Safety and tolerability of conversion to siponimod in patients with relapsing multiple sclerosis: interim results of the EXCHANGE study

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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 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 prospective, open label, single arm trial of safety and tolerability of immediate conversion to dose-titrated siponimod from other DMTs in patients with advancing RMS[a] or a history of RMS[b]
  - Includes a virtual study cohort pre-screened, recruited and monitored at home using telemedicine tools

[a]As defined by principal investigator; [b]with or without progressive features.

Objective

- **Report interim analyses of EXCHANGE, evaluating safety and tolerability of converting to siponimod from other DMTs**

Methods

Study design and patient population

- 6 month, prospective, multicenter, open label, single arm trial (**Figure 1**)
- ~300 adults with advancing RMS, as defined by the PI, or a history of RMS with or without progressive features (**Table 1**)
  - ~100 patients will enroll in remote patient cohort; recruitment and assessment conducted in patients' homes via telemedicine tools
- Most patients will undergo conversion to siponimod within 24 hours
  - Those transitioning from teriflunomide will undergo an 11-14 day washout with cholestyramine or activated charcoal*

Figure 1. EXCHANGE study design

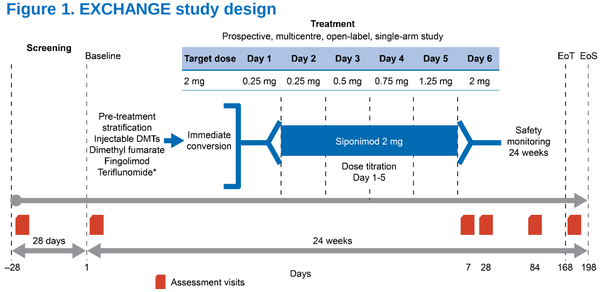


Table 1. Key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
Male or female outpatients, aged 18 to 65 years at screening	Immunological disease other than MS
Advancing RMS (as defined by PI)	CYP2C9*3/*3, CYP2C9*2/*3 and CYP2C9*1/*3 genotypes
History of RMS, with or without progressive features (2010 Revised McDonald or Lublin criteria)	History of malignancy of any organ system in the past 5 years
EDSS score at screening, ≥2.0 to 6.5	Diagnosis of macular edema 1 year before screening; certain conditions or treatments that may affect cardiovascular, pulmonary or hepatic function
Continuous DMT for ≥3 months at baseline • β-interferons, glatiramer acetate, fingolimod, dimethyl fumarate, teriflunomide, natalizumab or ocrelizumab	

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

- 113 patients included in interim analysis from 42 centers in the USA
  - 1 patient in the virtual arm
- 23 patients discontinued treatment (**Table 2**)
  - Reasons were patient decision (n=16), AE (n=5), physician decision (n=1), and progressive disease (n=1)
  - Proportion of patients who have discontinued from the study is broadly consistent with that seen in previous MS studies[1,3,4]
- 100% compliance reported by patients in interim analysis (**Table 2**)
- Most patients (74.1%) had relapsing-remitting MS; 21.4% had SPMS (**Table 3**)
- All patients had received previous MS treatments; fingolimod was the most common DMT (**Table 3**)
- 42% had ≥1 relapse in 12 months before screening

Table 2. EXCHANGE patient disposition and exposure (interim analysis)

Patient disposition	Siponimod N=112 n (%)
Study phase	
Ongoing treatment	38 (33.9)
Discontinued treatment	23 (20.5)
Completed study phase	51 (45.5)
Primary reason for premature discontinuation	
Patient decision	16 (14.3)
Adverse event	5 (4.5)
Physician decision	1 (0.9)
Progressive disease	1 (0.9)

Siponimod exposure	Median (min-max)
Exposure (days)	150 (7-196)
Compliance (overall)	100%

Table 3. Patient demographics and baseline characteristics

Baseline demographics	Siponimod N=112[c]
Characteristics	
Age (years)[a]	45.5 (20-65)
Females[b]	79 (70.5)
Race[b]	
White	96 (85.7)
Black or African American	15 (13.4)
Asian	1 (0.9)
EDSS	
EDSS score available for prior 2 years at screening	
Yes	11 (9.8)
No	101 (90.2)
EDSS score[a]	3.5 (2-6.5)
Previous MS treatments[a]	
Previously treated patients	112 (99.1)
Fingolimod	37 (32.7)
Glatiramer acetate	21 (18.6)
Dimethyl fumarate	19 (16.8)
Any IFN	18 (15.9)
Teriflunomide	17 (15.0)

MS history	Siponimod N=112[c]
Type of MS at study entry[b]	
Single demyelinating event	1 (0.9)
PPMS	4 (3.6)
SPMS	24 (21.4)
RRMS	83 (74.1)
Time since MS diagnosis (years)[a]	11.2 (0.4-39.8)
Relapses in 12 months before screening	
0	65 (58.0)
1	33 (29.5)
2	8 (7.1)
3	5 (4.5)
≥4	1 (0.9)
Relapses in 12-24 months before screening	
0	61 (54.5)
1	24 (21.4)
2	17 (15.2)
3	6 (5.4)
≥4	4 (3.6)

[a]Data are median (range); [b]data are number of patients (%); [c]baseline data are shown for 112 patients, except for previous MS treatments where N=113

Adverse events

- Proportion of patients reporting SAEs and AEs leading to drug discontinuation was low (**Table 4**)
  - 5 patients had ≥1 SAE[a]
    - asthenia, MS relapse, non-cardiac chest pain, pneumonia aspiration, seizure and tubulointerstitial nephritis
  - 6 patients had ≥1 AE leading to drug discontinuation[b]
    - abnormal behavior, cognitive disorder, edema peripheral, fatigue, insomnia, nausea, pain in extremity, tremor and vomiting

Table 4. Incidence of adverse events

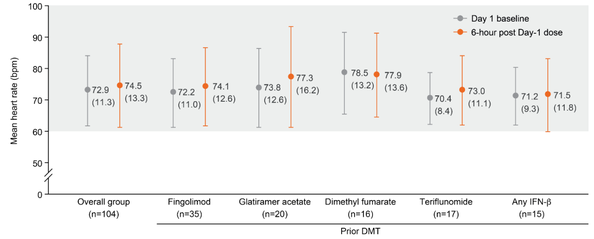
	Siponimod, N=112 n (%)	95% CI
Summary of AEs		
Patients with ≥1 AE	39 (34.8)	(26.2, 44.5)
Patients with ≥1 SAE	5 (4.5)	-
Patients with ≥1 AE leading to drug discontinuation	6 (5.4)	-
AEs related to study drug (>5% of patients, safety analysis set)		
Gastrointestinal disorders		
Total	10 (8.9)	(4.6, 16.2)
Infections and infestations		
Total	7 (6.3)	(2.8, 12.9)
Nervous system disorders		
Total	17 (15.2)	(9.3, 23.5)
Dizziness	6 (5.4)	(2.2, 11.8)
Headache	10 (8.9)	(4.6, 16.2)

[a]Multiple SAEs can occur in 1 patient; [b]multiple AEs leading to drug discontinuation can occur in 1 patient

Effect of siponimod conversion on heart rate

- No notable reductions from baseline in mean heart rate at 6-hour post Day-1 dose, in overall group or when stratified by previous DMT (**Figure 2**)

Figure 2. Mean heart rate at baseline and 6-hour post first dose



Data are shown as mean (SD). Gray shading normal heart rate range (60-100 bpm)

Conclusions

- Conversion from oral/injectable DMTs to siponimod without washout had an acceptable safety and tolerability profile, with no unexpected findings
- There was no evidence of a meaningful reduction in heart rate when initiating siponimod in the overall group or in subgroups stratified by previous DMT
- EXCHANGE will provide clinically relevant data to HCPs in providing management guidelines for switching patients to siponimod from other DMTs
  - Remote cohort recognizes impact of worsening disability on patients and is particularly important in context of the COVID-19 pandemic

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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; 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

Amit 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 Genzyme. **Bianca 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. **Yang Mao-Draayer** has received fees for consulting/non-CME/CE services from Biogen, Celgene, EMD Serono, Genentech, Novartis, Sanofi Genzyme and Teva, and fees for contracted research from Chugai, Novartis and Sanofi Genzyme. **Stanley L Cohan** has received speaking fees from Biogen, Novartis, Roche/Genentech and Sanofi Genzyme, serves on advisory boards or as a consultant to AbbVie, Biogen, Novartis and Sanofi Genzyme, and receives institutional research support (Providence Brain and Spine Institute) from AbbVie, Adamas, Biogen, Novartis, Roche/Genentech and Sanofi Genzyme. **Gina Cox**, **Linda-Ali Cruz**, **Xiangyi Meng** and **Wendy Su** are employees of Novartis Pharmaceuticals Corporation.

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