NOVARTIS

Clinical Development

Ofatumumab (OMB157)®

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

Statistical Analysis Plan (SAP)

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Signature Page

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
CI	Confidence interval
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of variation
eCRF	Electronic Case Report Form
EAS	Efficacy Analysis Set
DMT	Disease modifying therapy
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MNC	Mononuclear cells
MS	Multiple sclerosis
RAP	Report and Analysis Process
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAE	Serious adverse event
SOC	System Organ Class
SmPC	Summary of Procduc Characteristics
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) describes how the statistical analyses of this study will be implemented. Based on the tables/listings/figures (TFL) of resulting from this SAP the Clinical Study Report (CSR) will be written. The TFLs will be attached in section 14 of the CSR.

In addition this SAP describes which patient Data Listings to be attached in section 16.2.1 of the CSR will be generated.

This SAP is not used for other analyses or studies.

It is based on the Amended Study Protocol (CSP), Version 3 dated 28-MAR-2022

1.1 Study design

This is a two cohort, multicenter, open-label, prospective study of 40 patients (optionally up to 60) suffering from relapsing multiple sclerosis (RMS).

- The first cohort will be RMS patients receiving modRNA vaccine as part of clinical routine prior to starting ofatumumab treatment.
  Cohort 1a: will receive their 1st and 2nd SARS-CoV-2 vacines (and an optional booster vaccine)
  Cohort 1b: will receive a booster vaccine
- The second cohort will be 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: will receive their 1st and 2nd SARS-CoV-2 vaccines (and an optional booster vaccine)
  Cohort 2b: will receive a booster vaccine

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

The first interim analysis is planned when at least five patients per cohort have completed the study visit one week after the second SARS-CoV-2 modRNA vaccination or on September 1st 2021, whichever comes first. The data gathered at this time point will be examined as a preliminary evaluation of proof of concept.

The second interim analysis is planned when at least 10 patients that were vaccinated during stable ofatumumab-treatment have passes the primary endpoint, 1 month after the 2nd vaccination or after booster or on January 10th 2022, whichever comes first. The data gathered at this time point will be examined as a preliminary evaluation of proof of concept for the new study design.

An additional interim analysis is planned after all participants have completed the study visit 1 month after the second SARS-CoV-2 modRNA vaccination or booster vaccination, respectively. The data gathered at this time point will be the basis for the primary endpoint of this study.

Additional interim analyses may be conducted to support decision making concerning the current clinical study including an increase in participants (from 40 to 60), the sponsor's clinical development projects in general, or in case of any safety concerns.

1.2 Study objectives and endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
To estimate the proportion of RMS patients having established SARS-CoV-2-specific T-cells after receiving a mod RNA vaccine (initial or booster) either before or after starting ofatumumab treatment.	Proportion of RMS patients having established SARS-CoV-2-specific T-cells as defined by detection of SARS-CoV-2 reactive T-cells, measured by e.g. enzyme-linked immunosorbent spot (ELIspot) assay from T-cells that were stimulated with SARS-CoV-2 peptide mix, either one month after second dose of vaccine or one month after booster vaccine in participants who received the respective vaccine before or after starting ofatumumab treatment (yes/no)
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
To estimate the proportion of RMS patients maintaining for up to 18 months SARS-CoV-2-specific T cells after receiving a modRNA vaccine either before or after starting ofatumumab treatment.	Proportion of RMS patients with detectable SARS-CoV-2 reactive T-cells one week, 6 and 18 months 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 (yes/no)
To estimate the increase in specific T-cells after receiving a modRNA booster vaccine either before or after starting ofatumumab treatment.	Fold change of SARS-CoV-2 specific T-cell levels one week, 1 month, 6 months, 12 months and 18 months after the second dose of vaccine or 1 months, 6 months and 18 months after a booster vaccine compared to the last timepoint before the respective vaccine
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.	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 (yes/no)
To estimate the proportion of RMS patients maintaining for up to 18 months quantifiable levels of SARS-CoV-2 serum functional antibodies after receiving a modRNA vaccine either before or after starting ofatumumab treatment.	Proportion of RMS patients with quantifiable levels of SARS-CoV-2 serum functional antibodies one week, 1, 6, 12, and 18 months after receiving the second dose of modRNA vaccine or 1, 6, and 12 months after a booster shot either before or after starting ofatumumab treatment (yes/no)

Describing phenotypically the cellular response after receiving a modRNA vaccine either before or after starting ofatumumab treatment.	- Phenotypical characterization of peripheral blood mononuclear cells for CD45, CD3, CD4, CD8, CD62l, CD45RA, CD27, CCR7 - Immunophenotyping for naive, central memory, effector memory, and effector cells on CD4+ and CD8+ cells - Measuring cells positive for intracellular cytokine-staining for interferon-gamma and interleukin-4
Describing safety and tolerability, incl. patients developing coronavirus disease 2019 (COVID-19)	AEs, SAEs, incl. patients with clinical confirmed COVID-19

2 Statistical methods

2.1 Data analysis general information

Data analysis will be performed by the CRO [redacted]. The software SAS, version 9.2 or higher is used.

Categorical data will be summarized as frequencies and percentages. According to the small sample size of this study, percentages are presented without decimal places, i.e. as integers without digits.

For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

All listings and tables will be presented by cohort.

2.1.1 General definitions

Study treatments

The modRNA vaccine and the ofatumumab treatment are defined both as study treatments. The ofatumumab treatment which is started either before or after receiving a SARS-CoV-2 mRNA vaccine (either initial or booster) is considered as treatment of interest.

Screening failure

A screening failure is a patient not eligible for the study. Screening failures are identified by:

- any inclusion criterion is violated or
- any exclusion criterion applies

2.1.2 Handling with unscheduled vitis

In this study unscheduled visits may be performed for various reasons. If laboratory data (i. e. the primary and secondary parameters) are available for unscheduled visits it will be checked if the unscheduled visit replaces a scheduled visit. This will be done before analysis in the data review meeting and documented in the minutes.

2.1.3 Visits relevant for efficacy analyses

The following table shows which visits in each cohort are relevant for efficacy analysis and how they are numbered[1]:

	Baseline	Week 1	Month 1	Month 6	Month 12	Month 18
Cohort 1a (Ofatumumab after initial vaccination)	Screening/ Baseline (101; 10)	Visit 1 (104; 1000)	Visit 2 (105; 1010)	Visit 7 (110; 1060)	Visit 8 (112; 1120)	Visit 9 (113; 1180)

[1] The first number indicates the visit number of raw data. This visit number deviates in the different cohorts. The second number ist the visit number used in the analysis data. this number was assigned uniformly across all cohorts

Cohort 1b (Ofatumumab after booster vaccination)	Screening (701; 10)	n.a.	Visit 1 (705; 1010)	Visit 6 (710; 1060)	Visit 7 (713; 1120)	n.a.
Cohort 2a (Ofatumumab before initial vaccination)	Baseline (Visit 4) (205, 10)	Visit 5 (208, 1000)	Visit 6 (209, 1010)	Visit 8 (213, 1060)	Visit 9 (214, 1120)	Visit 10 (215; 1180)
Cohort 2b (Ofatumumab before booster vaccination)	Baseline (808; 10)	n.a.	Visit 4 (809, 1010)	Visit 6 (811; 1060)	Visit 7 (812; 1120)	n.a.

2.2 Analysis sets

For all analysis sets, participants will be analyzed according to the study treatment received.

The Safety Analysis Set (SAF) will include all participants that received any study drug.

The Efficacy Analysis Set (EAS) will include all patients of the Safety Set who received a mRNA vaccine. Patients who failed their second dose of mRNA vaccine are included in the Efficacy Analysis Set, but counted as non-responders. Patients with invalid or missing efficacy parameter at a respective time point are included in the EAS, but excluded from the denominator for that time point when calculating responder-rates.

2.2.1 Subgroup of interest

In general no subgroups are displayed. In selected tables (see Tables/Listings/Figures-Shells) the data are displayed separately for the subcohorts 1a, 1b, 2a, and 2b.

2.3 Patient disposition, demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by treatment group (ofatumumab before versus after vaccination) for the SAF and the Efficacy Analysis Set.

If major imbalance in relevant demographic or other baseline charateristics are discovered, the study results will be interpreted with more caution and post-hoc supportive analyses may be conducted to adjust for the imbalance.

2.3.1 Patient disposition

Patient disposition displays the absolute and relative frequency of screening failures, the number of patients included in the different analysis sets.

The reasons for screening failure, for missed study visits, for exclusion from analysis populations and for premature drop-out are described by frequency tables as well as protocol deviations.

The duration of intervals between relevant study visits are displayed by sample statistics.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The absolute and relative frequency of performed study visits (restricted to visits which are relevant for efficacy analysis) and performed vaccinations are presented. Sample statistics for the duration of intervals between screening and 1st resp. booster vaccination, 1st and 2nd vaccination, 2nd resp. booster vaccination and Week 1/Month 1/Month 6/ Month 12 after Vaccination 2 resp. booster vaccination are displayed. Here always the exact date of the respective vaccination is used but not the date of study visit called “Vaccination 1” or “Vaccination 2” or “Booster Vaccination” which displays the date of phone contact with the patient.

Two types of investigational study drugs are used in this study:

1. Ofatumumab for treatment of MS
2. mRNA vaccine

The interval of ofatumumab start is displayed relatively to the 1st resp. booster vaccination for cohort 2, and relatively to the 2nd resp. booster vaccination for cohort 1. Sample statistics are provided for these intervals. The frequencies of patients with temporary interruption respectively permanent discontinuation until each efficacy assessment time point (Week 1, Month 1, 6, 12, and 18) are provided.

The different vaccines are displayed by a frequency table separately for 1st and 2nd vaccination.

2.4.2 Prior, concomitant and post therapies

The number and types of all pretreatments for multiple sclerosis prior to screening are displayed. Here, all MS-therapies except ofatumumab which are starting before screening and ongoing after screening are included into counts.

The last disease modifying drug before ofatunumab respectively the number of treatment-naïve patients is displayed in a frequency table.

Concomitant medications are coded by WHO Drug-dictionary. Frequencies of Anatomic Therapeutical Chemical (ATC) categories and Preferred Names are presented. Here, a medication with multiple entries is counted only once in a ATC category respectively a preferred name category.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The **primary clinical question** of interest is: What is the proportion of RMS patients having developed a specific immune response after receiving a modRNA vaccine (either initial vaccination or booster) either before or after starting ofatumumab treatment. The justification for the primary estimand is that it will capture whether ofatumumab-treated patients will mount

a specific T-cell response after receiving a SARS-CoV-2 mRNA vaccine assessed by enzyme-linked immunosorbent spot (ELISpot) assays from T-cells that were stimulated with SARS-CoV-2 peptide mix. Patients will receive either their initial vaccination (1st and 2nd SARS-CoV-2 vaccines) or a booster vaccine before or after starting ofatumumab treatment. In both cases we want to assess if ofatumumab initiation negatively affects or prevents the immune response.

Since this is not a randomized trial, no randomization needs to be preserved and the ITT-principle and the associated estimands framework do not apply. However, this protocol will keep as close as appropriate to the terminology and the definitions established within that framework.

The primary estimand is described by the following attributes:

1. **Population**: Patients with relapsing MS (RMS) divided in two cohorts, each receiving a SARS-CoV-2 mRNA vaccine as part of clinical routine: (1) vaccination before start of ofatumumab treatment, (2) vaccination after having been on stable ofatumumab treatment for at least 4 weeks. The SARS-CoV-2 mRNA vaccine can be either the initial vaccination cycle (for patient that are exposed to the vaccine for the first time; cohort 1a and cohort 2a) or a booster vaccination (for patients that have already completed the initial vaccination cycle; cohort 1b and cohort 2b). Patients in cohort 1a or 2a who fail to receive their second dose of vaccine for whatever reason will be included in the analysis as non-responders. Patients in cohorts 1a and 2a who did receive their second dose of vaccine and patients in cohorts 1b and 2b who received their booster shot and do not have a valid determination of specific T-cell response to SARS-CoV-2 for whatever reason will be excluded from the analysis of vaccine efficacy.

2. **Variable:** Receiving the second dose of mRNA vaccine (for cohort 1a and 2a) or a booster vaccination (cohort 1b and 2b) and mounting a specific T cell response[2] one month after second dose of vaccine (cohort 1a and 2a) or booster vaccine (cohort 1b and 2b) defined by detection of SARS-CoV-2 specific T-cells by ELISpot assays after stimulation of T-cells with SARS-CoV-2 peptide mix (yes/no)

3. **Treatment of interest:** ofatumumab treatment, which is started either before or after receiving a SARS-CoV-2 mRNA vaccine (initial vaccination cycle or booster vaccine)

4. Intercurrent events:

a. Vaccination with a non-mRNA vaccine: patients will be excluded from the study

b. Failure to receive the second dose (for cohorts 1a and 2a) of vaccine: patients will be classified as non-responders

c. Failure to initiate ofatumumab treatment within six weeks after completion of the vaccination cycle (cohort 1a) or of the booster vaccine (cohort 1b): patients will be excluded from the efficacy analyses

[2] See appendix 5.3.1 for derivation

d. Failure to complete ofatumumab initiation or interruption of ofatumumab treatment prior to first vaccination (cohort 2a) or prior to booster vaccination (cohort 2b): patents will be excluded from the study

e. No valid detection of SARS-CoV-2 specific T-cells: patients will be excluded from the efficacy analyses if they received their second dose of vaccine (cohorts 1a and 2a) or booster vaccine (cohort 1b and 2b) and further analyses will be performed to confirm methodical reasons

5. **Summary measure:** n.a., there will be no formal comparison between cohorts. Response rates will only be calculated within each cohort.

2.5.2 Statistical hypothesis, model, and method of analysis

The efficacy analysis set is used for all analyses of the primary parameter.

The primary analysis will not use any statistical testing or modelling. The absolute numbers and the proportion of participants achieving SARS-CoV-2-specific T-cell response within each cohort will be calculated. It will be augmented by a (descriptive) two-sided 95% confidence interval (exact Clopper-Pearson).

2.5.3 Handling of missing values/censoring/discontinuations

Cohort 1a and cohort 2a: Patients who fail to receive their first dose of vaccine for whatever reason are excluded from the efficacy analysis Set(s). The number of these patients is displayed in the patient disposition table.

Patients who fail to receive their second dose of vaccine for whatever reason will be included in the analysis as non-responders. The number of these patients is displayed in the analysis table.

Patients who did receive their second dose of vaccine and do not have a valid determination of reactive T-cells to SARS-CoV-2 for whatever reason will be excluded from the analysis of vaccine efficacy at the respective time point. The number of these patients is displayed in the analysis table.

Cohort 1b and cohort 2b: Patients who fail to receive their booster vaccination for whatever reason are excluded from the efficacy analysis Sets(s). The number of theses patients is displayed in the patient disposition table.

Patients who did receive their booster vaccination and do not have a valid determination of reactive T-cells to SARS-CoV-2 for whatever reason will be excluded from the analysis of vaccine efficacy at the respective time point. The number of these patients is displayed in the analysis table.

2.5.4 Supportive analyses

The reactivity towards SARS-CoV-2 and towards PAN coronaviridae is analysed by frequency tables presenting each investigational visit. This applies to the parameters:

- IFNg (qualitative, i.e. reactive, equivocal, not reactive)
- IL-2 (qualitative, i.e. reactive, equivocal, not reactive)

The stimulation index towards SARS-CoV-2 and towards PAN coronaviridae is analysed by sample statistics and a boxplot graph for each investigational visit. This applies to the parameters:

- IFNg (quantitative)
- IL-2 (quantitative)

If relevant differences in demographic or other baseline chracteristics are observed post-hoc analysis will be performed to adjust the primary endpoint for theses inhomogeneities. A logistic regression model would be applied.

2.6 Analysis of the key secondary objective

Not applicable, because no key secondary objectives are specified.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

The secondary endpoints are analyzed descriptively within each cohort. The Efficacy Analysis Set is used for all analyses of the secondary parameters.

The proportion of patients achieving seroconversion[3] in SARS-CoV-2 neutralizing antibodies is presented for the time points Month 1, Month 6, and Month 12. Exact confidence intervals (95%, two-sided) are calculated by the Pearson-Clopper method.

The phenotypical parameters are displayed by sample statistics and boxplots per time point (Screening, Month 1, Month 6, and Month 12) by cohort. For the baseline visit the subcohorts are presented. This applies to these parameters:

- CD19+/CD20+ B cells (absolute and relative values)
- CD4+ cells (% of mononuclear cells)
- CD4: IL4 basal and stimulated, IFNg basal and stimulated (%)
- CD4 naïve: IL4 basal and stimulated, IFNg basal and stimulated (%)
- CD4 TCM: IL4 basal and stimulated, IFNg basal and stimulated (%)
- CD4 TEM CD27 – and CD27+: IL4 basal and stimulated, IFNg basal and stimulated (%)
- CD8+ cells (% of mononuclear cells)
- CD8: IL4 basal and stimulated, IFNg basal and stimulated (%)
- CD8 naïve: IL4 basal and stimulated, IFNg basal and stimulated (%)
- CD8 TCM: IL4 basal and stimulated, IFNg basal and stimulated (%)
- CD8 TEM CD27 – and CD27+: IL4 basal and stimulated, IFNg basal and stimulated (%)

[3] For derivation of seroconversion see Appendix 5.3.2

All other laboratory data (e. g. number of basal/background spots, spots, quality, comments, mutations and hemotology) are listed only.

The MS activity is measured by relapses. The crude annual relapse rate until end of study and the underlying sums (of relapses and patient-years) will be presented.

2.7.2 Statistical hypothesis, model, and method of analysis

Not applicable due to descriptive analysis.

2.7.3 Handling of missing values/censoring/discontinuations

Missing values are not replaced.

2.9 Safety analyses

All safety analyses are presented for the Safety Set (SAF). Descriptive statistics are presented within study treatment groups (cohorts 1 and 2).

2.9.1 Adverse events (AEs)

According to the CSP all adverse events starting in the on-treatment period, i. e. the treatment-emergent AEs, are analyzed.

The on-treatment period lasts from the date of first administration of study treatment[4] after informed consent to 30 days after the last visit.

[4] Study treatment is ofatumumab as well as the modRNA vaccine.

The number (and percentage) of subjects with treatment-emergent adverse events will be summarized in the following ways:

- by treatment group (cohort 1 and 2), primary system organ class and preferred term.
- by treatment group (cohort 1 and 2), primary system organ class, preferred term and maximum severity
- by type of modRNA (Biontech/Pfizer versus Moderna), primary system organ class and preferred term.

A subject with multiple AEs within a MedDRA primary system organ class is only counted once towards the total of the primary system organ class.

A subject with multiple AEs within a preferred term is only counted once towards the total of the preferred term class.

Separate summaries will be provided for study medication related AEs, death, SAEs, AEs leading to discontinuation and adverse events leading to dose adjustment.

The absolute and relative frequency of COVID-19 infections is presented.

Deaths and serious adverse events are listed in addition. Deaths outside the on-treatment period are listed in addition.

Rates of COVID-19 infections and the rate of COVID-19 infections starting >= 7 days after the 2nd vaccination are displayed. Alle COVID-19 infections are listed with the dates of all COVID-19 vaccinations.

2.9.1.1 Adverse events of special interest / grouping of AEs

Adverse events related to COVID-19 pandemic are listed.

2.9.2 Deaths

Deaths are listed. A frequency table with absolute numbers, percentages and 95% confidence interval is presented.

2.9.3 Laboratory data

Hematology is listed only. The analysis of other lab parameters are described in section 2.5 and section 2.7.

2.9.4 Other safety data

2.9.4.1 Physical examination

Clinically significant findings which were not present at screening but at any later visits are displayed by a frequency table.

2.9.4.2 Vital signs

The changes from screening to Week 1, to Month 1, to Months 6, to month 12, and to Month 18 as well as differences between last and first value are displayed for pulse, systolic/diastolic blood pressure and body weight.

2.10 Pharmacokinetic endpoints

Not applicable.

2.11 PD and PK/PD analyses

Not applicable.

2.12 Patient-reported outcomes

Not applicable.

2.13 Biomarkers

Not applicable.

2.14 Other Exploratory analyses

Not applicable.

2.15 Interim analysis

See section 1.1 Study design.

3 Sample size calculation

The sample size of 20 participants per arm is selected based on need for early availability of results for the current covid-19 pandemic and the feasibility to recruit sufficient participants. This sample size of 20 subjects will provide estimates of proportion responded with margin of error (half-width of a 95% confidence interval) of 20.1%, 19%, and 17.5% corresponding to response rates of 70%, 75%, and 80%, respectively. Adjusting for 10% drop-out, 22 subjects will be enrolled in each arm. In case of fast recruitment the sponsor is allowed to increase sample size in each arm by up to 10 additional patients to support the generation of meaningful data in a larger sample size.

4 Change to protocol specified analyses

The efficacy analysis set was defined in such a way that it can be applied to all efficacy analyses. With regard to the primary parameter, there is no change in content compared to the definition in the study protocol.

5 Appendix

5.1 Imputation rules

No imputations will be done except:

a. If differences between dates are calculated, partial dates are replaced by 15/6 for days/month. If negative date differences result from this replacement, the value is set to 0.

b. According to the Note to File dated 29 September 2023 the quantitative values and spots of IFGg and IL-2 were corrected (i. e. set to a missing value) when the respective qualitative assessment was “not evaluable”. This applied both to parameters “PAN corona” and “SARS CoV-2. This correction was performed also when the value for qualitative assessments was “missing” (see Note to file dated 20 Oct 2023).

5.2 Treatment-emergent adverse events

Treatment emergent AEs are those which start in the on-treatment period. The on-treatment period lasts from the date of first administration of study medication after informed consent to 30 days after the last visit.

The date of first administration of study medication is the date of 1st vaccination or the date of first ofatumumab at or after screening whichever is earlier.

5.3 Statistical models

5.3.1 Primary analysis

The primary parameter “T-cell response” is derived from the laboratory data. Patients who have either SARS-CoV-2 reactive INFg-secreting T-cells or SARS-CoV-2 reactive IL-2 secreting T-cells (or both) are classified are responders. The assement “equivocal” is rated as reactive for this analysis, which is based on observations made during the validation of the assay. It was noticed that the positiv control of the ELISpot assay repeatedly provoked lower signals than seen in healthy volunteers, which led to the conclusion that T-cells from MS patients in general show lower reactivity in this assay. Consequently, the cut-offs for “reactive”/”equivocal” and “not reactive” defined by the kit-manufacturer have to be adjusted to these circumstances and results that would be classified as “equivocal” for healthy patients can be considered as signal and hence as “reactive” for MS patients. The following table presents the derivation of T cell response:

		Reactivity to INFg SARS-CoV-2 (quantitative)			
Reactivity towards IL-2 SARS-CoV-2 (quantitative)		**reactive**	**equivocal**	**Not reactive**	**Missing value**
	reactive	response	response	response	response
	equivocal	response	response	response	response
	Not reactive	response	response	Non-response	Non-response
	Missing value	response	response	Non-response	m.v. (not included in denominator)

5.3.2 Secondary analysis

A patient achieves sercoconversion when the neutralizing SARS-CoV-2 antibodies have changed from negative at screening/baseline to positive at the respective Visit. If the neutralizing SARS-CoV-2 antibodies are already positive at baseline (e.g. in patients of cohorts b who received their initial COVID-19 vaccine before the study) seroconversion cannot be derived for the post-baseline visits. These cases are displayed in addition in the tables as ”already seroconverted at baseline”.

5.4 Rule of exclusion criteria of analysis sets

Deviation ID	Description of Deviation	Exclusion in Analyses
I01	Incl. crit. no. 1 (IFC) violated	Excluded form all analysis Sets
S02	Different vaccines at first and 2nd vaccination	Excluded form Efficacy Analysis Set

Table 2 Subject Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
SAF/Efficacy Analysis Set	NA	Not having any study treatment
Efficacy Analysis Set	NA	No mRNA vaccine administered: - Patients of cohort 1a and 2a who missed the 1st vaccliation - Patients of cohort 1b and 2b who missed the (study) booster vaccination

6 Reference

None.