Poster # 107

# Comparison of Natalizumab, Ocrelizumab, and Diroximel Fumarate in RRMS Patients Stable on Therapy to Characterize Divergent Proteomic, Radiomic, and Clinical Trajectories: Study Design

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## Introduction

The use of quantitative tools to guide therapy selection and monitor treatment response can enhance the standard of care for persons with multiple sclerosis (MS). The Octave Precision Care Solution[1] has been developed to improve monitoring and management of persons with multiple sclerosis (PwMS) and consists of: (1) a blood-based multivariate biomarker test that is correlated with MS disease activity (MSDA), (2) enhanced magnetic resonance imaging (MRI) reporting capabilities, and (3) a clinical insights (CI) program that provides personalized support to patients through continuous digital monitoring via apps, wearables, and MS certified nurse care partner engagement. Utilizing this precision care solution to characterize various disease modifying therapies (DMTs) may enable clinicians and patients to make more informed treatment decisions.

## Objectives

To characterize proteomic, radiomic, clinical, behavioral, and functional trajectories of patients stable on natalizumab, ocrelizumab, and diroximel fumarate disease modifying therapies (DMT), using the Octave Precision Care Solution.

## Methods

This is an open-label, observational study that aims to examine 153 participants with relapsing remitting MS (RRMS) across 3 US sites (Rocky Mountain Multiple Sclerosis Clinic, Oklahoma Medical Research Foundation, and MS Orlando Health) for a duration of 12 months. 51 participants will be enrolled per DMT group:

- Participants will meet the following key inclusion criteria:
  - 18-65 years old
  - stable on DMT for at least 6 months with no documented relapses
  - have the ability to walk at least 25 feet without assistive devices
- The clinically[2] and analytically[3] validated MSDA test will be assessed at baseline and months 3, 6, 9 and 12 (Table 1). The MSDA test measures the concentration of 18 protein biomarkers to determine 4 disease pathway scores and an overall disease activity score via the use of a stacked classifier logistic regression model with variable biological categorizations and weights of the features applied in the algorithm. (Figure 1)
- Standard of care MRIs (+/-1 year from screening) will be evaluated using Octave's MRI analysis pipeline. (Figure 2)
- The CI program will be administered throughout the study and includes:
  - monthly Nurse Care Partner virtual visits
  - scheduled patient-reported outcome measures (PROs; Table 2) e.g., Neuro-QoL, surveys to measure the 'feel good effect' and 'wearing off effect' phenomenon
  - passive collection of health metrics via the Oura ring (e.g.,resting heart rate, sleep quality, steps & activity level). (Figure 3)

| Tests and Assessments | Screening (Day -28 to 1) | Baseline (Day 1) | Month[5]3 (± 7 days) | Month[5]6 (± 7 days) | Month[5]9 (± 7 days) | Month[5]12 (± 7 days) | Unscheduled/ Early Termination |
|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | |
| Review of Eligibility Criteria | X | | | | | | |
| Medical History[1] | X | | | | | | |
| PDDS[2] | | X | | | | | |
| MSDA Test[3] | | X | X | X | X | X | X |
| Oura Ring Health Metrics | | Wear the ring regularly and passively share Oura health metrics | | | | | |
| MRI | X[4] | Standard of Care | | | | | |
| Adverse Events | X·····X | | | | | | |
| Octave Nurse Care Partner Video/Telephonic Visits | Monthly | | | | | | |

**Table 1: Schedule of activities (non ePROs).** [1]Medical history and collection of clinical characteristics is completed by the patient as part of the onboarding forms for the Clinical Insights Program. [2]Administered on the Octave app. [3]For patients on Ocrevus or Tysabri, the blood draw should occur within 7 days prior to the infusion. [4]No MRIs are intended to be collected outside of routine standard of care. This time point could include any MRI up to one year prior to the screening visit. [5]Month is defined as 28 days.

| Natalizumab SID Activities | Baseline | Infusion 1 | Infusion 7 | Infusion 13 |
|---|---|---|---|---|
| Baseline ePRO | X | | | |
| Custom ePRO[1] WOE | | X | X | |
| NeuroQoLs[2] & Custom ePRO FGE[1] | | X | X | X |

| Ocrelizumab Activities | Baseline | Infusion 1 | Infusion 2 | Infusion 3 |
|---|---|---|---|---|
| Baseline ePRO | X | | | |
| Custom ePRO[1] WOE | | X | X | |
| NeuroQoLs[2] & Custom ePRO FGE[1] | | X | X | X |

| Natalizumab EID Activities | Baseline | Infusion 1 | Infusion 5 | Infusion 9 |
|---|---|---|---|---|
| Baseline ePRO | X | | | |
| Custom ePRO[1] WOE | | X | X | |
| NeuroQoLs[2] & Custom ePRO FGE[1] | | X | X | X |

| Diroximel Fumarate Activities | Baseline | Month 1 | Month 6 | Month 12 |
|---|---|---|---|---|
| Baseline ePRO | X | | | |
| Custom ePRO[1] WOE | | X | X | |
| NeuroQoLs[2] & Custom ePRO FGE[1] | | X | X | X |

**Table 2: Schedule of activities - ePROs per Disease Modifying Therapy.** [1]Administered via Octave app weekly over the duration of an infusion cycle (from 1 infusion to the next); for diroximel fumarate the ePRO will be administered weekly for the duration of a month.

## Results

The primary endpoint, proteomic trajectories measured via the percentage of patients in each DMT group that had a significant change (≥ 1.5 score units) at any time point in their overall Disease Activity score relative to baseline throughout the 12 month period was used to power this study. With 153 subjects, we expect to be able to detect a 1.0 difference in MSDA scores (scale of 1 - 10) in pairwise comparisons between the DMT categories from baseline to Month 12 (SD: 1.8, Effect Size: MSDA delta -1.0, Power: 80%, Alpha: 0.05). An interim analysis will be performed when half of the participants (n=77, with no less than 15 participants in any individual treatment group) have completed their Month 6 visit. As of January 22nd, 2024, 48 participants have been enrolled in the study across the three sites with participants representing each of the 3 DMT categories.

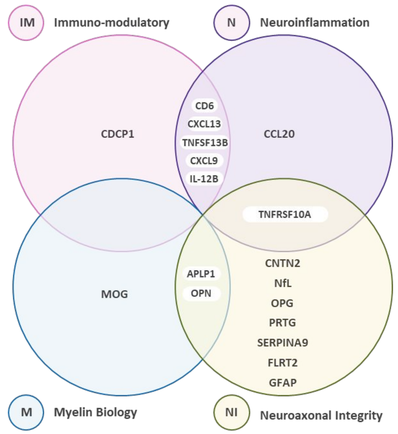


**Figure 1:** Octave MSDA Test Algorithm: Biomarkers and Pathways

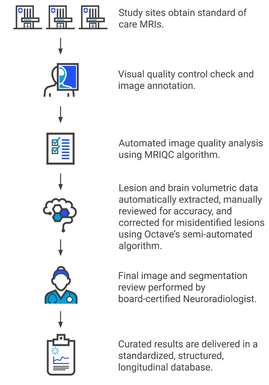


**Figure 2:** Octave MRI Analysis Program

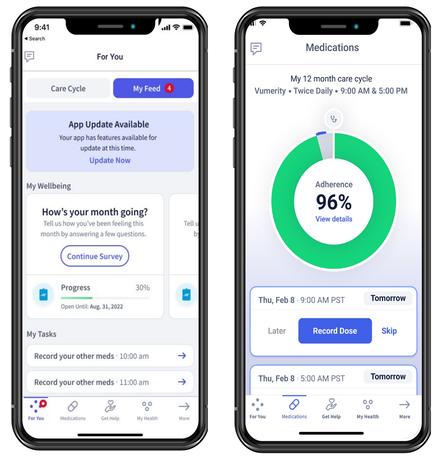


**Figure 3:** Octave Clinical Insights Program

## Conclusions

- This study was designed to characterize biological, imaging, and clinical trajectories of patients stable on MS DMTs to enable clinicians and patients in the future to make more informed treatment decisions.
- Based on current study progress we anticipate that the interim analysis will be completed in Q4 2024 and the final analysis will be completed in Q4 2025.

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**References:** [1] Miner et al. Improving Patient Outcomes through a Comprehensive Care Management Platform Measuring Outcomes and Value: an Integrated, Novel solution for Generating insights in MS. Poster #0091. MS Virtual 2020 Conference. [2] Chitnis et al. Clinical Validation of a Multi-protein, Serum-based Assay for Disease Activity Assessments in Multiple Sclerosis. Clinical Immunology. July 2023. https://doi.org/10.1016/j.clim.2023.109688 [3] Qureshi et al. Analytical Validation of a Multivariate Proteomic Serum Based Assay for Disease Activity Assessments in Multiple Sclerosis. Proteomics - Clinical Applications. Feb 2023. https://doi.org/10.1002/prca.202200018

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