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 & Objective

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)[1,2]
  - Approved in the USA for adults with relapsing MS (RMS), including clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS) and active SPMS[3]
  - Indicated in EU for adults with active SPMS as shown by relapses or magnetic resonance imaging (MRI) inflammatory activity[4]
  - Indicated in Japan and Australia for SPMS[5, 6]
- 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

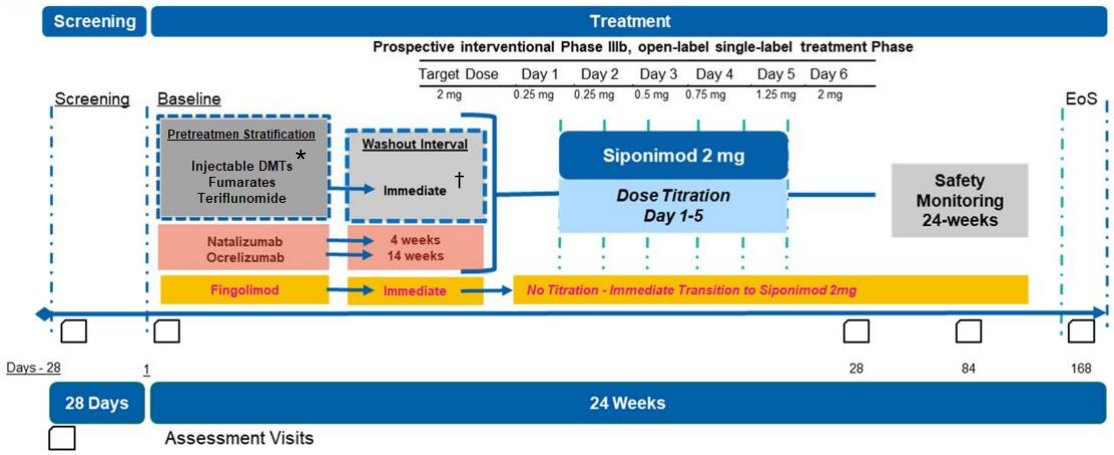
- To report interim analyses of EXCHANGE, evaluating safety and tolerability of converting to siponimod from other DMTs with and without dose titration

1. Kappos L, et al. *Lancet*. 2018;391:1263–1273. 2. Selmaj K, et al. *Lancet Neurol*. 2013;12:756-767. 3. Novartis Pharmaceuticals Corporation. Prescribing information. Mayzent® 2022. Available from: https://www.novartis.us/sites/www.novartis.us/files/mayzent.pdf (Accessed March 10, 2022). 4. European Medicines Agency. EPAR. Mayzent® 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/mayzent-epar-product-information_en.pdf (Accessed March 10, 2022). 5. PMDA. Mayzent® 2020. Available from: https://www.pmda.go.jp/files/000241414.pdf (Accessed March 10, 2022). 6. Australian Product Information. Mayzent® 2019. Available from: https://www.tga.gov.au/sites/default/files/auspar-siponimod-191211-pi.pdf (Accessed March 10, 2022).

Methods: Study Design, Patient Population, and Endpoints

- 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.

Results: EXCHANGE Patient Disposition & Exposure

- 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 (%)
Study phase	
Ongoing treatment*	27 (16.6)
Discontinued treatment	30 (18.4)
Completed study phase	106 (65.0)
Primary reason for premature discontinuation	
Patient decision	15 (9.2)
Adverse event	11 (6.7)
Physician decision	3 (1.8)
New therapy for study indication	1 (0.6)

Siponimod exposure	Median (min-max)
Exposure (days)	168.0 (1-198)
Compliance (overall)**	100%

*patients have not reached end of study visit
**n=153

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

Results: Patient Demographics and Baseline Characteristics

- 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
Baseline characteristics	
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)
Type of MS at study entry, n (%)	
Single demyelinating event	1 (0.6)
PPMS	4 (2.5)
SPMS	33 (20.2)
RRMS	125 (76.7)
Time since MS diagnosis (years), mean (SD)	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.

Results: Patient Baseline Characteristics and Prior Treatments

- 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/IFNβ, 20.9% dimethyl fumarate, and 17.2% teriflunomide

	Siponimod, N=163
Relapses in 12 months before screening, n (%)	
0	88 (54.0)
1	57 (35.0)
2	10 (6.1)
3	6 (3.7)
≥4	2 (1.2)
Relapses in 12-24 months before screening, n (%)	
0	86 (52.8)
1	39 (23.9)
2	24 (14.7)
3	7 (4.3)
≥4	7 (4.3)
Previous MS treatments, n (%) [duration (months), mean (SD)][a]	
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 IFNβ	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)]

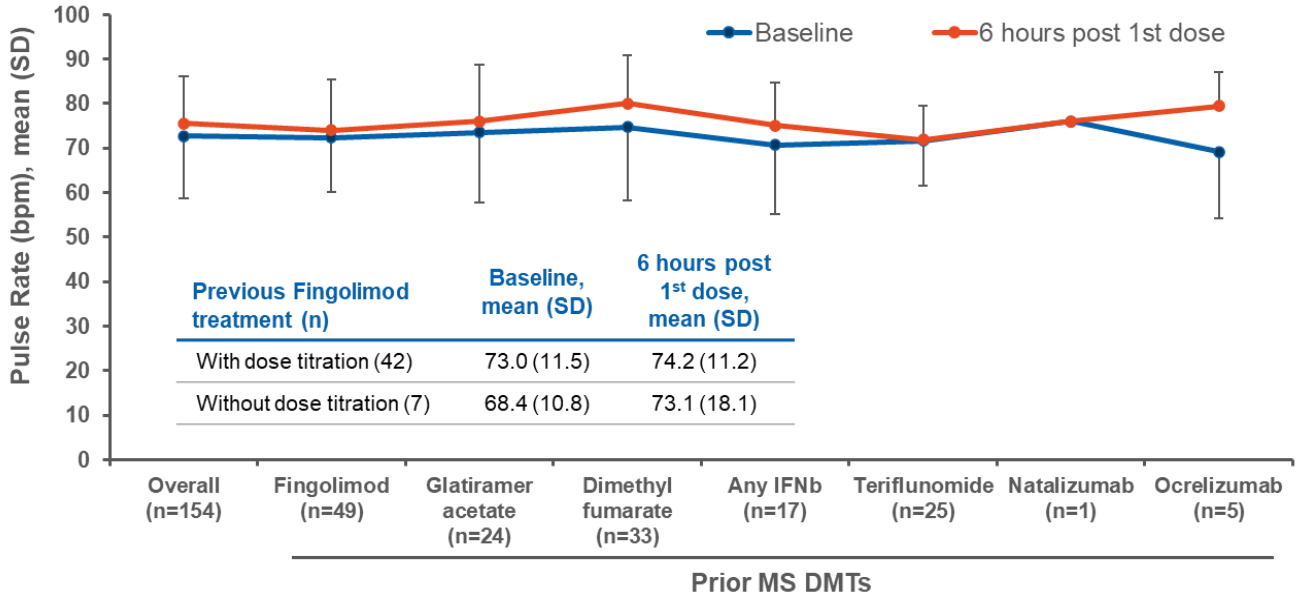
[a]Duration of previous MS treatments before switching to sipominod (months)

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

Results: Effect of Siponimod Conversion on Heart Rate

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



Previous Fingolimod treatment (n)	Baseline, mean (SD)	6 hours post 1st dose, mean (SD)
With dose titration (42)	73.0 (11.5)	74.2 (11.2)
Without dose titration (7)	68.4 (10.8)	73.1 (18.1)

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

Results: Safety

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

Incidence of AEs	Siponimod, N=163 n (%)	95% CI
Summary of AEs		
Patients with ≥1 AE	115 (70.6)	-
Patients with ≥1 SAE	8 (4.9)	-
Patients with ≥1 AE leading to permanent drug discontinuation	11 (6.7)	-
Patients with ≥1 AE possibly related to study medication	51 (31.3)	(24.4, 39.1)
Most common AEs by preferred term (≥ to 3%)		
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)
Infections and infestations		
Urinary tract infection	4 (2.5)	(0.8, 6.6)
Oral herpes	2 (1.2)	(0.2, 4.8)

Incidence of AEs possibly related to study medication by prior DMTs	Siponimod, n/N (%)	95% CI
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 IFNβ	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)

The patient on natalizumab experienced ≥1 AE (visual impairment)

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

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.