AGNOS Study Design: A Phase 4 Study Assessing Ofatumumab in Treatment-Naïve Young Adults with Early Relapsing Remitting MS Benchmarked Against Healthy Controls

Timothy Vollmer,[1] Daniel Pelletier,[2] Sibyl Wray,[3] Barry Hendin,[4] Linda-Ali Cruz,[5] Ratnakar Pingili,[5] Xiangyi Meng,[5] James Stankiewicz,[5] Andy Cheadle,[5] Jeffrey A Cohen[6]

[1]Rocky Mountain MS Center, Aurora, CO, USA; [2]USC Multiple Sclerosis Center, Los Angeles, CA, USA, Los Angeles, CA, USA; [3]Hope Neurology, Knoxville, TN, USA; [4]Center for Neurology and Spine, Phoenix, AZ, USA; [5]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [6]Cleveland Clinic Mellen Center, Cleveland, OH, USA

Presenter email address:
timothy.vollmer@cuanschutz.edu

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Background

- Early intervention with high efficacy DMTs has been shown to reduce long-term disability accrual in patients with MS
- OMB, a fully human anti-CD20 monoclonal antibody, is indicated for the treatment of adults with RMS in the US[1]
- In the Phase III ASCLEPIOS I and II studies, OMB significantly reduced ARR, CDW, and MRI lesions vs once daily oral teriflunomide[2]
- This study assesses early intervention with OMB in patients earlier in the MS disease continuum than the average patient studied in the pivotal Phase 3 ASCLEPIOS trials and will be the first multi-center study to provide comparative data using OMB relative to healthy control subjects (without a diagnosis of MS)

Objective

- To provide clinical, MRI (conventional and non-conventional), biometric, and biomarker data assessing the efficacy, safety, and tolerability of OMB in treatment-naïve young adults with early RMS, and to compare select endpoints to healthy subjects

Methods

Study design

- This is a Phase 4, open-label, multi-center, prospective 18-month trial (**Figure 1**)
- RMS patients will receive OMB 20 mg subcutaneously at Baseline/Week 0, 1, 2, and monthly thereafter starting at Week 4 (Month 1) until Month 18, with an optional open-label extension for an additional 12 months (up to Month 30 in the trial)

Study objectives

- **Primary objective:** To explore the impact of OMB on the ability to achieve NEDA-3 status (relapse-free, clinical disability progression-free, MRI activity-free) over an 18-month, open-label study period after a re-baseline of MRI at 6 months
- **Secondary objectives:**
  - To evaluate the effect of OMB on various clinical (NEDA, disability, relapse) and conventional MRI metrics, and PROs
  - To evaluate the effect of OMB vs HCs on whole brain and regional atrophy
  - To evaluate the safety and tolerability of OMB
- **Exploratory objectives:** To evaluate effects of OMB vs HCs on MRI, biomarkers, and digital biometric and physical/cognitive functional outcomes

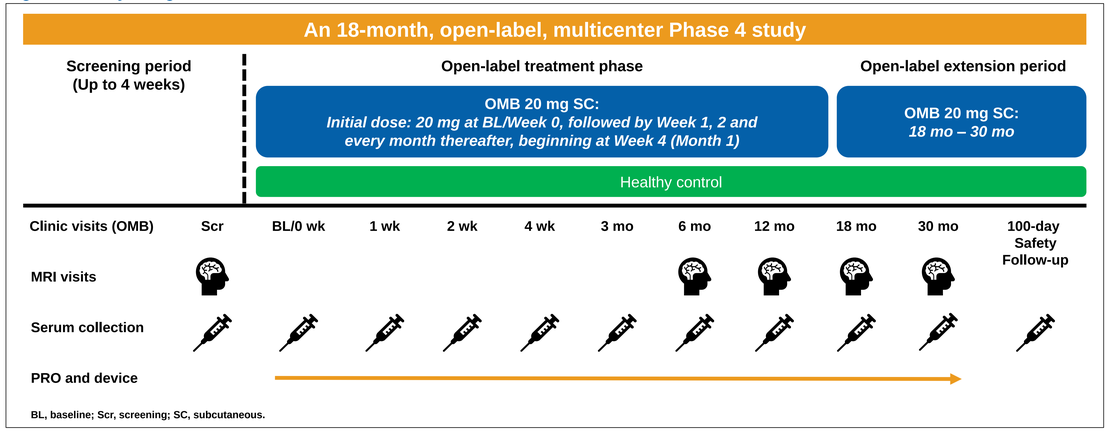
Participants and setting

- Key inclusion and exclusion criteria are described in **Table 1**
- OMB arm: treatment-naïve patients with early RMS (defined as within 6 months of diagnosis), aged 18-35 years, and EDSS score 0-3.0
- HC arm: will be used for comparison purposes and will not receive study treatment; those with abnormal MRI at Baseline will be excluded

Endpoints and assessments

- Study endpoints are summarized in **Table 2**
- Additional efficacy and safety assessments will be evaluated beyond Month 18, up to 30 months, necessitating OMB monotherapy over the course of up to 30 months
- Select endpoints will be benchmarked against age- and sex-matched HCs
- Clinic visits will be minimized (due to COVID-19 precautions) and digital monitoring technologies will be used when available

Figure 1. Study design



BL, baseline; Scr, screening; SC, subcutaneous.

Table 1. Key inclusion and exclusion criteria

Key inclusion criteria
All participants: Male or female patients, aged 18 to 35 years at Screening
HC arm: Able to obtain MRI, use wearable device, and provide blood sample
OMB arm: • Diagnosis of RMS per McDonald Criteria (2010/2017) • Within 6 months of diagnosis of CDMS • EDSS 0-3.0 (Inclusive) and treatment-naive to MS DMT • Able to obtain MRI and attend study visits at sites • Able to use wearable device and provide blood sample and potentially CSF (in a subgroup of N=15)

Key exclusion criteria	OMB arm	HC arm
Confounding medical condition as determined by the investigator		●
Abnormal MRI at Baseline		●
Diseases other than MS responsible for the clinical or MRI presentation, or other non-MS active chronic diseases of the immune system	●	
Patients with neuromyelitis optica, RIS/CIS, SPMS or PPMS diagnosis	●	
Prior use of experimental or investigational drugs for MS; prior use of DMT or chemotherapeutic medications for MS	●	
Relapse between Screening and Baseline visits	●	
Patients with active infections, neurological findings consistent with PML, confirmed PML, or IgG/IgM levels below LLN at Screening	●	

Table 2. Study endpoints

Primary endpoint	OMB arm	HC arm
NEDA-3 in Months 6 to 18 (y/n)	✓	
Secondary endpoints		
Number of relapse, 3-month disability worsening-free (y/n), NEDA clinical at study Month 18 (y/n), NEDA radiological at study Month 18 (y/n)	✓	
Change from Baseline in Conventional MRI metrics (at Months 6, 12, 18, and 30 from Baseline)	✓	✓
Change from Baseline in PROs (NeuroQOL™, PDDS); BVL assessment (whole brain and regional, at Months 18 and 30 from Baseline)	✓	✓
AEs, laboratory data, physical examination, and vital signs	✓	✓
Exploratory endpoints		
cCDP12 disability progression assessments (EDSS, 9HPT, T25FWT)	✓	
IgG/IgM level changes and AEs over the course of the study	✓	✓
Serum/CSF levels*: NfL, GFAP, B cell count, CXCL13, CHI3L1/YKL-40, MCP1, BDNF	✓	✓
Patient biometrics via device (e.g., activity, sleep quality); Physical and cognitive function (9HPT, T25FWT, SDMT)	✓	✓
Resting state functional MRI and magnetic resonance spectroscopy assessments, in regions of interest	✓	✓
Adherence to and persistence on OMB therapy through drug accountability and or possession diary	✓	

*CSF will not be collected in the HC group and will only be collected in 15 OMB-treated patients.

Data analyses

- The number and percentage of patients achieving outcomes will be presented
- The 95% confidence interval for the proportion of patients achieving outcomes will be calculated by using normal approximation method

Results

- This study plans to enroll up to 168 subjects (118 RMS patients, 50 HCs) at ~40 US centers
- The first study visit is expected to occur in 2021 with completion in 2025

Conclusions

- The AGNOS study will provide important data on clinical, imaging, and other outcomes in a treatment-naïve RMS population at first diagnosis, treated with OMB
- Further, it will provide the first data on OMB relative to HCs

References

1. Novartis Pharmaceuticals Corporation. Prescribing information. Kesimpta® 2020. Available from: https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf (Accessed September 9, 2021).
2. Hauser S, et al. N Engl J Med. 2020;383:546-557

Abbreviations

9HPT, 9-hole peg test; AE, adverse event; ARR, annual relapse rate; BDNF, brain-derived neurotrophic factor; BVL, brain volume loss; CSF, cerebrospinal fluid; CHI3L1/YKL-40, chitinase-3-like protein 1; CDMS, clinically definite MS; cCDP12, composite 12-week confirmed disability progression; CDW, confirmed disability worsening; CXCL13, C-X-C motif chemokine ligand 13; DMT, disease-modifying therapy; EDSS, expanded disability status scale; GFAP, glial fibrillary acidic protein; HC, healthy control; Ig, Immunoglobulin; LLN, lower limit of normal; MRI, magnetic resonance imaging; MCP1, monocyte chemoattractant protein-1; MS, multiple sclerosis; NfL, neurofilament light; NeuroQOL™, Quality of Life in Neurological Disorders; NEDA, no evidence of disease activity; OMB, ofatumumab; PRO, patient reported outcome; PDDS, patient determined disease steps; PPMS, primary progressive MS; PML, progressive multifocal leukoencephalopathy; RIS/CIS, radiologic/clinically isolated syndrome; RMS, relapsing MS; SPMS, secondary progressive MS; SDMT, symbol digit modalities test; T25FWT, timed 25-foot walk test; y/n, yes/no.

Disclosures

Timothy Vollmer has received compensation for lectures and consultancy from Biogen, Genentech/Roche, Siranax, Celgene, EMD Serono and Novartis and has received research support from Rocky Mountain Multiple Sclerosis Center, Celgene, Biogen, Anokion, Genentech, F. Hoffmann-La Roche Ltd, GW Pharma and TG Therapeutics, Inc.
Daniel Pelletier reports receiving consulting and/or speaking fees, along with grant and/or research support, from Biogen, Merck Serono, Novartis, Roche/Genentech, and Sanofi Genzyme.
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