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Safety and Tolerability of Conversion to Siponimod in Patients with Advancing Relapsing Multiple Sclerosis: A Subgroup Analysis by Race and Ethnicity of EXCHANGE Interim Data

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SUMMARY

1 **Minority groups are persistently underrepresented in clinical trials, resulting in limited data to inform clinical decision-making for these patients. EXCHANGE enrolled a higher proportion of minority groups vs other recent MS clinical trials**

2 **Findings of this subgroup analysis by race/ethnicity provide some insights into treatment patterns and safety/tolerability in minority MS patient populations**

3 **Siponimod safety/tolerability profile remained consistent with no new or unexpected safety findings identified through this analysis**

BACKGROUND

- Siponimod (Mayzent®), an oral S1P receptor type 1, 5 modulator approved in the USA for adults with RMS (including CIS, RRMS, and active SPMS), reduces relapses and disability progression in patients with SPMS[1-3]
- 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
- Minority groups are persistently underrepresented in clinical trials, resulting in limited data to inform clinical decision-making for these patients and presenting an urgent need for evidence-based clinical management[4]
- In four recent large-scale Phase 3 MS trials (OPERA, ORATORIO, RADIANCE, EXPAND), study populations included 0.5-5.3% Black and 0-6.5% Hispanic participants[4]
- The EXCHANGE study enrolled a diverse patient population and presents opportunity to assess MS treatment patterns and safety/tolerability in conversion to siponimod

OBJECTIVE

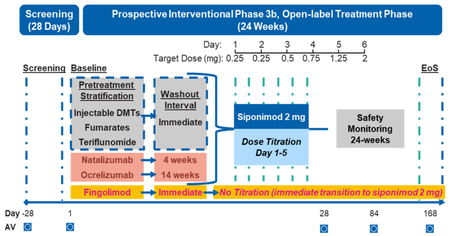
- Report on a subgroup analysis of EXCHANGE interim data in patients with advancing RMS who identified as Hispanic/Latino or Black/African American

METHODS

STUDY DESIGN

- EXCHANGE is a 6-month, prospective, multicenter, open label, single arm trial (**Figure 1**) that has recently completed enrollment; the current analysis is representative of an interim dataset
- The trial included patients aged 18–65 years with advancing RMS, EDSS 2.0–6.5, and on continuous oral/injectable/infusion DMTs for ≥3 months at time of consent; primary endpoint was drug-related AE incidence
- 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
- Subgroups were assessed according to patient-reported race/ethnicity

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; AV, Assessment Visit.

RESULTS

PATIENT DISPOSITION AND BASELINE CHARACTERISTICS

- Patient demographics and disposition are described in **Table 1**

Table 1. Patient demographics and baseline characteristics

Demographic, n (%) unless otherwise specified	Overall (N=163)	Black/African American (N=23)	Hispanic/Latino (N=36)
Age, years, mean (SD)	46.6 (10.3)	43.8 (8.6)	40.3 (11.3)
Gender			
Female	121 (74.2)	20 (87.0)	27 (75.0)
Male	42 (25.8)	3 (13.0)	9 (25.0)
Race			
White	138 (84.7)	-	-
Black or African American	23 (14.1)	23 (100.0)	-
Asian	2 (1.2)	-	-
Ethnicity			
Hispanic or Latino	36 (22.1)	-	36 (100.0)
Not Hispanic or Latino	126 (77.3)	-	-
Not Reported	1 (0.6)	-	-
Type of MS at study entry			
Single demyelinating event	1 (0.6)	-	1 (2.8)
PPMS	4 (2.5)	-	1 (2.8)
SPMS	33 (20.2)	3 (13.0)	3 (8.3)
RRMS	125 (76.7)	20 (87.0)	31 (86.1)
Time since MS diagnosis, years, mean (SD)	12.2 (8.7)	10.5 (7.1)	10.2 (7.7)
Time since first MS symptom, years, mean (SD)	14.4 (9.6)	12.3 (7.5)	13.0 (9.3)
EDSS score, median	3.5	3.5	3.0
Relapses in 12 months before screening			
0	88 (54.0)	8 (34.8)	15 (41.7)
1	57 (35.0)	7 (30.4)	17 (47.2)
2	10 (6.1)	5 (21.7)	2 (5.6)
3	6 (3.7)	1 (4.3)	2 (5.6)
≥4	2 (1.2)	2 (8.7)	-
Relapses in 24 months before screening			
0	86 (52.8)	10 (43.5)	10 (27.8)
1	39 (23.9)	5 (21.7)	13 (36.1)
2	24 (14.7)	4 (17.4)	8 (22.2)
3	7 (4.3)	2 (8.7)	3 (8.3)
≥4	7 (4.3)	2 (8.7)	2 (5.6)

- Of 163 patients in the overall EXCHANGE interim population (**Table 1**):
  - 126 (77.3%) identified as White, non-Hispanic/Latino
  - 23 (14.1%) identified as Black/African American
  - 36 (22.1%) identified as Hispanic/Latino
- The proportion of patients with no relapses in the year prior to screening were 54.0%, 34.8%, and 41.7% in the respective subgroups (**Table 1**)
- 77.8% of the Hispanic/Latino subgroup were on oral DMTs, vs 68.7% in the overall EXCHANGE interim population and 47.8% in the Black/African American subgroup (**Table 2**)
- 47.8% of the Black/African American subgroup were on injectable DMTs before switching to siponimod, vs 27.6% in the overall EXCHANGE interim population and 16.7% in the Hispanic/Latino subgroup (**Table 2**)

Table 2. Prior MS DMTs before switching to siponimod

Previous MS treatment, n (%)	Overall (N=163)	Black/African American (N=23)	Hispanic/Latino (N=36)
Previously treated patients	**163 (100)**	**23 (100)**	**36 (100)**
Oral DMTs			
Fingolimod	50 (30.7)	4 (17.4)	17 (47.2)
With dose titration	43 (26.4)	4 (17.4)	14 (38.9)
Without dose titration	7 (4.3)	-	3 (8.3)
Dimethyl fumarate	34 (20.9)	5 (21.7)	5 (13.9)
Teriflunomide	28 (17.2)	2 (8.7)	6 (16.7)
Injectable DMTs			
GA	26 (16.0)	5 (21.7)	5 (13.9)
Any IFNβ	19 (11.7)	6 (26.1)	1 (2.8)
Infusion DMTs			
Natalizumab	1(0.6)	1 (4.3)	-
Ocrelizumab	5 (3.1)	-	2 (5.6)

EFFECT OF SIPONIMOD CONVERSION ON HEART RATE

- Mean heart rate at baseline and 6-hour post first dose in both patient subgroups were comparable to the findings observed in the overall EXCHANGE interim population
- 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 either patient subgroup

SAFETY

- Incidence of AEs are described in **Table 3**; safety profile was consistent with what has been previously reported[5] and no unexpected safety signals emerged
- The most common AE related to siponimod treatment by preferred term was headache in the overall population (n=13; 8.0%), 11 of whom were Hispanic/Latino
- AEs that occurred in the Black or African American subgroup included: abscess limb, muscle spasms, MS relapse, peroneal nerve palsy, urinary incontinence – each n=1 (4.3%), 95% CI (0.2, 24.0)
- SAEs that occurred in the Black or African American subgroup included: asthenia, non-cardiac chest pain, cellulitis, hemiparesis, MS relapse, lymphoedema – each n=1 (4.3%)
- There were 4 patients who experienced AEs leading to permanent drug discontinuation in the Hispanic/Latino subgroup; the AEs were fatigue, oedema peripheral, pain in extremity, cognitive disorder, headache, MS relapse, tremor, insomnia – each n=1 (2.8%), except fatigue (n=2, 5.6%)

Table 3. Incidence of adverse effects

n (%) 95% CI	Overall (N=163)	Black/African American (N=23)	Hispanic/Latino (N=36)
Summary of AEs, n (%)			
Patients with ≥1 AE	115 (70.6)	18 (78.3)	26 (72.2)
Patients with ≥1 SAE	8 (4.9)	3 (13.0)	0
Patients with ≥1 AE leading to permanent drug discontinuation	11 (6.7)	0	4 (11.1)
≥1 AE possibly related to siponimod treatment	51 (31.3) (24.4, 39.1)	4 (17.4) (5.7, 39.5)	16 (44.4) (28.3, 61.7)
Most common AEs related to siponimod by preferred term			
Headache	13 (8.0) (4.5, 13.5)	0	11 (30.6) (16.9, 48.3)
Dizziness	7 (4.3) (1.9, 9.0)	0	3 (8.3) (2.2, 23.6)
Nausea	6 (3.7) (1.5, 8.2)	0	2 (5.6) (1.0, 20.0)
Bradycardia	5 (3.1) (1.1, 7.4)	0	0
Fatigue	5 (3.1) (1.1, 7.4)	0	1 (2.8) (0.1, 16.2)

Note: A patient with multiple AEs is counted only once in the "at least one AE" row

CONCLUSIONS

- **Representation of diverse patient populations in clinical trials is an important consideration; additional insights are needed on treatment patterns and safety/tolerability in minority patient populations in MS clinical trials**
- **Differences in baseline comorbidities and rates of AE reporting among patients and providers may provide limitations to interpretation of a differentiated profile**
- **Siponimod safety/tolerability profile remained consistent, with no new or unexpected safety findings identified through this analysis**

DISCLOSURES: A Bar-Or has participated as a speaker in meetings sponsored by and received consulting fees and/or grant support from: Atara Biotherapeutics, Biogen Idec, Celgene/Receptos, Janssen/Actelion, MAPI, Medimmune, Merck/EMD Serono, Novartis, Roche/Genentech and Sanofi-Genzyme. **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 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. **AR Chinea** is a speaker for Sanofi-Genzyme, Biogen, Teva, Novartis, Genentech, EMD Serono, and Allergan. **G Mavrikis Cox, LA Cruz,** and **X Meng** are employees of Novartis Pharmaceuticals Corporation. **SL Cohan** has received speaking honoraria from Biogen, Bristol Myer Squibb, Novartis, Roche Genentech and Sanofi Genzyme; and serves on advisory boards or as a consultant to Biogen, EMD Serono, Novartis, and Sanofi Genzyme. Institutional research support (the Providence Brain and Spine Institute) was received from AbbVie, Adamas, Biogen, Novartis, Roche Genentech, Sage Bionetworks and Sanofi Genzyme.

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.

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