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

Amit Bar-Or[1], Anne H. Cross[2], Anthony Cunningham[3], Yann Hyvert[4], Andrea Seitzinger[4], Elise E. Drouin[5], Nektaria Alexandri[4], Davorka Tomic[6], Xavier Montalban[7]

[1]Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [2]Neurology, Washington University School of Medicine, St. Louis, MO, USA; [3]Centre for Virus Research, The Westmead Institute for Medical Research, The University of Sydney, Westmead, NSW, Australia; [4]The healthcare business of Merck KGaA, Darmstadt, Germany; [5]EMD Serono, Billerica, MA, USA; [6]Ares Trading SA, Eysins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany; [7]Department of Neurology-Neuroimmunology, Centre d'Esclerosi Múltiple de Catalunya (Cemcat), Hospital Universitari Vall d'Hebron, Barcelona, Spain

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Evobrutinib is currently in Phase III trials for relapsing multiple sclerosis and has not yet been approved by any regulatory authority

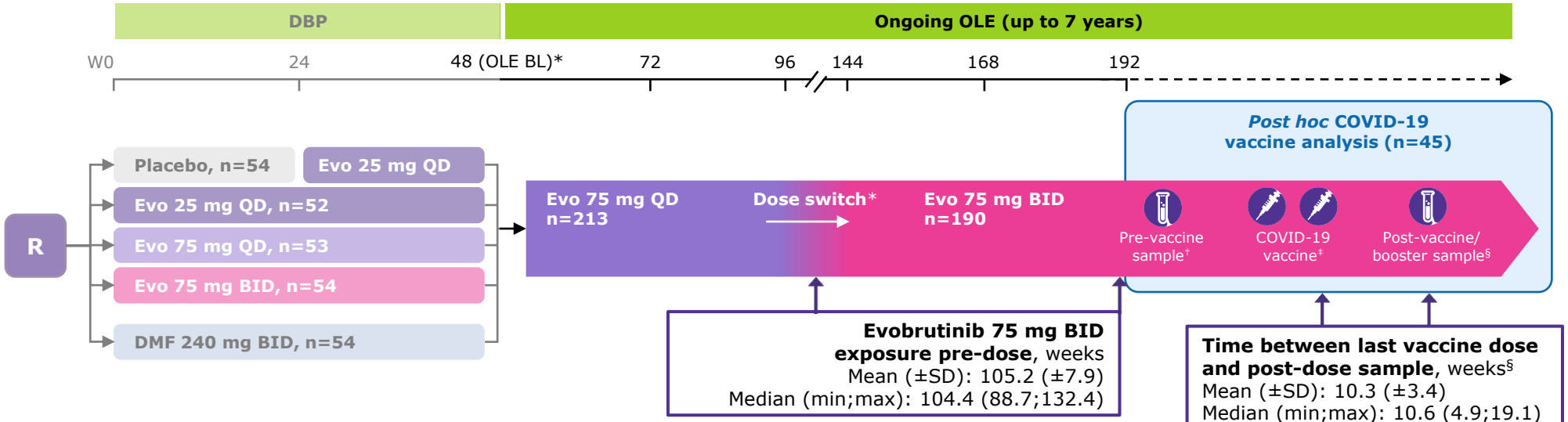
- Evobrutinib is an orally administered, highly selective, CNS-penetrant, covalent BTK inhibitor[1,2]
- There is evidence that MS disease-modifying therapies that work through B cell depletion (anti-CD20 monoclonal antibodies) or lymphocyte sequestration (S1PR modulators) adversely affect humoral responses to SARS-CoV-2 vaccination in people with MS[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

1. Haselmayer P, et al. *J Immunol*. 2019;202:2888–906; 2. Caldwell RD, et al. *J Med Chem*. 2019;62:7643–55; 3. Sormani MP, et al. *EBioMedicine*. 2021;72:103581; 4. Brill L, et al. *JAMA Neurol*. 2021;78:1510–4; 5. Pitzalis M, et al. *Front Immunol* 2021;12:781843; 6. Capuano R, et al. *Mult Scler Relat Disord*. 2022;60:103724; 7. Cross A, et al. *Eur J Neurol*. 2022;29(Suppl. 1):348 (EPR-253); 8. Bar-Or A, et al. *Mult Scler*. 2022;28(Suppl. 3):962 (P1188). **BTK**, Bruton's tyrosine kinase; **CNS**, central nervous system; **mRNA**, messenger ribonucleic acid; **MS**, multiple sclerosis; **RMS**, relapsing multiple sclerosis; **SARS-CoV-2**, severe acute respiratory syndrome coronavirus 2; **S1PR**, sphingosine-1-phosphate receptors; **SLE**, systemic lupus erythematosus

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)

mRNA, messenger ribonucleic acid; **OLE**, open-label extension; **RMS**, relapsing multiple sclerosis; **SARS-CoV-2**, severe acute respiratory syndrome coronavirus 2

- 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



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

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

Data cutoff: September 12, 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

AU, arbitrary units; **BID**, twice daily; **BL**, baseline; **COVID-19**, coronavirus disease 2019; **DBP**, double-blind period; **DMF**, dimethyl fumarate; **Evo**, evobrutinib; **IgG**, immunoglobulin G; **LLoQ**, lower limit of quantification; **mRNA**, messenger ribonucleic acid; **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; **ULoQ**, upper limit of quantification

Patient population

Patients who received SARS-CoV-2 vaccines during the OLE*
N=45

mRNA vaccine
n=37

Non-mRNA vaccine
n=8

Baseline characteristics

Age†
46.0 (±9.6) years

BMI†
24.6 (±4.6) kg/m^2

Female
68.9%

Prior to vaccination

32 patients were **seronegative**
(<15.0 AU/mL IgG anti-S1/S2 [spike protein domains] specific SARS-CoV-2-antibodies)

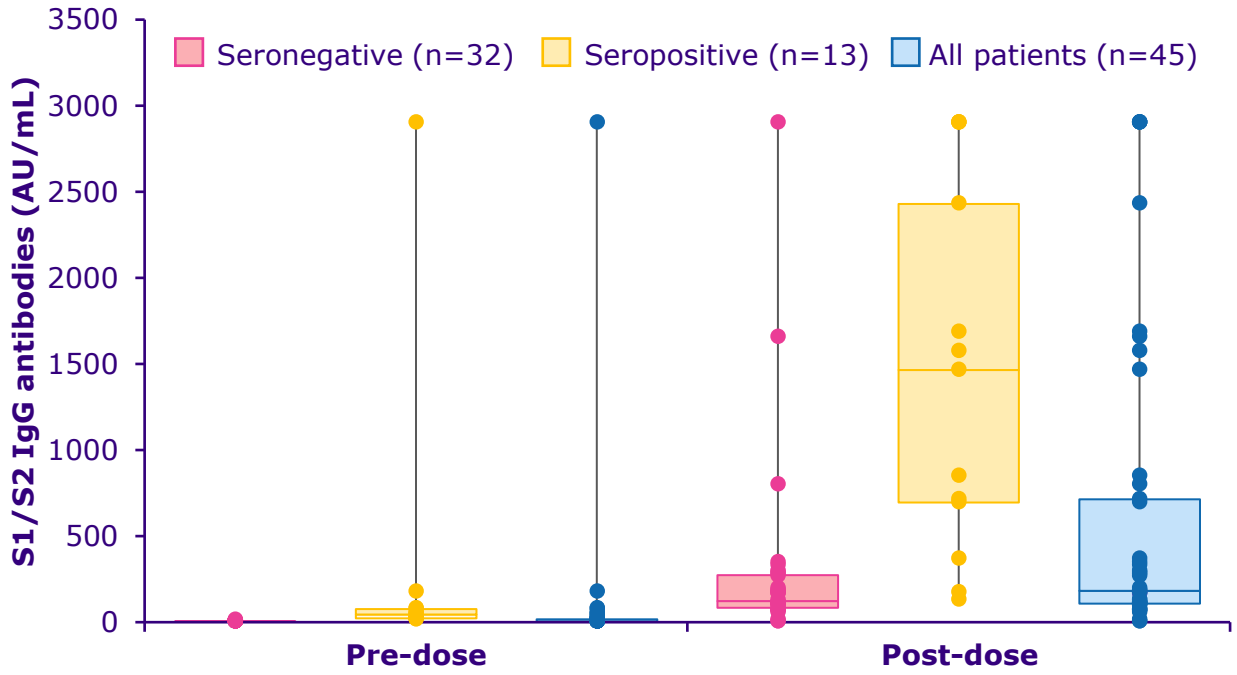
13 patients were **seropositive**‡
(≥15.0 AU/mL IgG anti-S1/S2 [spike protein domains] specific SARS-CoV-2-antibodies)

*Data cutoff: September 12, 2022; †mean (±SD); ‡seropositive status suggested prior exposure to SARS-CoV-2

AU, arbitrary units; **BMI**, body mass index; **IgG**, immunoglobulin G; **mRNA**, messenger ribonucleic acid; **OLE**, open-label extension; **SARS-CoV-2**, severe acute respiratory syndrome coronavirus 2; **SD**, standard deviation

S1/S2 IgG antibody response to vaccination

- 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[1]



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)

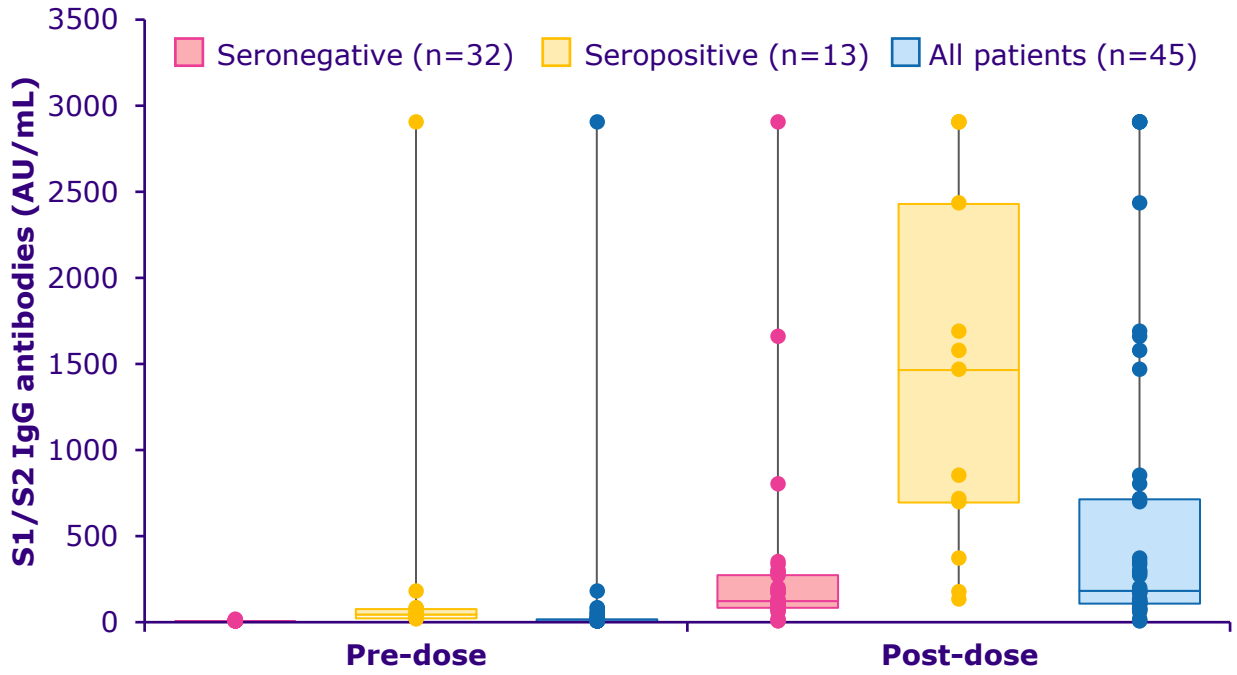
*Fold changes are the ratio between the post-dose and pre-dose IgG antibody levels

1. Brill L, et al. *JAMA Neurol*. 2021;78:1510–4

AU, arbitrary units; **IgG**, immunoglobulin G; **mRNA**, messenger ribonucleic acid; **MS**, multiple sclerosis; **SD**, standard deviation

S1/S2 IgG antibody response to vaccination

- 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
- 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



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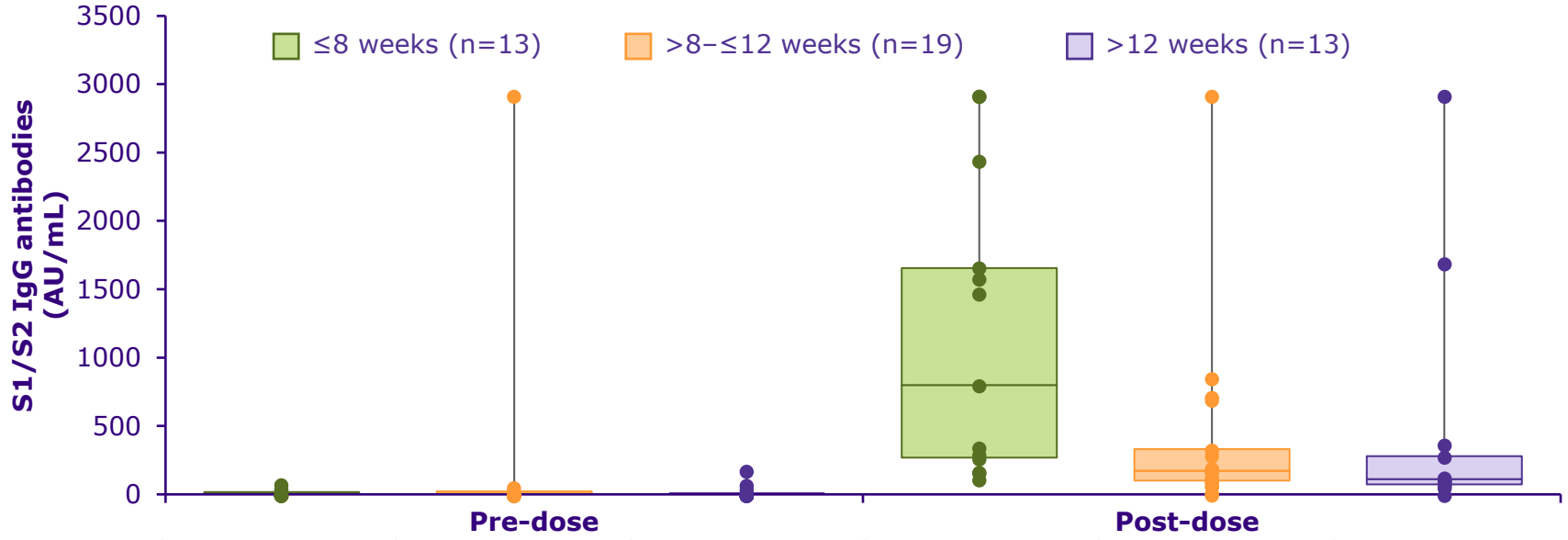
*Fold changes are the ratio between the post-dose and pre-dose IgG antibody levels

AU, arbitrary units; **IgG**, immunoglobulin G; **mRNA**, messenger ribonucleic acid; **SD**, standard deviation

Antibody levels over time following vaccination

- Time between last vaccine dose and post-dose sample was 4.9–19.1 weeks
- For most 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[1,2]



	≤8 weeks (n=13)	>8–≤12 weeks (n=19)	>12 weeks (n=13)	≤8 weeks (n=13)	>8–≤12 weeks (n=19)	>12 weeks (n=13)
	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

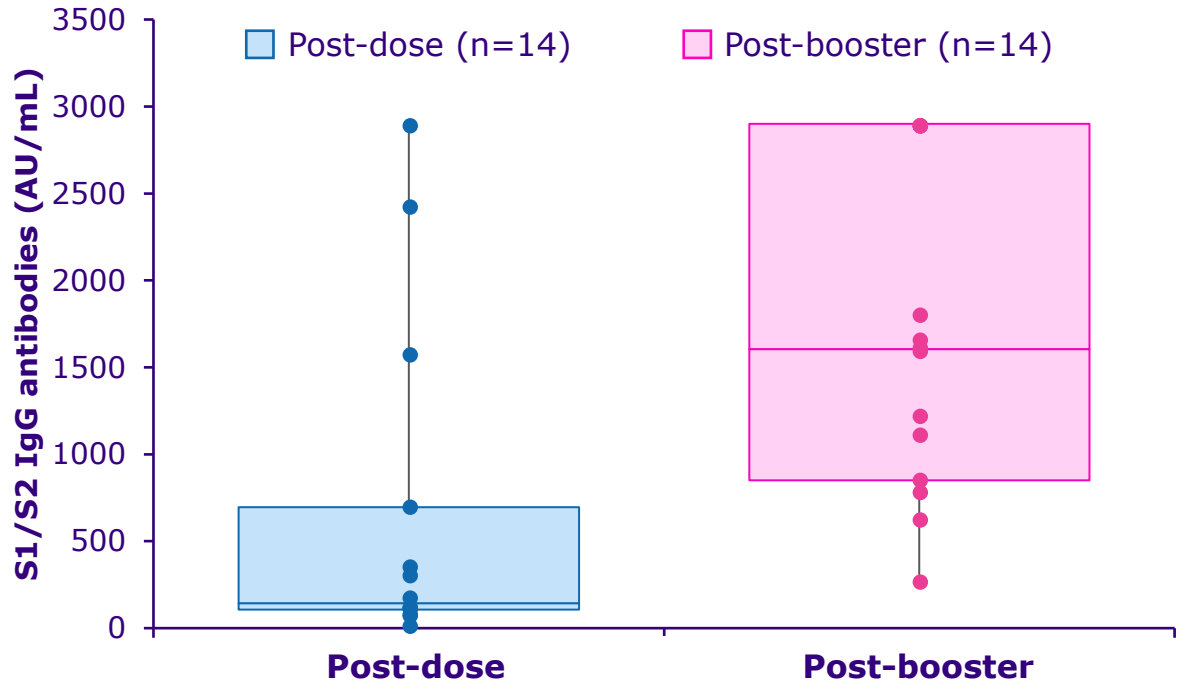
1. Favresse J, et al. *Emerg Microbes Infect*. 2021;10:1495–8; 2. Naaber P, et al. *Lancet Reg Health Eur*. 2021;10:100208

AU, arbitrary units; **IgG**, immunoglobulin G; **SARS-CoV-2**, severe acute respiratory syndrome coronavirus 2; **SD**, standard deviation

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

AU, arbitrary units; **IgG**, immunoglobulin G; **mRNA**, messenger ribonucleic acid; **SD**, standard deviation

- 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 evobrutinib-treated patients have a comparable humoral vaccination response to those previously reported for healthy controls and untreated patients with MS

mRNA, messenger ribonucleic acid; **MS**, multiple sclerosis; **RMS**, relapsing multiple sclerosis; **SARS-CoV-2**, severe acute respiratory syndrome coronavirus 2