

# Safety and Tolerability of Conversion to Siponimod With and Without Titration in Patients with Advancing Forms of RMS: Interim Results of the Phase 3b EXCHANGE Study

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## Background

- Siponimod (Mayzent®) is an oral sphingosine 1-phosphate (S1P) receptor type 1, 5 modulator that reduces relapses and disability progression in patients with secondary progressive multiple sclerosis (SPMS)<sup>1,2</sup>
  - Approved in the USA for adults with relapsing MS (RMS), including clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS) and active SPMS<sup>3</sup>
  - Indicated in EU for adults with active SPMS as shown by relapses or magnetic resonance imaging (MRI) inflammatory activity<sup>4</sup>
  - Indicated in Japan and Australia for SPMS<sup>5, 6</sup>
- Transient heart rate decreases following first dose are an expected effect of S1P receptor modulator drug class
  - Siponimod dose titration can mitigate this effect
- In clinical practice, patients may switch to siponimod following discontinuation of their disease modifying therapy (DMT)
  - It is important to study whether washout is required when converting to siponimod
- EXCHANGE (NCT03623243) is a Phase 3b trial of safety and tolerability of immediate conversion to dose-titrated siponimod from other DMTs in patients with advancing RMS

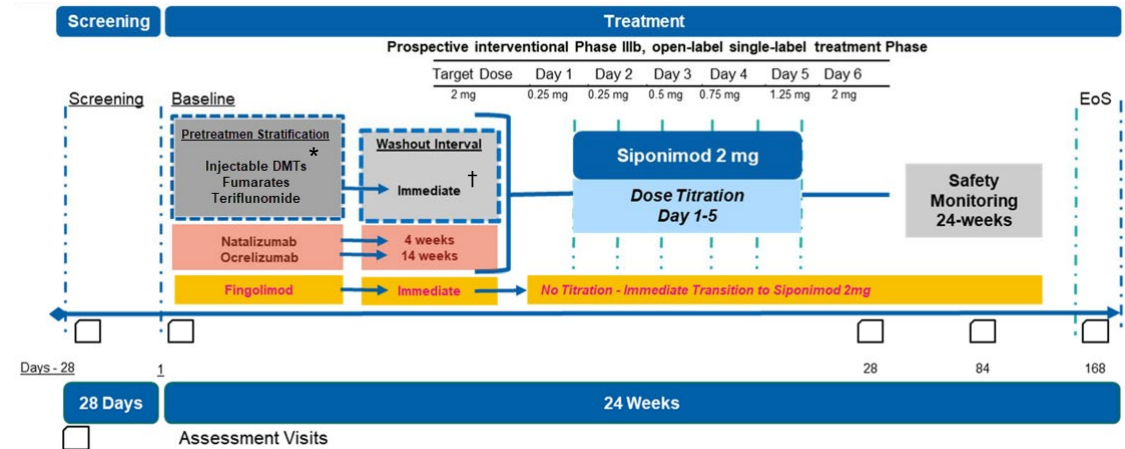
## Objective

- To report interim analyses of EXCHANGE, evaluating safety and tolerability of converting to siponimod from other DMTs with and without dose titration

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- This 6-month, prospective, multicenter, open label, single arm trial has recently completed enrollment; the current analysis is representative of an interim dataset
- Analysis included patients aged 18-65 years with advancing forms of RMS, EDSS 2.0–6.5, and on continuous oral/injectable DMTs for ≥3 months at time of consent
- Uniquely, some patients participated in a virtual cohort, which enabled certain visits to be conducted virtually, allowing for flexible participation during the COVID-19 pandemic
- Most patients initiating siponimod were titrated from 0.25 to 2 mg over 6 days
  - Patients transitioning from teriflunomide required 11-14 days' accelerated washout with cholestyramine or activated charcoal
  - Patients transitioning from natalizumab or ocrelizumab required ≥4- or ≥14-week washout period, respectively
  - Those converting from fingolimod immediately switched to siponimod 2 mg, with no dose-titration

## EXCHANGE study design



- **Primary endpoint:** AEs suspected to be related to siponimod over 6 months of treatment
- **Secondary endpoints:**
  - Any AE or hospitalizations
  - Change in heart rate from baseline to 6 hours after first dose

\*Injectable DMTs: IFN beta-1a, IFN beta-1b, glatiramer acetate, pegylated IFN beta-1a. †Defined as cessation of existing DMT and initiation of siponimod within 24 hours, followed by subsequent 5-day dose titration. COVID-19, coronavirus 2019; DMT, disease modifying therapy; EoS, end of study; EoT, end of treatment; EDSS, Expanded Disability Status Scale; RMS, relapsing multiple sclerosis.

- 163 patients from 42 US centers were eligible for inclusion in the safety analysis
  - 65.0% completed the study phase, 16.6% were receiving ongoing treatment, and 18.4% discontinued treatment

Patient disposition	Siponimod, N=163 n (%)
<b>Study phase</b>	
Ongoing treatment*	27 (16.6)
Discontinued treatment	30 (18.4)
Completed study phase	106 (65.0)
<b>Primary reason for premature discontinuation</b>	
Patient decision	15 (9.2)
Adverse event	11 (6.7)
Physician decision	3 (1.8)
New therapy for study indication	1 (0.6)
<b>Siponimod exposure</b>	
	<b>Median (min-max)</b>
Exposure (days)	168.0 (1-198)
Compliance (overall)**	100%

Max, maximum; min, minimum; N, number of patients; n, number of observations.

\*patients have not reached end of study visit

\*\*n=153

Background & Objective

Methods

Results

Conclusions



- 163 patients from 42 US centers were eligible for inclusion in the safety analysis
  - 74.2% were female, mean age was 46.6 years, and mean baseline EDSS score was 3.9
- EXCHANGE has enrolled a diverse patient demographic, including 22.1% who identified as Hispanic/Latino, and 14.1% as Black/African American
- At screening, 76.7% had RRMS, 20.2% SPMS, 2.5% PPMS, and 0.6% single demyelinating event

	Siponimod, N=163
<b>Baseline characteristics</b>	
Age (years), mean (SD)	46.6 (10.3)
Females, n (%)	121 (74.2)
Race, n (%)	
White	138 (84.7)
Black or African American	23 (14.1)
Asian	2 (1.2)
Ethnicity, n (%)	
Hispanic or Latino	36 (22.1)
Not Hispanic or Latino	126 (77.3)
Not Reported	1 (0.6)
EDSS score, mean (SD)	3.9 (1.5)
<b>Type of MS at study entry, n (%)</b>	
Single demyelinating event	1 (0.6)
PPMS	4 (2.5)
SPMS	33 (20.2)
RRMS	125 (76.7)
<b>Time since MS diagnosis (years), mean (SD)</b>	12.2 (8.7)

EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; N, number of patients; n, number of observations; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

- The majority of patients (54%) had no relapses in the year prior to screening
- Most common prior DMTs were oral and injection therapies: 30.7% fingolimod, 27.7% glatiramer acetate/IFN $\beta$ , 20.9% dimethyl fumarate, and 17.2% teriflunomide

	Siponimod, N=163
<b>Relapses in 12 months before screening, n (%)</b>	
0	88 (54.0)
1	57 (35.0)
2	10 (6.1)
3	6 (3.7)
≥4	2 (1.2)
<b>Relapses in 12-24 months before screening, n (%)</b>	
0	86 (52.8)
1	39 (23.9)
2	24 (14.7)
3	7 (4.3)
≥4	7 (4.3)
<b>Previous MS treatments, n (%) [duration (months), mean (SD)]<sup>a</sup></b>	
Previously treated patients	163 (100)
Fingolimod	50 (30.7) [48.3 (31.0)]
Glatiramer acetate	26 (16.0) [83.4 (68.7)]
Dimethyl fumarate	34 (20.9) [34.9 (25.9)]
Any IFN $\beta$	19 (11.7) [82.7 (65.6)]
Teriflunomide	28 (17.2) [29.6 (26.9)]
Natalizumab	1 (0.6) [3.9 (NA)]
Ocrelizumab	5 (3.1) [15.2 (12.7)]

DMT, disease modifying therapy; IFN, interferon; MS, multiple sclerosis; N, number of patients; n, number of observations; SD, standard deviation.

<sup>a</sup>Duration of previous MS treatments before switching to siponimod (months)

Background & Objective

Methods

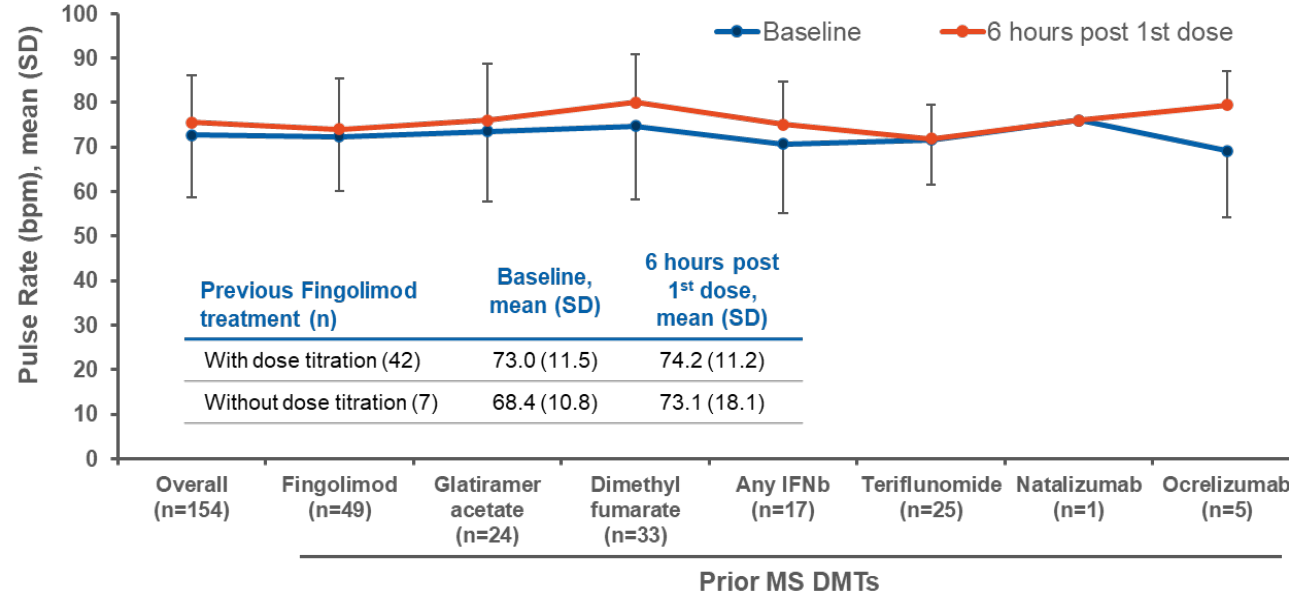
Results

Conclusions



## Mean heart rate at baseline and 6-hour post first dose by prior MS DMTs

- There was no decrease in heart rate at 6 hours post first dose from baseline in the overall or any of the prior DMT groups
- In the fingolimod subgroup (n=7) who were switched to siponimod without dose titration, mean heart rate (SD) was 73.1 bpm (18.1) at 6 hours post 1st dose vs 68.4 bpm (10.8) at baseline



bpm, beats per minute; DMT, disease modifying therapy; IFN, interferon; MS, multiple sclerosis; N, number of patients; n, number of observations; SD, standard deviation.



- In safety analysis, 31.3% of patients reported  $\geq 1$  AE possibly related to siponimod treatment

Incidence of AEs	Siponimod, N=163 n (%)	95% CI
<b>Summary of AEs</b>		
Patients with $\geq 1$ AE	115 (70.6)	-
Patients with $\geq 1$ SAE	8 (4.9)	-
Patients with $\geq 1$ AE leading to permanent drug discontinuation	11 (6.7)	-
<b>Patients with <math>\geq 1</math> AE possibly related to study medication</b>	51 (31.3)	(24.4, 39.1)
<b>Most common AEs by preferred term (<math>\geq</math> to 3%)</b>		
Headache	13 (8.0)	(4.5, 13.5)
Dizziness	7 (4.3)	(1.9, 9.0)
Nausea	6 (3.7)	(1.5, 8.2)
Bradycardia	5 (3.1)	(1.1, 7.4)
Fatigue	5 (3.1)	(1.1, 7.4)
<b>Infections and infestations</b>		
Urinary tract infection	4 (2.5)	(0.8, 6.6)
Oral herpes	2 (1.2)	(0.2, 4.8)
<b>Incidence of AEs possibly related to study medication by prior DMTs</b>		
	<b>Siponimod, n/N (%)</b>	<b>95% CI</b>
Fingolimod	16/50 (32.0)	(19.9, 46.8)
Glatiramer acetate	9/26 (34.6)	(17.9, 55.6)
Dimethyl fumarate	8/34 (23.5)	(11.4, 41.6)
Any IFN $\beta$	4/19 (21.1)	(7.0, 46.1)
Teriflunomide	11/28 (39.3)	(22.1, 59.3)
Ocrelizumab	3/5 (60.0)	(17.0, 92.7)

AE, adverse event; CI, confidence interval; IFN, interferon; SAE, serious adverse event; DMT, disease modifying therapy; N, number of patients; n, number of observations.

The patient on natalizumab experienced  $\geq 1$  AE (visual impairment)

Background & Objective

Methods

Results

Conclusions



- In this interim analysis, immediate conversion over 6 days from other DMTs to siponimod was generally well tolerated, with no unexpected findings
- Furthermore, there was no evidence of a meaningful reduction in heart rate when initiating siponimod in the overall group or in subgroups stratified by prior DMTs, including subjects transitioning from fingolimod to siponimod without dose titration
- EXCHANGE will provide clinically relevant data to HCPs in providing management guidelines for switching patients to siponimod from other DMTs

DMT, disease-modifying therapy; HCP, healthcare provider.

Background & Objective

Methods

Results

Conclusions

