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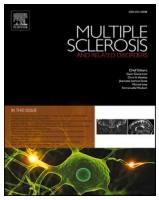

Demographics and baseline disease characteristics of Black and Hispanic patients with multiple sclerosis in the open-label, single-arm, multicenter, phase IV CHIMES trial

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ABSTRACT

Background: Black/African American patients with multiple sclerosis (BpwMS) and Hispanic/Latino patients with multiple sclerosis (HpwMS), who historically have been underrepresented in multiple sclerosis (MS) clinical trials, exhibit greater disease severity and more rapid disease progression than White patients with MS (WpwMS). The lack of diversity and inclusion in clinical trials, which may be due to barriers at the system, patient and study levels, impacts the ability to effectively assess risks, benefits and treatment responses in a generalized patient population.

Methods: CHIMES (Characterization of Ocrelizumab in Minorities With Multiple Sclerosis), an open-label, single-arm, multicenter, phase IV study of self-identified BpwMS and HpwMS aged 18–65 years with relapsing MS and an Expanded Disability Status Score (EDSS) of $\leq$5.5, was developed in collaboration with patients with MS, national advocacy groups and clinical researchers. Patients were enrolled at study centers across the US, including Puerto Rico, and 1 site in Kenya.

Results: A total of 182 patients enrolled in CHIMES: 113 (62.1%) were BpwMS, and 69 (37.9%) were HpwMS; the mean (SD) baseline EDSS score was 2.4 (1.4), and 62.6% of patients were treatment naive. Using the pooled non–BpwMS/HpwMS group in the OPERA ocrelizumab trials as a reference population, patients enrolled in CHIMES were younger, had a higher mean body mass and had a greater T2 lesion volume but similar T2 lesion number on MRI.

Abbreviations: AE, adverse event; BMI, body mass index; BpwMS, Black/African American patients with multiple sclerosis; CHIMES, Characterization of Ocrelizumab in Minorities With Multiple Sclerosis; CSF, cerebrospinal fluid; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Score; Gd, gadolinium; HpwMS, Hispanic/Latino patients with multiple sclerosis; ICF, informed consent form; ICH, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; IRB, institutional review board; ITT, intention to treat; IV, intravenous; MRI, magnetic resonance imaging; MS, multiple sclerosis; NEDA, no evidence of disease activity; PPMS, primary progressive multiple sclerosis; PRO, patient-reported outcome; RMS, relapsing multiple sclerosis; WpwMS, White patients with multiple sclerosis.

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Conclusion: BpwMS and HpwMS have been consistently underrepresented in clinical trials, limiting the understanding of disease biology and response to treatment in this population. Data from the CHIMES study revealed differences in demographics and some baseline disease characteristics and disease burden between BpwMS and HpwMS vs WpwMS. These differences could have an impact when assessing clinical outcomes in BpwMS and HpwMS.
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1. Introduction

Multiple sclerosis (MS) is a heterogenous, autoimmune, neurodegenerative, demyelinating disease of the central nervous system that results from a complex interaction between genetic factors, sex and environmental factors (Filippi et al., 2018; Hollenbach and Oksenberg, 2015). The incidence and prevalence of MS vary by race and ethnicity (Khan et al., 2015; Langer-Gould et al., 2013; Langer-Gould et al., 2022; Rivas-Rodríguez and Amezcua, 2018; Wallin et al., 2012; Wallin et al., 2004). Retrospective studies from the United States have shown that the incidence of MS is higher in Black/African American patients (10.2%−12.1%) and lower in Hispanic/Latino patients (2.9%−8.2%) compared with White patients (6.9%−9.3%) (Rivas-Rodríguez and Amezcua, 2018). The prevalence of MS is similarly high among Black/African American and White patients and lower among Hispanic/Latino patients (Langer-Gould et al., 2022).

Differences in MS clinical characteristics in Black/African American patients with MS (BpwMS) and Hispanic/Latino patients with MS (HpwMS) were previously thought to result from genetic factors; (Rivas-Rodríguez and Amezcua, 2018) however, systemic bias likely accounts for a large proportion of outcome disparities. Structural racism can lead to prejudice, stereotyping, discrimination and imbalances in power and wealth that influence social determinants of health (eg, economic stability, community, education, health and healthcare, food stability) (Amezcua et al., 2021). Together, these complex socioeconomic, environmental and cultural factors may lead to health inequities and health disparities, including greater disease severity (Amezcua and McCauley, 2020). MS disease characteristics vary among racial and ethnic groups, and differences in the demographic characteristics of patients with MS in the US have been reported (Langer-Gould et al., 2013; Wallin et al., 2004). Recent studies of prospectively acquired data and smaller, retrospective studies have shown that BpwMS and HpwMS experience greater disease severity, faster disease progression and greater eventual disease-related disability than WpwMS and are more likely to present with optic neuritis, transverse myelitis (in BpwMS) or cerebellar dysfunction (Khan et al., 2015; Amezcua et al., 2017; Ventura et al., 2017; Cree et al., 2009; Naismith et al., 2006; Gray-Roncal et al., 2021; Vasileiou et al., 2021). In addition, age at death due to MS is lower in non-Hispanic BpwMS than in non-Hispanic WpwMS (Amezcua et al., 2018). Potential differences in MS disease characteristics in BpwMS from North America and BpwMS from Africa should also be considered since the extent and experience of systematic bias may differ (Jamal et al., 2021; Kioy, 2001).

BpwMS and HpwMS historically have had low enrollment in clinical trials, including trials of disease-modifying therapies (DMTs) for the treatment of MS (Langer-Gould et al., 2013; Avasarala, 2014; Geller et al., 2018; Rae-Grant et al., 2018; Robers et al., 2020). Barriers to clinical trial participation for BpwMS and HpwMS include physician reluctance to provide an accurate MS diagnosis, lack of outreach to make patients in these communities aware of the opportunity to participate, geographic location of the study, type of institute conducting the study, insurance requirements, strict inclusion and exclusion criteria, patient financial and logistical burden of frequent study visits and patient distrust of clinical research (Clark et al., 2019; Schmotzer, 2012; Cree et al., 2004). In addition, implicit bias based on racial stereotypes and systemic racism, as well as lack of racial and cultural sensitivity, may affect which patients are offered the opportunity to participate in clinical trials (Hamel et al., 2016). Underrepresentation of diverse racial and ethnic groups in clinical trials limits the understanding of MS and hinders the collection of accurate safety and efficacy data related to therapies across all patient populations (Khan et al., 2015; Telesford et al., 2020). To enhance clinical trial participation in underrepresented populations and to better understand the relationship between race and ethnicity (as socially constructed) and response to DMTs, these barriers need to be considered in the inception of trial design (Cree et al., 2004).

Ocrelizumab is a humanized monoclonal antibody DMT that selectively depletes CD20 B cells while preserving pre-existing humoral immunity. It has shown significant and sustained benefits in patients with relapsing MS (RMS) (Hauser et al., 2017; Hauser et al., 2020) and primary progressive MS (PPMS) (Montalban et al., 2017; Wolinsky et al., 2020). However, participation of BpwMS and HpwMS in the pivotal ocrelizumab OPERA and ORATORIO trials was <10%, which is consistent with other MS DMT trials (Cree et al., 2011; Cascione et al., 2018; Okai et al., 2019). Study of ocrelizumab in BpwMS is warranted, as these patients may have greater B-cell–mediated pathology, different B-cell depletion/repletion biology and a higher IgG index compared with WpwMS (Khan et al., 2015; Rinker et al., 2007). Additionally, a recent retrospective study of samples from patients who received ocrelizumab found that BpwMS had significantly more rapid repletion of CD19+ B cells at 6–12 months after ocrelizumab treatment compared with WpwMS (Saidenberg et al., 2022). In a post hoc analysis of a small number of patients of African descent with RMS in the OPERA I and II studies, ocrelizumab treatment suggested benefits consistent with those observed in the complete OPERA cohorts, but this type of post hoc analysis has many limitations (Cree et al., 2021). CHIMES (Characterization of Ocrelizumab in Minorities With Multiple Sclerosis)—a prospective, open-label, single-arm, phase IV study—is the first dedicated MS study in BpwMS and HpwMS to investigate the efficacy and safety of ocrelizumab.

2. Material and methods

2.1. Trial design

This open-label, single-arm, multicenter, phase IV study (NCT04377555) was conducted at centers in the mainland US, Puerto Rico and Kenya. The latter was included to promote inclusive enrollment of BpwMS, expand understanding of MS biology in an African population and assess the impact of genetic and environmental factors in BpwMS from an African nation that has a much lower reported incidence of MS than the US (Kioy, 2001; Heine et al., 2020). CHIMES was developed in collaboration with patients with MS, patient advocacy groups (Accelerated Cure Project and Multiple Sclerosis Association of America), industry leaders and clinical investigators to tailor the study design to ensure participation of BpwMS and HpwMS. Study sites included academic institutions, hospitals, outpatient clinics, community centers and provider practices. To promote inclusive enrollment, study-related patient materials (informed consent forms [ICFs] and patient-reported outcomes [PROs]) were available in multiple languages (English, Spanish and Swahili); patient materials were reviewed by an advisory panel to ensure understanding and cultural appropriateness; flexible scheduling options were available based on population needs; and compensation for loss of earnings, childcare reimbursement, accommodation, reimbursement for travel and meals and utilization of

ride-sharing companies for patient transportation were offered to participants.

Ocrelizumab 600 mg was administered every 24 weeks, with the first dose administered as two 300-mg intravenous (IV) infusions given 14 days apart; for subsequent doses, ocrelizumab was administered as a single 600-mg IV infusion consistent with the US prescribing information (Fig. 1) (Genentech, Inc. 2017).

Patients were evaluated at baseline and followed up for 1 year. Assessments included clinical evaluations, PROs, magnetic resonance imaging (MRI; at Weeks 24 and 48) and laboratory assessments. Patients can elect to continue the study on a 3-year extension. In this extension period, ocrelizumab will be administered at Weeks 48, 72, 96, 120, 144 and 168, with a final MRI performed at Week 192 (assessed yearly after Week 48). Those who complete their infusion at Week 24 (main study only) and at Week 168 (3-year extension) or who discontinue treatment early will enter the safety follow-up period and will return for a final assessment 24 weeks after the last dose. The end of the study is expected to occur 48 months after the last patient is enrolled. The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 7 years.

This study was conducted in full conformance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research was conducted, whichever afforded greater protection to the individual. The study complied with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). This protocol, the ICFs, any information to be given to patients and relevant supporting information were approved by a central institutional review board (IRB) and local IRBs for the US sites and an ethics committee for the Kenya site before study initiation. The study website, as well as ICFs and written materials for patients, were available in English, Spanish and Swahili. All patient materials were reviewed by an MS patient advocacy group to ensure consistency, patient understanding and patient centricity.

2.2. Patient population

Full inclusion and exclusion criteria are listed in **Supplemental Table 1**. Self-identified Black/African American and Hispanic/Latino patients aged 18–65 years with a diagnosis of RMS in accordance with the 2017 revised McDonald criteria (Thompson et al., 2018) and an Expanded Disability Status Scale (EDSS) score of ≤5.5 at screening were eligible for enrollment. Each patient's treating neurologist was required to make an independent medical assessment and decision to initiate ocrelizumab treatment as the most appropriate standard of care per the most current US prescribing information (Genentech, Inc. 2017).

Patients were treatment naive or switching from treatment with ≤2 prior DMTs due to lack of efficacy (**Supplemental Table 1**). For patients switching from dimethyl fumarate, diroximel fumarate, fingolimod, ozanimod, siponimod or teriflunomide, a minimum treatment-free period of 1 month was required before the baseline screening. For patients switching from natalizumab, a washout period of ≥12 weeks before enrollment was required. For patients switching from teriflunomide, an accelerated elimination procedure (per the product label) was performed.

Key exclusion criteria included any medical or neurological condition that in the opinion of the investigator posed a risk for the patient to participate in the study; systemic corticosteroid therapy use ≤4 weeks before enrollment; previous use of IV immunoglobulins or plasmapheresis ≤6 weeks before enrollment or chronic treatment with systemic corticosteroids, B-cell–targeted therapies or immunosuppressants; and inability to tolerate the MRI procedure.

Patients who did not initially meet the criteria for participation in this study (screen failure) qualified for 2 additional rescreening opportunities (for a total of 3 screenings per participant) at the investigator's discretion.

2.3. Planned outcome measures

The primary endpoint is the proportion of patients with no evidence of disease activity (NEDA) during a 48-week period of treatment with ocrelizumab (full list of endpoints in **Supplemental Table 2**). Key secondary endpoints include the proportion of patients free of a protocol-defined event during a 24-week period; confirmed disability progression at Weeks 24 and 48; and serum biomarkers, including neurofilament light protein levels, B-cell subpopulations and other markers of inflammation.

Exploratory outcomes include imaging (volume/area change of whole brain, cervical spine and other structures/regions; changes in gadolinium [Gd]-enhancing lesions and T2 lesion counts; change in T1 nonenhancing lesion volumes; change in T2 lesion volume; changes in slowly expanding lesion count and volume); and genetic analysis.

Safety endpoints include the nature, frequency, severity and timing of adverse events (AEs), as well as vital signs, physical findings and clinical laboratory results during and following ocrelizumab administration. Grade 3–5 AEs, serious AEs, AEs leading to treatment discontinuation, time to withdrawal from the study due to an AE, AEs leading to infusion adjustment and treatment-related AEs will be summarized.

2.4. Planned statistical analyses

It was estimated that 38% of BpwMS would be free of protocol-defined events during the 48 weeks, based on the CHORDS study (NCT02637856 (Weinstock-Guttman et al., 2022). Assuming the same expected proportion for HpwMS, this study plans to enroll approximately 182 patients. This sample size provides a 95% confidence interval of 30.2%−46.3% for the proportion of patients with NEDA, using the exact Clopper-Pearson method.

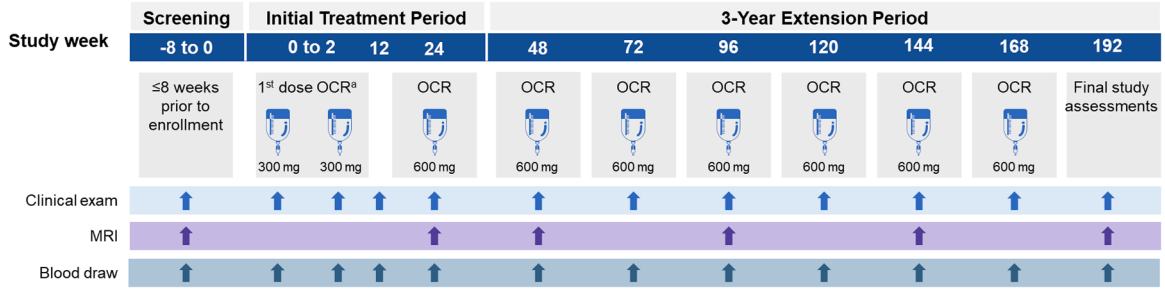

Fig. 1. Study design timeline.
MRI, magnetic resonance imaging; OCR, ocrelizumab.
[a] The first OCR infusion was administered as two 300-mg doses 14 days apart.

For continuous variables, the mean, median, standard deviation, 25th and 75th percentiles, minimum and maximum are provided. For categorical variables, number and percentage in each category are displayed. The statistical summaries presented here for baseline demographic and clinical characteristics are descriptive and hypothesis generating, and no direct statistical comparisons were made to other clinical trials. The pivotal OPERA clinical trials (Hauser et al., 2017) were used as a benchmark reference to further understand differences between BpwMS, HpwMS and WpwMS.

3. Results

3.1. Patient demographics at baseline

Overall, 182 patients have been enrolled in the CHIMES clinical study: 113 Black/African American patients (62.1%) and 69 Hispanic/Latino patients (37.9%) (Table 1).

When referencing the non–Black/Hispanic pooled population from the OPERA trial as a benchmark (Hauser et al., 2017), younger age and higher body mass index (BMI) were observed in BpwMS and HpwMS in CHIMES. The mean (SD) age of the intention-to-treat (ITT) population in CHIMES and OPERA was 35.5 (10.5) and 37.4 (9.1) years, and BMI was 31.0 (7.4) and 25.75 (5.64) kg/m^2, respectively. Most patients in both populations were female (CHIMES, 72.0%; OPERA, 65.7%). Among HpwMS, 63 identified their race as White (91.3%), 3 Black (4.3%), 2 American Indian/Alaska Native (2.9%) and 1 reported multiple races (1.4%). The most common comorbidities reported by BpwMS and HpwMS were anxiety (19%), depression (18%), hypertension (18%), asthma (15%), migraine (14%) and fatigue (11%) (**Supplemental Table 3**).

Table 1
Patient demographics and baseline characteristics.

Characteristic[a]	CHIMES Black/ African American patients (n = 113)	Hispanic/ Latino patients (n = 69)	All patients (N = 182)	Pooled OPERA non–Black/ Hispanic patients (N = 1378)
Age, mean (SD), years	36.3 (10.4)	34.2 (10.5)	35.5 (10.5)	37.4 (9.1)
Age group, years				
≤40	76 (67.3)	54 (78.3)	130 (71.4)	1074 (77.9)[b]
>40	37 (32.7)	15 (21.7)	52 (28.6)	304 (22.1)[c]
Female	87 (77.0)	44 (63.8)	131 (72.0)	906 (65.7)
Ethnicity				
Hispanic	–	69 (100)	69 (37.9)	0
Not Hispanic	110 (97.3)	–	110 (60.4)	1261 (91.5)
Unknown	3 (2.7)	–	3 (1.6)	117 (8.5)
Race				
American Indian or Alaska Native	–	2 (2.9)	2 (1.1)	4 (0.3)
Black	113 (100)	3 (4.3)	116 (63.7)	0
White	–	63 (91.3)	63 (34.6)	1351 (98.0)
Multiple	–	1 (1.4)	1 (0.5)	6 (0.4)
Country				
Kenya	9 (8.0)	1 (1.4)	10 (5.5)	–
United States	104 (92.0)	68 (98.6)	172 (94.5)	319 (23.1%)
BMI, mean (SD) [n], kg/m^2	31.6 (8.0) [112]	29.9 (6.3) [69]	31.0 (7.4) [181]	26.0 (5.9) [1365]

BMI, body mass index.
[a] Represented as n (%) unless otherwise stated; [n] represents the number of patients with data available.
[b] Age group ≤45 years.
[c] Age group >45 years.

3.2. Baseline MS disease history and prior DMT use

The ITT population in this study had a shorter disease duration and time to diagnosis than the pooled OPERA trial reference population, with a mean (SD) time since MS symptom onset of 4.9 (5.6) years in CHIMES and 6.8 (6.3) years in OPERA (Table 2).

Time since RMS diagnosis was 2.9 (4.5) years in CHIMES and 4.1 (5.0) years in OPERA. Baseline mean (SD) EDSS score in BpwMS and HpwMS in CHIMES was 2.4 (1.4), and 62.6% were treatment naive. In OPERA, baseline mean (SD) EDSS was 2.8 (1.3), and 74.2% were treatment naive.

3.3. Brain MRI results at baseline

The mean (SD) number of T1 Gd-enhancing lesions in the ITT population in this study was 1.9 (4.3), which is higher than that in the referenced OPERA population (1.7 [4.3]) (Table 3).

A higher T2 lesion burden was observed in the CHIMES ITT population when using the OPERA population as a reference: the overall population in CHIMES had a mean (SD) T2 lesion volume of 18.9 (18.1) cm^3, whereas the reference OPERA population had a T2 lesion volume of 10.2 (12.9) cm^3. The mean (SD) T2 lesion number was similar between all patients in CHIMES (49.3 [31.6]) and the OPERA reference population (49.6 [38.0]). Within the CHIMES population, BpwMS and HpwMS had a similar mean number of T2 lesions; a higher T2 lesion volume was observed in BpwMS.

4. Discussion

The CHIMES trial was developed in collaboration with patients with MS, patient advocacy groups, investigators and the pharmaceutical industry and is the first prospective trial to address the historical lack of racial/ethnic representativeness in MS clinical trials and to focus on meeting the needs of BpwMS and HpwMS. This initial report from the CHIMES trial notes differences in demographic and baseline disease characteristics in BpwMS and HpwMS using the patient population of the pivotal OPERA studies as a reference, (Hauser et al., 2017; Hauser

Table 2
Baseline MS clinical characteristics.

Characteristic[a]	CHIMES Black/ African American patients (n = 113)	Hispanic/ Latino patients (n = 69)	All patients (N = 182)	Pooled OPERA non–Black/ Hispanic patients (N = 1378)
Time since symptom onset, years	5.15 (5.71)	4.60 (5.52)	4.94 (5.63)	6.76 (6.30)
Time since RMS diagnosis, years	2.87 (4.62)	2.91 (4.43)	2.89 (4.54)	4.08 (5.04)
Baseline EDSS	2.58 (1.41)	2.18 (1.25)	2.43 (1.36)	2.81 (1.28)[b]
No. of relapses in the past 24 months	0.77 (0.58)	0.64 (0.51)	0.72 (0.56)	–
Prior DMT use, n (%)	41 (36.3)	27 (39.1)	68 (37.4)	356 (25.8)
Time from end of last DMT to OCR initiation, months	10.20 (17.96)	7.23 (11.03)	9.02 (15.55)	–

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; OCR, ocrelizumab; RMS, relapsing MS.
[a] Represented as mean (SD) unless otherwise stated.
[b] n = 137.

Table 3
Brain MRI assessments at baseline.

Characteristic	CHIMES Black/African American patients ($n = 113$)	Hispanic/ Latino patients ($n = 69$)	All patients ($N = 182$)	Pooled OPERA non–Black/ Hispanic patients ($N = 1378$)
T1 Gd-enhancing lesions				
n	111	68	179	1369
Mean (SD)	2.3 (5.1)	1.2 (2.5)	1.9 (4.3)	1.7 (4.3)
T2 lesions				
n	113	68	181	1373
Number of lesions, mean (SD)	49.8 (32.9)	48.4 (29.6)	49.3 (31.6)	49.6 (38.0)
Volume, mean (SD), cm^3	21.4 (20.7)	14.9 (11.9)	18.9 (18.1)	10.2 (12.9)
Normalized brain volume				
n	112	68	180	1368
Mean (SD), cm^3	1506.8 (94.2)	1533.7 (95.5)	1516.9 (95.3)	1501.6 (87.8)

Gd, gadolinium.

et al., 2020), which predominately included WpwMS. BpwMS and HpwMS enrolled in CHIMES tended to be younger and to have a higher BMI than the non–Black/Hispanic pooled OPERA population. The most common comorbidities reported by BpwMS and HpwMS in the CHIMES study were anxiety, depression, hypertension, asthma, migraine and fatigue (**Supplemental Table 3**). A systematic review of 249 articles from a global MS population found that the most prevalent comorbidities are depression (23.7%), anxiety (21.9%), hypertension (18.6%), hypercholesterolemia (10.9%) and chronic lung disease (10%) (Marrie et al., 2015). Additionally, the CHIMES population had a shorter disease duration and time to diagnosis and greater T2 lesion burden than the OPERA population. Findings from other studies, most of which are retrospective, on disease duration and time to diagnosis for Black/-African American and Hispanic/Latino persons compared with White persons are mixed (Khan et al., 2015; Amezcua et al., 2021; Amezcua et al., 2011) but may reflect inequities in access to MS healthcare. Compared with White patients, longer diagnostic delays among Hispanic/Latino patients in a public system (Marrie et al., 2015) and longer time to a referral center for Black/African American patients (Kaufman et al., 2003) have been reported; diagnostic delays are similar between Asian, Black/African American, Hispanic/Latino and White individuals with equal healthcare access in a large, managed healthcare system (Langer-Gould et al., 2013; Amezcua et al., 2021). These initial findings provide evidence of the importance of evaluating patient populations that are historically underrepresented in clinical studies of MS. How these clinical differences may affect outcomes is currently unclear.

Black/African American and Hispanic/Latino persons collectively comprise approximately one-third of the US population (US Census Bureau 2021), yet only a small fraction (Black/African American, 2%−16%; Hispanic/Latino, 7%−7.5%) have been enrolled in major clinical trials in MS (Robers et al., 2020). A systematic review of 136 published articles on MS in underrepresented populations concluded that BpwMS have a more severe clinical course and worse outcomes than WpwMS, including later age at onset, higher disease severity scores, more frequent relapses, faster disease progression, greater T1 and T2 lesion volumes on MRI and higher cerebrospinal fluid (CSF) oligoclonal bands and CSF immunoglobulin index (Khan et al., 2015). The same study showed that HpwMS have a higher frequency of optic neuritis and transverse myelitis compared with WpwMS.

Despite evidence of greater disease severity and faster disease progression in BpwMS and HpwMS, which suggests that B-cell and antibody biology may be driving disease in this population (Khan et al., 2015; Amezcua et al., 2017; Ventura et al., 2017), the overall risk/benefit analysis for many therapies is based on data generated in predominantly White cohorts.

The prospective phase IV CHIMES trial seeks to explore the underlying mechanisms of disease and pathophysiology of MS exclusively in BpwMS and HpwMS before and during treatment with ocrelizumab, an anti-CD20 antibody that depletes B cells. Ocrelizumab was chosen because BpwMS may have greater B-cell–mediated pathology (Khan et al., 2015) and a higher frequency of antibody-secreting B cells than WpwMS (Telesford et al., 2020). This study was conducted to further our understanding of MS biology in underrepresented populations and address the lack of past representation. Results from the study will also help to understand the role of social determinants of health in the recruitment and retention of these populations. Additionally, this study will help us to understand if the observed differences in MS clinical phenotypes result from specific demographics and social barriers (PROs related to social determinants of health in **Supplemental Table 2**).

Previous study designs in MS clinical research have not prioritized solutions to the historical, cultural and socioeconomic barriers to clinical trial enrollment that BpwMS and HpwMS face. In the CHIMES North American sites, 20 patients used ICFs in Spanish, and 16 used PROs in Spanish; all patients in Kenya used ICFs and PROs in English. Of 182 patients, 45 (24.7%) used RideHealth patient transportation services, and 25 of those patients have continued use within the past 6 months. The tailored inclusion and exclusion criteria and initiatives to overcome circumstantial barriers to recruitment that were applied in CHIMES led to successful enrollment rates that are equal to or better than those in other clinical studies in MS; this is notable since study enrollment has occurred during the COVID-19 pandemic, when clinical trial recruitment has universally been a challenge (Mitchell et al., 2020). Tailoring clinical research to the needs of an ethnically diverse population of patients, especially those who have been historically underrepresented in clinical trials, is vital to increase trial inclusivity and access to beneficial therapies.

Increasing diversity and inclusion in clinical research requires a deeper understanding of the communities we serve. A recent study that evaluated the perceptions of patients with MS in a multiethnic cohort found that barriers to MS research participation were more common among BpwMS and HpwMS. Hispanic/Latino patients were more concerned about receiving poor-quality medical care (91%), being taken advantage of by the research team (81%) and the risk of losing their job or legal status (62%) than non-Hispanic/Latino respondents, regardless of race (79%, 72% and 50%, respectively) (Pimentel Maldonado et al., 2021). Black respondents were also more concerned about being taken advantage of by the research team (83%) compared with Hispanic/Latino and non-Hispanic/Latino White respondents (71%) (Pimentel Maldonado et al., 2021). In addition, previous trials have been primarily conducted at large academic centers; this must be addressed by increasing participation at nontraditional trial sites, including rural areas, public hospitals and community-based institutions, which in many cases are underresourced and provide care for a greater proportion of underrepresented racial and ethnic minority patients and those without access to private insurance.

The CHIMES trial was specifically designed to address barriers to trial inclusion in BpwMS and HpwMS, including (1) selecting study sites that serve large underrepresented racial and ethnic communities; (2) broadening eligibility requirements; (3) using the appropriate baseline laboratory values for the intended patient population; (4) providing written patient materials and study websites in English, Spanish and Swahili and ensuring linguistic and cultural sensitivity in all patient materials; and (5) widening the screening duration to 8 weeks and using visit windows of ±14 days to allow more schedule flexibility. In addition, the CHIMES study includes proactive measures to promote retention and decrease the burden on patients enrolled in the trial, including a stipend/compensation for loss of earnings, childcare reimbursement, accommodation, reimbursement for travel and meals and ride-share

coverage for patient transportation. Future trials should focus on optimizing study visits and testing to accommodate for patient and site availability and to make studies more attractive to patients and investigators.

5. Conclusion

CHIMES is investigating the efficacy and safety of ocrelizumab in BpwMS and HpwMS. Findings from the CHIMES study are expected to improve the current understanding of MS in BpwMS and HpwMS, with the ultimate goal of accumulating high-quality prospective data and contributing to improving the standard of care in these traditionally underserved populations. This study may also help dispel commonly held beliefs about disadvantages of including these patient populations in clinical studies by providing evidence that study design methodologies that consider the needs of specific populations can enhance inclusive clinical research without compromising study deliverables.

CRediT authorship contribution statement

MJ Williams: Conceptualization, Methodology, Writing – Review & Editing. **AF Okai:** Conceptualization, Investigation, Methodology, Writing – Review & Editing. **AH Cross:** Investigation, Writing – Review and Editing. **NL Monson:** Conceptualization, Supervision and Review and Editing of the manuscript. **T Vartanian:** Conceptualization, Investigation, Methodology, Resources, Writing – Review & Editing. **BW Thrower:** Writing – Review & Editing. **AT Reder:** Conceptualization, Investigation, Writing – Original Draft Preparation, Writing – Review & Editing. **JB English:** Investigation, Writing - Review & Editing. **GF Wu:** Conceptualization, Methodology, Writing – Review & Editing. **E Bernitsas:** Conceptualization, Investigation, Supervision and Review and Editing of the manuscript. **S Yap:** Project Administration and Resources. **J Ndrio:** Investigation, Writing –Original Draft Preparation, Writing – Review & Editing. **J Pei:** Statistical analysis, Methodology, Data interpretation, Conclusion, Review & Editing of the manuscript. **EM Mowry:** Investigation, Writing – Review & Editing. **F Magrini:** Investigation and Supervision. **J Acosta:** Conceptualization, Investigation, Supervision and Review & Editing of the manuscript. **L Amezcua:** Conceptualization, interpretation of data, review & editing for important intellectual content of the manuscript.

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Data sharing statement

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/innovation/process/clinical-trials/data-sharing/).

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

MJ Williams has received consulting fees from Alexion, Biogen Idec, Bristol Myers Squibb, EMD Serono, Genentech, Inc., Janssen, Novartis, Sanofi Genzyme and TG Therapeutics and serves on speakers bureaus for Biogen, Bristol Myers Squibb, EMD Serono, Janssen, Genentech and TG Therapeutics. **AF Okai** has received consulting fees from Alexion, Biogen, Bristol Myers Squibb, EMD Serono, Greenwich Biosciences, Novartis, Roche, Genentech, Inc., Sanofi Genzyme and TG Therapeutics and serves on speakers bureaus for Alexion, Biogen, EMD Serono and Sanofi Genzyme. **AH Cross** has, in the past year, received fees or honoraria for consulting for Biogen, EMD Serono, F. Hoffmann-La Roche Ltd, Genentech, Inc., Horizon Therapeutics, Janssen Pharmaceuticals, Jazz Pharmaceuticals, Novartis and TG Therapeutics. **NL Monson** has received consulting fees from EMD Serono and Genentech, Inc.; is a founder of GenRab; and holds patent US 8,394,583 B2 on MSPreciseTM, a diagnostic tool for predicting conversion to multiple sclerosis. **T Vartanian** reports personal compensation for consulting, speaking or serving on steering committees or advisory boards for Biogen Idec, Novartis, Genentech, Inc., EMD Serono, the National Multiple Sclerosis Society and the National Institutes of Health. **BW Thrower** serves on speakers bureaus for Biogen, Horizon Therapeutics, Genentech, Inc. and Bristol Myers Squibb. **AT Reder** has received consulting fees from Bayer, Biogen, F. Hoffmann-La Roche Ltd, Genentech, Inc., Merck Serono, Novartis and TG Therapeutics; is an editor for MedLink; and has received unrestricted research grant support from Bayer, Biogen, F. Hoffmann-La Roche Ltd, Genentech, Inc., Mallinckrodt, Merck Serono and Novartis. **JB English** has received consulting fees from Biogen, EMD Serono, Sanofi Genzyme, Bristol Myers Squibb and IT Therapeutics, contracted research support from Biogen, EMD Serono, Novartis and Genentech, Inc. and serves on speakers bureaus for Biogen, EMD Serono, Sanofi Genzyme and Bristol Myers Squibb. **GF Wu** has received honoraria for consulting from Novartis and Genentech, Inc. and research funding from Biogen, EMD Serono and F. Hoffmann-La Roche Ltd. **E Bernitsas** has received grant support from F. Hoffmann-La Roche Ltd, Genentech, Inc., Sanofi Genzyme, MedImmune, Novartis, EMD Merck Serono, Chugai, Mallinckrodt and TG Therapeutics; is a Chief Editor for the "Brain Sciences" Neuroimaging section; and has received consulting fees/honoraria from Biogen, Merck Serono, Bristol Myers Squibb, Horizon, Janssen Pharmaceuticals and Genentech, Inc. **S Yap** is an employee of Genentech, Inc., and a shareholder of F. Hoffmann-La Roche Ltd. **J Ndrio** is an employee of Genentech, Inc., and a shareholder of F. Hoffmann-La Roche Ltd. **J Pei** is an employee of Genentech, Inc., and a shareholder of F. Hoffmann-La Roche Ltd. **EM Mowry** has received grant support from Biogen, Genentech and Teva and royalties for editorial duties from UpToDate and has participated in data safety monitoring boards for the NIAID and TRIM trials. **F Magrini** was an employee of Genentech, Inc., at the time of the study. **J Acosta** is an employee of Genentech, Inc., and a shareholder of F. Hoffmann-La Roche Ltd. **L Amezcua** reports personal compensation for consulting or serving on steering committees or advisory boards for Biogen Idec, Novartis, Genentech, Inc. and EMD Serono and has received research support from the National Multiple Sclerosis Society, NIH NINDS and Biogen.

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Supplementary materials

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