Analysis of Influenza and Varicella Zoster Virus Vaccine Antibody Titers in Patients with Relapsing Multiple Sclerosis Treated with Cladribine Tablets

Sanjeev Roy[1], Ursula Boschert[1]

[1]Ares Trading S.A., Eysins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany

SUMMARY

In this small retrospective investigation, vaccination close to cladribine tablets initiation in year 1 and in year 2 provided protective immunity against varicella zoster virus and seasonal influenza.

Seroprotective antibody levels against varicella zoster and seasonal influenza were maintained or increased for at least 6 months independent of lymphocyte counts measured at the time of vaccination in year 1 or 2 of cladribine tablets treatment.

Results from another study of vaccine protection in patients treated with cladribine tablets are also being presented at ACTRIMS 2021 (poster #P071—Wu GF, et al. Evaluating the Impact of Cladribine Tablets on the Development of Antibody Titres: Interim Results from the CLOCK-MS Influenza Vaccine Sub-Study)

ALC, absolute lymphocyte count; **BL**, baseline; **CladT**, cladribine tablets; **DMD**, disease-modifying drug; **ELISA**, enzyme-linked immunosorbent assay; **Gd+**, gadolinium enhancing; **HAI**, hemagglutination inhibition; **Ig**, immunoglobulin; **M**, month; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis; **Pat**, patient; **Scr**, screening; **VZV**, varicella zoster virus

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- **SR** and **UB** are employees of Ares Trading S.A., Eysins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany.

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The MAGNIFY-MS study: NCT03364036.

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BACKGROUND INFORMATION

- Recent studies have shown that patients with MS can mount a protective immune response to the influenza vaccine.[1] However, the use of DMDs may increase the risk of infections and alter vaccine efficacy.[2]
- The MAGNIFY-MS study (NCT03364036)[3] aims to determine the onset of action of cladribine tablets (3.5 mg/kg cumulative dose over 2 years) in patients with highly active relapsing MS.†
- As some patients enrolled in MAGNIFY-MS received vaccinations during the course of the trial as standard of care, this presented an opportunity to investigate the vaccine response.
  - Although this investigation was not part of the protocol, it was driven by the COVID-19 pandemic and the need of urgent vaccination data to better manage patients with MS.

OBJECTIVES

To investigate the immunoprotective response to VZV and seasonal influenza vaccination in patients treated with cladribine tablets for relapsing MS in the MAGNIFY-MS study.

†Highly active relapsing MS as defined by: one relapse in the previous year and at least 1 T1 Gd+ lesion, or 9 or more T2 lesions, while on therapy with other DMDs, or two or more relapses in the previous year, whether on DMD treatment or not.

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METHODS

Blood samples from 15 patients with relapsing MS treated with cladribine tablets who received VZV (n=3) or seasonal influenza vaccinations (n=12) as a standard of care, were retrospectively investigated.

Two control blood samples (baseline sample before starting cladribine tablets and closest sample available just before vaccination) and two post-vaccination blood samples (closest sample available after vaccination) were examined.

Quantitative antibody titers in response to the VZV and seasonal influenza vaccine were measured by ELISA and HAI assay, respectively.

The seroprotection titer levels for the VZV vaccine are ≥100 IU/L* and ≥40† for the seasonal influenza vaccine.

*As per the ELISA test protocol. †As per the EMA cut-off.

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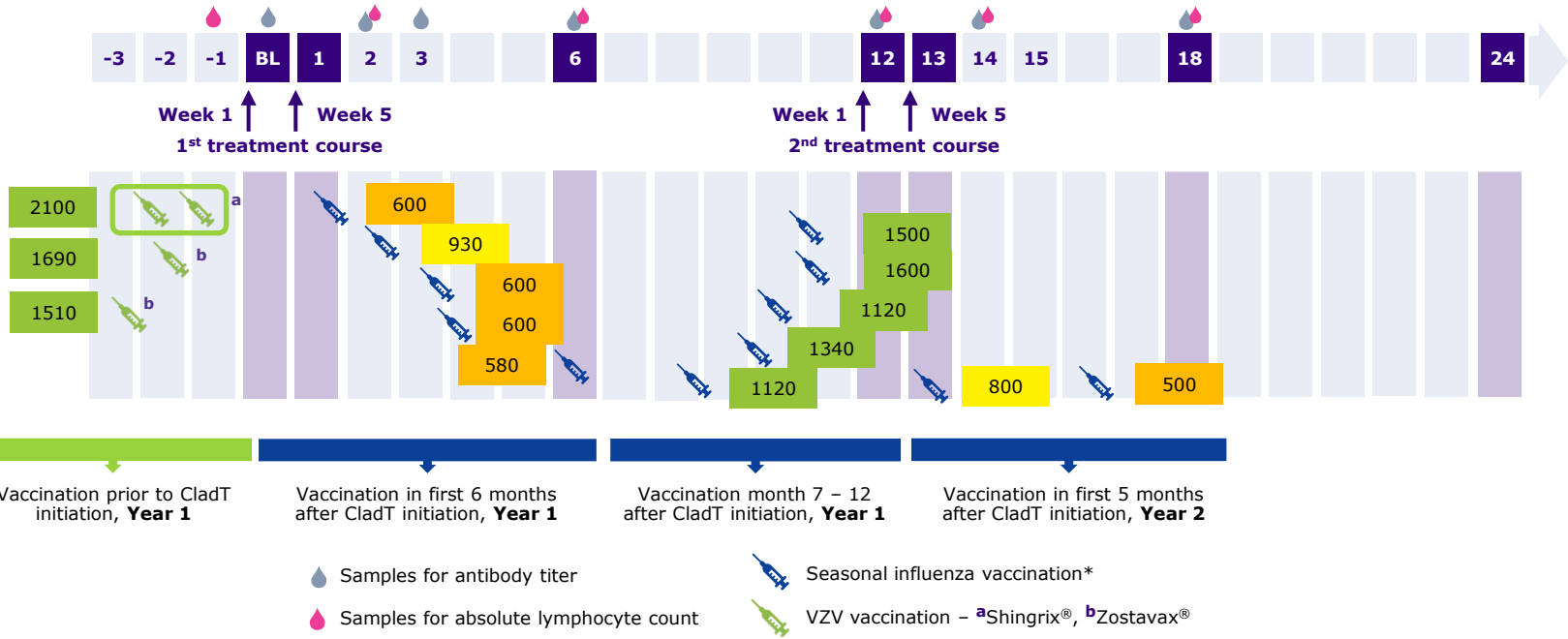
METHODS

Lymphopenia status: Normal range | Grade 1 | Grade 2 | Grade 3

Administration and sampling timeline for vaccinations



Each syringe represents a different patient (with the exception of the Shingrix® vaccine). ALC counts (cells/µL) are represented next to each syringe.

*The vaccine strains for seasonal influenza differed each year.

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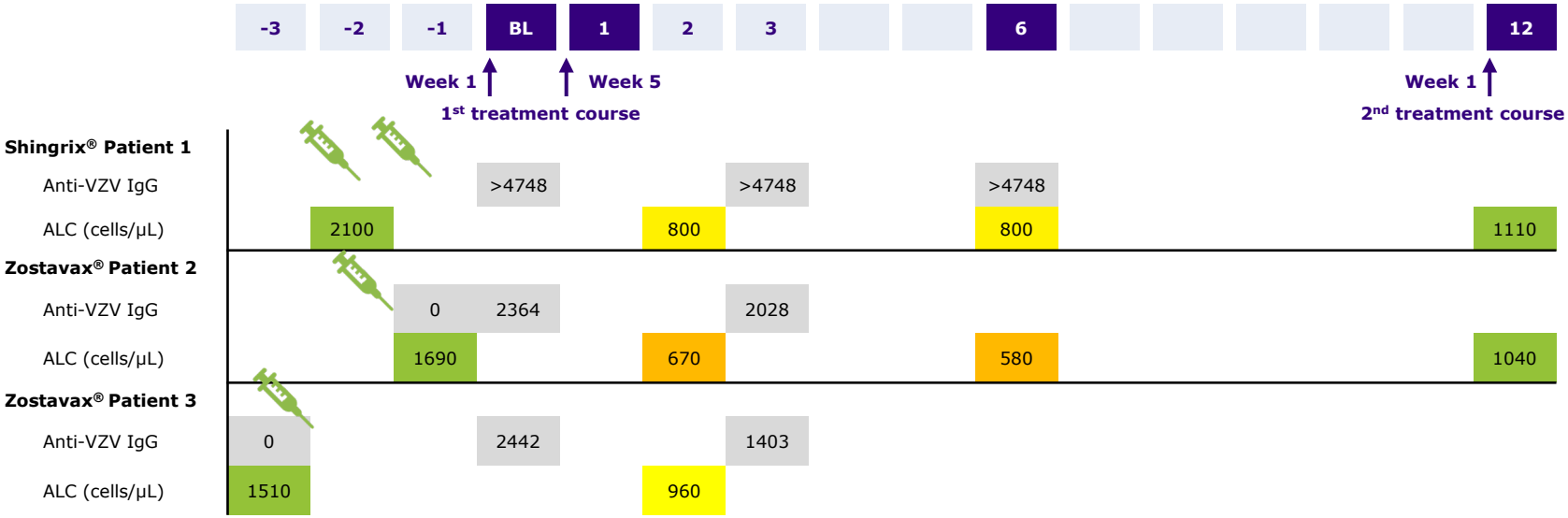
RESULTS

Lymphopenia status: Normal range | Grade 1 | Grade 2 | Grade 3

VZV vaccination before Year 1 initiation of cladribine tablets treatment



- Seroprotective* VZV titers were maintained over 6 months post-initiation with cladribine tablets, despite lymphocyte depletion.

*Seroprotection was defined as titers ≥100 IU/L.

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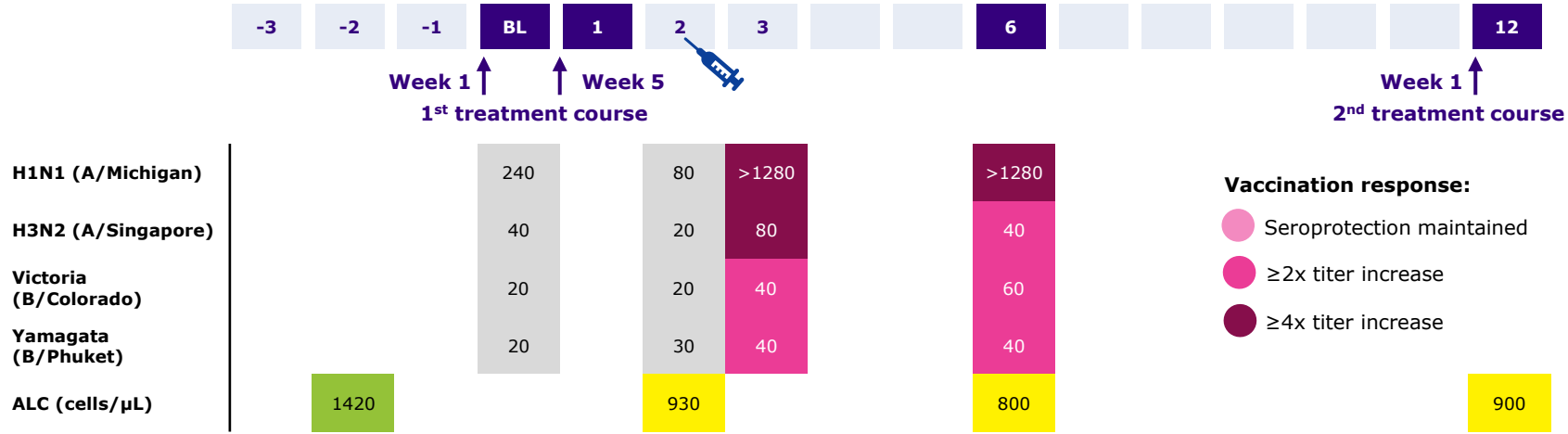
Lymphopenia status: Normal range | Grade 1 | Grade 2 | Grade 3

RESULTS

Example of seasonal influenza vaccination during Year 1 of cladribine tablets treatment



- In this individual patient example, influenza vaccination 2.5 months after cladribine tablets initiation in Year 1 induced protective serology.
- A ≥4-fold rise in titers for two A strains was seen up to 6 months after cladribine tablets initiation, or 3.5 months after vaccination. No samples were available for later time points.
- In two strains, titers were raised 1.5–2-fold and then maintained above protective levels (≥40).

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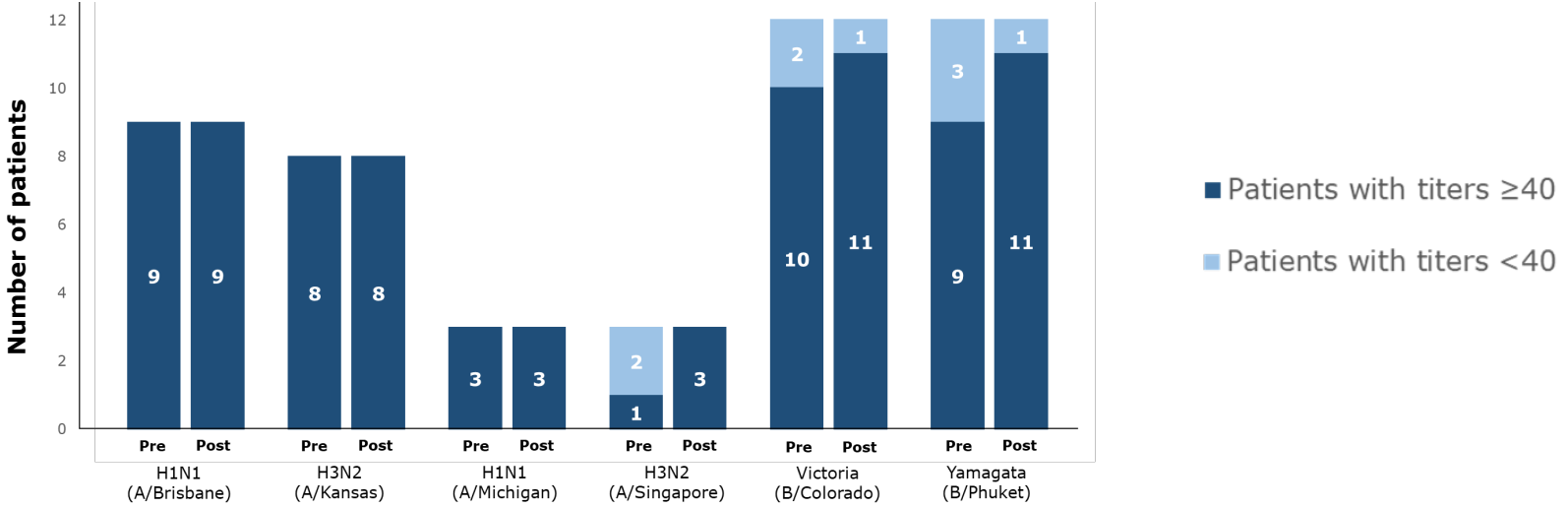
RESULTS

Seasonal influenza vaccination – seroprotection*



- The majority of patients had seroprotective antibody titers even before vaccination; post-vaccination seroprotective titers were maintained in those patients.
- The number of patients with seroprotective antibody titers increased for three strains (H3N2 and two B strains).

*Seroprotection was defined as HAI titers ≥40.

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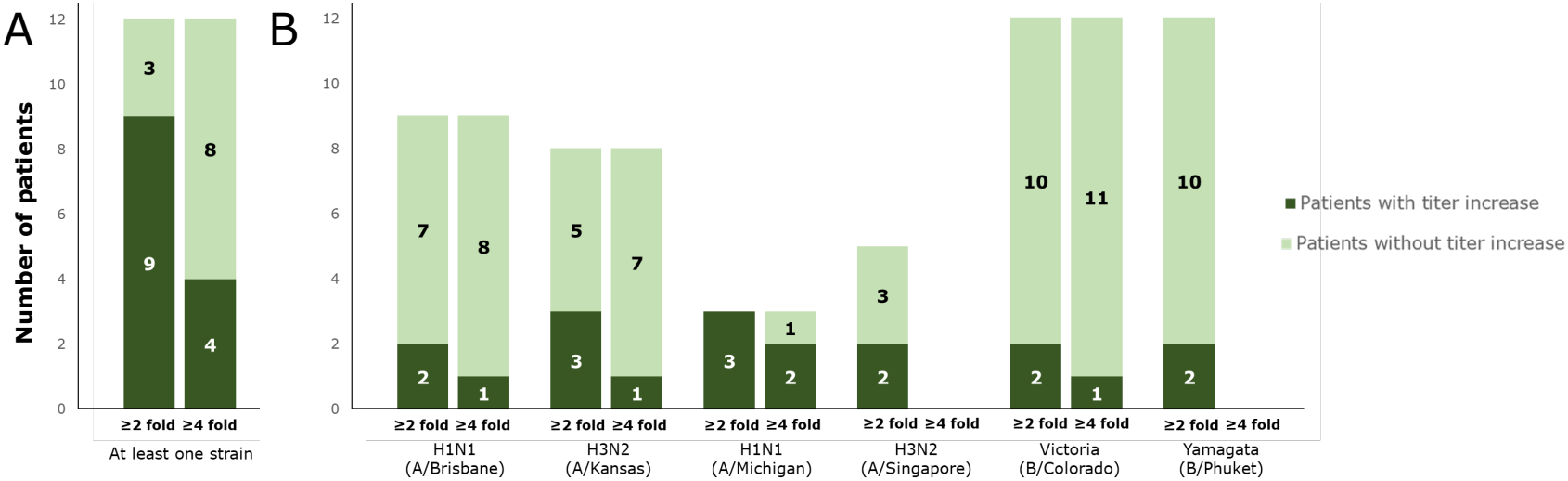
RESULTS

Seasonal influenza vaccination – titer increase



- Nine out of 12 patients exhibited a ≥2-fold titer increase, and 4 out of 12 patients exhibited a ≥4-fold increase, for at least one strain of influenza.
- Titers were increased to a greater extent for A influenza strains than B.

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RESULTS

Seasonal influenza – vaccine response in relation to lymphocyte count

Early Vaccination Year 1:
Grade 1 or 2 lymphopenia

Vaccination during or after CladT	Vaccination ALC* cells/μL
M 1.5	600
M 2.5	930
M 3.5	600
M 3.8	600
M 6	580

Late Vaccination Year 1:
Normal ALC

Vaccination after CladT	Vaccination ALC# cells/μL
M 8.5	1120
M 9.8	1340
M 10	1120
M 10.5	1600
M 10.5	1500

Early Vaccination Year 2:
Grade 1 or 2 lymphopenia

Vaccination during or after CladT	Vaccination ALC# cells/μL
M 1	800
M 4.5	500

Best vaccination response per patient: Seroprotection maintained | ≥2x titer increase | ≥4x titer increase

- Seroprotection or increase in seasonal influenza titers occurred in cladribine tablet treated patients who were vaccinated early (M1.5 – 6 Year 1 and M1 – 4.5 Year 2) or late (M8.5 – 10.5 Year 1).
- Seroprotection was maintained or increased irrespective of lymphocyte count.

Approx. ALC defined with pre- and/or post-vaccination time points: *ALC up to +/- 0.5 M from vaccination, #ALC up to +/- 2 M from vaccination.

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