An Observational Study to Assess Brain MRI Change and Disease Progression in Multiple Sclerosis Clinical Practice—The MS-MRIUS Study

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ABSTRACT

BACKGROUND & PURPOSE: To describe methodology, interim baseline, and longitudinal magnetic resonance imaging (MRI) acquisition parameter characteristics of the multiple sclerosis clinical outcome and MRI in the United States (MS-MRIUS).

MATERIAL & METHODS: The MS-MRIUS is an ongoing longitudinal and retrospective study of MS patients on fingolimod. Clinical and brain MRI image scan data were collected from 600 patients across 33 MS centers in the United States. MRI brain outcomes included change in whole-brain volume, lateral ventricle volume, T2- and T1-lesion volumes, and new/enlarging T2 and gadolinium-enhancing lesions.

RESULTS: Interim baseline and longitudinal MRI acquisition parameters results are presented for 252 patients. Mean age was 44 years and 81% were female. Forty percent of scans had 3-dimensional (3D) T1 sequence in the preindex period, increasing to 50% in the postindex period. Use of 2-dimensional (2D) T1 sequence decreased over time from 85% in the preindex period to 65% in the postindex. About 95% of the scans with FLAIR and 2D T1-WI were considered acceptable or good quality compared to 99–100% with 3D T1-WI. There were notable changes in MRI hardware, software, and coil (39.5% in preindex to index and 50% in index to postindex). MRI sequence parameters (orientation, thickness, or protocol) differed for 36%, 29%, and 20% of index/postindex scans for FLAIR, 2D T1-WI, and 3D T1-WI, respectively.

CONCLUSIONS: The MS-MRIUS study linked the clinical and brain MRI outcomes into an integrated database to create a cohort of fingolimod patients in real-world practice. Variability was observed in MRI acquisition protocols overtime.

Keywords: Multiple sclerosis, fingolimod (Gilenya®), MRI, brain volume, lesion.

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Introduction

Multiple sclerosis (MS) is primarily a demyelinating disease of the central nervous system. Neurodegeneration is observed from a young age and leads to irreversible neurological impairment.[1] Among the magnetic resonance imaging (MRI) measurements that have become available to research labs in the last 10 years, the quantification of brain atrophy, defined by decrease in brain volume, appears to be one of the most important with regard to providing information on the extent of neurodegeneration during the course of the disease.[2] It has become increasingly clear that MS patients experience a significant and progressive decrease in brain volume as compared to healthy controls, especially affecting the gray matter (GM).[3–5] Loss of brain volume plays a particularly prominent role in cognitive and physical decline in MS.[6–8]

In clinical trials and single center academic studies, disease-modifying therapies (DMTs) have demonstrated reduction in the rate of brain atrophy, lesion burden, and disability progression as well as improvement in relapse rate in relapsing MS patients (RRMS).[2,9–13] More importantly, it is not clear whether the results will be similar in routine clinical practice where lesions may not be systematically analyzed and new/enlarging T2 lesions are often missed.

In routine clinical practice, brain volume can be measured using cross-sectional or longitudinal MRI techniques on 3-dimensional (3D) and 2-dimensional (2D) T1-weighted images (WIs).[14,15] Cross-sectional methods, such as brain parenchymal fraction (BPF) and structural image evaluation, using normalization, of atrophy–cross-sectional (SIENAX) measure whole-brain (WB) volume at a single time point using an MRI scan. SIENAX can also provide information on global or regional tissue volumes.[16,17] Longitudinal methods, eg, structural image evaluation, using normalization, of atrophy (SIENA) measure change in WB volume over time from images acquired at two different time points. BPF and SIENA are the two most commonly used techniques for measuring brain volume in clinical trials.[10] A recent extension of the SIENA approach, named VIENA, allows for the estimation of ventricular volume change.[18] While the most appropriate MRI sequence for measurement of brain volume is high-resolution 3D T1-WI that allows for the acquisition of 1 mm^3 isotropic voxels in less than 5 minutes using parallel imaging techniques on modern 1.5 or 3 T scanners, it is proposed only as an optional sequence in recent MAGNIMS[19] and Consortium of MS Centers (CMSC)[20] consensus MRI acquisition protocol guidelines. This limits the widespread availability of this sequence within the clinical routine at this time. However, both MAGNIMS and CMSC consensus MRI acquisition protocol guidelines[19,20] propose the mandatory use of 3D or 2D fluid-attenuated inversion recovery (FLAIR) with 1-3-mm-thick gapless slices, for baseline and follow-up evaluation of MS patients, which will likely increase the availability of this sequence in real-world clinical practice. Neurological Software Tool for REliable Atrophy Measurement (NeuroSTREAM), a research-based fully automated software, can also be used to compute cross-sectional and longitudinal ventricular cerebrospinal fluid volumes on low- and high-resolution 2D and 3D FLAIR and T1-WI in MS patients.[21,22]

Here, we describe the design and setup of the multicenter, observational, longitudinal, and retrospective chart review MS clinical outcome and MRI in the United States (MS-MRIUS) study. MS-MRIUS will create a structured and integrated electronic clinical and MRI research database to help understand disease progression in relapsing MS patients with respect to evolution of brain volume changes, lesion burden, and clinical outcomes, including relapse rate and Expanded Disability Status Scale (EDSS) score. The MS-MRIUS study will be the first large-scale multicenter observational study to link quantitative MRI metrics and clinical outcomes among MS patients across the United States. The primary objectives are:

1. To describe whether retrospective, multicenter collection of MRI scan data collected in real-world clinical practice can be utilized to observe brain volume and brain lesion activity among patients initiated on fingolimod.
2. To describe brain volume changes and presence of brain lesions before and after initiation of fingolimod, and assess whether changes posttherapy initiation are similar to those observed in clinical trials.
3. To assess whether changes in brain volume are associated with clinical outcomes such as relapses, mobility measures, and changes in EDSS scores among patients initiated on fingolimod.

Secondary objectives include:

1. To assess the proportion of patients who exhibit no evidence of disease activity (NEDA): A composite measure of (1) absence of relapses AND (2) no new or enlarging T2 or T1 gadolinium-enhancing lesions on MRI scans over the follow-up period.
2. To compare changes in brain volume by sequence type, specifically 2D T1 versus 3D T1-WI for WB volume and 2D FLAIR versus 3D T1 versus 2D T1-WI for lateral ventricular volume (LVV).
3. To investigate impact of hardware, software, and protocol changes on MRI measures over the follow-up.
4. To assess whether the association with clinical outcomes such as relapses, mobility measures, and EDSS scores varies by scan type and hardware, software, and protocol changes used in the analyses.

This paper describes study methodology, interim baseline, and longitudinal MRI acquisition parameters characteristics.

Material and Methods

Study Design

The MS-MRIUS study is a multicenter, longitudinal, retrospective, chart review of MS patients treated with fingolimod (Gilenya®) in clinical routine practice. The retrospective clinical information and brain MRI image data were collected from participating MS centers across the United States and integrated into a central research database (Fig 1). All data to be integrated into the database have already been collected by physicians at the centers as part of their routine clinical practice; this is thus a noninterventional and retrospective cohort study.

Study Population

Retrospective data were collected from 600 fingolimod patients with MS across 33 MS centers in the United States. For each patient, clinical information was collected for a 48-month time period, including 12–24 month's data in the preindex period and 12–24 month's data in the postindex period (see Fig 2). The index date was defined as the date the patient first received treatment with fingolimod.

Inclusion criteria included RRMS patients, received fingolimod for at least 28 days and 18–65 years of age at index date. Additionally, patients needed to have brain MRI scans performed within the following windows: (1) index scan performed between 6 months before and 1 month after fingolimod initiation and (2) postindex scan performed 9 to 24 months after initiation of fingolimod. A preindex scan performed 9 to 24 months before fingolimod initiation was desired but was not a required inclusion criterion (see Fig 2).

Exclusion criteria included prior use of fingolimod or natalizumab. Additionally, any patients who participated in an interventional trial during the study period, as well as patients with other neurological diseases that affect the central nervous system and those with history of alcohol or substance abuse were excluded.

Center Identification and Selection

About 141 centers in the United States were asked to participate in the study. Centers interested in participation were required to

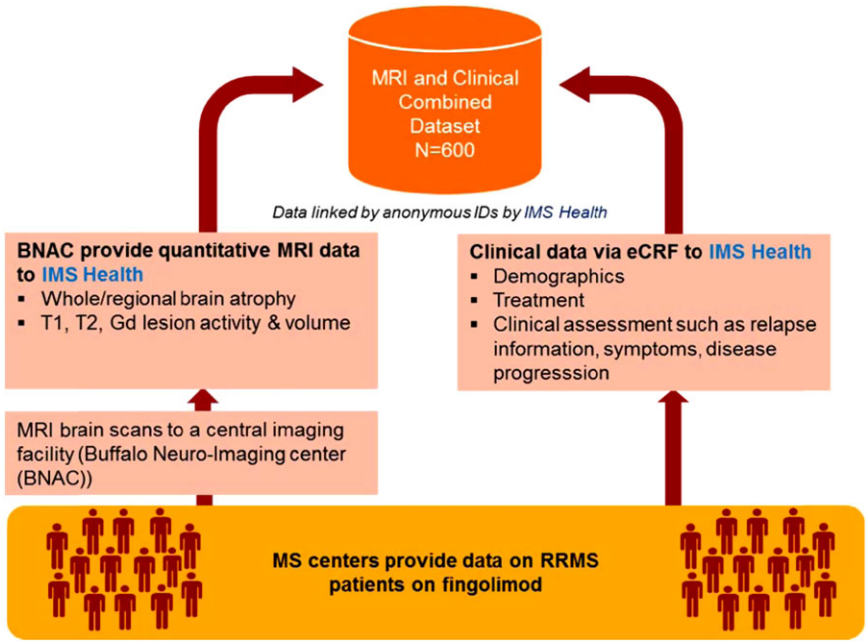


Fig 1. Diagrammatic representation of study approach. Gd = gadolinium; MS = multiple sclerosis; MRI = magnetic resonance imaging; eCRF = electronic Case Report Form; RRMS = relapsing-remitting multiple sclerosis.

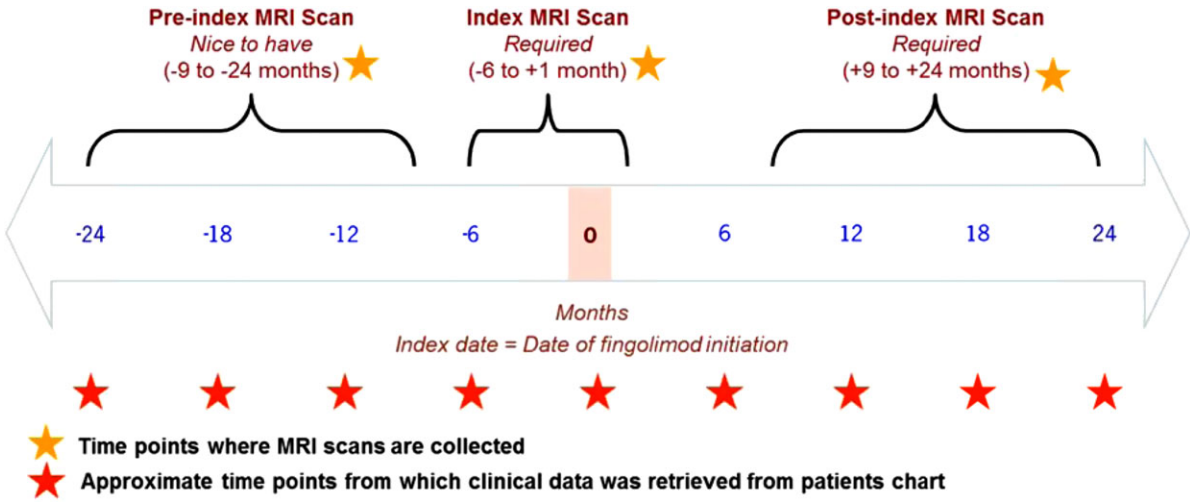


Fig 2. Study design.

fill out a site feasibility survey (SFS). The SFS assessed site ability to provide data, resource availability, scanner strength, and the number of scanning centers used by the sites. Additionally, sites were required to send 2–6 sample scans of brain MRI images to assess scans quality to a central imaging center–the Buffalo Neuroimaging Analysis Center (BNAC), University of Buffalo, Buffalo, NY. The BNAC is a specialized neuroimaging center with experience in qualitative and quantitative analyses of MRI scans. Sites that met scan quality standards and had resource availability were then enrolled into the study.

Data Collection Procedure

Participating centers identified patients who met the inclusion and exclusion criteria of the study and provided anonymized clinical data for patients using an electronic Case Report Form (eCRF). Additionally, MRI scans of included patients were sent by centers to a central neuroimaging analysis center (BNAC). Scans were analyzed across MRI outcomes of interest and the resultant measures were provided to the analytical team (IMS Health®, Plymouth Meeting, PA)–where this information was linked to the clinical data using anonymized identification (see Fig 1).

Clinical Data Collection

All retrospective data required for this study were collected from patients' medical records into a study-specific eCRF. Sites were requested to provide baseline and all visit-specific information that occurred between 24 months preindex and 24 months postindex. If there were more than nine visits during this period, then a site could provide information on one visit per 6 months. Sites were requested to prioritize more extensive visits and visits closest to the scan dates.

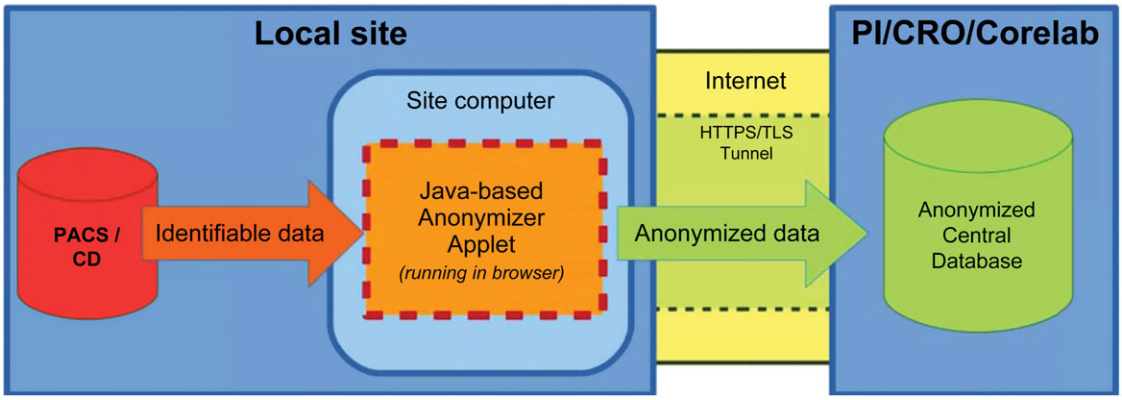


Fig 3. Anonymization pathway. Pathway 1: Scans are parsed through a local secure Java applet running within the local site computer's browser, where they are stripped of all protected health information by an anonymizer compliant with Digital Imaging and Communications in Medicine (DICOM) PS3.15 2015b Annex E. Only after anonymization, does any data leave the local site through an encrypted Internet tunnel. PACS = picture archiving communication system; CD = CD-ROM; HTTPS = Hyper Text Transfer Protocol Secure; TLS = transport layer security; PI = principal investigator; CRO = clinical research organization.

Table 1. Clinical Information and MRI Data Collected

Data Variables and Time Points of Collection[a]	−24 Months	−18 Months	−12 Months	−6 Months	Index Date	6 Months	12 Months	18 Months	24 Months
Clinical information via eCRF									
I/E criteria					X				
Demographics					X				
MS history					X				
BMI	X	X	X	X	X	X	X	X	X
MS medication	X	X	X	X	X	X	X	X	X
Other medication	X	X	X	X	X	X	X	X	X
MS symptoms	X	X	X	X	X	X	X	X	X
Relapses	X	X	X	X	X	X	X	X	X
FSS/EDSS[b]					X				X
T25-FW	X	X	X	X	X	X	X	X	X
Comorbidities	X	X	X	X	X	X	X	X	X
Hospitalizations	X	X	X	X	X	X	X	X	X
ER visits	X	X	X	X	X	X	X	X	X
MRI measures via brain MRI scans									
Global atrophy measures	X[c]				X[c]				X[c]
Lesion measures	X[c]				X[c]				X[c]

[a]Note that the time does not represent explicit time points rather any visit that happened between the current visit and last reported visit. In routine practice, they are generally 6 months apart.
[b]Required to record or estimate an EDSS score for the visits closest to the index and postindex MRI scan dates; other EDSS scores may be captured as well.
[c]MRI data are collected at the following intervals: Preindex scan: 9–24 months before index date (optional); index scan: 6 months before to 1 month after index date; postindex scan: 9–24 months after index date.
eCRF = electronic Case Report Form; BMI = body mass index; MS = multiple sclerosis; EDSS = Expanded Disability Status Scale; ER = emergency room; I/E = inclusion/exclusion; FSS = Functional Systems Scores; MRI = magnetic resonance imaging; T25-FW = Timed 25-Feet Walk.

Table 1 provides variables that were collected as baseline information at index date and at each visit during the study period. Data on medical history and sociodemographics were collected at the baseline visit (also defined as visit corresponding to index date). During the visit-specific data entry, the minimum data to be included were relapse information, MS medication, and disability progression. Disability progression was assessed using ambulation score, Functional Systems Scores (FSS), EDSS,[23] and Timed 25-Foot Walk (T25-FW) scores.[24] Where EDSS scores were not recorded in the patient charts, FSS and ambulatory scores were estimated by centers' trained staff using available clinical information. Any additional information available from the physician notes was recorded but not as mandatory. Additional information could include, but was not limited to, hospitalizations, emergency room (ER) visits, and relapse severity.

MRI Data Collection

Scans need to have been performed on 1.5 or 3 T scanners. Individual patients did not need to have study scans performed on the same scanner type and strength. However, scans acquired within 30 days after receiving high dose steroid treatment could not be included in the study due to their impact on the brain volume changes. All eligible scans needed to have a 2D or a 3D FLAIR sequence or a 2D or 3D T1-WI with or without contrast.

All scans were visually inspected by an experienced rater at BNAC. The following metrics were evaluated: slice thickness, excessive patient motion ("Yes" or "No"), image contrast ("Bad," "Acceptable," or "Good") and overall quality ("Bad," "Acceptable," or "Good"). The overall quality metric reflects anatomical coverage, presence of imaging artifacts, noise level, and contrast. Scans with excessive

patient motion or bad image contrast automatically received a "Bad" rating in terms of overall quality. Additionally, for each MRI scan, differences in machine, software, and coil between preindex/index and index/postindex were evaluated. For each MRI sequence (FLAIR, 2D T1-WI, and 3D T1-WI), differences in orientation, thickness, and protocol changes between preindex/index and index/postindex were examined. Then, overall hardware, software or protocol differences between preindex/index and index/postindex scans were also evaluated.

In addition, WB volume and LVV as well as lesion measures were systematically assessed, results of which will be presented in subsequent work. In particular, impact of hardware, software, and protocol changes over the follow-up on MRI efficacy measures will be investigated. Atrophy measures were assessed by an experienced rater. The use of different scanners or significant changes in the pulse sequence between time points resulted in SIENA and VIENA measures being considered invalid. On the other hand, LVV changes, as assessed by NeuroSTREAM, were retained as the algorithm has been shown to be robust to differences in imaging parameters.[21,22] In particular, the stability of NeuroSTREAM across scanners was tested on a dataset consisting of 125 MS patients and 76 healthy controls scanned randomly at both 1.5 and 3 T in 72 hours. Seventy-two percent of subjects were female, with a mean age of 42.5 ± 11.1 years. Out of 402 total scans, four analyses failed (<1%). R2 correlation coefficient was .99, interclass correlation coefficient was .99, and relative coefficient of variations was 2.15%.[25]

For the baseline analyses of WB and LVV on 2D or 3D T1-WI, SIENAX software was used (version 2.6) with corrections for lesion segmentation misclassification using an in-house developed in-painting program.[25] For the baseline LVV analyses on 2D or 3D FLAIR images, NeuroSTREAM software was used.[21,22] For longitudinal changes of the WB volume on 2D or 3D T1-WI, SIENA was applied to calculate the percent brain volume change (PBVC).[26] Longitudinal volume enlargement of the lateral ventricles was calculated as a measure of central atrophy on 2D or 3D T1-WI using the VIENA software[18] and on 2D or 3D FLAIR images using NeuroSTREAM software.[21,22]

Lesion Measures

The T2-, T1- and contrast-enhancing (CE) lesion number and lesion volumes were measured on FLAIR and pre- and post-T1 contrast images, respectively, using a semiautomated edge detection contouring/thresholding technique previously described.[27] Using FLIRT, the follow-up FLAIR and T1-WI pre- and postcontrast images for a given subject were coregistered to its baseline FLAIR image using a 6 degrees-of-freedom rigid-body model. All subsequent lesion analyses were done using the coregistered images.

Human Protection and Patient Privacy

This study was required to adhere to the Health Insurance Portability and Accountability Act (HIPAA) and Internal Review Board (IRB) directives regarding participant privacy and has gone through central and local IRB approvals. These various regulations and guidance were in place to safeguard individual protected health information (PHI).

In addition, while transferring brain MRI images, participating sites transfer digital images using the standard Digital Imaging and Communications in Medicine (DICOM) format. DICOM files may contain potentially revealing PHI. To ensure patient privacy was protected and relevant regulations were adhered to, BNAC followed guidance from DICOM PS3.15 2015b–Security and System Management Profiles–Annex E: Attribute Confidentiality Profiles.[28] Automatic deidentification via the online BNAC transfer portal (Fig 3) was performed for all study scans. This pathway was the simplest and least burdensome for the sites, as all sites had digital transfer capability. DICOM images were automatically anonymized prior to transmission to the BNAC via encrypted channels and there was no "burned-in" information on the images (uncommon for MRI acquired in the last decade).

Statistical Analyses

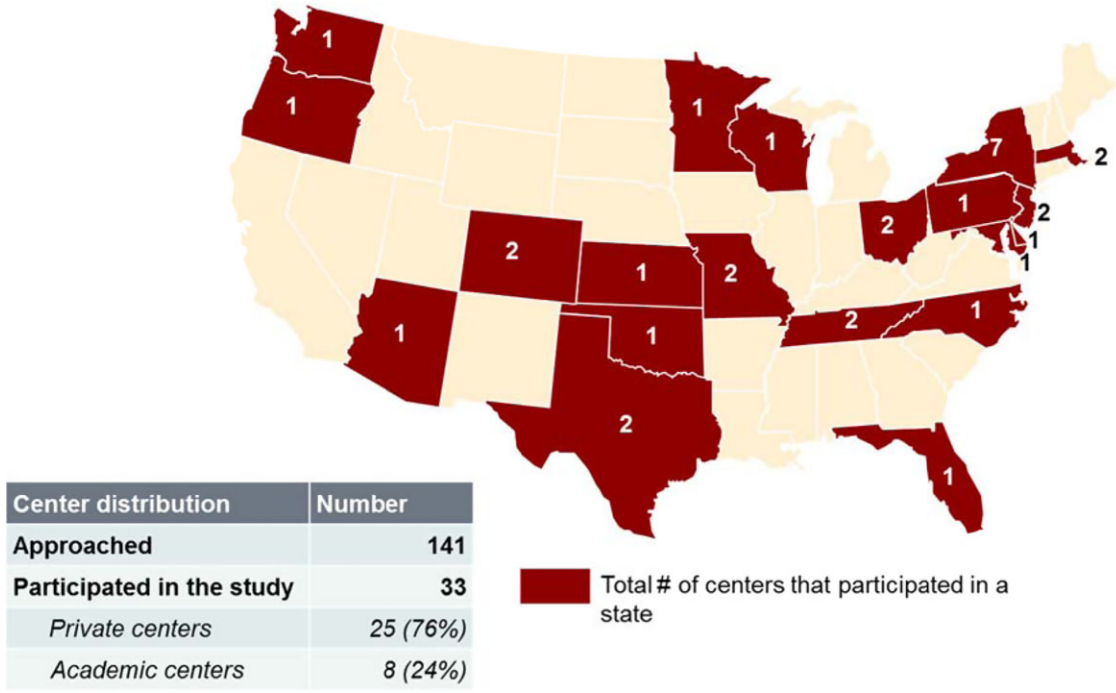
All statistical analyses were performed by using the SAS statistical software system (SAS Institute, Cary, NC). All analyses were performed based on an a priori defined statistical analysis plan (SAP). Summary statistics for continuous variables include the number of patients with valid/missing observations, mean, standard deviation, median, 95% confidence interval, minimum, and maximum. Summary statistics for categorical variables included frequencies and related percentages per class level.

Results

An initial feasibility assessment was conducted to determine each site's qualification for the study in terms of staff resources and data availability. The majority of sites were started using electronic medical record (EMR) systems only after 2012 and were relying on paper versions before. While all sites kept paper records, few also scanned them into the EMR system once the system was running. All the sites indicated that they recorded longitudinal data on demographics, medication use, relapses, and disability progression. Recording of FSS and EDSS scores was a rare occurrence and was mainly associated with participation in a clinical trial.

The study opened for recruitment on August 4th, 2015. About 141 centers were contacted for participation from across the United States, of which 33 centers are participating in the study, demonstrating a robust participation rate of 23%. The reasons for nonparticipation included: (a) no response from centers (45%); (b) capacity constraint (11%); *c) low reimbursement (2%); (d) failure to meet qualification criteria (5%); and (d) no reason/other (14%). Others included lack of interest in retrospective studies, conflicts of interest, Principal Investigator (PI) retirement, and other PI at sister sites already participating. Of the 33 centers that participated, 22% were academic and 78% were private centers. Reasons for participation were similar across academic and private centers except for refusal due to low reimbursement that was only present in academic centers due to high overhead costs. The geographical distribution of centers is shown in Figure 4 and indicates a wide geographical reach.

Characteristics of the patients enrolled in the study at the time of interim database lock ($N = 252$) are presented in Table 2. The number of patients per center ranged from 1 to 46 with an average of 13 patients per center. About 34% of patients in the dataset also had preindex scans. Mean age was 44 years and 81% were female. The average preindex scan period was



Center distribution	Number
Approached	**141**
Participated in the study	**33**
Private centers	*25 (76%)*
Academic centers	*8 (24%)*

Fig 4. Geographical distribution of centers. The numbers illustrate the total numbers of centers interested in the study as of end of February 2016 and the numbers in brackets the number of enrolled sites.

1.03 years and postindex period 1.49 years. Mean number of relapses in the 2 years prior to diagnosis was .58.

Table 3 presents MRI sequencing and scan quality indicators. In the preindex period, 73% of the scans were performed on 1.5 T compared to 27% on 3 T. This changed to 60% and 40% on 1.5 and 3 T scanner in the postindex period, respectively. The use of 2D T1-WI sequence decreased over time from 85% in the preindex period to 70% at index to 64% in the postindex period, whereas use of 3D T1-WI sequences increased from 40% in the preindex period to 50% in the postindex period. Between 40% and 50% of the 2D T1-WI scans were $< = 5$ mm thickness, there was minimal to no excessive patient motion, and scanner contrast and overall quality were generally acceptable or good. Quality of 3D T1-WI sequence was superior to 2D T1-WI between 83% and 85% of the 3D T1-WI scans had $< = 2$ mm thickness and scanner contrast and overall quality were generally good. Similar to 2D T1, 58–66% of the FLAIR scans had $< = 5$ mm thickness and scanner contrast and overall quality were generally acceptable or good.

In addition, for each patient, MRI scan and sequence, we calculated several parameters to assess differences in MRI acquisition protocols between preindex/ index scans and index/post index scans (Table 4). Among index/post index scan, hardware or software was different in 50% of the scans, remained consistent in 30%, and was unknown in 15%. Among index/postindex FLAIR sequence analysis, orientation, thickness, or protocol were different among 35.5% of scans and consistent for 64.5%. 2D T1-WI scans analysis showed that orientation, thickness, or protocol were different for 29% of patient's scans between index/postindex scan, whereas 3D T1-WI scan orientation, thickness, or protocol were different for 20% of scans between index/postindex scan.

Discussion

The clinical efficacy and safety of fingolimod, a sphingosine-1-phosphase receptor modulator, in RRMS patients have been assessed in three controlled clinical trials, TRANSFORMS, FREEDOMS, FREEDOMS II.[11,12,29] Results from these randomized clinical trials provide strong evidence that fingolimod treatment reduces relapse rates and brain volume loss. However, it is not clear whether these findings are similar in real-world practice with wider inclusion/exclusion criteria and no strict adherence to protocol.

Here, we report on the MS-MRIUS study design, interim baseline characteristics, and brain MRI scan acquisition parameters. MS-MRIUS cohort mean age was 44 years and 81% were female. Average duration of MS was 9.3 years and mean number of relapses in the 2 years prior to index was .58. These baseline characteristics are comparable with retrospective claims analysis and prospective studies of patients treated in clinical practice.[30–32] For instance, in the PASSAGE cohort,[32] mean age was 42 years and higher in U.S. patients (47 years), the majority of patients were female (69.1%), mean duration of MS was 12.3 years, and average number of relapses one year prior to index was 1.0. However, similar to other prospective and retrospective studies, MS-MRIUS baseline characteristics differ slightly from fingolimod phase 3 clinical trial patients.[11,12] In TRANSFORMS and FREEDOMS trial, patients were comparatively slightly younger with mean age of 36 years, average duration of MS around 7.5-8 years, and had higher average number of preindex relapses around 2.0.

One of the unique aspects of this study is provision of longitudinal retrospective MRI brain scans to a central imaging center. Longitudinal brain imaging is useful in the analysis of response to treatment of MS patients. Standard structural

Table 2. Characteristics of the Included Patients

Characteristics	N = 252	
Patients with index and postindex scan[a]	250	99.2%
Patients with preindex, index, and postindex scan	86	34.1%
Age at index date (years): mean (SD)	43.3	(9.3)
Gender: (*n*, %)		
Male	49	19.4%
Female	203	80.6%
Race/Ethnicity: (*n*, %)		
Caucasian/White	211	83.7%
Non-Caucasian	23	9.1%
Unknown	18	7.1%
Health insurance: (*n*, %)		
Private	193	77.6%
Public	43	17.1%
Mixed	4	1.6%
Other	1	.4%
Unknown	11	4.4%
Marital Status: (*n*, %)		
No partner (single/divorced/separated/widowed)	58	23.0%
Partner (married/cohabitating/partnered)	175	69.4%
Unknown	19	7.5%
Preindex days (first visit to index MRI): mean (SD)	379.0	(239.2)
Postindex days (index MRI to postindex MRI): mean (SD)	505.9	(145.5)
Duration with MS (years): mean (SD)	9.6	(6.8)
Number of relapses in 2 years before index: mean (SD)	.58	(.85)

[a]Two patients were excluded as there was scan quality indicator data that were not available for these patients at the time of analysis.
SD = standard deviation; *n* = number; % = percentage; MRI = magnetic resonance imaging.

Table 3. Description of Scan Collection and Quality Control Assessment

Characteristics	Preindex (*n* = 86) %	Index (*n* = 252) %	Postindex (*n* = 250) %
Scanner strength			
1.5 T	73.3	63.5	59.6
3 T	26.7	36.5	40.4
Pulse sequence:			
2D T1-WI	84.9	70.2	64.4
3D T1-WI	39.5	43.3	50.0
2D or 3D FLAIR	100.0	100.0	99.6
2D T1-WI and 3D T1-WI	26.7	16.7	17.2
2D or 3D FLAIR quality:			
Slice thickness:			
< = 5 mm	50.7	40.9	39.5
>5 mm	49.3	59.1	60.5
Excessive patient motion:			
Yes	.0	1.1	1.1
No	100.0	98.9	98.9
Scanner contrast:			
Bad	1.4	3.3	.5
Acceptable	27.4	16.0	19.5
Good	71.2	80.7	80.0
Overall scan quality:			
Bad	4.1	5.0	1.1
Acceptable	46.6	54.1	53.0
Good	49.3	40.9	45.9
3D T1-WI quality:			
Slice thickness:			
< = 2 mm	85.3	83.2	85.6
>2 mm	14.7	16.8	14.4
Excessive patient motion:			
Yes	.0	.0	.0
No	100.0	100.0	100.0
Scanner contrast:			
Bad	.0	.0	.8
Acceptable	5.9	4.4	1.5
Good	94.1	95.6	97.7
Overall scan quality:			
Bad	.0	.9	.8
Acceptable	17.6	21.2	14.4
Good	82.4	77.9	84.8
2D FLAIR quality:			
Slice thickness:			
< = 5 mm	58.1	61.9	66.0
>5 mm	41.9	38.1	34.0
Excessive patient motion:			
Yes	5.8	.8	2.4
No	94.2	99.2	97.6
Scanner contrast:			
Bad	.0	.4	1.2
Acceptable	22.1	19.0	25.6
Good	77.9	80.6	73.2
Overall scan quality:			
Bad	3.5	4.0	7.2
Acceptable	25.6	21.4	25.6
Good	70.9	74.6	67.2

T = Tesla; WI = weighted image; FLAIR = fluid-attenuated inversion recovery; mm = millimeter.

imaging pulse sequences, such as FLAIR, has been used in the clinical practice to detect lesion burden and volumetric changes in the white matter. However, detection of focal GM lesions by standard methods is less reliable. As such, more advanced techniques with greater specificity are required to gain a better understanding of disease progression in MS patients. Use of 3D pulse sequence with T1 weighing can help improve spatial resolution thereby enhancing measurement of atrophy changes over time.[14] In this study, we used NeuroSTREAM, VIENA, and SIENA methodology to assess LVV and WB volume. Centers were asked to provide retrospective data on patient clinical measures and send MRI brain scan images to a central imaging facility. Scans should have been acquired within a specific time window, on 1.5 or 3 T, should have had FLAIR and 2D T1-WI or 3D T1-WI sequences. A very small percentage of scans (4%) did not fall within the specified scan windows (data not shown in table) suggesting minor protocol deviations. The majority of the scans that were supplied by centers met all criteria, and 96% of patients had FLAIR available at good or acceptable quality, allowing LVV to be measured. WB volume was calculated in roughly 70% of patients using 2D T1-WI and 45% using 3D T1-WI, and there was a growth in the use of 3 T scanner and 3D T1-WI sequence over time. Over 90% of scan sequences were of acceptable or good quality; as expected, quality of the 3D T1-WI sequence was better than other sequences. Changes in scanner or pulse sequence resulted in SIENA and VIENA measures being considered invalid; however, even with changes to the scanner or pulse sequence, results using FLAIR were retained as the algorithm has previously been shown to be robust to changes in

Table 4. Description of MRI Scan Hardware, Software, and Protocol Changes over the Follow-Up

Characteristics	Preindex to Index ($n = 86$)	Index to Postindex ($n = 250$)
Machine difference: (%)		
Yes	31.4%	26.0%
No	68.6%	74.0%
Software difference: (%)		
Yes	17.4%	26.4%
No	82.6%	73.6%
Coil difference: (%)		
Yes	20.9%	36.0%
No	50.0%	39.6%
Unknown	29.1%	24.4%
Hardware or software difference: (n, %)		
Yes	39.5%	50.0%
No	41.9%	35.2%
Unknown	18.6%	14.8%
2D or 3D FLAIR		
Orientation, thickness, or protocol different: (%)		
Yes	55.8%	35.5%
No	44.2%	64.5%
Hardware, software, or protocol difference: (%)		
Yes	57.0%	55.4%
No	32.6%	32.1%
Unknown	10.5%	12.4%
2D T1-WI		
Orientation, thickness, or protocol difference: (%)		
Yes	31.9%	29.1%
No	68.1%	70.9%
Hardware, software, or protocol difference: (%)		
Yes	44.9%	55.7%
No	36.2%	31.6%
Unknown	18.8%	12.7%
3D T1-WI		
Orientation, thickness, or protocol difference: (%)		
Yes	26.7%	20.4%
No	73.3%	79.6%
Hardware, software, or protocol difference: (%)		
Yes	30.0%	44.7%
No	66.7%	44.7%
Unknown	3.3%	10.7%

FLAIR = fluid-attenuated inversion recovery; WI = weighted image.

imaging parameters.[14,21,22] Variability was observed in the MRI scans (differences in machine/hardware/software/differences in coil) and in sequences (orientation/thickness/protocol) over the follow-up period (preindex to index and index to postindex) in more than 50% of the scans. Therefore, it would be important to estimate the impact of these changes on the MRI measures in real-world clinical setting.

Limitations

This is an observational retrospective database study and thus will not be able to infer causality. Information is limited by the level of detail and quality of information recorded by the physician. For instance, there may be an absence of clinical measures, especially MS severity, not typically available through chart/EMR data that can provide additional detail and insight into treatment outcomes. Date of first MS diagnosis may not be established within this data as the patient's complete medical history may not be available. Not all concomitant medications may be captured in the database, both because they are available over-the-counter and thus patients can self-medicate or because a patient may receive treatment from a physician or pharmacist outside the centers. This is anticipated to be a rare occurrence as most centers record all data relating to medication use retrospectively in their records. Most importantly, the choice of treatment is likely not random. It is possible that patients are prescribed fingolimod because of a physician's prescribing pattern or patient characteristics not observed in the dataset. While no attempt will be made to limit this potential bias, its potential presence in any conclusions made is acknowledged.

The retrospective study MS-MRIUS has an innovative design, linking MRI images with clinical parameters, from a large cohort of MS patients in real-world practice, in an integrated database from multiple centers across United States for the first time. Other ongoing international studies such as PANGAEA[33] or MSBase[34] report clinical safety and efficacy data on fingolimod from multiple centers. However, they do not include imaging outcomes. In addition, MS-MRIUS will provide valuable information on clinical-MRI correlations and impact of MRI parameters differences over time in real-world practice.

References

1. Compston A, Coles A. Multiple sclerosis. Lancet 2002;359:1221-31.
2. Zivadinov R, Reder AT, Filippi M, et al. Mechanisms of action of disease-modifying agents and brain volume changes in multiple sclerosis. Neurology 2008;71:136-44.
3. Geurts JJ, Stys PK, Minagar A, et al. Gray matter pathology in (chronic) MS: modern views on an early observation. J Neurol Sci 2009;282:12-20.
4. Hulst HE, Geurts JJ. Gray matter imaging in multiple sclerosis: what have we learned? BMC Neurol 2011;11:153.
5. Zivadinov R, Pirko I. Advances in understanding gray matter pathology in multiple sclerosis: are we ready to redefine disease pathogenesis? BMC Neurol 2012;12:9.
6. Benedict RH, Bruce JM, Dwyer MG, et al. Neocortical atrophy, third ventricular width, and cognitive dysfunction in multiple sclerosis. Arch Neurol 2006;63:1301-6.
7. Houtchens MK, Benedict RH, Killiany R, et al. Thalamic atrophy and cognition in multiple sclerosis. Neurology 2007;69:1213-23.
8. Roosendaal SD, Bendfeldt K, Vrenken H, et al. Grey matter volume in a large cohort of MS patients: relation to MRI parameters and disability. Mult Scler 2011;17:1098-106.
9. Tsivgoulis G, Katsanos AH, Grigoriadis N, et al. The effect of disease modifying therapies on brain atrophy in patients with relapsing-remitting multiple sclerosis: a systematic review and meta-analysis. PLoS One 2015;10:e0116511.
10. De Stefano N, Airas L, Grigoriadis N, et al. Clinical relevance of brain volume measures in multiple sclerosis. CNS Drugs 2014;28:147-56.

11. Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010;362:387-401.
12. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med 2010;362:402-15.
13. Khan O, Bao F, Shah M, et al. Effect of disease-modifying therapies on brain volume in relapsing-remitting multiple sclerosis: results of a five-year brain MRI study. J Neurol Sci 2012;312:7-12.
14. Zivadinov R, Dwyer MG, Bergsland N. Brain atrophy measurements should be used to guide therapy monitoring in MS - YES. Mult Scler 2016;22:1522-4.
15. Zivadinov R, Jakimovski D, Gandhi S, et al. Clinical relevance of brain atrophy assessment in multiple sclerosis. Implications for its use in a clinical routine. Expert Rev Neurother 2016;16:777-93.
16. Giorgio A, Battaglini M, Smith SM, et al. Brain atrophy assessment in multiple sclerosis: importance and limitations. Neuroimaging Clin N Am 2008;18:672-86.
17. Durand-Dubief F, Belaroussi B, Armspach JP, et al. Reliability of longitudinal brain volume loss measurements between 2 sites in patients with multiple sclerosis: comparison of 7 quantification techniques. AJNR Am J Neuroradiol 2012;33:1918-24.
18. Vrenken H, Vos EK, van der Flier WM, et al. Validation of the automated method VIENA: an accurate, precise, and robust measure of ventricular enlargement. Hum Brain Mapp 2014;35:1101-10.
19. Rovira A, Wattjes MP, Tintore M, et al. Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis-clinical implementation in the diagnostic process. Nat Rev Neurol 2015;11:471-82.
20. Traboulsee A, Simon JH, Stone L, et al. Revised recommendations of the consortium of MS centers task force for a standardized MRI protocol and clinical guidelines for the diagnosis and follow-up of multiple sclerosis. AJNR Am J Neuroradiol 2016;37:394-401.
21. Dwyer MG, Ramasamy DP, Durfee J, et al. Accurate and reliable atrophy measurement on clinical quality FLAIR scans. 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis, Barcelona, Spain, October 7-10, 2015:P437.
22. Dwyer M, Silva D, Bergsland N, et al. Neurological software tool for reliable atrophy measurement (NeuroSTREAM) in multiple sclerosis. 68th Annual Meeting of American Academy of Neurology, Vancouver, BC, Canada, April 21, 2016:S45.005.23.
23. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444-52.
24. Learmonth YC, Dlugonski DD, Pilutti LA, et al. The reliability, precision and clinically meaningful change of walking assessments in multiple sclerosis. Mult Scler 2013;19:1784-91.
25. Zivadinov R, Heininen-Brown M, Schirda CV, et al. Abnormal subcortical deep-gray matter susceptibility-weighted imaging filtered phase measurements in patients with multiple sclerosis: a case-control study. Neuroimage 2012;59:331-9.
26. Smith SM, Zhang Y, Jenkinson M, et al. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. Neuroimage 2002;17:479-89.
27. Zivadinov R, Bergsland N, Dolezal O, et al. Evolution of cortical and thalamus atrophy and disability progression in early relapsing-remitting MS during 5 years. AJNR Am J Neuroradiol 2013;34:1931-9.
28. Fetzer DT, West OC. The HIPAA privacy rule and protected health information: implications in research involving DICOM image databases. Acad Radiol 2008;15:390-5.
29. Calabresi PA, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol 2014;13:545-56.
30. Agashivala N, Wu N, Abouzaid S, et al. Compliance to fingolimod and other disease modifying treatments in multiple sclerosis patients, a retrospective cohort study. BMC Neurol 2013;13:138.
31. Bergvall N, Petrilla AA, Karkare SU, et al. Persistence with and adherence to fingolimod compared with other disease-modifying therapies for the treatment of multiple sclerosis: a retrospective US claims database analysis. J Med Econ 2014;17:696-707.
32. Giacomini P, Butzkueven H, Cohan S, et al. Baseline characteristics and interim analysis results of the fingolimod cohort in the world-wide post-approval safety program (PASSAGE). Neurology 2014;82:202A.
33. Ziemssen T, Kern R, Cornelissen C. The PANGAEA study design - a prospective, multicenter, non-interventional, long-term study on fingolimod for the treatment of multiple sclerosis in daily practice. BMC Neurol 2015;15:93.
34. Warrender-Sparkes M, Spelman T, Izquierdo G, et al. The effect of oral immunomodulatory therapy on treatment uptake and persistence in multiple sclerosis. Mult Scler 2016;22:520-32.