# Humoral immune responses to SARS-CoV-2 vaccines in an ozanimod open-label extension study

**Freddy Caldera,[1] Rachel Maddux,[2] Ryan Ungaro,[3] Amandeep Kaur,[2] Elizabeth Brown,[2] Sarah Hu,[2] James K. Sheffield,[2] Diego Silva,[2] Sarah Harris,[2] Bruce A. C. Cree[4]**

[1]University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; [2]Bristol Myers Squibb, Princeton, NJ, USA; [3]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [4]Weill Institute for Neurosciences, Department of Neurology, University of California San Francisco, San Francisco, CA, USA

## Introduction

- Ozanimod, an oral sphingosine 1-phosphate (S1P) receptor modulator selectively targeting $S1P_1$ and $S1P_5$, prevents lymphocyte migration to the intestines through S1P receptor internalization[1-3]
- Ozanimod is approved in the United States and European Union for the treatment of moderately to severely active ulcerative colitis (UC) and relapsing multiple sclerosis (RMS)[2,3]
- A previous analysis of data from UC and multiple sclerosis (MS) open-label extension studies (True North [NCT02435992] and DAYBREAK [NCT02576717], respectively) showed that most participants with confirmed coronavirus infection (COVID-19) had nonserious infections, recovered, and did not require discontinuation of ozanimod[4]
- Some immunomodulators and biologics may attenuate the response of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine; this analysis evaluated serologic response and predictors of response to SARS-CoV-2 vaccination in participants with RMS treated with ozanimod[5-8]

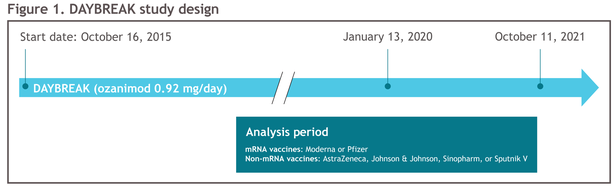
## Objectives

- To describe the serological response and predictors of response to SARS-CoV-2 vaccination in participants with RMS treated with ozanimod in the DAYBREAK study

## Methods

- Participants with RMS who completed a phase 1–3 ozanimod clinical trial could enter the single-arm, open-label, phase 3 DAYBREAK trial (**Figure 1**)
- This analysis (January 2020–October 2021) included DAYBREAK participants receiving mRNA or non-mRNA SARS-CoV-2 vaccines (1 or 2 doses, vaccine-dependent) and had serum samples available postvaccination
- Receptor binding domain (RBD) antibody titers were analyzed prevaccination, after 1 dose, and at 1–229 days after full vaccination (defined as 2 doses of Moderna, Pfizer, AstraZeneca, Sinopharm, or Sputnik V vaccine received or 1 dose of Johnson & Johnson vaccine received)
  - The Elecsys Anti-SARS-CoV-2 S assay (Roche Diagnostics, Indianapolis, IN, USA) and Cobas e 411 analyzer (Roche Diagnostics) were used to measure SARS-CoV-2 spike protein RBD antibodies
  - Seroconversion rates were defined as immunoglobulin G levels ≥0.8 U/mL
- Nucleocapsid antibody levels were measured before and after vaccination to confirm whether participants had a natural exposure to SARS-CoV-2
  - Nucleocapsid antibody negative indicated no exposure to SARS-CoV-2 and nucleocapsid antibody positive indicated exposure to SARS-CoV-2
- Student's t-test, Fisher's exact test, and regression models tested the association with seroconversion and log2 antibody levels

**Figure 1. DAYBREAK study design**

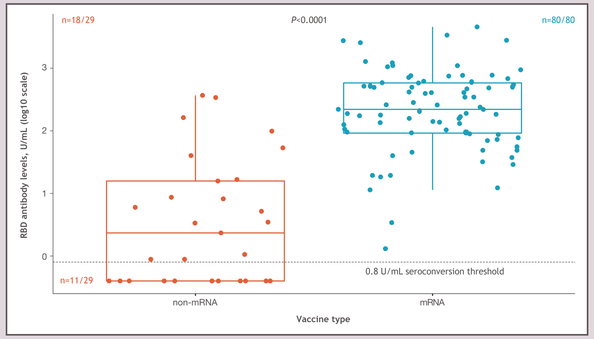



## Results

- Demographic and clinical characteristics were similar between recipients of the mRNA and non-mRNA vaccines (**Table 1**)

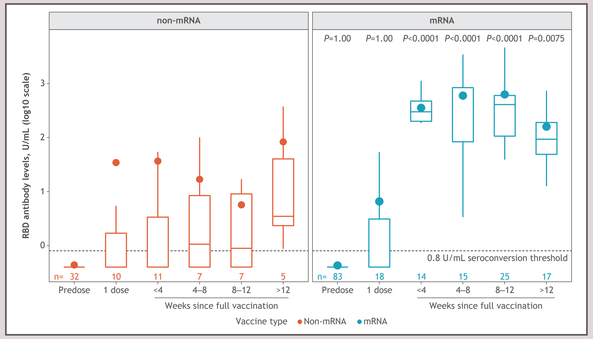
## Seroconversion occurred in 100% of fully vaccinated mRNA vaccine recipients receiving ozanimod

**Figure 2. RBD antibody levels in fully vaccinated participants by vaccine type**




Data are representative of fully vaccinated participants who were nucleocapsid antibody negative. The box-and-whisker plots show the median (horizontal line), interquartile range (box), and minimal and maximal values excluding any outliers (vertical line). The *P*-value was determined by comparing log2 SARS-CoV-2 RBD titer differences between the mRNA and non-mRNA groups using a Student's t-test.
RBD, receptor binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

**Figure 3. RBD antibody levels at each time point after mRNA and non-mRNA vaccination**




Group-level analyses of serum samples from participants with prevaccine and ≥1 postvaccine samples (N=115) who were nucleocapsid antibody negative. The box-and-whisker plots show the median (horizontal line), mean (large circles), interquartile range (box), and minimal and maximal values excluding any outliers (vertical line). *P*-values were determined by comparing log2 SARS-CoV-2 spike protein RBD titer differences between mRNA and non-mRNA participants at each time point in the linear regression model.
RBD, receptor binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

**Table 2. RBD antibody levels in mRNA and non-mRNA vaccine recipients**

| Vaccine type | n | RBD antibody levels, U/mL | | | | Percent of participants by RBD antibody level, U/mL | | |
|---|---|---|---|---|---|---|---|---|
| | | Mean | Median | SD | Range | <0.8 | ≥0.8 to ≤250 | ≥0.8 to ≤250 |
| mRNA | 80 | 512.6 | 220.2 | 789.8 | 1.3–4572.0 | 0 | 52% | 48% |
| Non-mRNA | 29 | 39.3 | 2.3 | 94.1 | 0.4–368.5 | 38% | 55% | 7% |

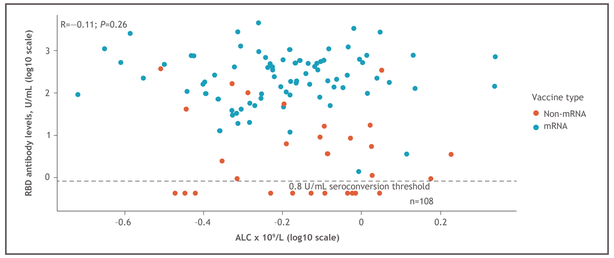
**Table 1. Demographic and clinical characteristics of fully vaccinated[a] participants without serological evidence of virus exposure[b]**

| Characteristics | mRNA vaccine recipients (n=80) | Non-mRNA vaccine recipients (n=29) | Total vaccinated participants (N=109) |
|---|---|---|---|
| Presence of RBD antibodies, n (%) | 80 (100) | 18 (62) | 98 (90) |
| White, n (%) | 78 (97.5) | 29 (100.0) | 107 (98.2) |
| Non-Hispanic, n (%) | 76 (95.0) | 28 (96.6) | 104 (95.4) |
| Eastern European, n (%) | 41 (51.3) | 22 (75.9) | 63 (57.8) |
| North America, n (%) | 10 (12.9) | 1 (3.4) | 11 (10.1) |
| Age, y, mean (range) | 40.4 (23.0–56.0) | 41.6 (28.0–56.0) | 40.7 (23.0–56.0) |
| ALC x $10^9$/L, mean (range) | 0.7 (0.2–2.2) | 0.8 (0.3–1.7) | 0.7 (0.2–2.2) |
| BMI, kg/m$^2$, mean (range) | 24.6 (16.8–42.0) | 25 (17.3–33.8) | 24.7 (16.8–42.0) |
| Female, n (%) | 59 (74) | 21 (72) | 80 (73) |
| Concomitant steroid use, n (%) | 1 (1.3) | 2 (6.9) | 3 (2.8) |
| Days on ozanimod, mean (range) | 1676.9 (1398.0–1967.0) | 1620.5 (1448.0–1869.0) | 1661.9 (1398.0–1967.0) |

[a]Fully vaccinated defined as 2 doses of Moderna, Pfizer, AstraZeneca, Sinopharm, or Sputnik V vaccine received or 1 dose of Johnson & Johnson vaccine received.
[b]All 109 participants were nucleocapsid antibody negative before and after vaccination.
ALC, absolute lymphocyte count; BMI, body mass index; RBD, receptor binding domain.

- Seroconversion occurred in 100% (80/80) of fully vaccinated mRNA vaccine recipients and 62% (18/29) of fully vaccinated non-mRNA vaccine recipients (**Figure 2**)
  - Participants who did not seroconvert received the following non-mRNA vaccines (n=11/29):
    - Johnson & Johnson (n=3/6)
    - Sinopharm (n=6/16)
    - Sputnik V (n=2/2)
  - Seroconversion occurred in all 5 patients who received the AstraZeneca non-mRNA vaccine
- Higher RBD antibody levels were observed in participants who received mRNA vs non-mRNA vaccines (**Table 2**)
  - A wide range of RBD antibody levels were detected in both vaccine groups
- RBD antibody levels in participants receiving mRNA vaccines increased after the second dose at all time points tested and were higher compared to those receiving non-mRNA vaccines (**Figure 3**)
- Absolute lymphocyte count (ALC) levels were not correlated with and were not predictive of RBD antibody seroconversion in vaccinated participants at matched time points (**Figure 4**)
- Age, body mass index (BMI), and sex were not predictors of antibody levels or seroconversion in vaccinated participants
- Vaccination with a non-mRNA vaccine predicted lower antibody levels (beta coefficient: -5.90 [95% CI: -6.99 to -4.82]; *P*<0.0001) and seroconversion (Fisher's exact test: *P*<0.0001)
  - These findings were from a linear model of log2 antibody levels: log2 (RBD) ~ vaccine type + log2 (ALC) + age + sex + BMI

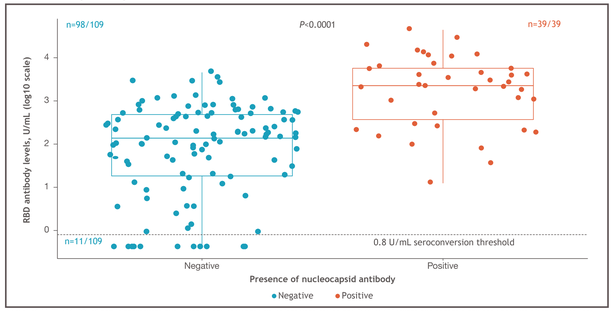
**Figure 4. RBD antibody levels vs ALC levels in fully vaccinated participants**




Prediction analyses were performed using postvaccination serum samples for fully vaccinated participants who were nucleocapsid antibody negative (n=109; n=108 for ALC, as 1 patient's time point was missing).
ALC, absolute lymphocyte count; RBD, receptor binding domain.

- Seroconversion rates and RBD antibody levels were higher in fully vaccinated participants with confirmed exposure to SARS-CoV-2 (**Figure 5**)
  - Seroconversion occurred in 100% of mRNA and non-mRNA vaccine recipients who were nucleocapsid antibody positive (n=39/39)
  - In patients who are nucleocapsid antibody positive, RBD antibody levels were higher in mRNA vaccine recipients compared with those who received non-mRNA vaccine (*P*=0.01)

**Figure 5. RBD antibody levels by presence of nucleocapsid antibodies in fully vaccinated participants**




A total of 66.7% (26/39) of participants were nucleocapsid antibody positive before vaccination and 2.6% (1/39) were nucleocapsid antibody positive after vaccination; for the remaining 30.8% (12/39), the timing of nucleocapsid antibody positivity with regard to vaccination could not be determined from these data. A level of 0.8 U/mL, which was the positive cutoff of the test, indicated seroconversion. The box-and-whisker plots show the median (horizontal line), interquartile range (box), and minimal and maximal values (vertical line). The *P*-value was determined between the groups that were nucleocapsid antibody negative and positive using a Student's t-test for log2 SARS-CoV-2 RBD titers.
RBD, receptor binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

## Conclusions

- Independent of demographic characteristics and ALC levels at time of vaccination, participants receiving ozanimod developed serologic response to SARS-CoV-2 vaccines, with 100% seroconversion after mRNA vaccination
- Fully vaccinated participants with evidence of natural infection have higher levels of RBD antibodies, possibly suggesting a primed immune response
- Some participants, however, developed low antibody levels and may benefit from booster doses
- These findings provide important information for physicians managing ozanimod-treated patients with UC or MS

## References

1. Scott FL et al. *Br J Pharmacol*. 2016;173:1778-1792.
2. Zeposia (ozanimod) [package insert]. Princeton, NJ: Bristol Myers Squibb; April 2022.
3. Zeposia (ozanimod) [summary of product characteristics]. Utrecht, Netherlands: Celgene Distribution B.V.; December 2021.
4. Ungaro RC et al. Presented at: ECCO 2022; February 16-19, 2022; Virtual. Poster 486.
5. Iancovici L et al. *Rheumatology*. 2022;61:3439-3447.
6. Edelman-Klapper H et al. *Gastroenterology*. 2022;162:454-467.
7. Reder AT et al. *CNS Drugs*. 2021;35:317-330.
8. Achiron A et al. *Ther Adv Neurol Disord*. 2021;14:17562864211012835.

## Acknowledgments

- This study was sponsored by Bristol Myers Squibb, Princeton, NJ, USA
- All authors contributed to and approved the presentation
- Yicong Li provided statistical support for this analysis
- Writing and editorial assistance was provided by Anny Wu, PharmD, of Peloton Advantage, LLC, an OPEN Health company, and was funded by Bristol Myers Squibb

## Disclosures

**FC:** received research support from Takeda; and has been a consultant for Arena, Celgene, GlaxoSmithKline, and Takeda. **RM, AK, EB, SHu, JKS, DS, and SHa:** employees and/or shareholders of Bristol Myers Squibb. **RU:** advisory board member or consultant for Eli Lilly, Janssen, Pfizer, and Takeda; and has received research support from AbbVie, Boehringer Ingelheim, and Pfizer. **BACC:** received personal compensation for consulting from Alexion, Atara, Autobahn Therapeutics, Avotres, Biogen, EMD Serono, Gossamer Bio, Horizon Therapeutics, Neuron23, Novartis, Sanofi, TG Therapeutics, and Therini Bio; and received research support from Genentech.

Presented at American College of Gastroenterology 2022; October 21-26, 2022; Charlotte, NC, USA, and Virtual.
*Previously presented at the 8th Congress of the European Academy of Neurology – Europe 2022; June 25-28, 2022; Vienna, Austria, and Virtual.*

Email: fcaldera@medicine.wisc.edu