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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P672

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Background

- Siponimod (Mayzent®) is an oral S1P receptor type 1, 5 modulator that reduces relapses and disability progression in patients with SPMS[1,2]
  - Approved in the USA for adults with RMS, including CIS, RRMS and active SPMS
  - Indicated in EU for adults with active SPMS as shown by relapses or MRI inflammatory activity
  - Indicated in Japan and Australia for SPMS
- 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 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

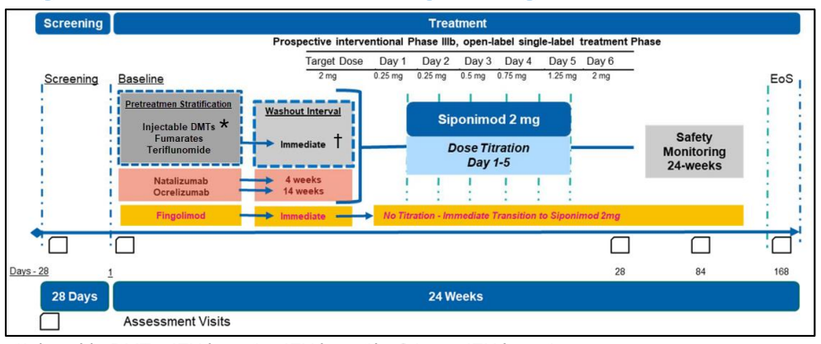
- **To report interim analyses of EXCHANGE, evaluating safety and tolerability of converting to siponimod from other DMTs with and without dose titration**

Methods

Study design and patient population

- This 6-month, prospective, multicenter, open label, single arm trial (**Figure 1**) has completed 50% subject enrollment
- 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

Figure 1. EXCHANGE study design



*Injectable DMTs: IFN beta-1a, IFN beta-1b, GA, pegIFN beta-1a
†Defined as cessation of existing DMT and initiation of siponimod within 24 hours, followed by subsequent 5-day dose titration

Study endpoints

- **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

Results

Patient disposition and demographics

- 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 (**Table 1**)
  - 74.2% were female, mean age was 46.6 years, and mean baseline EDSS score was 3.9 (**Table 2**)
- 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 (**Table 2**)
- The majority of patients (54%) had no relapses in the year prior to screening (**Table 2**)
- 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 (**Table 2**)

Table 1. EXCHANGE patient disposition and exposure (interim analysis)

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%

*n=153

Table 2. Patient demographics and baseline characteristics

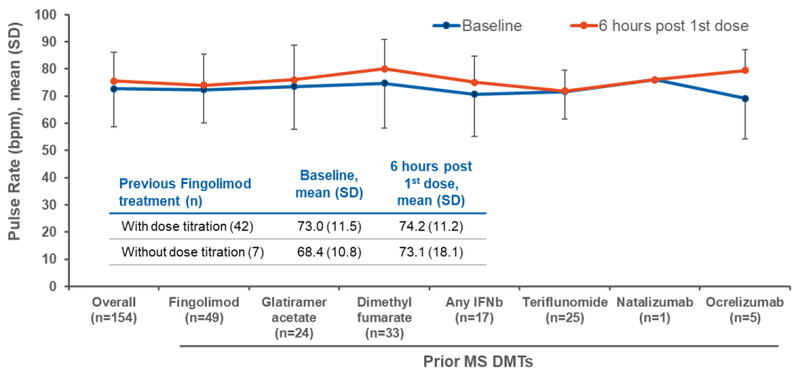
	Siponimod N=163
Baseline characteristics	
Age (years), mean (SD)	46.6 (10.3)
Females, n (%)	121 (74.2)
Race, n (%)	
White	138 (84.7)
Black or African American	23 (14.1)
Asian	2 (1.2)
Ethnicity, n (%)	
Hispanic or Latino	36 (22.1)
Not Hispanic or Latino	126 (77.3)
Not Reported	1 (0.6)
EDSS score, mean (SD)	3.9 (1.5)
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)]
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)
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)

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

Effect of siponimod conversion on heart rate

- 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 (**Figure 2**)
- 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

Figure 2. Mean heart rate at baseline and 6-hour post first dose by prior MS DMTs



Adverse events

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

Table 3. Incidence of adverse events

	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		
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)

Table 4. Incidence of adverse events 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)

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

References

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Abbreviations

AE, adverse event; bpm, beats per minute; CI, confidence interval; CIS, clinically isolated syndrome; DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; EoS, end of study; EoT, end of treatment; GA, glatiramer acetate, HCP, healthcare professional; IFN, interferon; MS, multiple sclerosis; N, number of patients; n, number of observations; PI, principal investigator; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; S1P, sphingosine 1-phosphate; SAE, serious adverse event; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

Disclosures

A. Bar-Or has participated as a speaker in meetings sponsored by, and received consulting fees and/or grant support from, Actelion, Atara Biotherapeutics, Biogen Idec, Celgene/ Receptos, Genentech/Roche, Mapi, MedImmune, Merck/EMD Serono, Novartis and Sanofi. **B. Weinstock-Guttman** has received consulting fees from Biogen, Celgene, EMD Serono, Genentech and Janssen, and research support from Biogen, Celgene, EMD Serono, Genentech and Novartis. **Y. Mao-Draayer** has received research support from NIH NINDS R01-NS080821, NIAID Autoimmune Center of Excellence UM1-AI110557, UM1 AI144298-01, PCORI, Sanofi-Genzyme, Genentech-Roche, Novartis, and Chugai; consulting/speaker fees from Acorda, Biogen, Bayer Pharmaceutical, Celgene/Bristol Myers Squibb, Teva, Genentech-Roche, Novartis, Janssen, Sanofi-Genzyme, and EMD Serono. **S.L. Cohan** has received speaking fees from Biogen, Bristol Myers Squibb, Novartis, Roche/Genentech and Sanofi Genzyme, serves on advisory boards or as a consultant to Biogen, EMD Seromo, Novartis and Sanofi Genzyme, and receives institutional research support (Providence Brain and Spine Institute) from Adamas, Biogen, Novartis, Roche/Genentech and Sanofi Genzyme. **L.-A. Cruz, X. Meng,** and **G.M. Cox** are employees of Novartis Pharmaceuticals Corporation.

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