Immune response following COVID-19 vaccination (mRNA or non-mRNA) in patients with relapsing multiple sclerosis treated with the Bruton's tyrosine kinase inhibitor evobrutinib: an update

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CONCLUSIONS

- **The data reported here show a humoral response to both mRNA and non-mRNA vaccination, building upon an earlier assessment of mRNA SARS-CoV-2 vaccinations in evobrutinib-treated patients with RMS**
- **The observed increase in antibody levels in seronegative and seropositive patients demonstrates the ability to mount humoral responses to both novel and recall antigens in evobrutinib-treated patients with RMS**
- **Following booster vaccinations, antibody levels increased further compared with after the first vaccination cycle**

These results provide additional evidence that the evobrutinib-treated patients have a comparable humoral vaccination response to healthy controls and untreated patients with MS

INTRODUCTION

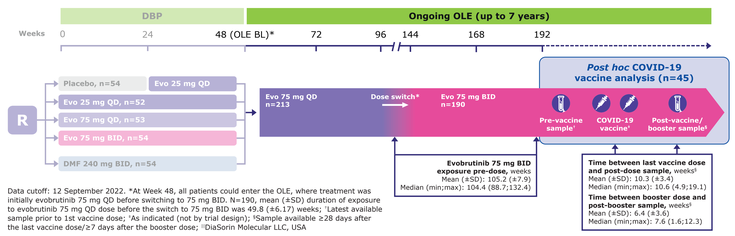
- Evobrutinib is an orally administered, highly selective, CNS-penetrant, covalent BTK inhibitor[1,2]
- In MS, some disease-modifying therapies, including S1PR modulators and anti-CD20 monoclonal antibodies, have been shown to suppress humoral immunity in response to vaccination[3–6]
- Previous analyses showed that evobrutinib-treated patients with SLE mounted a humoral immune response to seasonal influenza vaccination[7], and evobrutinib-treated patients with RMS (n=24) could mount an antibody response to mRNA SARS-CoV-2 vaccines[8]
- As BTK inhibition is a novel treatment strategy in MS, further understanding the impact of BTK inhibition on vaccination responses is of high interest and is characterized further here

OBJECTIVE

To examine the humoral response to mRNA and non-mRNA SARS-CoV-2 vaccination in patients with RMS receiving evobrutinib during the OLE of a Phase II trial (NCT02975349)

METHODS

- This *post hoc* analysis included patients with RMS who received evobrutinib 75 mg BID (fasted) and SARS-CoV-2 vaccination (mRNA or non-mRNA) during the Phase II OLE
- Samples were not collected by trial design, but selected:
  - Pre-dose: the latest available sample prior to 1st vaccine dose
  - Post-dose: sample available ≥28 days after last vaccine dose
  - Post-booster: sample available ≥7 days after booster dose



Data cutoff: 12 September 2022. *At Week 48, all patients could enter the OLE, where treatment was initially evobrutinib 75 mg QD before switching to 75 mg BID. N=190, mean (±SD) duration of exposure to evobrutinib 75 mg QD dose before the switch to 75 mg BID was 49.8 (±6.17) weeks; †Latest available sample prior to 1st vaccine dose; ‡As indicated (not by trial design); §Sample available ≥28 days after the last vaccine dose/≥7 days after the booster dose; ¶DiaSorin Molecular LLC, USA

IgG anti-S1 and anti-S2 specific antibodies to SARS-CoV-2 were measured using an indirect chemiluminescence immunoassay[11]

- **LLoQ: 3.8 AU/mL**
- **ULoQ: 2900.0 AU/mL**
- **Seronegative: <15.0 AU/mL**
- **Seropositive: ≥15.0 AU/mL**

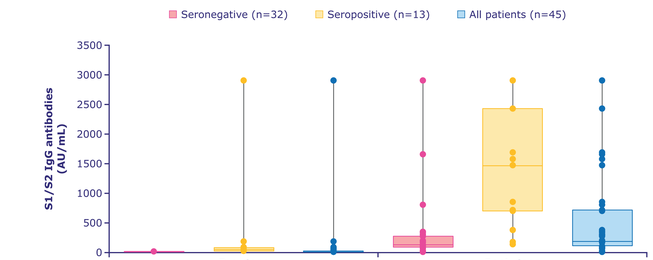
RESULTS

S1/S2 IgG antibody response to vaccination

- N=45 patients received COVID-19 vaccines during the OLE (data cutoff: 12 September 2022)
  - mRNA vaccine: n=37
  - Non-mRNA vaccine: n=8
- At baseline, patients had a mean (±SD) age of 46.0 (±9.6) years, 68.9% were female, and mean (±SD) BMI was 24.6 (±4.6) kg/m^2
- Prior to vaccination, **32** patients were **seronegative** and **13** patients were **seropositive**

- Of 45 evobrutinib-treated patients, 43 developed or increased S1/S2 IgG antibody levels after vaccination
- The antibody response observed was higher in patients seropositive prior to vaccination versus those patients seronegative prior to vaccination
- The levels were in the range of those observed for healthy controls and untreated MS patients receiving an mRNA vaccine[9]

- Only two patients did not have a change in S1/S2 IgG antibody levels after vaccination
  - One patient was seronegative both pre- and post-vaccination. The other patient had S1/S2 IgG antibody levels >2900 AU/mL both pre- and post-vaccination
- Overall, there was no substantial difference in the antibody response with the mRNA versus non-mRNA vaccines



	Pre-dose			Post-dose		
Geometric mean (±SD)	4.3 (±1.3)	55.5 (±4.0)	9.0 (±4.0)	133.6 (±3.7)	984.4 (±2.9)	237.8 (±4.7)
Median	3.8	44.7	3.8	123.0	1465.0	182.0
Geometric mean fold change* (±SD)				31.0 (±3.4)	17.7 (±3.3)	26.4 (±3.4)
Median fold change* (min;max)				30.3 (1.0;557.9)	18.3 (1.0;90.5)	28.4 (1.0;557.9)

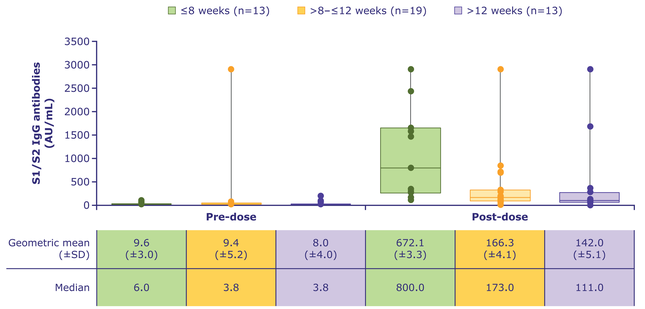
*Fold changes are the ratio between the post-dose and pre-dose IgG antibody levels

- The geometric mean (±SD) fold change of S1/S2 IgG antibody levels for all patients was 26.4 (±3.4) AU/mL
  - The majority of patients (n=36/45), had at least a 10–100 fold induction of S1/S2 IgG antibody levels from pre- to post-vaccination

Antibody levels over time following vaccination

- Time between last vaccine dose and post-dose sample was 4.9–19.1 weeks
- For the majority of patients, the time between the last vaccine dose and antibody assessment was >8 weeks (n=32/45, 71.1%)

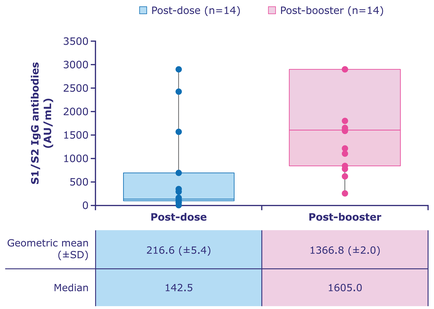
- With increasing time between the last vaccine dose and antibody assessment, a lower antibody level was observed, as has been reported for SARS-CoV-2 vaccines in the general population[10,11]



	Pre-dose			Post-dose		
Geometric mean (±SD)	9.6 (±3.0)	9.4 (±5.2)	8.0 (±4.0)	672.1 (±3.3)	166.3 (±4.1)	142.0 (±5.1)
Median	6.0	3.8	3.8	800.0	173.0	111.0

Response to booster vaccination

- S1/S2 IgG antibody levels increased in n=12/14 evobrutinib-treated patients who received an mRNA booster compared with after the initial vaccination cycle
- Two patients did not have a change in S1/S2 IgG antibody levels after the booster
  - One patient had S1/S2 IgG antibody levels of 1575.0 and 1615.0 AU/mL post-vaccination and post-booster, respectively. The other patient had levels ≥2900 AU/mL at both timepoints



	Post-dose	Post-booster
Geometric mean (±SD)	216.6 (±5.4)	1366.8 (±2.0)
Median	142.5	1605.0

Abbreviations: AU, arbitrary units; **BID**, twice daily; **BL**, baseline; **BMI**, body mass index; **BTK**, Bruton's tyrosine kinase; **COVID-19**, coronavirus disease 2019; **CNS**, central nervous system; **DBP**, double-blind period; **DMF**, dimethyl fumarate; **Evo**, evobrutinib; **IgG**, immunoglobulin G; **LLoQ**, lower limit of quantification; **mRNA**, messenger ribonucleic acid; **MS**, multiple sclerosis; **OLE**, open-label extension; **QD**, once daily; **R**, randomization; **RMS**, relapsing multiple sclerosis; **SARS-CoV-2**, severe acute respiratory syndrome coronavirus 2; **SD**, standard deviation; **S1PR**, sphingosine-1-phosphate receptors; **SLE**, systemic lupus erythematosus; **ULoQ**, upper limit of quantification; **W**, week

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