Evaluating the Impact of Cladribine Tablets on the Development of Antibody Titers: Interim Results from The CLOCK-MS Influenza Vaccine Substudy

G.F. Wu[1] , U. Boschert[2], B. Hayward[3], L.A. Lebson[3], A.H. Cross[1]

[1]Washington University in St. Louis, St. Louis, MO, USA; [2]Merck KGaA, Darmstadt, Germany; [3]EMD Serono, Inc., Rockland, MA, USA, an affiliate of Merck KGaA, Darmstadt, Germany

SUMMARY

The COVID-19 pandemic, and recent vaccine availability, have raised interest around the impact of MS disease-modifying therapies on vaccine efficacy generally

The antibody response to influenza vaccination will be measured within 21 days pre-vaccination, and at 4 weeks and 6 months post-vaccination

A subset of patients with RRMS or active SMPS enrolled in the CLOCK-MS study who had received treatment with cladribine tablets and planned to receive the influenza vaccine as part of standard care will be enrolled in this vaccine sub-study

Seroprotective antibody levels against seasonal influenza were maintained or increased at 4 weeks post-vaccination in three patients treated with cladribine tablets, two of whom were experiencing lymphopenia around the time of vaccination

Results from another study of vaccine protection in patients treated with cladribine tablets are also being presented at ACTRIMS 2021 *(Poster #P059—S. Roy and U. Boschert "Analysis of Influenza and Varicella Zoster Virus Vaccine Antibody Titers in Patients with Relapsing Multiple Sclerosis Treated with Cladribine Tablets")*

Abbreviations: ALC, absolute lymphocyte count; **DMT**, disease modifying therapy; **EC50**, half-maximal; **EDSS**, Expanded Disability Status Scale; **M**, month; **MS**, multiple sclerosis; **OD**, optical density; **RMS**, relapsing forms of MS; **RRMS**, relapsing-remitting MS; **SPMS**, secondary progressive MS; **Tet-Dip**: tetanus/diphtheria; **USPI**, United States Prescribing Information; **y**, years.

References: **1.** Metze C, et al. *CNS Neurosci Ther* 2019;25(2):245-254. **2**. Olberg HK, et al. *Mult Scler* 2014;20(8):1074-80. **3**. Olberg HK, et al. *Eur J Neurol* 2018;25(3):527-534. **4**. Turner JS, et al. *Nature* 2020;586:127–132. **5.** Mavenclad [package insert]. Rockland, MA: EMD Serono, Inc.; 2020.

Presented at ACTRIMS Forum 2021 | February 25–27 2021

DISCLOSURES & ACKNOWLEDGMENTS

The CLOCK study (NCT03963375) is sponsored by EMD Serono, Inc., Rockland, MA, USA, an affiliate of Merck KGaA, Darmstadt, Germany, who reviewed and provided feedback on this poster. Writing and editorial support for the preparation of this poster was provided by Jenna Steere and Nick White of of Ashfield MedComms, an Ashfield Health company (New York, NY, USA); funding was provided by the study sponsor. The authors had full control of the poster and provided their final approval of all content.

GFW: has served as a consultant for: Genzyme, Novartis, Roche, and the US Department of Justice; has received research grant funding from the NIH, National MS Society, Doris Duke Foundation, Biogen, EMD Serono, Inc., Rockland, MA, USA, an affiliate of Merck KGaA, Darmstadt, Germany, and Roche.

UB: employee of Ares Trading SA, Eysins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany.

BH and LAL: employees of EMD Serono, Inc., Rockland, MA, USA, an affiliate of Merck KGaA, Darmstadt, Germany.

AHC: has received honoraria and/or research support from: Biogen, Celgene, EMD Serono, Inc., Rockland, MA, USA, an affiliate of Merck KGaA, Darmstadt, Germany, Genentech/Roche, NOVARTIS, and TG Therapeutics.

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BACKGROUND INFORMATION

- Previous studies have suggested that seroprotection following vaccination may be reduced in patients with MS receiving some DMTs suppressing the immune system[1-3]
- The COVID-19 pandemic and vaccine availability have increased the urgency around further investigating the impact of MS DMTs on vaccine efficacy
- Cladribine tablets have been approved in more than 80 countries for the treatment of relapsing forms of MS, and are hypothesized to function as an immune reconstitution therapy with potential to cross the blood-brain barrier
- The CLOCK-MS study (CLadribine tablets: collaborative study to evaluate impact On Central nervous system biomarKers in MS) is a 24-month, open-label, randomized, multicenter, collaborative Phase IV biomarker research study in patients with RRMS or active SPMS

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OBJECTIVE

- To evaluate the potential impact of recent treatment with cladribine tablets on the development of antibody titers post-influenza vaccination via a sub-study of CLOCK-MS

METHODS

Patient Selection

CLOCK-MS main study

- The CLOCK-MS main study (NCT03963375) will enroll approximately 50 patients across 5 sites who:
  - Are age 18–65
  - Have been diagnosed with RRMS or active SPMS
  - Had inadequate response to, or were unable to tolerate, an alternate drug indicated for the treatment of RMS

Vaccine substudy

- The CLOCK-MS vaccine substudy is an *ad hoc* snapshot evaluation of patients vaccinated during the study who:*
  - Have received at least one dose of cladribine tablets
  - Are planning to obtain one standard-of-care influenza vaccine
  - Consent to blood sampling

*In addition to main study inclusion criteria

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METHODS

Vaccine Substudy Design

- Patients were treated with cladribine tablets as per the USPI
- Blood sampling for antibody titers to Flucelvax 20-21 and Tet-Dip control were collected:
  - 0—3 Weeks pre-vaccine (within 21 days prior to obtaining a standard of care vaccine)
  - 4 Weeks post-vaccine (+/- 7 days)
  - 6 Months post-vaccine (+/- 7 days)
- As a control, titers were determined for responses to Tet-Dip, to which patients had not received recent vaccination

Quantitative Antibody Titer Measurement

- The ELISA technique was used to measure OD of the samples at each serial dilution point for both the Flucelvax 20-21 and Tet-Dip control[4]
- An ELISA was performed on the samples with two vaccines, the Flucelvax 20-21 (1:300 dilution) and the Tet-Dip vaccine (1:100 dilution) as a control
  - Wells on the plate were coated with the serially diluted samples and the diluted vaccines, then incubated overnight
  - Plates were blocked and incubated, and the goat anti-human IgG-HRP (secondary antibody) was diluted to 1:2,500, added to the plates, and incubated
  - Optical density measurements were taken using an ELISA plate reader
- Titer dilutions were calculated by finding the EC50 OD point of the fitted curve to determine the corresponding dilution factor, using GraphPad Prism v9

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RESULTS

- 4 patients diagnosed with RRMS, aged 36 to 59, with disease durations >10 years and EDSS score 2.5 to 5 have been enrolled in the study

Patient demographics and baseline characteristics

	Age (y)	Gender	Disease duration (y)	EDSS score
Patient #1	59.1	Female	21	4.5
Patient #2	45.7	Female	10	2.5
Patient #3	36	Female	13	3
Patient #4	40.6	Male	15	5

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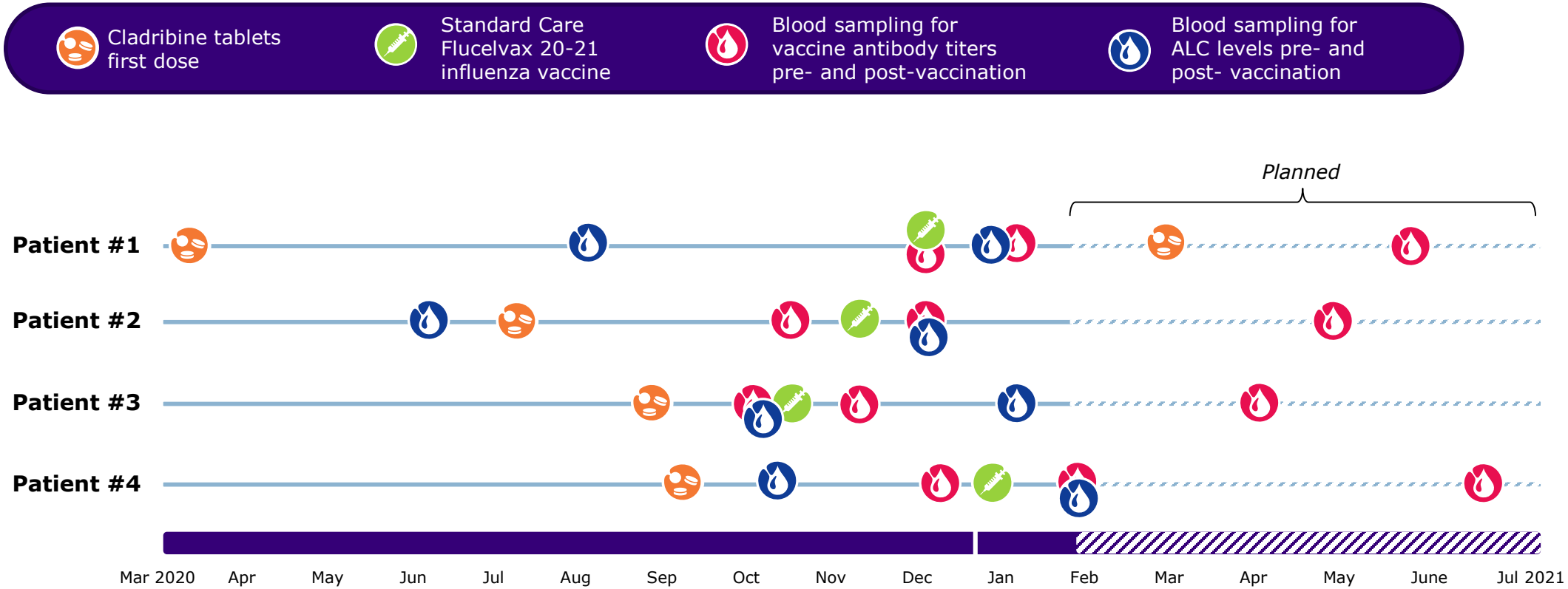
RESULTS

Timeline for Vaccine Substudy Assessments by Patient



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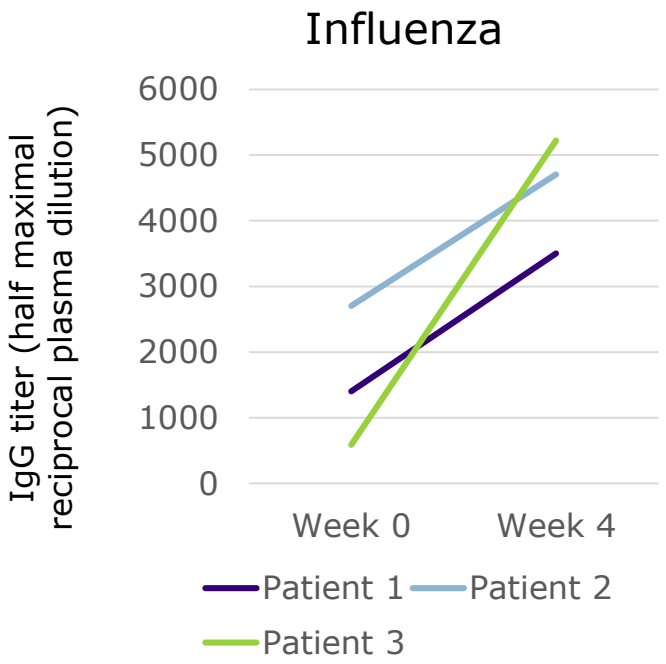
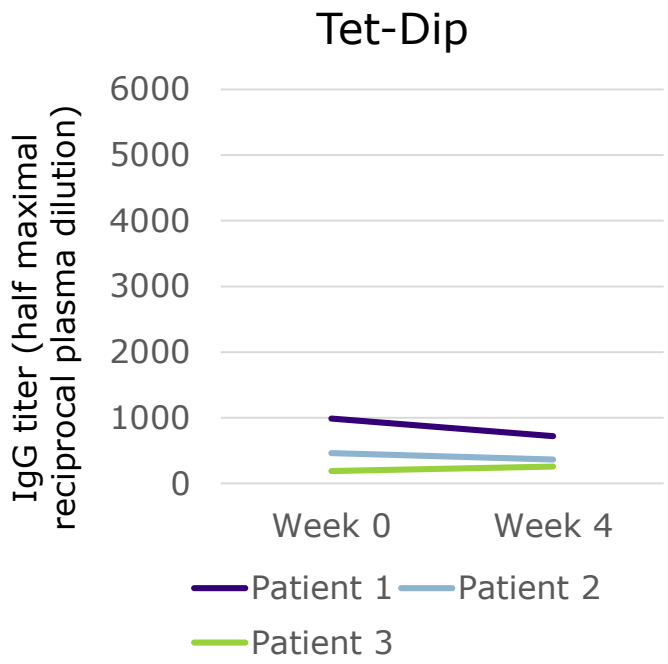
RESULTS

Immune Response to Vaccination and Concurrent ALC Status

	Influenza titers		Tet-Dip control titers		ALC (cells/uL)	
	Pre-vaccination	Post-vaccination	Pre-vaccination	Post-vaccination	Pre-vaccination	Post-vaccination
Patient #1	1402	3504	990	720	**1476** (8/5/20)	**1887** (1/7/21)
Patient #2	2702	4705	464	365	**818** (6/3/20)	**381** (12/9/20)
Patient #3	588	5220	188	256	**608** (10/9/20)	**622** (1/13/21)
Patient #4	TBD	TBD	TBD	TBD	**1470** (10/15/20)	N/A

Lymphopenia status
- Normal range
- Grade 1
- Grade 2
- Grade 3





- All 3 patients with 4-week data demonstrated an increase in influenza titers
  - 2 of these patients were experiencing lymphopenia around vaccination date and had received treatment with cladribine tablets 4 (Patient 2) and 2 (Patient 3) months prior to vaccination

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CONCLUSIONS

- **Vaccine effectiveness in MS patients treated with DMTs is particularly important following the availability of COVID-19 vaccines**
- **Seroprotective antibody levels against seasonal influenza were increased at 4 weeks post-vaccination in all three patients treated with cladribine tablets for whom data has been collected.**
  - **Two of these patients, who had received treatment with cladribine tablets 2 and 4 months prior to vaccination, were experiencing lymphopenia around the time of vaccination**
- **This study is ongoing and aims to collect samples from all participants receiving vaccination in the future to assess vaccine efficacy**

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