $S1P_5$-dependent Pro-remyelination Effect

In vivo mechanistic model for $S1P_5$-dependent remyelination[1]





- Siponimod has potent pro-remyelination properties at up to 30–60 nM levels in brain homogenates, promoting a >2 fold acceleration of remyelination in the model used[2]
  - At such exposure, siponimod is expected to have full efficacy on $S1P_1$/$S1P_5$ receptors
- The pro-remyelination effect of siponimod is reduced at tissue exposures >100 nM

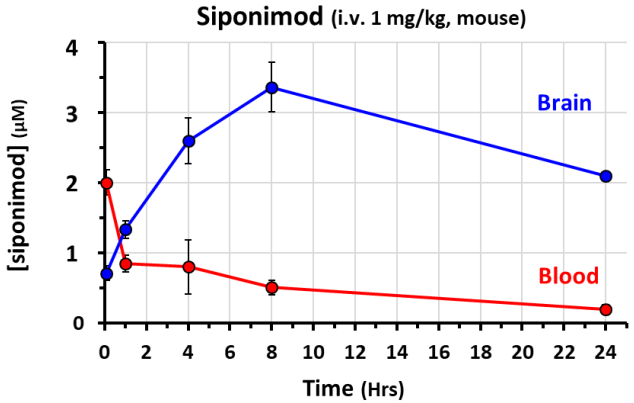
CNS, central nervous system; MTZ, metronidazole; S1P, spingosine 1-phosphate

1. Mannioui A et al. Mult Scler. 2018;24:1421-1432; 2. Martin E et al. Poster presented at ECTRIMS 2019. P1376

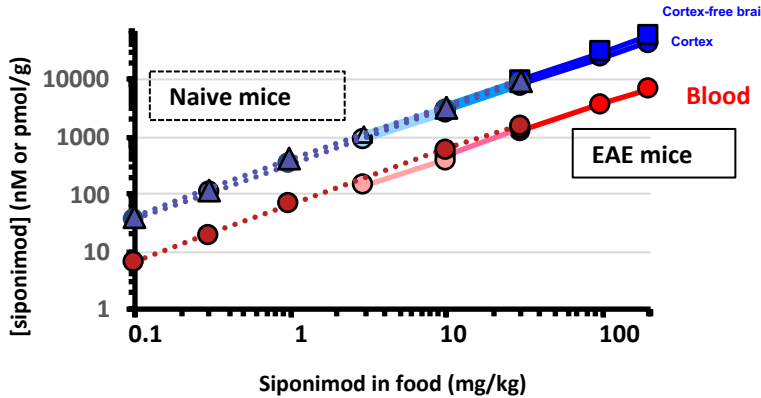
Mice: Siponimod Penetrates the CNS

- In healthy and EAE mice, a siponimod-loaded diet achieved dose-proportional steady-state levels in the blood, concomitant with 6- to 8-fold higher levels in brain homogenates

Acute ^{24h}Blood/Brain PK in healthy mice



Steady state ^{24h}Blood/Brain PK in healthy mice and EAE mice[1]



- Fast brain penetration of siponimod, showing a strong contrast versus the PK profile of blood
- At 8 hours, the **brain/blood ratio** peaks at **~6**

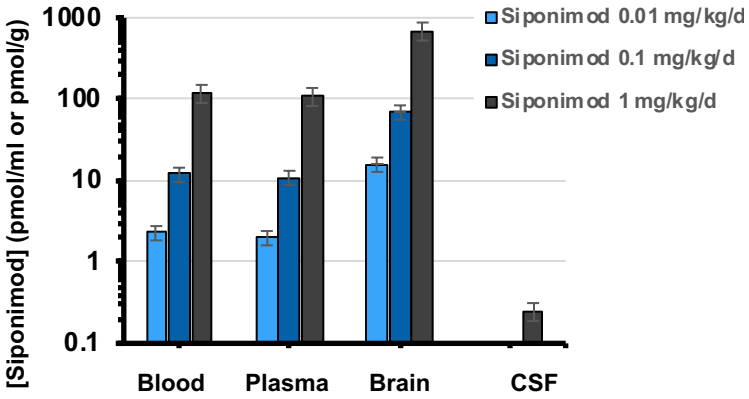
- Dose-proportional increase in steady-state siponimod levels in both the brain and blood
- The **brain/blood ratio** is steady at **~6**

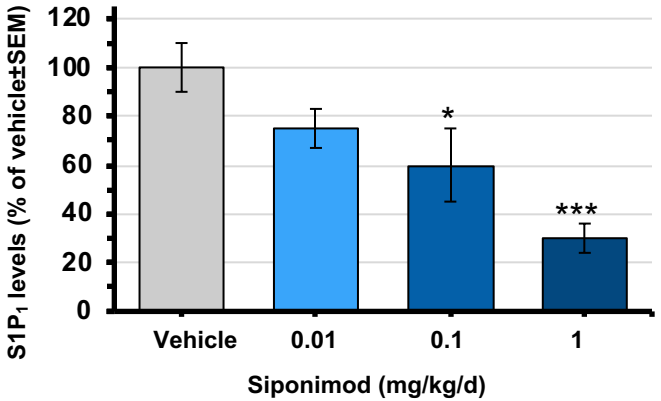
CNS, central nervous system; EAE, experimental autoimmune encephalomyelitis; h, hour; i.v., intravenous; PK, pharmacokinetics

1. Bigaud M et al. Poster presented at ECTRIMS 2019. P622

Rats: Siponimod Penetrates into the CNS and Down Modulates $S1P_1$ Receptors

Siponimod levels at 8 hours post-treatment





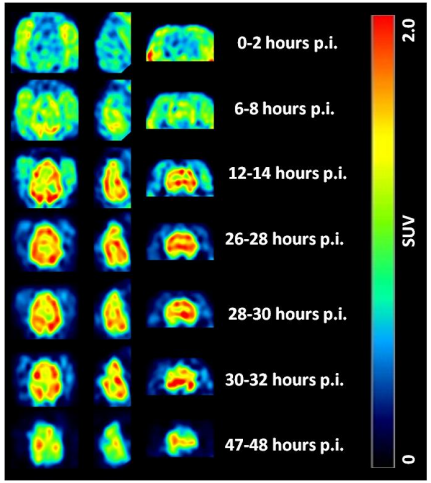
- Dose-proportional increase of siponimod levels in the blood, plasma and brain, with a steady **brain/blood ratio at ~6**
- Siponimod can be detected in the CSF with a CSF/plasma ratio of 0.0025
- Siponimod induced a dose-dependent down-modulation of $S1P_1$ receptors as indicated by $S1P_1$ protein levels measured in brain homogenates

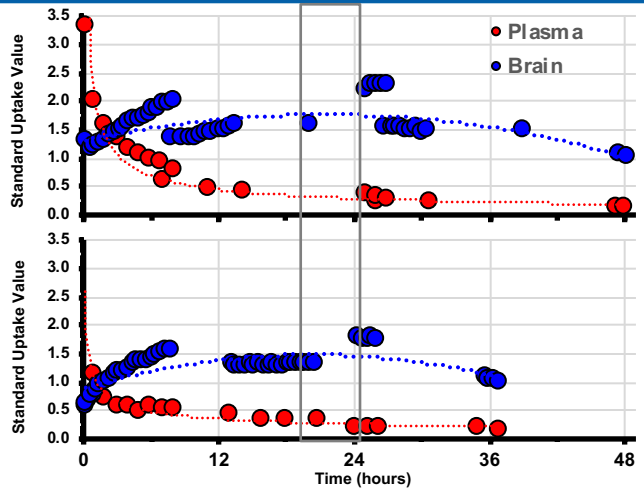
*p<0.05; ***p<0.001

CNS, central nervous system; CSF, cerebrospinal fluid; SEM, standard error of the mean; S1P, sphingosine 1-phosphate

Non-human Primates: Siponimod Penetrates the CNS

^{123}I radiolabelled SPECT-imaging of the siponimod analog (MS565) in two NHPs





Peak brain uptake: **18-24 hours**

Brain/plasma ratio at peak brain uptake: **5–6**

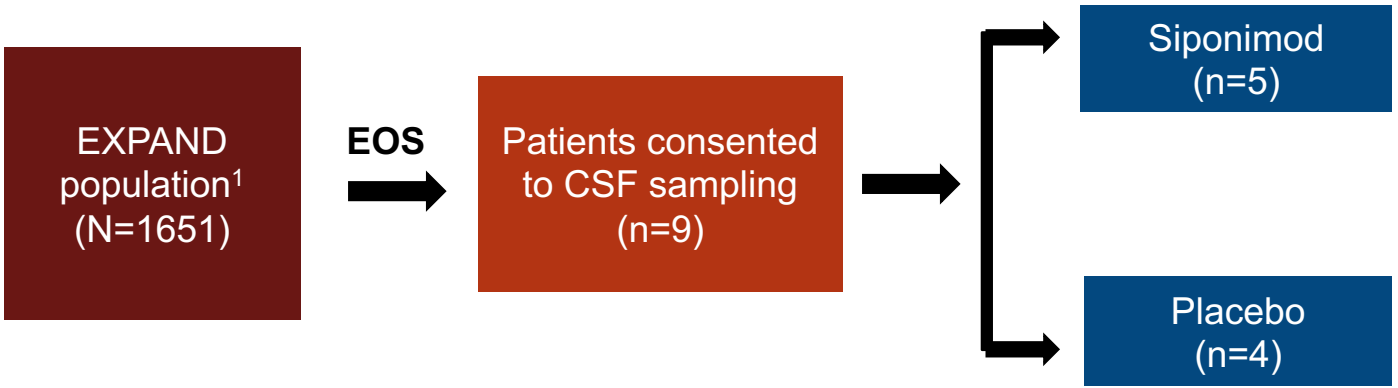
- Siponimod analogue [^{123}I]MS565 displayed good brain penetration with an uptake initially increasing and then slowly washing out[1]
- SPECT monitoring in NHPs revealed CNS distribution of siponimod with a brain/blood ratio of **6–8**, as observed in rodents
- Non-human primates were considered as translational species for estimating the brain penetration in humans

CNS, central nervous system; NHPs, non-human primates; SPECT, single-photon emission computerized tomography; SUV, Standard Uptake Value

1. Tavares A et al. Poster presented at AAN 2014. P1.168

Humans: Siponimod is Found in the CSF of Patients Treated in the Phase 3 EXPAND study

- **EXPAND study[1]:**
  - **Phase 3 study in SPMS patients (EDSS score of 3–6.5)**
  - **Randomised, double-blind, placebo-controlled, event- and exposure-driven study**
  - **Siponimod 2 mg/d (n=1105) vs placebo (n=546)**



Siponimod was detected in the CSF of all siponimod-treated patients (sub-nM range)

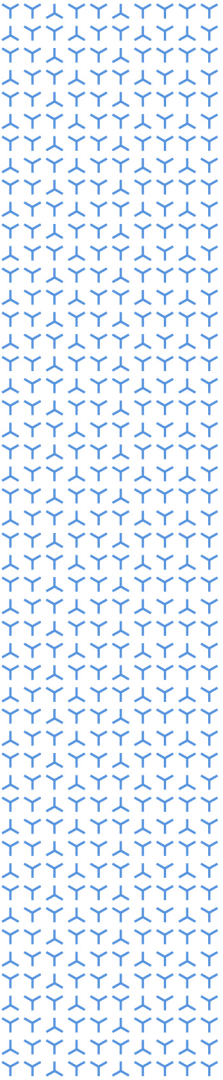
CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Scale; EOS, end of study; SPMS, secondary progressive multiple sclerosis

1. Kappos L et al. Lancet. 2018;391:1263–1273

Conclusions

- Translational evidence from animal models and SPMS patients suggests consistent penetration and distribution of siponimod in the CNS across species (with DER around 6)
- A follow-up study is required for strengthening human data and understanding PK profiles of siponimod in the CNS
- This data provides biological basis for a central MOA that is relevant especially in SPMS and so contribute to explain siponimod efficacy observed in the EXPAND study

CNS, central nervous system; DER, drug exposure ratio; MOA, mechanism of action; PK, pharmacokinetics; SPMS, secondary progressive multiple sclerosis



Thank you