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## Sponsor

Novartis Pharmaceuticals

## Generic Drug Name

Ofatumumab

## Trial Indication(s)

Relapsing multiple sclerosis

## Protocol Number

COMB157GDE01

## Protocol Title

Tracking the immune response to SARS-CoV-2 modRNA vaccines in an open-label multicenter study in participants with relapsing multiple sclerosis treated with ofatumumab s.c. (KYRIOS)

## Clinical Trial Phase

Phase 4

## Phase of Drug Development

Phase IV

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## Study Start/End Dates

Study Start Date: May 27, 2021 (Actual)
Primary Completion Date: May 10, 2022 (Actual)
Study Completion Date: June 13, 2023 (Actual)

## Reason for Termination (If applicable)

## Study Design/Methodology

This was a two cohort, multicenter, open-label, prospective study of 40 (optionally up to 60) RMS patients.

• The first cohort consisted of RMS patients receiving modRNA vaccine as part of clinical routine prior to starting ofatumumab treatment.

Cohort 1a: received their 1st and 2nd SARS-CoV-2 vaccines (and an optional booster vaccine)
Cohort 1b: received a booster vaccine

• The second cohort consisted of participants receiving modRNA vaccine as part of clinical routine while already stable on ofatumumab treatment for at least 4 weeks (since first dose).

Cohort 2a: received their 1st and 2nd SARS-CoV-2 vaccines (and an optional booster vaccine)
Cohort 2b: received a booster vaccine

Ofatumumab treatment initiation and maintenance was performed as per approved SmPC. SARS-CoV-2 mRNA vaccination was performed as part of clinical routine.

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## Centers

Germany(6)

## Objectives:

Primary objective::

To estimate the proportion of RMS patients having established SARSCoV- 2-specific T-cells after receiving a modRNA vaccine (initial vaccination or booster) either before or after starting ofatumumab treatment.

Secondary objectives:

To estimate the proportion of RMS

- patients maintaining for up to 18 months1 SARS-CoV-2-specific T cells after receiving a modRNA vaccine either before or after starting ofatumumab treatment.
- To estimate the increase in specific Tcells after receiving a modRNA booster vaccine either before or after starting ofatumumab treatment.
- To estimate the proportion of RMS patients achieving seroconversion (i.e. having SARS-CoV-2 serum neutralizing antibodies) after receiving a modRNA vaccine either before or after starting ofatumumab treatment.
- To estimate the proportion of RMS patients maintaining for up to 18 months quantifiable levels of SARSCoV- 2 serum functional antibodies after receiving a modRNA vaccine either before or after starting ofatumumab treatment.
- Describing phenotypically the cellular response after receiving a modRNA vaccine either before or after starting ofatumumab treatment.

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## Test Product (s), Dose(s), and Mode(s) of Administration

Ofatumumab initiation and treatment in this study was performed as per approved SmPC to resemble clinical routine as closely as possible. The used dose was 20 mg subcutaneous injection. monthly.

## Statistical Methods

Categorical data are summarized as frequencies and percentages. For continuous data, mean, standard deviation are presented. For all analysis sets, participants were analyzed according to the study treatment(s) received. The Safety Analysis Set (SAF) included all participants that received any study drug. The Efficacy Analysis Set (EAS) included all participants of the SAF who received a mRNA vaccine. The primary analysis did not use any statistical testing or modelling. The percentage of participants achieving SARS-CoV-2-specific T-cell response within each cohort was calculated. This was augmented by a (descriptive) two-sided 95% confidence interval (exact Clopper-Pearson).

Immunophenotyping was inconclusive due to low participant numbers and high heterogeneity within cohorts.

## Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Relapsing Multiple Sclerosis (RMS) diagnosis
- eligible for ofatumumab treatment
- willing and eligible to receive SARS-CoV-2 mRNA vaccine

Exclusion Criteria:

- known prior or current COVID-19 infection
- previous treatment with BTK inhibitor or anti-CD20 therapy other than ofatumumab
- no previous vaccination with a non-modRNA SARS-CoV-2 vaccine.

Other protocol-defined inclusion/exclusion criteria may apply

## Participant Flow Table

### Overall Study

| | Cohort 1a | Cohort 1b | Cohort 2a | Cohort 2b | Total |
|---|---|---|---|---|---|
| **Arm/Group Description** | Patients received first SARS-CoV-2 vaccination within the study prior to starting ofatumumab treatment. | Patients had already completed initial vaccination cycle and received a booster vaccine within the study prior to starting ofatumumab treatment. | Patients who received their first SARS-CoV-2 vaccination within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose). | Patients who had already completed their initial vaccination cycle and received a booster vaccine within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose). | |
| **Started** | 6 | 8 | 5 | 15 | 34 |
| **Completed** | 5 | 8 | 5 | 15 | 33 |
| **Not Completed** | 1 | 0 | 0 | 0 | 1 |
| Wish to have children. | 1 | 0 | 0 | 0 | 1 |

## Baseline Characteristics

| | Cohort 1a | Cohort 1b | Cohort 2a | Cohort 2b | Total |
|---|---|---|---|---|---|
| **Arm/Group Description** | Patients received first SARS-CoV-2 vaccination within the study prior to starting | Patients had already completed initial vaccination cycle and received a booster vaccine | Patients who received their first SARS-CoV-2 vaccination within the study while | Patients who had already completed their initial vaccination cycle and received a | |

| | | | | | |
|---|---|---|---|---|---|
| | ofatumumab treatment. | within the study prior to starting ofatumumab treatment. | already stable on ofatumumab treatment for at least 4 weeks (since the first dose). | booster vaccine within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose). | |
| **Number of Participants [units: participants]** | 6 | 8 | 5 | 15 | 34 |
| Baseline Analysis Population Description | | | | | |
| **Age Continuous**<br>(units: years)<br>Analysis Population Type: Participants<br>Mean ± Standard Deviation | | | | | |
| | 32.5±8.1 | 47.1±14.1 | 32.4±7.7 | 45.5±12.4 | 41.6±12.9 |
| **Sex: Female, Male**<br>(units: )<br>Analysis Population Type: Participants<br>Count of Participants (Not Applicable) | | | | | |
| Female | 5 | 5 | 4 | 9 | 23 |
| Male | 1 | 3 | 1 | 6 | 11 |
| **Race/Ethnicity, Customized**<br>(units: Participants)<br>Analysis Population Type: Participants | | | | | |
| Caucasian | 6 | 8 | 5 | 13 | 32 |
| Missing | 0 | 0 | 0 | 2 | 2 |

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# Primary Outcome Result(s)

## Percentage of participants having established SARS-CoV-2-specific T cells after receiving a modRNA vaccine

| | |
|---|---|
| Description | Participants who established SARS-CoV-2-specific T cells as defined by detection of SARS-CoV-2 reactive T-cells, measured by e.g. ELIspot assay from T-cells that were stimulated with SARS-CoV-2 peptide mix, either 1 month after second dose of vaccine or 1 month after booster vaccine in participants who received the respective vaccine before or after starting ofatumumab treatment. |
| Time Frame | 1 month after second dose of vaccine or booster vaccine |
| Analysis Population Description | Efficacy and safety analysis sets |

| | Cohort 1a | Cohort 1b | Cohort 2a | Cohort 2b | Total |
|---|---|---|---|---|---|
| **Arm/Group Description** | Patients received first SARS-CoV-2 vaccination within the study prior to starting ofatumumab treatment. | Patients had already completed initial vaccination cycle and received a booster vaccine within the study prior to starting ofatumumab treatment. | Patients who received their first SARS-CoV-2 vaccination within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose). | Patients who had already completed their initial vaccination cycle and received a booster vaccine within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose). | All cohorts |
| **Number of Participants Analyzed [units: participants]** | 5 | 8 | 4 | 15 | 32 |
| **Percentage of participants having established SARS-CoV-2-specific T cells after receiving a modRNA vaccine** (units: percentage of participants) | **Number (95% Confidence Interval)** | **Number (95% Confidence Interval)** | **Number (95% Confidence Interval)** | **Number (95% Confidence Interval)** | **Number (95% Confidence Interval)** |
| Month 1 after Vacc - n=5,7,4 15,32 | 80.0 (28.4 to 99.5) | 87.5 (47.3 to 99.7) | 100.0 (39.8 to 100.0) | 46.7 (21.3 to 73.4) | 68.8 (50 to 83.9) |

# Secondary Outcome Result(s)

## Percentage of participants who maintained T-cell response after receiving a modRNA vaccine

| | |
|---|---|
| Description | Participants who maintained detectable SARS-CoV-2 reactive T-cells (measured by e.g. ELIspot assay from T-cells that were stimulated with SARS-CoV-2 peptide mix) after second dose of vaccine or 6 and 12 months after booster vaccine in participants who received the vaccine before or after starting ofatumumab treatment. First booster vaccination was optional for cohorts 1a and 2a. In cohorts 1b and 2b the time points "Month 1 after Vacc" and "1 Month after booster" are identical. |
| Time Frame | At Week 1, Months 6, 12 and 18 after second dose of vaccine or 1 Month after 1st booster, 1 Month after 2nd booster |
| Analysis Population Description | Efficacy and safety analysis sets |

| | Cohort 1a | Cohort 1b | Cohort 2a | Cohort 2b | Total |
|---|---|---|---|---|---|
| **Arm/Group Description** | Patients received first SARS-CoV-2 vaccination within the study prior to starting ofatumumab treatment. | Patients had already completed initial vaccination cycle and received a booster vaccine within the study prior to starting ofatumumab treatment. | Patients who received their first SARS-CoV-2 vaccination within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose). | Patients who had already completed their initial vaccination cycle and received a booster vaccine within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose). | All cohorts |
| **Number of Participants Analyzed [units: participants]** | 6 | 8 | 5 | 15 | 34 |

| **Percentage of participants who maintained T-cell response after receiving a modRNA vaccine** (units: percentage of participants) | **Number (95% Confidence Interval)** | **Number (95% Confidence Interval)** | **Number (95% Confidence Interval)** | **Number (95% Confidence Interval)** | **Number (95% Confidence Interval)** |
|---|---|---|---|---|---|
| Week 1 after vacc n=4,0,5,0,9 | 100.0 (39.8 to 100.0) | | 100.0 (47.8 to 100.0) | | 100.0 (66.4 to 100.0) |
| Month 6 after vacc n=4,8,5,14,31 | 100 (39.8 to 100.0) | 62.5 (24.5 to 91.5) | 60.0 (14.7 to 94.7) | 57.1 (28.9 to 82.3) | 64.5 (45.4 to 80.8) |
| Month 12 after vacc n=5,5,5,15,30 | 100.0 (47.8 to 100.0) | 100.0 (47.8 to 100.0) | 80.0 (28.4 to 99.5) | 93.3 (68.1 to 99.8) | 93.3 (77.9 to 99.2) |
| Month 18 after vacc n=4,0,4,0,8 | 50.0 (6.76 to 93.2) | | 100.0 (39.8 to 100.0) | | 93.3 (77.9 to 99.2) |
| Month 1 after 1st booster n=4,8,3,15,30 | 75.0 (19.4 to 99.4) | 87.5 (47.3 to 99.7) | 66.7 (9.43 to 99.2) | 46.7 (21.3 to 73.4) | 63.3 (43.9 to 80.1) |
| Month 1 after 2nd booster n=2,4,0,10,16 | 100.0 (15.8 to 100.0) | 75.0 (19.4 to 99.4) | | 80.0 (44.4 to 97.5) | 81.3 (54.4 to 96.0) |

## Increase in specific T-cells after receiving an modRNA booster vaccine

| | |
|---|---|
| Description | Patients having established SARS-CoV-2-specific T cells as defined by detection of SARS-CoV-2 reactive T-cells, measured by e.g. ELIspot assay from T-cells that were stimulated with SARS-CoV-2 peptide mix 1 month after booster vaccine in participants who received the respective vaccine before or after starting ofatumumab treatment. The fold change of SI from last value before booster to Month 1 is the ratio of SI at Month 1 divided by SI at last value before booster. |
| Time Frame | Last value before booster to 1 month after booster |
| Analysis Population Description | All patients in the efficacy analysis set, for whom ELISpot data for the time points "last visit before booster" and "month 1 after booster" were available, were included in the analysis. |

| | **Cohort 1a** | **Cohort 1b** | **Cohort 2a** | **Cohort 2b** | **Total** |
|---|---|---|---|---|---|
| **Arm/Group Description** | Patients received first SARS-CoV-2 vaccination within the | Patients had already completed initial vaccination cycle and | Patients who received their first SARS-CoV-2 | Patients who had already completed their initial | All cohorts |

| | study prior to starting ofatumumab treatment. | received a booster vaccine within the study prior to starting ofatumumab treatment. | vaccination within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose). | vaccination cycle and received a booster vaccine within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose). | |
|---|---|---|---|---|---|
| **Number of Participants Analyzed [units: participants]** | 4 | 7 | 3 | 14 | 28 |
| **Increase in specific T-cells after receiving an modRNA booster vaccine** (units: stimulation index) | **Mean ± Standard Deviation** | **Mean ± Standard Deviation** | **Mean ± Standard Deviation** | **Mean ± Standard Deviation** | **Mean ± Standard Deviation** |
| Fold change | 0.8 ± 0.9 | 12.6 ± 25.5 | 2.0 ± 2.1 | 3.6 ± 4.4 | 5.3 ± 13.2 |

## Percentage of RMS participants with quantifiable levels of SARS-CoV-2 serum functional antibodies by visits and subcohorts (EAS)

| | |
|---|---|
| Description | Level of SARS-CoV-2 serum functional antibodies were measured by a central laboratory using a neutralizing antibody detection kit. |
| Time Frame | Baseline, Week 1 after Vacc, Month 1, 6, 12 after Vacc, 1 month after 1st booster, 1 month after 2nd booster |
| Analysis Population Description | Efficacy analysis set |

| | **Cohort 1a** | **Cohort 1b** | **Cohort 2a** | **Cohort 2b** |
|---|---|---|---|---|
| **Arm/Group Description** | Patients received first SARS-CoV-2 vaccination within the study prior to starting ofatumumab treatment. | Patients had already completed initial vaccination cycle and received a booster vaccine within the study prior to starting ofatumumab treatment. | Patients who received their first SARS-CoV-2 vaccination within the study while already stable on ofatumumab treatment for at least 4 | Patients who had already completed their initial vaccination cycle and received a booster vaccine within the study while already stable on ofatumumab treatment |

| | | | | |
|---|---|---|---|---|
| | | | weeks (since the first dose). | for at least 4 weeks (since the first dose). |
| **Number of Participants Analyzed [units: participants]** | 6 | 8 | 5 | 15 |
| **Percentage of RMS participants with quantifiable levels of SARS-CoV-2 serum functional antibodies by visits and subcohorts (EAS)** (units: percentage of participants) | **Number (95% Confidence Interval)** | **Number (95% Confidence Interval)** | **Number (95% Confidence Interval)** | **Number (95% Confidence Interval)** |
| Baseline0 positive n=6,8, 5,14 | 0 (0 to 45.9) | 100.0 (63.1 to 100.0) | 0 (0 to 52.2) | 71.4 (41.9 to 91.6) |
| Week 1 after Vacc positive n=5,0,5,0 | 100.0 (47.8 to 100.0) | | 40.0 (5.27 to 85.3) | |
| Month 1 after Vacc positive n=5,8,4,15 | 100.0 (47.8 to 100.0) | 100.0 (63.1 to 100.0) | 25.0 (0.63 to 80.6) | 93.3 (68.1 to 99.8) |
| Month 6 after Vacc positive n=5,8,5,15 | 100.0 (47.8 to 100.0) | 100.0 (63.1 to 100.0) | 40.0 (5.3 to 85.3) | 73.3 (44.9 to 92.2) |
| Month 12 after Vacc positive n=5,7,5,14 | 100.0 (47.8 to 100.0) | 100.0 (59.0 to 100.0) | 40.0 (5.3 to 85.3) | 92.9 (66.1 to 99.8) |
| Month 1 after 1st booster postive n=5,8,5,15 | 100.0 (47.8 to 100.0) | 100.0 (63.1 to 100.0) | 66.7 (9.4 to 99.2) | 93.3 (68.1 to 99.8) |
| Month 1 after 2nd booster positive n=2,4,0,10 | 100.0 (15.8 to 100.0) | 100.0 (39.8 to 100.0) | | 90.0 (55.5 to 99.7) |

## SARS-CoV-2 specific CD4+ effector memory T-cells

| | |
|---|---|
| Description | Phenotypic description of the cellular immune response was performed at the central laboratory. T-cells were stimulated with SARS-CoV-2 peptide mix and analyzed for IFNg- and IL4 secretion using FACS analysis. Results are inconclusive due to low participant numbers. |
| Time Frame | Baseline, Months 1 ,6, 12 and 18 after vaccinationse of vaccine or 1,6 and 12 months after booster vaccine |
| Analysis Population Description | Full analysis set -available participant data varied across time points |

| | Cohort 1 | Cohort 2 |
|---|---|---|
| **Arm/Group Description** | Patients received first SARS-CoV-2 vaccination within the study prior to starting ofatumumab treatment or patients had already completed initial vaccination cycle and received a booster vaccine within the study prior to starting ofatumumab treatment. | Patients who received their first SARS-CoV-2 vaccination within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose) or patients who had already completed their initial vaccination cycle and received a booster vaccine within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose). |
| **Number of Participants Analyzed [units: participants]** | 14 | 20 |
| **SARS-CoV-2 specific CD4+ effector memory T-cells** (units: % of CD4+/CD8+ cells) | **Mean ± Standard Deviation** | **Mean ± Standard Deviation** |
| BL before initial Vacc IL4 basal n=4,5 | 2.458 ± 4.915 | 0.262 ± 05.86 |
| BL before initial Vacc IL4 stim.n=4,5 | 2.583 ± 5.165 | 0.264 ± 0.59 |
| BL before initial Vacc INFg basal n=4,5 | 0.555 ± 0.549 | 0.03 ± 0.067 |
| BL before initial Vacc INGg stim n=4,5 | 0.235 ± 0.191 | 0.146 ± 0.326 |
| Month 1 after Vacc Il4 basal n=12,19 | 0.396 ± 2.318 | 1.209 ± 6.919 |
| Month 1 after Vacc IL4 stim. n=12,19 | 0.719 ± 0.62 | 2.449 ± 0.283 |
| Month 1 after Vacc INFg basal n=12,19 | 0.258 ± 2.165 | 0.171 ± 0.917 |
| Month 1 after Vacc INFg stim. n=12,19 | 0.947 ± 2.165 | 0.381 ± 0.917 |
| Month 6 after Vacc Il4 basal n=12,20 | 0.662 ± 1.44 | 0.061 ± 0.273 |
| 0Month 6 after Vacc IL4 stim.n=12,20 | 0.93 ± 2.043 | 0.44 ± 0.197 |
| Month 6 after Vacc INFg basal n=12,20 | 0.236 ± 0.344 | 0.123 ± 0.205 |
| Month 6 after Vacc INFg stim.n=12,20 | 0.305 ± 0.352 | 0.342 ± 0.644 |
| Month 12 after Vacc Il4 basal n=10,17 | 0.361 ± 1.142 | 1.078 ± 2.468 |
| Month 12 after Vacc IL4 stim.n=10,17 | 0.174 ± 0.55 | 1.031 ± 2.491 |
| Month 12 after Vacc INFg basal n=10,17 | 0.132 ± 0.192 | 0.226 ± 0.478 |

| | | |
|---|---|---|
| Month12 after Vacc INFg stim. n=10,17 | 0.122 ± 0.26 | 0.757 ± 2.332 |
| Month 18 after Vacc IL4 basal n=4,5 | 2.368 ± 4.735 | 0.118 ± 0.264 |
| Month 18 after Vacc IL4 stim.l n=4,5 | 1.833 ± 3.665 | 0.176 ± 0.394 |
| Month 18 after Vacc INFg basal l n=4,5 | 0.148 ± 0.295 | 0.11 ± 0.246 |
| Month 18 after Vacc INFg stim.l n=4,5 | 0.138 ± 0.159 | 0.12 ± 0.268 |

## Other Pre-Specified Outcome Result(s)

No data identified.

## Post-Hoc Outcome Result(s)

No data identified.

## Safety Results

| | |
|---|---|
| **Time Frame** | Adverse events were reported from first dose of study treatment until the end of the treatment period plus an additional 30 day safety follow up period for a maximum time of 22 months. |
| **Source Vocabulary for Table Default** | MedDRA (23.1) |
| **Collection Approach for Table Default** | Systematic Assessment |

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## All-Cause Mortality

| | Cohort 1a N = 6 | Cohort 1b N = 8 | Cohort 2a N = 5 | Cohort 2b N = 15 |
|---|---|---|---|---|
| **Arm/Group Description** | Patients received first SARS-CoV-2 vaccination within the study prior to starting ofatumumab treatment. | Patients had already completed initial vaccination cycle and received a booster vaccine within the study prior to starting ofatumumab treatmen | Patients who received their first SARS-CoV-2 vaccination within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose). | Patients who had already completed their initial vaccination cycle and received a booster vaccine within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose) |
| **Total Number Affected** | 0 | 0 | 0 | 0 |
| **Total Number At Risk** | 6 | 8 | 5 | 15 |

## Serious Adverse Events

| | |
|---|---|
| **Time Frame** | Adverse events were reported from first dose of study treatment until the end of the treatment period plus an additional 30 day safety follow up period for a maximum time of 22 months. |
| **Source Vocabulary for Table Default** | MedDRA (23.1) |
| **Collection Approach for Table Default** | Systematic Assessment |

| | Cohort 1a N = 6 | Cohort 1b N = 8 | Cohort 2a N = 5 | Cohort 2b N = 15 |
|---|---|---|---|---|
| **Arm/Group Description** | Patients received first SARS-CoV-2 vaccination | Patients had already completed initial | Patients who received their first SARS-CoV-2 | Patients who had already completed their initial |

| | within the study prior to starting ofatumumab treatment. | vaccination cycle and received a booster vaccine within the study prior to starting ofatumumab treatmen | vaccination within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose). | vaccination cycle and received a booster vaccine within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose) |
|---|---|---|---|---|
| **Total # Affected by any Serious Adverse Event** | 0 | 0 | 1 | 1 |
| **Total # at Risk by any Serious Adverse Event** | 6 | 8 | 5 | 15 |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | | | | |
| Neurilemmoma benign | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) |
| **Nervous system disorders** | | | | |
| Multiple sclerosis relapse | 0 (0.00%) | 0 (0.00%) | 1 (20.00%) | 0 (0.00%) |

## Other (Not Including Serious) Adverse Events

| | |
|---|---|
| **Time Frame** | Adverse events were reported from first dose of study treatment until the end of the treatment period plus an additional 30 day safety follow up period for a maximum time of 22 months. |
| **Source Vocabulary for Table Default** | MedDRA (23.1) |
| **Collection Approach for Table Default** | Systematic Assessment |

**Frequent Event Reporting Threshold** 2%

| | Cohort 1a N = 6 | Cohort 1b N = 8 | Cohort 2a N = 5 | Cohort 2b N = 15 |
|---|---|---|---|---|
| **Arm/Group Description** | Patients received first SARS-CoV-2 vaccination within the study prior to starting ofatumumab treatment. | Patients had already completed initial vaccination cycle and received a booster vaccine within the study prior to starting ofatumumab treatmen | Patients who received their first SARS-CoV-2 vaccination within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose). | Patients who had already completed their initial vaccination cycle and received a booster vaccine within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose) |
| **Total # Affected by any Other Adverse Event** | 6 | 6 | 5 | 15 |
| **Total # at Risk by any Other Adverse Event** | 6 | 8 | 5 | 15 |
| **Blood and lymphatic system disorders** | | | | |
| Lymphadenopathy | 1 (16.67%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| **Ear and labyrinth disorders** | | | | |
| Tinnitus | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) |
| **Gastrointestinal disorders** | | | | |
| Abdominal pain upper | 0 (0.00%) | 0 (0.00%) | 1 (20.00%) | 0 (0.00%) |
| Dental caries | 0 (0.00%) | 1 (12.50%) | 0 (0.00%) | 0 (0.00%) |
| Dry mouth | 0 (0.00%) | 1 (12.50%) | 0 (0.00%) | 0 (0.00%) |
| Nausea | 0 (0.00%) | 0 (0.00%) | 1 (20.00%) | 1 (6.67%) |
| **General disorders and administration site conditions** | | | | |
| Asthenia | 1 (16.67%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |

| | | | | |
|---|---|---|---|---|
| Chills | 0 (0.00%) | 1 (12.50%) | 1 (20.00%) | 1 (6.67%) |
| Fatigue | 0 (0.00%) | 1 (12.50%) | 0 (0.00%) | 1 (6.67%) |
| Gait disturbance | 0 (0.00%) | 0 (0.00%) | 1 (20.00%) | 1 (6.67%) |
| Influenza like illness | 0 (0.00%) | 0 (0.00%) | 1 (20.00%) | 1 (6.67%) |
| Injection site pain | 3 (50.00%) | 0 (0.00%) | 1 (20.00%) | 0 (0.00%) |
| Injection site swelling | 0 (0.00%) | 0 (0.00%) | 1 (20.00%) | 0 (0.00%) |
| Peripheral swelling | 0 (0.00%) | 0 (0.00%) | 1 (20.00%) | 0 (0.00%) |
| Swelling face | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) |
| Vaccination site reaction | 1 (16.67%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| **Immune system disorders** | | | | |
| Immune-mediated adverse reaction | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) |
| **Infections and infestations** | | | | |
| Abscess limb | 0 (0.00%) | 0 (0.00%) | 1 (20.00%) | 0 (0.00%) |
| Bacterial infection | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) |
| COVID-19 | 2 (33.33%) | 2 (25.00%) | 5 (100.00%) | 9 (60.00%) |
| Folliculitis | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) |
| Fungal skin infection | 0 (0.00%) | 0 (0.00%) | 1 (20.00%) | 0 (0.00%) |
| Gastroenteritis | 0 (0.00%) | 0 (0.00%) | 2 (40.00%) | 0 (0.00%) |
| Influenza | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) |
| Nasopharyngitis | 1 (16.67%) | 0 (0.00%) | 1 (20.00%) | 3 (20.00%) |
| Oral herpes | 1 (16.67%) | 1 (12.50%) | 0 (0.00%) | 0 (0.00%) |
| Pneumonia | 0 (0.00%) | 0 (0.00%) | 1 (20.00%) | 0 (0.00%) |
| Rhinitis | 0 (0.00%) | 1 (12.50%) | 0 (0.00%) | 0 (0.00%) |
| Sinusitis | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) |
| Upper respiratory tract infection | 1 (16.67%) | 0 (0.00%) | 1 (20.00%) | 0 (0.00%) |

| | | | | |
|---|---|---|---|---|
| Urinary tract infection | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) |
| **Injury, poisoning and procedural complications** | | | | |
| Contusion | 0 (0.00%) | 0 (0.00%) | 1 (20.00%) | 1 (6.67%) |
| Epicondylitis | 1 (16.67%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Infusion related reaction | 0 (0.00%) | 2 (25.00%) | 0 (0.00%) | 0 (0.00%) |
| Radius fracture | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) |
| Skin abrasion | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 2 (13.33%) |
| **Metabolism and nutrition disorders** | | | | |
| Hypercholesterolaemia | 0 (0.00%) | 1 (12.50%) | 0 (0.00%) | 0 (0.00%) |
| Vitamin D deficiency | 1 (16.67%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Arthralgia | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) |
| Back pain | 1 (16.67%) | 0 (0.00%) | 1 (20.00%) | 0 (0.00%) |
| Intervertebral disc protrusion | 1 (16.67%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Muscle spasms | 0 (0.00%) | 1 (12.50%) | 0 (0.00%) | 0 (0.00%) |
| Muscle twitching | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) |
| Musculoskeletal chest pain | 0 (0.00%) | 0 (0.00%) | 1 (20.00%) | 0 (0.00%) |
| Musculoskeletal stiffness | 0 (0.00%) | 1 (12.50%) | 0 (0.00%) | 0 (0.00%) |
| Pain in extremity | 0 (0.00%) | 1 (12.50%) | 2 (40.00%) | 1 (6.67%) |
| Spinal pain | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) |
| **Nervous system disorders** | | | | |
| Carpal tunnel syndrome | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) |
| Dizziness | 1 (16.67%) | 0 (0.00%) | 1 (20.00%) | 0 (0.00%) |

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|---|---|---|---|---|
| Headache | 3 (50.00%) | 2 (25.00%) | 4 (80.00%) | 3 (20.00%) |
| Meralgia paraesthetica | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) |
| Multiple sclerosis | 1 (16.67%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Multiple sclerosis relapse | 1 (16.67%) | 1 (12.50%) | 1 (20.00%) | 0 (0.00%) |
| Peripheral nerve lesion | 0 (0.00%) | 1 (12.50%) | 0 (0.00%) | 0 (0.00%) |
| Restless legs syndrome | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) |
| Sciatica | 1 (16.67%) | 1 (12.50%) | 0 (0.00%) | 0 (0.00%) |
| **Pregnancy, puerperium and perinatal conditions** | | | | |
| Pregnancy | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) |
| **Psychiatric disorders** | | | | |
| Adjustment disorder | 0 (0.00%) | 0 (0.00%) | 1 (20.00%) | 0 (0.00%) |
| Sleep disorder | 0 (0.00%) | 0 (0.00%) | 1 (20.00%) | 1 (6.67%) |
| **Renal and urinary disorders** | | | | |
| Renal colic | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) |
| **Reproductive system and breast disorders** | | | | |
| Benign prostatic hyperplasia | 0 (0.00%) | 1 (12.50%) | 0 (0.00%) | 0 (0.00%) |
| Breast mass | 0 (0.00%) | 1 (12.50%) | 0 (0.00%) | 0 (0.00%) |
| Erectile dysfunction | 0 (0.00%) | 1 (12.50%) | 0 (0.00%) | 0 (0.00%) |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Asthma | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) |
| Dry throat | 0 (0.00%) | 1 (12.50%) | 0 (0.00%) | 0 (0.00%) |
| Oropharyngeal pain | 1 (16.67%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Pleurisy | 0 (0.00%) | 0 (0.00%) | 1 (20.00%) | 0 (0.00%) |

| | | | | |
|---|---|---|---|---|
| Throat irritation | 1 (16.67%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| **Skin and subcutaneous tissue disorders** | | | | |
| Acne | 0 (0.00%) | 1 (12.50%) | 0 (0.00%) | 0 (0.00%) |
| Alopecia | 0 (0.00%) | 0 (0.00%) | 1 (20.00%) | 1 (6.67%) |
| Hand dermatitis | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) |
| Onychoclasis | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) |
| Rash | 0 (0.00%) | 1 (12.50%) | 0 (0.00%) | 0 (0.00%) |
| Skin exfoliation | 0 (0.00%) | 1 (12.50%) | 0 (0.00%) | 0 (0.00%) |
| Urticaria | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (6.67%) |
| **Vascular disorders** | | | | |
| Flushing | 0 (0.00%) | 0 (0.00%) | 1 (20.00%) | 0 (0.00%) |
| Haematoma | 0 (0.00%) | 0 (0.00%) | 1 (20.00%) | 0 (0.00%) |
| Hypertension | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 2 (13.33%) |

## Other Relevant Findings

## Conclusion:

Results should be interpreted with limitations due to the small sample size.

All participants developed SARS-CoV-2-specific humoral or cellular response or both as soon as one week and still one month after the full initial vaccination cycle, irrespective of being vaccinated prior to or during ofatumumab treatment. Furthermore, booster vaccination increased neutralizing antibody titer to similar levels in patients being vaccinated prior to or during ofatumumab treatment. The data of this study indicate that both humoral and cellular response need to be considered for interpretation of vaccination efficacy.

No new safety signals were observed.

## Date of Clinical Trial Report

December 14, 2024