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SOSTOS Study Design: Assessing Transition to Ofatumumab From Other Disease-Modifying Therapies in RRMS After Elevation of Serum Neurofilament Light Levels

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SUMMARY

1. **SOSTOS is a randomized, open-label, prospective, active comparator, phase 4 study**
2. **The study will highlight the potential clinical benefits of transitioning to OMB vs continuing on a current DMT in patients with RRMS not experiencing a relapse in the past year but who may exhibit imaging/biomarker evidence of ongoing disease activity**
3. **The study will also provide clinical insights into the utility of NfL as a potential biomarker of underlying disease activity and the identification of patients who may benefit from a switch to OMB from their current DMT**

INTRODUCTION

- Ongoing disease activity in relapsing-remitting multiple sclerosis (RRMS) may not be clinically apparent and may remain under the threshold of detection[1]
- Patients who appear stable on their current disease-modifying therapy (DMT) may benefit from transitioning to a higher-efficacy agent
- Serum neurofilament light (NfL) holds promise as a biomarker for clinical and subclinical disease activity, with the potential to be used as a risk-stratifying tool[2]
  - The NfL threshold at which a patient might benefit from a transition to a higher-efficacy DMT is currently not defined
- Ofatumumab (OMB), a fully human anti-CD20 monoclonal antibody, is indicated for the treatment of adults with relapsing MS in the United States[3]
- In the phase 3 ASCLEPIOS I and II studies, OMB significantly reduced annualized relapse rates, confirmed disability worsening, and magnetic resonance imaging (MRI) lesions vs once-daily oral teriflunomide[4]

OBJECTIVES

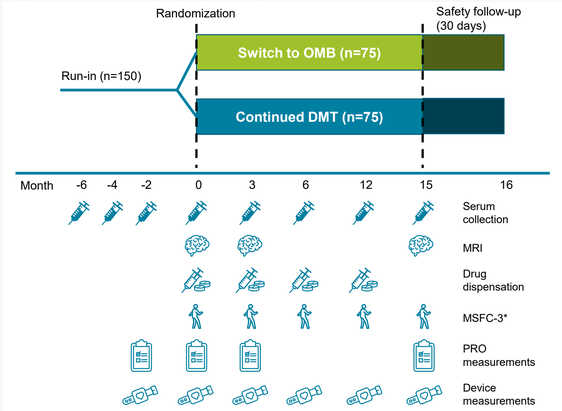
- The Multicenter Study of Continued Current Therapy vs Transition to Ofatumumab After Neurofilament Elevation (SOSTOS; ClinicalTrials.gov identifier, NCT05090371) will assess whether patients with RRMS without a relapse in the past year would benefit from a transition to OMB vs continuing on their current DMT
- This study will also investigate the potential benefits of using baseline and serial NfL measures to inform treatment switch decisions

METHODS

STUDY DESIGN

- SOSTOS is a randomized, open-label, prospective, active comparator, phase 4 study (**Figure 1**)
- Following screening, patients will enter a 6-month run-in period, during which NfL levels will be obtained every 2 months
- Following the run-in period, patients will be randomized (1:1) to either switch to OMB or continue on their current DMT. This is regardless of baseline NfL levels (investigators and patients are blinded to NfL levels). Patients will then be followed for 15 months with a 4-week safety follow-up

Figure 1. SOSTOS Study Design



DMT, disease-modifying therapy; MRI, magnetic resonance imaging; MSCF-3, Multiple Sclerosis Functional Composite-3; OMB, ofatumumab; PRO, patient-reported outcome. Patients will be randomly selected 3:2 to wear a digital measuring device with a 1:1 randomization by treatment arm (OMB vs continue current therapy); the wearable device will be distributed to patients at Month -2. At Month 9, patients are not required to come to the study site; a 3-month supply of OMB can be sent to the patient's home, or the patient may return to the office to pick up the supply for at-home administration; *MSFC-3 includes Symbol Digit Modalities Test, Timed 25-Foot Walk, and 9-Hole Peg Test

PARTICIPANTS AND SETTING

- Key inclusion and exclusion criteria are described in **Table 1**
- The OMB arm comprises patients with RRMS randomized to receive open-label OMB in an autoinjector containing 20 mg (20 mg/0.4 mL) for subcutaneous administration once monthly, following 20-mg loading doses at weeks 0, 1, and 2,[3] after switching
- Patients randomized to the continued therapy arm will continue to take their DMT as commercially prescribed by their physician

Table 1. Key Inclusion and Exclusion Criteria

Key inclusion criteria
Age 18 to 45 years
Diagnosis of RRMS per McDonald criteria (2017)
EDSS 0 to 5.5 (inclusive)
Able to obtain MRI and attend study visits at sites
Willing to use wearable device as specified in the protocol
Able to provide blood sample
On a current DMT with approved label use of RRMS ≥6 months before screening
No relapse reported within 6 months before screening
Key exclusion criteria
Primary progressive or secondary progressive phenotype
Diseases other than MS responsible for clinical or MRI presentation
Use of experimental/investigational MS drugs within <2 years of screening
Known sensitivity to gadolinium
CNS anomalies better accounted for by another disease process
Other active chronic diseases (or stable but treated with immune therapy) of the immune system
Known active malignancies or infections, neurological finding consistent with PML, confirmed PML or IgG/IgM levels below LLN at screening
Currently treated with cladribine, alemtuzumab, natalizumab, mitoxantrone, or anti-CD20 therapy (longer-lived drugs) at time of screening (Month -6) or thereafter

CNS, central nervous system; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IgG, immunoglobulin G; IgM, immunoglobulin M; LLN, lower limit of normal; MRI, magnetic resonance imaging; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy; RRMS, relapsing-remitting multiple sclerosis

STUDY ENDPOINTS

- Study objectives and corresponding endpoints are summarized in **Table 2**

DATA ANALYSIS

- Treatment difference in terms of proportion of participants in the full analysis set (all randomized patients) achieving 3-parameter no evidence of disease activity (NEDA-3; primary endpoint), and its 2-sided 95% confidence interval (CI) and associated p-values will be calculated using normal approximation or exact method
- Those discontinuing therapy will be included in primary analysis until switching
- Superiority of ofatumumab to continued therapy will be established if the lower limit of the 95% CI mentioned above is >0
- Secondary endpoints will be reported using descriptive statistics
- NfL levels and change from Month 3 will be summarized by treatment and visit/time

Table 2. Study Endpoints

Primary endpoint
• Achieving NEDA-3* in Months 3 to 15 (yes/no)
Secondary endpoints
• Achieving NEDA-3 in Months 3 to 15 (yes/no) by subgroup of baseline NfL level (10 pg/mL cutoff, with age and BMI as confounding factors)
• Number of relapses in Months 3 to 15 • 3-month disability worsening free in Months 3 to 15 (yes/no) • NEDA clinical (no relapses or disability progression) in Months 3 to 15 (yes/no) • NEDA radiological (no MRI activity) in Months 3 to 15 (yes/no) • MSFC-3 (includes SDMT, T25FW, and 9-HPT)
• Conventional MRI metrics (Gd+ lesion count and volume, T2 lesion count and volume [new and enlarging], T1) • Brain volume loss assessment (whole brain and regional)
• Patient-reported outcomes (MSQOL-54)
• Adverse events, serious adverse events, events leading to discontinuation
Exploratory endpoints
• Serum NfL, serum GFAP, CD19+ B cell count • Patient biometrics via device† • Drug accountability and/or possession diary • Treatment burden questionnaire

9-HPT, 9-Hole Peg Test; BMI, body mass index; Gd+, gadolinium-enhancing; GFAP, glial fibrillary acidic protein; MRI, magnetic resonance imaging; MSFC-3, Multiple Sclerosis Functional Composite-3; MSQOL-54, Multiple Sclerosis Quality of Life-54; NEDA-3, 3-parameter no evidence of disease activity; NfL, neurofilament light; SDMT, Symbol Digit Modalities Test; T25FW, Timed 25-Foot Walk
*NEDA-3 is met if the patient is relapse free, 3-month clinical disability progression free, and MRI activity free during Months 3 to 15;
†A biometric monitoring wearable device will be used in the study to passively collect physical activity, sleep, and vitals; participants will be instructed to wear the device 24 hours per day, 7 days per week, starting at Visit 4/Month -2 through to study completion/end of study; compliance on device use will be monitored and follow-up will be requested as needed

RESULTS

- The SOSTOS study is currently recruiting and plans to enroll up to ~150 patients at up to 40 US and 10 Canadian centers
- The first study visit occurred in March 2022, and the study is planned to be completed in 2025
- Additional information can be found at: https://clinicaltrials.gov/ct2/show/NCT05090371

ABBREVIATIONS: 9-HPT, 9-Hole Peg Test; **BMI**, body mass index; **CI**, confidence interval; **CNS**, central nervous system; **DMT**, disease-modifying treatment; **EDSS**, Expanded Disability Status Scale; **Gd+**, gadolinium-enhancing; **GFAP**, glial fibrillary acidic protein; **IgG**, immunoglobulin G; **IgM**, immunoglobulin M; **LLN**, lower limit of normal; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis; **MSFC-3**, Multiple Sclerosis Functional Composite-3; **MSQOL-54**, Multiple Sclerosis Quality of Life-54; **NEDA-3**, 3-parameter no evidence of disease activity; **NfL**, neurofilament light; **OMB**, ofatumumab; **PML**, progressive multifocal leukoencephalopathy; **PRO**, patient-reported outcome; **RRMS**, relapsing-remitting multiple sclerosis; **SDMT**, Symbol Digit Modalities Test; **T25FW**, Timed 25-Foot Walk

DISCLOSURES: Gina Mavrikis Cox, **Harald Kropshofer**, **Xiangyi Meng**, and **James Stankiewicz** are employees of Novartis. **Jeffrey A. Cohen** has received personal compensation for consulting from Adamas, Atara, Bristol Myers Squibb, Convelo, MedDay, and Mylan, and for serving as an editor of *Multiple Sclerosis* journal

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