CLadribine Tablets: Collaborative Study to Evaluate the Impact On CNS Biomarkers in Multiple Sclerosis (CLOCK-MS) – Current Baseline Characteristics

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CLOCK-MS STUDY CONCLUSIONS



Recruitment for CLOCK-MS is ongoing. The results will elucidate the impact of cladribine tablets on pathological B and T cell subsets, and inflammatory and neurodegeneration biomarkers in blood and CSF



The first 26 patients enrolled in CLOCK-MS were 50% female, with a median EDSS of 3.3, mean age of 44.7 years, and mean time since diagnosis of 9.5 years



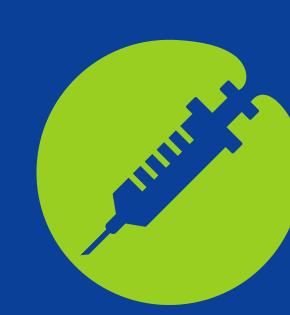
Lymphocyte subsets were detectable in the blood and CSF at baseline, and changes will be evaluated following treatment with cladribine tablets

X Have malignancy, infections, signs/symptoms suggestive of PML

1.75 mg/kg total^{e,f}

X Have been previously treated with ocrelizumab, alemtuzumab, or daclizumab





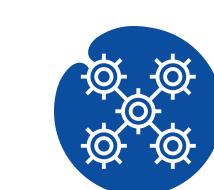
COVID-19 vaccination in cladribine tablets-treated patients produces humoral responses



BACKGROUND

- In RMS, early signs of neuronal degeneration are dependent on inflammatory activity in the CNS¹
- Cladribine tablets, approved for RMS, are proposed to function as an immune reconstitution therapy² with potential CNS effects³
- The ongoing CLOCK-MS trial is investigating effects of cladribine tablets on CNS biomarkers.⁴ A substudy of CLOCK-MS is also looking at seroprotection following vaccination
- Previously reported results from the seroprotection substudy showed that in patients given cladribine tablets, seroprotective antibody levels against seasonal influenza were maintained or increased at 4 weeks after vaccination⁵

Goals of the CLOCK-MS study are to:



Understand the mechanism of action of cladribine tablets in MS



Shed light on the pathophysiology



Identify reliable biomarkers for the efficacy of cladribine tablets



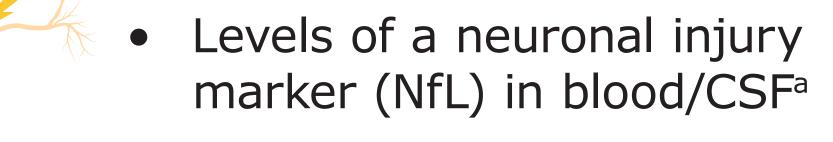
- To present baseline characteristics to date in the CLOCK-MS study, including B cell, T cell, and leukocyte levels
- To show COVID-19 vaccine titers in a subgroup of patients from CLOCK-MS

CLOCK-MS STUDY ENDPOINTS

Primary endpoints



 Levels of CD45+ leukocytes, CD3+ T cells, and CD19+ B cells in blood/CSF^a



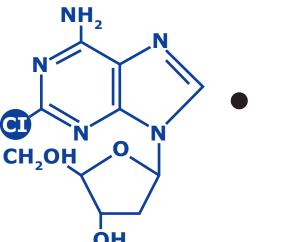
Vaccine substudy endpoint



COVID-19 vaccine titers in

Data from any third, optional end of Year 2 LP will be included with the data from protocolrequired end of Year 2 LPs. bMeasured at baseline and second LP (end of 5 weeks).

Secondary endpoints

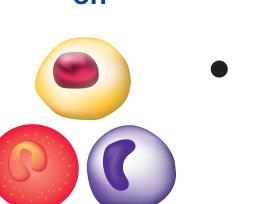


Cladribine levels



MRI changes at 12

Safety



Immune cell

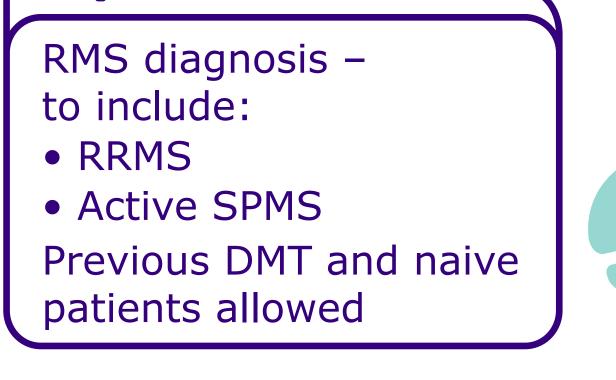


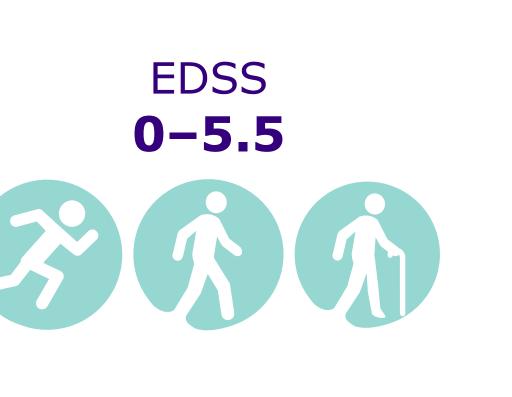
STUDY DESIGN

Selected Inclusion Criteria 18-65 years old

Selected Exclusion Criteria

Have any contraindication for LP





CLOCK-MS Study Design

Willing and able

to undergo

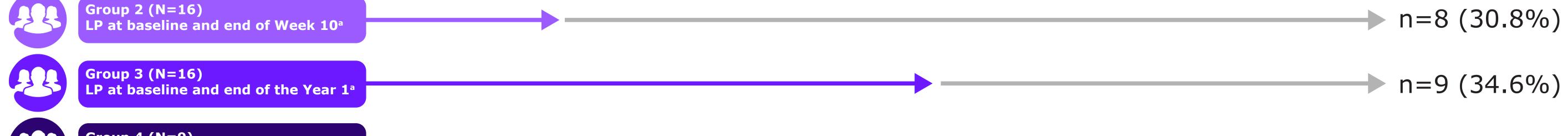
Enrolled to date:

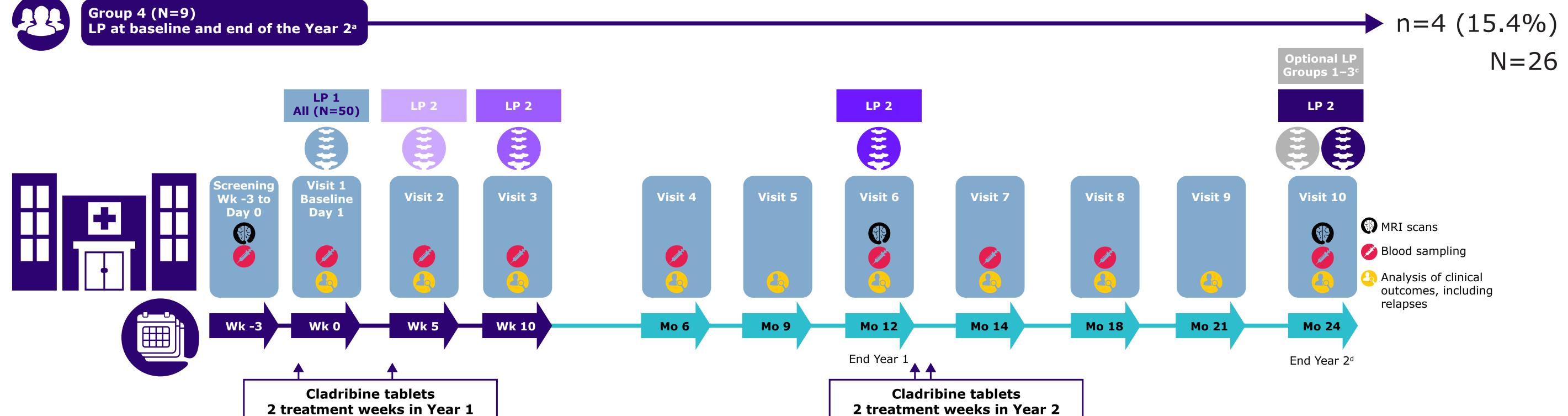
n=5 (19.2%)

≥2 LP

Patients (N=50) will be randomized 1:2:2:1 to undergo 2 LP procedures according to 1 of the 4 following schedules:

X Have received natalizumab during the last 6 months





^aFor patients assigned to a LP, the LP-aligned blood sample needs to be obtained on the same day as the LP. ^bFor patients in Group 1, the LP and aligned blood samples need to be obtained on the same day of and following the last intake of the Week 5 cladribine tablets treatment course. All patients randomized to Groups 1-3 will have the option to volunteer for a third, optional LP at the end of Year 2, the timing of which would be aligned with the second LP of Group 4. If the start of the second treatment year needs to be delayed (eg, to allow for lymphocyte recovery to ≥800 cells/µL), to maintain the protocol-specified time interval between start of cladribine Year 2 treatment and all following assessments, Year 2 visits and procedures for this participant will be delayed accordingly (for up to 6 months). Patients to receive cladribine tablets 3.5 mg/kg per the USPI. Feach treatment week consists of daily treatment over 4-5 consecutive days. The second treatment week is administered 23 to 27 days after the last dose of the first treatment week. 9The second treatment week after the last dose of the first treatment vear and can be delayed for up to 6 months. 9

1.75 mg/kg total^{e,f,g}



- Blood and CSF samples (LP) were collected at the first visit (baseline), and leukocytes (CD45+), B cells (CD20+), and T cells (CD3+) were measured by flow cytometry conducted at each individual site
- A subset of patients in CLOCK-MS who were treated with cladribine tablets (as per the USPI) and planned to receive the COVID-19 vaccines as part of standard care were enrolled in a substudy
- Blood samples were collected at 0-3 weeks pre-vaccine (within 21 days before a standard of care COVID-19 vaccine), 4 weeks post-vaccine (+/- 7 days), and 6 months post-vaccine (+/- 7 days), for both original doses and booster doses
- ELISA was used to measure titers (reciprocal EC50 in serum) against SARS-CoV-2 spike protein in response to COVID-19 vaccines, with titers against nucleocapsid protein as control (no response

RESULTS

Baseline Characteristics (N=26)



Age 44.7 years $(mean, \pm 12.2 years)$



9.5 years since diagnosis (mean, \pm 8.5 years)

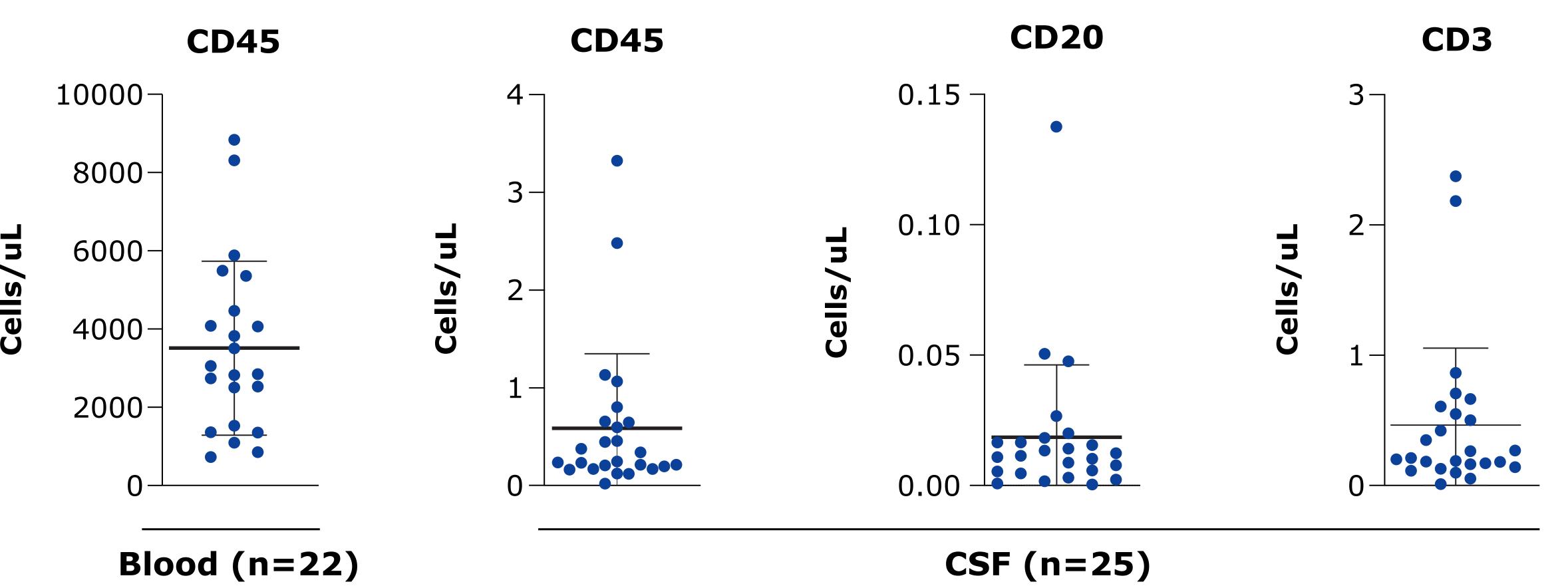


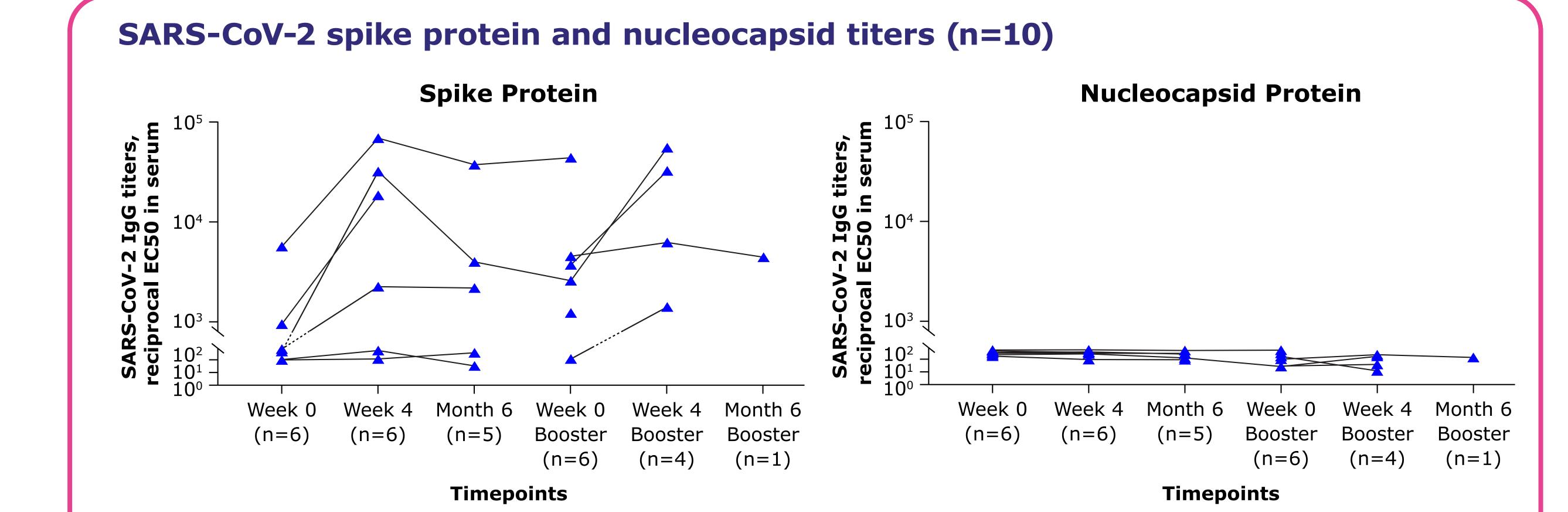
EDSS score of 3.3 (median, range 1.5 – 4.0)



50% female

Baseline measurements of leukocytes, B cells, and T cells in blood and CSF





] Enterosis; NfL, neurofilament light chain; PML, relapsing forms of MS; RRMS, relapsing forms of MS; RRMS, relapsing forms of MS; RRMS, relapsing forms of MS; SPMS, secondary progressive multifocal leukoencephalopathy; RMS, relapsing forms of MS; RRMS, relapsing forms of MS; RRMS, relapsing forms of MS; WSI, united States Prescribing Information. . References: 1. Sandi D, et al. Molecules 2021; 26 (11):3423; 2. Comi G, et al. Poster presentation at ACTRIMS Forum 2021; 6. EMD Serono. MAVENCLAD® (cladribine) tablets Full Prescribing Information, April 2019.
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 Image of the rapeutics without monetary compensation, and Exalys. He serves on the editorial boards of Therapeutic Advances in Meurological Disorders, and Genzyme; AB-O has participated as a speaker in meetings sponsored on data monitoring committees for Genentech, TG Therapeutics, and Genzyme; AB-O has participated as a speaker in meetings sponsored on data monitoring committees for Genentech, TG Therapeutics, and Genzyme; AB-O has participated as a speaker in meetings sponsored on data monitoring committees for Genentech, TG Therapeutics, and Genzyme; AB-O has participated as a speaker in meetings sponsored on data monitoring committees for Genentech, TG Therapeutics without monetary compensation, and has advised EMD Serono, Rockland, MA, USA, Celgene, Genentech, TG Therapeutics without monetary compensation, and the calculation and received grant support to the University of Pennsylvania from Biogen Idec, Roche/Genentech, and Novartis; GP has received grant support to the University of Pennsylvania from Biogen Idec, Roche/Genentech, Merck KGaA, Darmstadt, Germany/EMD Serono, Rockland, MA, USA, and Novartis; GP has received speaker honoraria and/or consulting fees from Alexion, Biogen Idec, Roche/Genentech, and Sanofi-Genzyme, and Novartis; GP has received speaker honoraria and/or consulting fees from Alexion, Biogen Idec, Roche/Genentech, and Novartis; GP has received speaker honoraria and/or consulting fees from Alexion, Biogen Idec, Roche/Genentech, Ma, USA, and Novartis; GP has received speaker honoraria and/or consulting fees from Alexion, Biogen Idec, Roche/Genentech, Ma, USA, Novartis; GP has received speaker honoraria and/or consulting fees from Alexion, Biogen Idec, Roche/Genentech, Ma, USA, Novartis; GP has received speaker honoraria and/or consulting fees from Alexion, Biogen Idec, Roche/Genentech, Ma, USA, Novartis; GP has received speaker honoraria and/or consulting fees from Alexion, Biogen Idec, Roche/Genentech, Ma, USA, Novartis; GP has received speaker honoraria and/or consulting fees from Alexion, Biogen Idea, Roche/Genentech, Ma, USA, Novartis; GP has received speaker honoraria and/or consulting fees from Alexion, Biogen Idea, Roche/Genentech, B received honoraris, and Teva; BH/JK/LAL are employee of Ares Trading SA, Eysin, Switzerland, MA, USA; AHC has received honoraria and/or research support (to the institution) from Abbvie, Rockland, MA, USA, Roche/Genentech, Sanofi Genzyme, Novartis, and Teva; BH/JK/LAL are employees of EMD Serono, Rockland, MA, USA, Roche/Genentech, Sanofi Genzyme, TG Therapeutics; and has received honoraria and/or research support from Biogen, EMD Serono, Rockland, MA, USA, Roche/Genentech, Sanofi Genzyme, Novartis, and Teva; BH/JK/LAL are employees of EMD Serono, Rockland, MA, USA, Roche/Genentech, Sanofi Genzyme, TG Therapeutics; and has received honoraria and/or research support (to the institution) from Abbvie, Adamas, Alkermes, Biogen Idec, EMD Serono, Rockland, MA, USA, Roche/Genentech, Sanofi Genzyme, To the institution) from Abbvie, Adamas, Alkermes, Biogen Idec, EMD Serono, Rockland, MA, USA, Roche/Genentech, Sanofi Genzyme, To the institution of the institu Genentech/Roche, Greenwich Biosciences, Horizon Pharmaceuticals, and Novartis; BKS and DHF have nothing to disclose.