EMA/572648/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Spikevax

Common name: COVID-19 mRNA Vaccine (nucleoside-modified)

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted and personal data anonymised.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	13 Sep 2021	13 Sep 2021
☐	CHMP Rapporteur Assessment Report	23 Sep 2021	23 Sep 2021
☐	CHMP members comments	29 Sep 2021	29 Sep 2021
☐	Updated CHMP Rapporteur Assessment Report	01 Oct 2021	01 Oct 2021
☒	Opinion	04 Oct 2021	04 Oct 2021

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Table of contents

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Moderna Biotech Spain, S.L. submitted to the European Medicines Agency on 20 August 2021 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

To update sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to introduce a third dose of Spikevax in the primary vaccination schedule for individuals 18 years of age and older who have undergone a solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise, based on updated clinical literature; the Package Leaflet is updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

GLP/GCP inspections

No (non)-clinical/clinical study site inspections are needed.

2. Introduction

On 6 January 2021, a conditional marketing authorisation (cMA) for Spikevax was granted under Article 8.3 of Directive 2001/83/EC -complete and independent application. The approved indication is 'active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus in individuals 12 years of age and older'. The approved posology is a course of two doses administered 28 days apart. One dose (0.5 mL) contains 100 micrograms of messenger RNA (mRNA), embedded in SM-102 lipid nanoparticles.

Recent vaccine effectiveness data from the USA show that approximately 44% of breakthrough cases with COVID-19 hospitalisation occur in individuals with an immunocompromising condition, including active solid organ or hematologic malignancy and prior solid organ transplant (Tenforde et al. 2021, https://www.medrxiv.org/content/10.1101/2021.07.08.21259776v1). Published data indicate that the vaccinated immunosuppressed individuals continue to have an increased risk of severe COVID-19. In this specific population the standard 2-doses vaccination strategy have been associated with reduced immune responses to SARS-CoV-2 mRNA vaccines including Spikevax (Boyarsky et al. 2021; Stumpf et al. 2021; Greenberger et al. 2021; Stampfer et al. 2021, Rincon-Arevalo et al. 2021, Narasimhan et al. 2021, Thakkar et al. 2021, Addeo et al. 2021, Moor et al. 2021). Since optimal protection of this high-risk group require an appropriate immune response induced by vaccination to prevent severe COVID-19 there is a need to evaluate the benefit and risk of a further dose.

The MAH submitted the results reported by Hall et al. 2021 to support the implementation of a third dose of Spikevax (also referred to as mRNA-1273) for immunocompromised individuals such as patients who have undergone a solid organ transplant or who are diagnosed with conditions of equivalent immune compromise. Based on this publication, the MAH recommends updating the product information accordingly.

It should be noted that no data are yet available from the post authorisation study initiated by the MAH in solid organ transplant recipients and healthy controls to assess the safety and immunogenicity of Spikevax in immunocompromised adults aged 18 years and older as agreed during the initial approval in the RMP. This study is currently ongoing and data are expected in 2022/2023.

2.1. List of references

Hall et al. 2021, Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients

Rincon-Arevalo et al. 2021, Impaired humoral immunity to SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients and dialysis patients

Boyarsky et al. 2021, Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients

Stumpf et al. 2021 Humoral and cellular immunity to SARS-CoV-2 vaccination in renal transplant versus dialysis patients: A prospective, multicenter observational study using mRNA-1273 or BNT162b2 mRNA vaccine

Greenberger et al. 2021, Antibody response to SARS-CoV-2 vaccines in patients with hematologic malignancies

Stampfer et al. 2021, Response to mRNA vaccination for COVID-19 among patients with multiple myeloma

Narasimhan et al. 2021, Serological Response in Lung Transplant Recipients after Two Doses of SARS-CoV-2 mRNA Vaccines

Thakkar et al. 2021, Seroconversion rates following COVID-19 vaccination among patients with cancer

Addeo et al. 2021, Immunogenicity of SARS-CoV-2 messenger RNA vaccines in patients with cancer

Moor et al. 2021, Humoral and cellular responses to mRNA vaccines against SARS-CoV2 in patients with a history of CD20-B-cell depleting therapy

2.2. Submitted Data

The MAH submitted the publication of Hall et al. 2021 together with one corresponding appendix and the study protocol to support the application. The submitted documents refer to a (randomised) sub-study of an observational, comparative, cohort study "The PREVent-COVID" Study (CAPCR ID 20-6069).

Upon request further data were provided by the investigators of the PREVent-COVID study.

Study design

This study was conducted by the University Health Network organ transplant program. It is a randomised, placebo-controlled, double blind study of transplant recipients already enrolled in the PREVENT-COVID Study. 120 adult solid organ transplant (SOT) recipients who were stable outpatients with functioning allograft and who have already received both doses of Spikevax at 0 and 1 months have been enrolled in the study. Consented patients were randomised 1:1 to receive a third dose of Spikevax (0.5 mL intramuscular injection of Spikevax) or saline placebo (0.5 mL intramuscular injection of normal saline) in the deltoid muscle of the arm. Both, participant and healthcare provider who administers the vaccine were blinded to intervention versus placebo. The contents of both mRNA-1273 and placebo vaccine for injection were concealed with opaque tape to ensure blinding. Blood

work was performed 4-6 weeks after immunisation to determine immunogenicity. A subset of 50 participants were asked to provide an additional 20 mL of blood for cell-mediated immunity. These were the same 50 participants that consented to the PBMC substudy in PREVenT-COVID.

Follow-up

Patients were followed every 2 weeks for 3 months after the third Spikevax (or placebo) dose. This is 6 months after enrolment in the main PREVenT-COVID study. They were to be telephoned every 2 weeks to determine whether they were diagnosed with COVID or if they have any COVID-related symptoms (fever, cough, myalgias, sore throat, runny nose, diarrhoea, shortness of breath).

Study population

Adult patients (aged ≥18 years) who had received an organ transplant (kidney, liver, heart, lung and pancreas, or combined organs) and had a functioning allograft. Patients were eligible if they had already received both doses of the mRNA-1273 vaccine at the 0,1- month interval.

Exclusion criteria for the current trial were as follows:

1. within 1-month post-transplant
2. had a febrile illness within 1-week prior
3. previous microbiologically confirmed COVID-19 infection
4. active cytomegalovirus (CMV) infection
5. received intravenous immunoglobulin in the 4 weeks prior
6. received rituximab in the last 6 months
7. had treatment for acute rejection in the 30 days prior
8. an allergic reaction to the previous mRNA-1273 vaccination

Patients were enrolled without a-priori knowledge of their antibody response after the second dose. In the initial COVID-19 vaccine rollout at transplant centre, since there were limited data on vaccine safety, patients who were >6 months post-transplant were initially prioritised. Some of the patients in the current trial were enrolled in an observational study (n=84) that analysed antibody and T-cell responses after the first and second doses of vaccine. (Hall VG FV, Ierullo M, Ku T, Marinelli T, Majchrzak-Kita B, Yousuf A, Kulasingam V, Humar A, Kumar D. Humoral and Cellular immune response and Safety of 2-dose SARS-CoV-2 mRNA-1273 (Moderna) vaccine in Solid Organ Transplant Recipients. Am J Transplant. 2021 (In press)).

Study aim and objectives

Study Aim

To investigate if a third dose of Spikevax at 3 months post initial vaccination will boost the antibody titer and immune response in solid organ transplant recipients.

Hypothesis

A third dose of COVID-19 vaccine will provide a greater immune response compared to only two doses.

Study objectives

Primary objective

To determine the immunogenicity of a third dose of Spikevax given at 3 months post-initial vaccination in solid organ transplant recipients.

Secondary objectives

Vaccine safety and side effects that occur daily up to 7 days after vaccination. Follow-up will occur for graft rejection and any health-care contact up to 3 months post-study vaccine.

Study endpoints

Primary endpoint

The primary endpoint was the serologic response, i.e. the percentage of patients that achieve an anti–receptor-binding domain (RBD) antibody level of ≥100 units/ml at the 4-6 week time-point post intervention, measured with an Elecsys Anti-SARS-CoV-2 immunoassay (Roche).

Secondary endpoints

Secondary immunogenicity endpoints included the percent neutralisation, as measured with a validated surrogate virus neutralisation assay (Genscript), and the polyfunctional T-cell response.

Safety endpoints included local and systemic adverse events recorded until 7 days after injection and episodes of acute organ rejection, hospitalisation, other adverse events, and COVID-19 (i.e. microbiology proven by PCR from appropriate clinical specimen and compatible clinical syndrome) in the 6 months following vaccination.

Details regarding the immunogenicity and safety endpoints are described in the corresponding efficacy and safety sections of this AR.

Blood take for immunogenicity

In all participants, pre-third dose blood was obtained 6±2 weeks after the second dose (mean 37±14 days placebo; 37±15 days mRNA-1273). Only in a subgroup of 84 patients immunogenicity evaluations prior to the first and prior to the second dose were performed.

Statistical methods

Sample Size

It was assumed that at least 33% of participants who were to be randomised to receive a third dose of Spikevax will have an antibody titer >100 AU/mL when measured at 4-6 weeks post vaccination compared to the expected 10% that have received two doses of vaccine. For two independent study groups, to achieve a power of 80% with an alpha level 0.05, and 1:1 randomisation a sample size of 98 patients was required. It was aimed to enrol all 120 patients from the main PREVENT-COVID study to account for any loss to follow-up.

In case it was not possible to enrol all 120 patients from the main PREVENT-COVID study, it was planned to contact as many participants as needed from the MOT vaccine clinic to fulfil this sample size calculation.

Safety analyses

The safety analysis was to be performed in all patients who received the study vaccine regardless of whether they returned for follow-up serum (intention-to-treat population). Demographics and safety analysis were to be summarised using descriptive statistics.

Immunogenicity analyses – Primary endpoint

The immunogenicity analysis was to be performed in those who received the third vaccine dose and returned for follow-up serum (per-protocol population). The primary endpoint was defined as a post-intervention (4-6 weeks after third dose) anti-RBD titer of ≥ 100 U/ml as a threshold for response. The hypothesis of no difference in response rate between placebo and mRNA-1273 groups was to be assessed in the primary analysis with a Yates-corrected chi-square test; an unadjusted relative risk (RR) was to be calculated and a 95% confidence interval (CI) for the unadjusted RR was to be calculated using the normal approximation to the distribution of the log-relative risk. For the primary outcome, an adjusted marginal relative risk (RR) was also to be computed, along with a 95% CI. To obtain the adjusted RR estimate, a logistic regression model was used with baseline log(anti-RBD) titer as a covariate.

Immunogenicity analyses – Secondary endpoints

Analyses for the secondary endpoints were defined as follows:

- Assess pre-intervention antibody levels (i.e. baseline): absolute level (median; IQR) and percentage meeting threshold value (≥100) to ensure groups are balanced pre-intervention. Change in pre-post antibody level (paired data; Wilcoxon rank sum test).
- Median levels of antibody post-intervention at the 4-6 week time period (median; IQR); compare using Mann-Whitney U test assuming non-parametric distribution.
- Calculate fold-change in antibody level by using post-antibody divided by pre-antibody. If pre-or post-intervention antibody is negative use a value of 1/2 the detection threshold for calculation. Compare fold-change difference in two groups (median and mean fold change).
- Calculate T-cell response by using the number of SARS-CoV-2 specific CD4 and CD8 T-cells that produce both IFN-γ and IL-2 (defined as polyfunctional). The number is expressed as number of positive cells per 106 CD4 cells or CD8 cells respectively; (median; IQR with comparison between Placebo and Spikevax post-third dose using Mann-Whitney U test). Baseline (pre-intervention) median number of positive cells to ensure balance of the groups pre-intervention (median; IQR).
- The Genscript SVNT (surrogate virus neutralisation test) provides a neutralisation percentage (0-100%). As per test manufacturer's instructions, a threshold value of greater than 30% is considered positive for neutralising antibody. Analysis plan was to compare both the absolute SVNT percentage value between Spikevax and placebo (median percent neutralisation) using a Mann-Whitney test and the percentage of patients that achieve >30% threshold value in the two study arms using a corrected Chi-square test.

CHMP's comment

The description of statistical analyses in the protocol or SAP remains vague in many places and is not to the standard of pivotal trials usually submitted to the authorities.

Details of the adjusted (marginal) RR and for confidence intervals for change from baseline were only provided post hoc in the supplement of Hall et al. but not pre-specified in the protocol or SAP. The supplement explained the analyses as follows:

First the responses were predicted using the baseline log(anti-RBD) titer as a covariate and assuming everyone was in the vaccinated group. Then the responses were predicted using the baseline log(anti-RBD) titer as a covariate assuming everyone was in the non-vaccinated group. The ratio of the averages of the two sets of probabilities was used as the estimate of the marginal adjusted RR. The

95% BCa CI for this RR was calculated based on 4000 bootstrap replications of the calculation of this model based RR. Confidence intervals for the fold-change from pre-to post, and the absolute values of anti-RBD titers were computed using the nonparametric bootstrap with 4000 replicates and the BCa method.

Computation of confidence intervals for secondary endpoints was not pre-specified in either protocol or SAP. Only the supplement described the computations post hoc as follows:

For secondary outcomes, confidence internals for the differences in median, percent virus neutralisation, and SARS-CoV-2-specific T-cells were computed using the nonparametric bootstrap with 4000 replicates and the BCa method. Confidence intervals for the RR for secondary binary outcomes were calculated using the normal-based approximation.

Likewise, treatment of multiple testing was not defined in the SAP or protocol. The supplement stated in that regard:

Statistical significance for the primary outcome was defined as a p value < 0.05. Because no provision for correcting for multiplicity when conducting tests for secondary outcomes was pre-specified, all secondary results were reported as point estimates and 95% CIs. The widths of the CIs have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes.

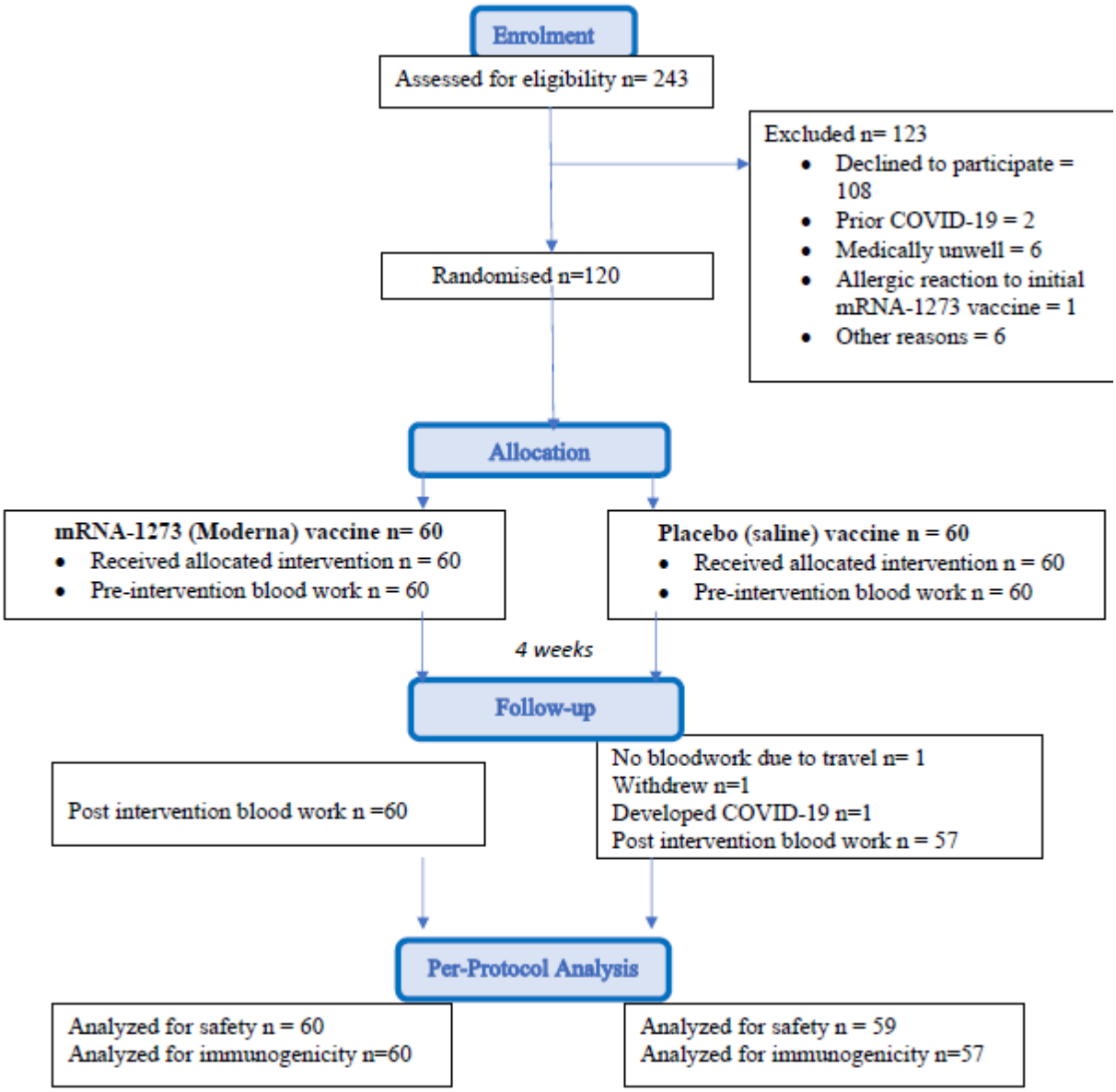
For safety analyses the protocol and the SAP are contradictory. The protocol states that "Rate of biopsy-proven or clinically treated rejection will be compared between the two groups using Chi-squared or Fisher's exact test." The SAP states that "No statistical comparison between placebo and Spikevax are planned" and does not give any details on how transplant rejections will be treated.

Immunogenicity analyses were performed in a "per protocol" population. No imputation for missing values was pre-specified or performed. Given that drop-outs only occurred in the placebo group this can be considered acceptable in this case as any sensible imputation strategy would increase the difference between groups in that case.

Overall, the conducted analyses seem acceptable.

Conduct of the study and baseline characteristics

Participants Flow



Demography

No patient had a previous diagnosis of COVID-19. The median age of the patients was 66.9 years (64.0 – 71.8) in the mRNA-1273 vaccine group and 65.9 years (62.9 – 70.3) in the placebo group. The median time from transplantation to the third dose was 3.57 (1.99 – 6.75) and 2.20 (1.44 – 5.55) years in the two groups, respectively. One subject each in the two groups had experienced an organ rejection within the preceding 3 months. An overview of demography for subjects in the vaccine and the placebo group including kind of transplant and the immunosuppressive therapy used is provided in Table 1.

Table 1: Patient characteristics at enrolment, mRNA-1273 vaccine vs placebo groups

Characteristic	mRNA-1273 (n=60)	Placebo (n=60)
Age (years), median (IQR)	66.9 (64.0 – 71.8)	65.9 (62.9 – 70.3)
Male sex, n (%)	37 (61.7%)	42 (70.0%)
Time from transplantation to intervention (years), median (IQR)	3.57 (1.99 – 6.75)	2.20 (1.44 – 5.55)
Rejection within the preceding 3 months n (%)	1 (1.7%)	1 (1.7%)
Anti-thymocyte globulin in the preceding 6 months	0	0
Type of transplant (%)		
Thoracic	21 (35.0%)	26 (43.3%)
Lung	11	18
Heart	10	8
Abdominal	39 (65.0%)	34 (56.7%)
Kidney	20	9
Pancreas and Kidney-Pancreas	15	9
Liver	4	16
Immunosuppression		
Prednisone (%)	50 (83.3%)	42 (70.0%)
Prednisone daily dose, mg; median (IQR)	5 (5–5)	5 (5-7.5)
Calcineurin inhibitor (%)	59 (98.3%)	59 (98.3%)
Tacrolimus	47 (78.3%)	46 (76.7%)
Tacrolimus trough level, ng/mL (IQR)	7.6 (5.9 – 9.8)	6.7 (5.3 – 8.6)
Cyclosporine	12 (20.0%)	13 (21.7%)
Mycophenolate mofetil/ mycophenolate sodium (%)	44 (73.3%)	46 (76.7%)
Mycophenolate daily dose; mg, median (IQR)	1080 (720-1440)	720 (585 – 1440)
Azathioprine (%)	8 (13.3%)	4 (6.7%)
Sirolimus (%)	6 (10.0%)	5 (8.3%)
Lymphocyte count at time of intervention (10^3 cells/μL), median (IQR)	1.15 (0.90 – 1.60)	1.3 (0.825 – 1.70)
Pre-third dose anti-RBD titre (U/ml), median (IQR)	0.37 (0.2 – 27.64)	0.44 (0.2 – 18.19)
Anti-RBD ≥ 100 U/ml pre-3rd dose	7 (11.7%)	5 (8.8%)*
Positive surrogate virus neutralization assay pre-3rd dose (threshold ≥30%)	22 (36.7%)	18 (31.6%)*

*denominator represents per-protocol population (n=57)

CHMP`s comment:

The kind of organ transplants slightly differed in the two groups. The immunosuppressive therapy was in general comparable, as well as lymphocyte count at time of intervention. In both groups more males than females were enrolled. One subject each in the two groups had experienced an organ rejection within the preceding 3 months.

3. Clinical Efficacy aspects

3.1. Methods – analysis of data submitted

Assessment of SARS-CoV-2 status

Although a previous diagnosis of COVID-19 was an exclusion criteria, in order to further confirm that measured immune responses were not due to natural infection, post-third dose sera were tested for anti-nucleocapsid protein antibody. The nucleocapsid protein is not encoded by the vaccine and thus a positive result due to vaccination is not expected. Testing was done using a commercially available chemiluminescent microparticle immunoassay (Abbott Laboratories, USA) as per manufacturer's instructions. As recommended by the manufacturer, an index measurement of ≥1.4 was considered positive.

Assessment of the antibody responses

Antibody levels were determined prior to the intervention as a baseline (preintervention antibody level) and following administration of a third dose. Sera were collected 4±1 weeks after the third dose of vaccine. The primary endpoint was defined as the percentage of patients that achieve a threshold response (i.e. a positive response) following vaccination.

Anti-spike receptor binding domain antibodies (anti-RBD) were measured using the Roche Elecsys anti-SARS-CoV-2 S enzyme immunoassay. This assay is a double-antigen sandwich electrochemiluminescence immunoassay that quantitatively detects antibodies to RBD of the spike protein. It has a lower limit of detection (LOD) of 0.4 U/mL although positive detection is defined as ≥ 0.8 U/mL. Testing was performed as per manufacturer's instructions in a certified biochemistry laboratory.

A serologic response characterised by an anti–receptor-binding domain (RBD) antibody level of at least 100 U/ml at month 4 was prespecified in the protocol as threshold of a positive antibody response. This cut-off was based on the protective anti-RBD titer determined in a challenge study involving nonhuman primates (McMahan et al. Nature 2021). A anti-RBD ELISA titer of approximately 100 U/ml was required for protection against SARS-CoV-2 infection.

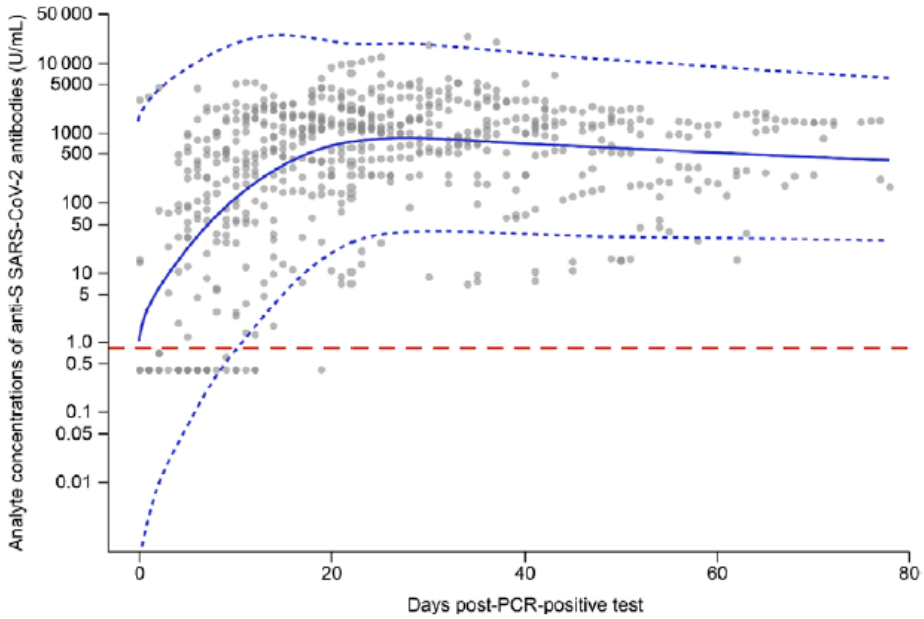
Moreover, use of this threshold was further justified by published data from Khoury et al. (Nature 2021) that looked at correlates of protection in a large cohort, validating the primary endpoint as the upper bound of the estimated 95% CI that correlates with 50% protective neutralisation. They estimated a 50% protective neutralisation level equates to approximately an anti-RBD titer of 54 U/ml with a 95% CI 30-96 U/ml. This validates our primary endpoint as the upper bound of the estimated 95% confidence interval that correlates with 50% protective neutralisation. Marinelli et al. in their prospective cohort study found a median convalescent anti-RBD antibody titre of 64.3 U/ml (interquartile range (IQR) 5.7 – 185) in solid organ transplant patients infected with COVID-19.

CHMP's comment:

As this assay was not employed in the clinical evaluation of the pivotal study for approval of Spikevax the study results do not allow to draw any conclusions on the vaccine efficacy of a third dose of Spikevax in patients under immune suppression. Moreover, no internationally recognised immunological surrogate of protection is yet established.

Published data by Riester et al, 2021 on independent performance evaluation of the Elecsys anti-SARS-CoV-2 S enzyme immunoassay using presumed negative samples collected prior October 2019 (n=7880) and samples from SARS-CoV-2 RT-PCR positive individuals (n=240) indicate a high

sensitivity (97.92%; 95% CI: 95.21–99.32) and specificity (99.95%; 95% CI: 99.87–99.99) for the detection of anti-Spike antibodies. The range of anti-RDB antibody responses observed and the decline of antibodies in convalescent sera over time (sequential samples) were provided (see below).



Longitudinal antibody titers of all subjects. Concentration of anti-S SARS-CoV-2 602 antibodies, as measured by the Elecsys Anti-S SARS-CoV-2 S immunoassay, over time (days 0 to 78) 603 in sequential samples from all study sites. Each grey circle represents a different data point, with 604 darker circles representing overlapping data points. The solid blue line represents the combined curve 605 and the blue dashed lines represent the upper and lower confidence limits. The red dashed line indicates the assay cut-off limit (0.80 U/mL).

In conclusion, it was found that the Elecsys anti-SARS-CoV-2 S enzyme immunoassay provides reliable results on anti-RDB antibody concentrations.

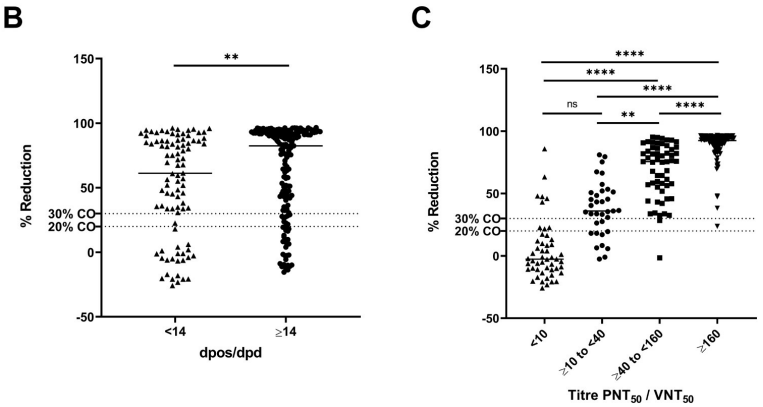
During the trial, a surrogate virus neutralisation assay became available in Canada and was added as a secondary endpoint before any post-third dose sera was collected. Neutralising antibodies were assessed via the SARS-CoV-2 Surrogate Virus Neutralization Test (SVNT) assay (GenScript), according to the manufacturer's specifications. The assay was originally described by Tan et al. in Nature Biotechnology and has been used in several peer-reviewed studies to assess neutralising antibodies. This assay has received emergency use authorisation from the FDA. Briefly, serum is incubated with horseradish peroxidase (HRP)-conjugated spike-RBD and transferred to ACE2 coated wells. Neutralising antibodies present in serum will inhibit RBD-ACE2 interactions. The assay provides the percent neutralisation, with <30% classified as negative; 30-100% represents a range of low-to-high neutralisation ability. The negative and positive percent agreement with conventional plaque reduction neutralisation test (PRNT)50 and PRNT90 assays is approximately 100%. The manufacturer reported sensitivity and specificity for the assay is 93.80% and 99.4%, respectively.

CHMP's comment:

The SARS-CoV-2 surrogate virus neutralisation (SVNT) assay is not a classical cell-based neutralisation assay measuring the ability of antibodies to inhibit infection of SARS-CoV-2 or pseudovirions of cells but is based on antibody-mediated blockage of the interaction between the angiotensin-converting enzyme 2 (ACE2) receptor protein and the receptor-binding domain of the spike protein. The read out is semi-quantitative and no specific neutralising ab titers were determined.

An independent evaluation of the robustness, specificity and sensitivity of the SVNT assay was performed on a panel of sera from 269 PCR-confirmed COVID-19 cases and 259 unmatched samples

collected before 2020 and compared it to cell-based neutralisation assays (ref to Meyer et al. 2021, https://doi.org/10.1080/22221751.2020.1835448). Comparison with cell-based neutralisation assays determined an analytical sensitivity of 74.3 (56.4–86.9) and 98.2 (89.4–99.9) for titres ≥10 to <40 and ≥40 to <160, respectively. While samples with a PNT50/VNT5O neutralising titre of <10 were found positive in the SVNT, some samples with a neutralising antibody titre of ≥10-<160 as measured by PNT50/VNT50 were determined negative in the SVNT. Only samples with a titre of ≥160 as measured in cell-based assays (PNT50/VNT50) were consistently positive in the SVNT.



In this study, % inhibition measured by the SVNT showed a moderate correlation with the cell-based assays PNT50 and VNT50 titres with R^2 values of 0.4937 and 0.6548, respectively. This is considerably lower than the correlation found in the study by Tan et al. which reported a R^2 of 0.8374 for a pseudovirus-based assay and 0.8591 for a conventional virus neutralisation assay. It should be noted that in the study by Tan et al. the half-maximum inhibitory concentration was determined by the SVNT instead of the % inhibition as calculated by Meyer et al. and as determined in the clinical study by Hall et al. Furthermore, the SVNT measures only neutralising antibodies directed against the RBD and not all neutralising antibodies directed against the full-length spike protein.

In conclusion, neutralising antibody responses based on the % inhibition as measured by the SVNT are of limited value and do not allow any meaningful interpretation of the neutralising antibody results reported by Hall et al.

T-Cell mediated immunity assessment

As a pre-specified secondary outcome, SARS-CoV-2 specific CD4+ and CD8+ T-cell responses were assessed pre and post intervention in patients who consented for additional blood. According to the authors methods have previously been validated using healthy controls post-vaccine and post-recovery from COVID-19 infection samples. Briefly, peripheral blood mononuclear cells (PBMCs) were isolated from whole blood and cryopreserved for batch testing. For testing, a total of 10^6 PBMCs were rested for two hours and incubated with overlapping peptides encompassing the full SARS-CoV-2 spike protein.

Peptides consisted mainly of 15-mer sequences with 11 amino acid overlaps (PepTivator, Miltenyi Biotec)(final concentration of 5 µg/mL per peptide). Cells were incubated overnight with peptides, a CD28/CD49d co-stimulatory antibody cocktail (BD Biosciences) and a protein transport inhibitor to prevent cytokine release (ThermoFisher Scientific). Intracellular cytokine staining (ICS) was used to measure the frequency of spike-specific T-cells. IFN-γ and IL-2 were used as the markers for this study, as has been also reported with other mRNA-1273 vaccine studies. The positive control was PMA/ionomycin and the negative (media) control was cells treated with media alone. Following overnight incubation at 37°C, PBMCs were stained with a viability dye (Zombie Aqua, Biolegend), Fc blocked (BD Biosciences) and incubated with a surface marker antibodies (CD3, CD4, CD8). Cells were then fixed, permeabilised and incubated with antibodies for intracellular markers (IFN-γ, and IL-2).

Flow cytometry was performed on an LSR II BGRV (BD Biosciences) instrument. A representative gating strategy and a patient with a positive CD4+ and a negative CD8+ response is shown in the supplementary information. As a robust, validated, yet conservative measure of vaccine-induced T-cell responses, frequencies of CD4+ and CD8+ T-cells that expressed two cytokines (IFN-γ and IL-2 positive; after subtraction of concurrent untreated comparator) were specifically measured. A minimum number of 100,000 live, CD3+ T-cells were required for samples to be included in the flow analysis.

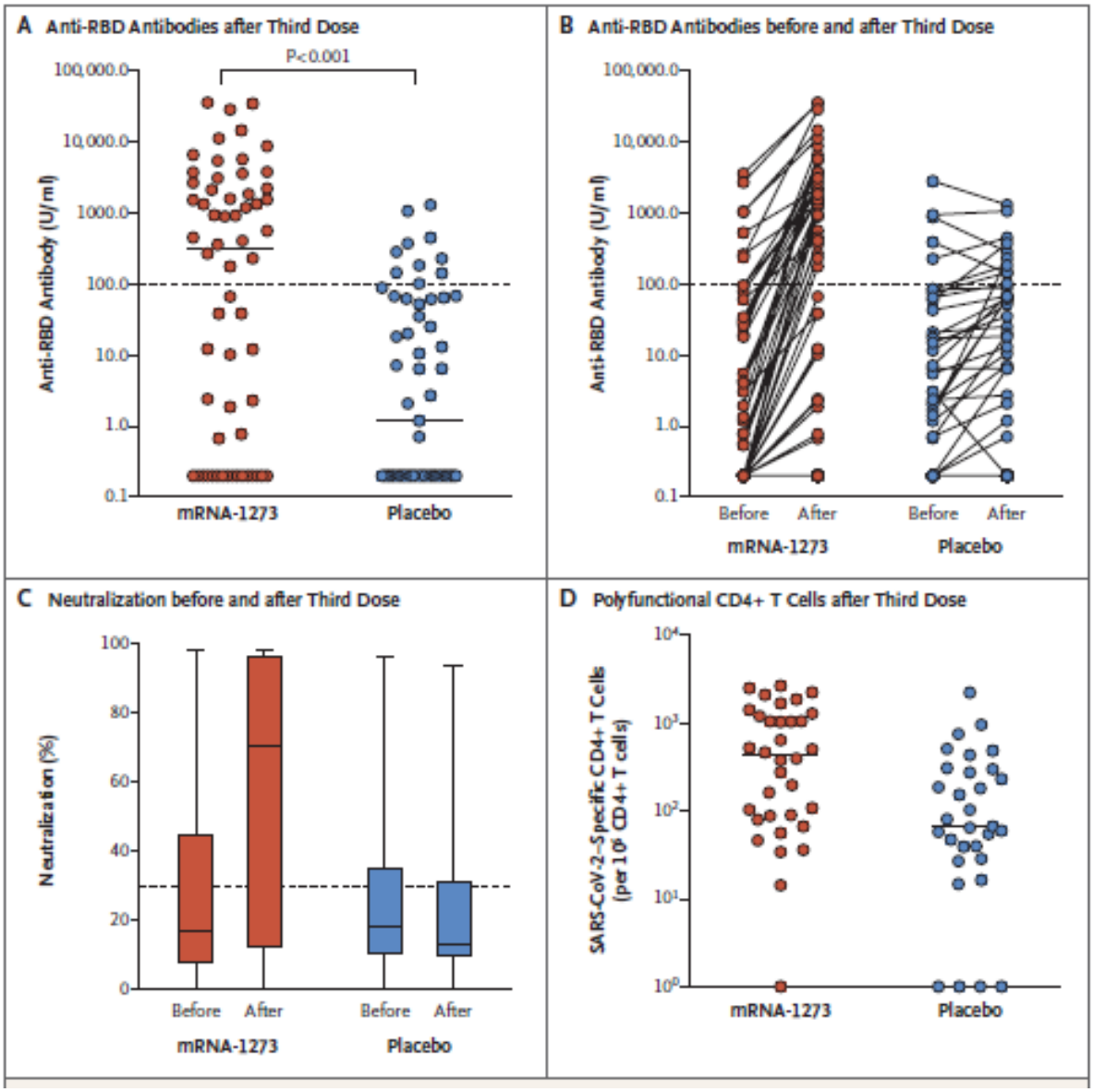
3.2. Results

At month 4, an anti-RBD antibody level of at least 100 U per millilitre was present in 33 of 60 patients (55%) in the mRNA-1273 group and in 10 of 57 patients (18%) in the placebo group (relative risk, 3.1; 95% confidence interval [CI], 1.7 to 5.8; P<0.001) (Figure 1A and Table 2). The changes in anti-RBD antibody levels from before to after the third dose are shown in Figure 1B. The mean anti-RBD antibody concentration was significantly higher in the group of IC patients having received a third dose of Spikevax compared to the control group having received placebo (GMC: 3145 U/ml vs 86 U/ml). The mean fold change was 75 times as high in the Spikevax group vs. the placebo group (95%CI: 21-220).

After the third dose, the median percent virus neutralisation was 71% in the mRNA-1273 group and 13% in the placebo group (95% CI for the between-group difference, 11 to 76 percentage points), and the percentage of patients above the 30% threshold for neutralising antibody positivity was 60% and 25%, respectively (relative risk, 2.4; 95% CI, 1.5 to 4.0) (Figure 1C and Table 2).

Median severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–specific T-cell counts were greater after the third dose in the mRNA-1273 group than in the placebo group (432 vs. 67 cells per 10^6 CD4+ T cells; 95% CI for the between-group difference, 46 to 986) (Figure 1D). There was a minimal polyfunctional CD8+ T-cell response in both groups.

Figure 1 . Immune Responses in Transplant Recipients Who Received a Third Dose of mRNA-1273 or Placebo.



Panel A shows the anti–receptor-binding domain (RBD) antibody levels in the mRNA-1273 group (60 patients) and the placebo group (57 patients) after the third dose. Each point represents an individual patient, and horizontal lines indicate the median. The dotted line indicates the threshold value of 100 U per millilitre. Values below the detection limit are plotted as 0.2 U per millilitre.
Panel B shows the anti-RBD antibody levels before and after the third dose.
Panel C shows box-and-whisker plots of the percent neutralisation before and after the third dose. The whiskers indicate the range, the top and bottom of the boxes indicate the interquartile range, and the horizontal line within each box indicates the median. The dotted line indicates the 30% threshold for neutralising antibody positivity.
Panel D shows the polyfunctional CD4+ T-cell response (i.e., cells producing both interleukin-2 and interferon-γ) before and after the third dose in the mRNA-1273 group (34 patients) and the placebo group (31 patients).

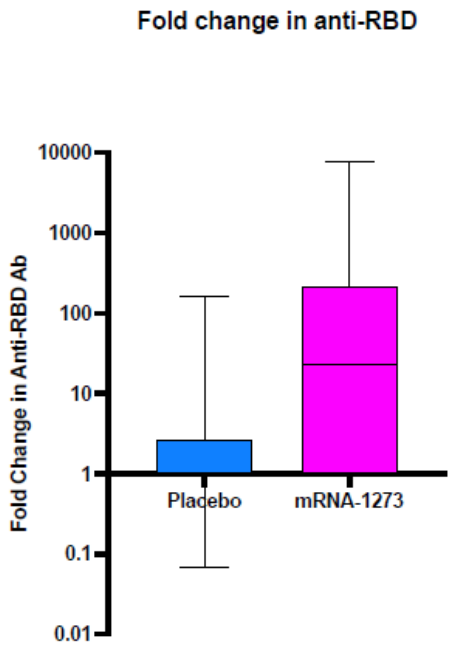
Table 2: Immunogenicity outcomes comparing a third dose of mRNA-1273 vs. placebo

Outcome	mRNA-1273 n=60	Placebo N=57	Comparison and 95% confidence interval*
Anti-RBD ≥100 U/ml post-dose 3	33 (55.0%)	10 (17.5%)	RR 3.1 (1.7-5.8) unadjusted; RR 2.9; (2.0-4.7) adjusted for baseline anti-RBD
Absolute anti-RBD titer (U/ml) post dose 3; mean (SD), median [IQR]	3145 (7517) 313.8 [0.2-2191]	86 (231) 1.19 [0.2-63.4]	Ratio of means: 36.5 (12.9-94)
Anti-nucleocapsid antibody post-dose 3 positive; n (%)	0 (0%)	1(1.8%)**	
Positive surrogate virus neutralization assay post-dose 3 (threshold ≥30%)	36 (60.0%)	14 (24.6%)	RR 2.4 (1.5-4.0)

*Widths of confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects for secondary outcomes.

**Borderline positive anti-nucleocapsid antibody level (1.56 U/ml); Patient had positive anti-RBD titer (>100 U/ml) both pre-and post-dose 3.

Figure 2 : Fold-change in anti-RBD titer for placebo and mRNA-1273 groups. For calculation of fold-change, values below the threshold were assigned a value of 0.2 U/ml. The mean fold change was 75 times as high in the treatment arm vs. the placebo arm (95%CI: 21-220). Horizontal lines in box represent median fold change. *Widths of confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects for secondary outcomes.*



CHMP's comment:

The study authors kindly provided further data on the immunogenicity assessment. Approximately half of the subjects having received a third dose of Spikevax did not achieve a titer above 100 U/ml, i.e., did not respond to it (27/60), while 10 out of 60 subjects had anti-RDB-titers of ≥100-<1000 U/ml and 23/60 immunocompromised (IC) patients developed anti-RBD titers of ≥ 1000 U/ml. In the placebo group 8/57 IC subjects had anti-RDB titers of ≥100-<1000 U/ml and only 2 IC subjects had still an antibody response of ≥1000 U/ml. Of note, one subject in the placebo group had evidence of a prior SARS-CoV-2 infection as determined by anti-NC antibodies and for 3 subjects no immunogenicity results were available.

3.3. Discussion

Immunogenicity of Spikevax in immunocompromised (IC) patients was assessed in a randomised, placebo-controlled trial conducted in Canada by Kumar and colleagues. The study results were published by Hall et al, 2021. In this study 243 IC patients were enrolled and of those 120 randomised to receive either a third dose of Spikevax or placebo, respectively, within 2 months. No control arm of healthy individuals was included.

The trial was not planned with the usual standards of pivotal trials but was conducted and analysed seemingly in an acceptable manner. Although no correlate of protection is yet established the immunogenicity data reported by Hall et al. suggest that a third dose of Spikevax is able to elicit a pronounced antibody response in a substantial number IC patients at risk for severe COVID-19. IC patients having received a third dose of Spikevax were compared to IC patients treated with placebo. Prior to the third dose 11.7% in the vaccine group and 8.8% in the placebo group had anti-RBD-antibody titers ≥100 U/ml, an antibody response considered by the investigators as seropositive. The median anti-RBD titre reported for both groups was low with 0.37 U/ml (IQR: 0.2-27.64) for the Spikevax group and 0.44 U/ml (IQR: 0.2-18.19) for the placebo group. Following administration of a third dose of Spikevax a significant rise in antibodies was observed with 55% of the IC patients showing at least an antibody titer of 100 U/ml with a calculated mean anti-RBD titer of 3145 U/ml (median: 313.8 U/ml, IQR: 0.2-2191). In the placebo group only 17.5% of IC patients had antibodies ≥100 U/ml and a GMC of 86 U/ml (median: 1.19 U/ml, IQR: 0.2-63.4) was reported.

Data from routine vaccination of healthcare workers (HCW) with a standard 2-dose regimen suggest that the level of anti-RDB antibody response achieved in IC patients following a third dose of Spikevax is in the same range as in the healthy population post-second dose. Steensels et al., 2021 compared the humoral immune response following vaccination of 1647 HCW with mRNA vaccines including Spikevax. In this prospective study the antibody responses were evaluated 6 to 10 weeks after they received a second dose using the Elecsys anti-SARS-CoV-2 S enzyme immunoassay. In total, 688 individuals were vaccinated with Spikevax (mRNA-1273: mean age, 43.2 years; 76.7% women; 21.8% previously infected with SARS-CoV-2). Post-second dose a GMT of 3836 U/mL [95%CI, 3586-4104] was determined for individuals having received two doses of Spikevax. Further evaluation according to baseline status showed that previously uninfected individuals had lower antibody responses compared with previously infected individuals (GMT: 2881 U/mL, 95% CI, 2721-3051 and 10708 U/mL 95% CI,9311-12 315, respectively).

Currently no data are available, however, on the duration of the antibody response in IC patients following a third dose or whether it correlates with a higher chance to prevent serious disease.

As no immune correlate of protection exists to infer vaccine efficacy so far, the interpretation of the available immunogenicity results based on anti-RDB antibody responses is limited. The assay does not

measure the antibody response to the full-length spike protein, nor does it provide information on the neutralising capacity of the immune response. Results provided by Hall et al. on the neutralising antibody responses in IC patients following a third dose were not determined with a standard cell-based assay but a semiquantitative surrogate assay. The SNVT assay has various flaws and limitations and therefore the data provided should be interpreted with caution. The results provide no additional value to conclude on the benefit of a third dose.

In conclusion, the limited published data on the immunogenicity in solid organ transplant recipients cannot provide direct estimates of the protective benefit of a third dose of Spikevax in patients under immunosuppressant therapy.

No immunogenicity data are available on other immunocompromised patients, i.e. due to specific therapies or due to hereditary immunodeficiencies. B cell targeted therapies have a strong but selective impact on antibody responses that might not be overcome by additional doses for primary immunisation.

Although, in this study the third dose was given 2 months after the second dose, a time interval of at least 28 days would be more appropriate considering the high number of no and low responders in immunocompromised and their high risk of serious complications following a SARS-CoV-2 infection.

4. Clinical Safety aspects

4.1. Methods – analysis of data submitted

Data on safety of a third dose of Spikevax in solid organ transplant (SOT) recipients are derived from the published placebo controlled trial.

Pertinent exclusion criteria were: 1) within 1-month post-transplant, 2) had a febrile illness within 1-week prior, 3) previous microbiologically confirmed COVID-19 infection, 4) active cytomegalovirus (CMV) infection, 5) received intravenous immunoglobulin in the 4 weeks prior, 6) received rituximab in the last 6 months, 7) had treatment for acute rejection in the 30 days prior, and 8) an allergic reaction to the previous mRNA-1273 vaccination.

Immunosuppressive treatment was adapted according to standard practise also during the trial (information by one of the authors in teleconference).

Safety assessments included reporting of local or systemic AE by the vaccinee via a diary each day for 7 days after injection. Thereafter patients were followed every 2 weeks for up to 3 months after the third Spikevax or placebo dose. They were called by telephone every 2 weeks to determine whether they were diagnosed with COVID or if they have any COVID-related symptoms (fever, cough, myalgias, sore throat, runny nose, diarrhoea, shortness of breath). Participants were reminded to let the study team know immediately if they had been diagnosed with COVID. Non-routine health-care contacts including hospitalisation and the reasons for these healthcare visits were recorded every two weeks up to 3 months post-vaccination. These were to be judged as related or unrelated to vaccine according to investigator judgement. In addition, within the phone calls and chart review episodes of acute organ rejection and whether a biopsy was done, and whether rejection treatment was started was recorded. Rate of biopsy-proven or clinically treated rejection will be compared between the two groups. Passive follow-up was planned to occur from 3 to 9 months after the third dose of Spikevax or placebo (i.e. from 6 to 12 months post-first dose).

Adverse events were categorised by the Food and Drug Administration toxicity grading scale for volunteers in vaccine trials:

- grade 1 (no interference in daily activities)
- grade 2 (some interference in daily activities)
- grade 3 (participants unable to perform daily activities)
- grade 4 (potentially life threatening)

CHMP's Comment

The reason for the SOT is unknown in the included population. Therefore, any interaction of underlying disease (e.g. autoimmune disease) is unknown. From the specified exclusion criteria, it is apparent that only a fairly stable population after solid organ transplantation was eligible for the trial.

4.2. Results

Safety data are available for n=60 subjects in the Spikevax group and for n=59 subjects in the placebo group.

Patient characteristics as regards immunosuppressive treatment is shown in the following table (from supplement to publication).

Table 3: Patient characteristics

Characteristic	mRNA-1273 (n=60)	Placebo (n=60)
Age (years), median (IQR)	66.9 (64.0 – 71.8)	65.9 (62.9 – 70.3)
Male sex, n (%)	37 (61.7%)	42 (70.0%)
Time from transplantation to intervention (years), median (IQR)	3.57 (1.99 – 6.75)	2.20 (1.44 – 5.55)
Rejection within the preceding 3 months n (%)	1 (1.7%)	1 (1.7%)
Anti-thymocyte globulin in the preceding 6 months	0	0
Type of transplant (%)		
Thoracic	21 (35.0%)	26 (43.3%)
Lung	11	18
Heart	10	8
Abdominal	39 (65.0%)	34 (56.7%)
Kidney	20	9
Pancreas and Kidney-Pancreas	15	9
Liver	4	16
Immunosuppression		
Prednisone (%)	50 (83.3%)	42 (70.0%)
Prednisone daily dose, mg; median (IQR)	5 (5–5)	5 (5-7.5)
Calcineurin inhibitor (%)	59 (98.3%)	59 (98.3%)
Tacrolimus	47 (78.3%)	46 (76.7%)
Tacrolimus trough level, ng/mL (IQR)	7.6 (5.9 – 9.8)	6.7 (5.3 – 8.6)
Cyclosporine	12 (20.0%)	13 (21.7%)
Mycophenolate mofetil/ mycophenolate sodium (%)	44 (73.3%)	46 (76.7%)
Mycophenolate daily dose; mg, median (IQR)	1080 (720-1440)	720 (585 – 1440)
Azathioprine (%)	8 (13.3%)	4 (6.7%)
Sirolimus (%)	6 (10.0%)	5 (8.3%)
Lymphocyte count at time of intervention (10^3 cells/μL), median (IQR)	1.15 (0.90 – 1.60)	1.3 (0.825 – 1.70)

CHMP's comment

The trial population involves only individuals after solid organ transplantation that are immunosuppressed by commonly used immunosuppressive regimen consisting of glucocorticoids, calcineurin-inhibitors and antimetabolites. Thus, any conclusions on the safety of a third dose of Spikevax in immune-compromised individuals other than the studied populations rely on a full extrapolation without support by data. From a safety perspective it is unknown how e.g. hereditary immunodeficiencies and medically induced immunodeficiencies using other treatments would behave. It is also likely that the underlying disease that is the reason for the medical immuno-suppression is important for judging safety.

Local and systemic adverse events 4 weeks post-third dose are presented in the following table. No grade 3 or 4 adverse events were reported. According to the publication, no clinically treated or biopsy proven rejection events occurred.

	mRNA-1273, n = 60		Placebo, n = 59	
	Grade 1, n (%)	Grade 2, n (%)	Grade 1, n (%)	Grade 2, n (%)
Local adverse event				
Pain	46 (76.7)	0	6 (10.2)	1 (1.7)
Erythema	0	2 (3.3)	0	1 (1.7)
Swelling	9 (15.0)	0	0	0
Systemic adverse event				
Fever	5 (8.3)	0	1 (1.7)	0
Chills	13 (21.7)	1 (1.7)	6 (10.2)	0
Fatigue	26 (43.3)	4 (6.7)	16 (27.1)	1 (1.7)
Myalgia	17 (28.3)	1 (1.7)	11 (18.6)	1 (1.7)
Arthralgia	7 (11.7)	0	6 (10.2)	1 (1.7)
Headache	11 (18.3)	0	5 (8.5)	1 (1.7)
Nausea or vomiting	4 (6.7)	1 (1.7)	3 (5.1)	0
Diarrhea	2 (3.3)	0	3 (5.1)	0
Rash	0	0	0	1 (1.7)

SAE and deaths

There is no mentioning of SAE in the publication. On request the authors provided the following information:

"There were medical visits for the following reasons during the 4 weeks post-intervention: patients sought outpatient medical attention for diverticulitis (n=1; placebo), blurry vision (n=1; placebo). Hospitalisation occurred in three patients in the placebo arm, one each for COVID-19 infection, fall, gastrointestinal bleed."

CHMP's comment

The duration of data collection overall is not entirely clear and the safety database is limited. Strength of this dataset is the randomised comparison to placebo.

AE overall were grade 1 and 2 of the chosen scale which could be considered acceptable as regards severity. No information is available on the duration and reversibility of the AE so it can only be assumed that they were fully reversible. As with any medicinal product that relies on unspecific elements of immune system stimulation this could lead to rejection in SOT, thus it is important to note that no rejection episodes were observed.

Three SAE (hospitalisation events) were recorded that occurred in the placebo arm. No deaths were observed.

An evaluation of safety in other immune-compromised individuals was not part of this submission.

4.3. Discussion

Given that generally the observed reactogenicity is a function of a working immune system there is a priori no specific safety concern related to vaccination of a normally immune-competent individual that is medically immune-suppressed. The limited dataset in this application and the observed AE appear to support this assumption.

This reasoning would also apply to the immunisation of individuals with malignancies that cause immuno-compromise per se and that is caused in addition by the administered oncologic therapy (with the possibly important exception of checkpoint inhibitors). A survey of safety of mRNA vaccines in patients with haematological malignancies did not indicate vast differences in the different safety profile compared to healthy subjects (https://www.lls.org/news/covid-19-vaccine-safety-among-blood-cancer-patients). A specific concern in some haematological malignancies is lymphadenopathy following vaccination (observed in 5% of the above survey) that either indicate disease or could be an AE to vaccination. Only reversibility would indicate that this is more likely related to vaccination.

The situation is considered to be different in auto-immune or auto-inflammatory diseases that are pharmacologically immuno-suppressed. Here the inflammatory stimulus by the vaccine could cause a flare of the underlying disease. Since the concept of mRNA vaccination is relatively new, the experience in these conditions is clearly limited at the present point in time. One prospective cohort study of patients with autoimmune disease under immunosuppressive therapy was conducted (Conolly et al. 2021). This study included individuals who reported receipt of a single booster dose of SARS-CoV-2 mRNA or adenovirus vector vaccine between 10 April and 11 June 2021. The publication however does not comment on safety. A recently conducted survey in SLE patients suggests that there is no high risk of flare induced by mRNA vaccination (https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913%2821%2900221-6/fulltext). However, in 3% of the patients AE were observed that were judged to be consistent with a flare. Without concomitant control it is difficult to evaluate this finding. A third dose was not used in this population and thus no specific information is available. Therefore, any decision on a third dose in these populations should factor in type of immunosuppression and severity of underlying disease.

Other means of pharmacological immune-suppression involve neutralisation of cytokines such as TNF-alpha, IL-6, IL-1beta, IL-12, IL-23 etc by monoclonal antibodies, depleting antibodies such as rituximab, antimetabolites such as methotrexate and inhibitors of the JAK-STAT signalling pathway. No information on the safety in patients treated with these types of medicinal products has been submitted and as outlined above the underlying disease may be an important modifier that has to be considered for safety. It should be noted that e.g. under therapy with TNF-alpha inhibitors paradoxical auto-immune phenomena have been observed.

Hereditary immunodeficiencies are most often caused by changes to the function of different components of adaptive immune system that ultimately lead to impaired immune responses. No information on safety of Spikevax in these populations has been submitted.

Altogether the submitted documentation is severely limited especially with regard to the different populations of immunocompromised patients, no new safety signals were observed. The MAH provided a high-level overview of the available literature on the safety of a third dose of Spikevax as part of a primary series in immunocompromised individuals. All published literature refers to solid organ recipients and no safety data for Spikevax in patients with other types of immunocompromise is available.

5. Changes to the Product Information

As a result of this variation, sections 4.2 and 4.4 of the SmPC are being updated to introduce a third dose of Spikevax in the primary vaccination schedule for individuals 12 years of age and older who are severely immunocompromised. The Package Leaflet (PL) is updated accordingly (see Attachment 1).

6. Request for supplementary information

6.1. Other concerns

Clinical aspects

The MAH should provide a high level overview of the available literature for the safety of a third dose in immune-compromised individuals to support extrapolation to other types of immune-compromise.

7. Assessment of the responses to the request for supplementary information

7.1. Other concerns

Clinical aspects

Question

The MAH should provide a high level overview of the available literature for the safety of a third dose in immune-compromised individuals to support extrapolation to other types of immune-compromise.

Summary of the MAH's response

The MAH conducted a literature search for publications containing safety data for the third dose of mRNA SARS CoV-2 vaccine in immunocompromised patients which identified nine articles. Currently, there are limited data available from the publications and all publication concern SOT recipients. Four publications describe expected reactogenicity, and almost all commented on the acceptable safety profile or tolerability at a high level; however, most of the data focused on immunogenicity not safety. Four articles were letters to the editor with study data, two were preprint, and one was "Observations: case reports". Four articles presented third dose data for Spikevax, and one study described the third

dose of Spikevax administered after a primary series of Comirnaty (BNT162b2, Pfizer/BioNTech), and another study presented data on mix-and match vaccine administration including the Janssen COVID-19 vaccine.

Reference Article	Type of Publication	Patient Population	COVID-19 mRNA Vaccine	Reactogenicity	Serious adverse events/additional safety data	Other findings
Hall et al 2021	NEJM, letter to the editor and supplementary appendix	Organ-transplant recipients (n=120)	Moderna	No grade 3 or 4 reactogenicity; graphs in supplementary appendix	None	No organ transplant rejection
Massa et al 2021	Lancet, PREPRINT	Kidney transplant (n=61)	Pfizer	Frequency (not severity) after Dose 1,2, and 3 presented	Limited, 1 subject had de novo Abs to donor after dose 2 which increased after Dose 3, although had not complied with immunosuppressive medication	No rejection
Kamar et al 2021	NEJM, letter to the editor	Solid-organ transplant (n=101)	Pfizer	None provided	No serious adverse events were reported after the administration of the third dose, and no acute rejection episodes occurred	No additional safety data in appendix
Werbel et al 2021	Annals of Internal Medicine, Observations: Case Reports	Solid organ Transplant Recipients (n=30)	n= 2 of Moderna primary series and Moderna 3rd dose, n=7 Pfizer primary series and Moderna 3rd dose, n=3 Pfizer primary series and 3rd dose Pfizer; also included Janssen	Does not delineate Pfizer and Moderna third dose recipients; present mRNA reactogenicity for 12 mRNA vaccinees; "the vaccine reactions seem acceptable given the benefits these vaccines can confer."	None	One heart transplant patient had rejection 7 days after third dose (vaccine not specified)
Del Bello, et al 2021	American Journal of Transplantion, Letter to the Editor	Solid organ transplant (n=396 [note, on these n=101 were presented in the	Pfizer	None provided	No serious adverse event or acute rejection episode was observed after the administration of the third dose	
Westhoff, et al 2021	Kidney International, Letter to the Editor	Renal transplant patients (n=10)	4 weeks after second dose of Pfizer received Moderna	None provided	None	"well-tolerated"
Espi, et al 2021	MedRxRIV, PREPRINT	Hemodialysis, Pfizer (n=75)	Pfizer	Reactogenicity presented for optimal and suboptimal responders. "Tolerance to 3D of BNT162b2 was excellent"	"Although, the safety of the 3D of BNT162b2 vaccine was excellent and comparable to that of the 2D with no critical local or systemic side-effect reported, the tolerance was worst in patients with already optimal humoral response, who did not improve significantly their immune response against the spike protein of SARS-Cov-2 after this additional injection."	
Longlune, et al 2021	Nephrology Dialysis Transplantation, published by Oxford Univeristy Press on behalf of ERA-EDTA	Hemodialysis (n=12, received third dose)	Pfizer	The article discusses dose 1,2, and 3 – does not delineate reactogenicity for each of the doses. Summary statement: "With respect to adverse events, 20 patients experienced fatigue (n=15), myalgia (n=15) and low fever (n=7) for 24 hours."	No serious adverse events were reported by patients who received the vaccine.	
Benotmane, et al 2021	JAMA, Research Letter	Kidney transplant recipients (n=159)	Moderna	None provided	"No severe adverse events were observed after the third dose"	

On a monthly basis, the MAH reviews and summarises the literature and the data from the MAH's global safety database for both immunocompromised (defined by medical history and medications) and

autoimmune/inflammatory disease subpopulations. This information is reported in the MSSRs, and the MAH presented a cumulative review in the PBRER (provided on 26 August 2021). In MSSR #8 (provided on 15 September 2021), a subsection was provided for third dose AE reports on both subpopulations.

Assessment of the MAH's response

Safety
The MAH conducted a literature search for publications containing safety data for the third dose of mRNA SARS CoV-2 vaccine in immunocompromised patients and submitted the findings subsequently after request. All publications refer to SOT recipients and no safety data for Spikevax in patients with other types of immunosuppression are available.

One study evaluates a third dose of Comirnaty in in maintenance haemodialysis patients (Espi et al. 2021). The objective of this observational study was to evaluate the protection of MHD patients against COVID-19 after two doses of BNT162b2, and the safety and impact on immune responses of a third dose. A third dose of BNT162b2 mRNA vaccine was offered to all 66 MHD patients with suboptimal anti-RBD IgG response and effectively administered to 56 of them. The lowest titer observed in a cohort of 30 healthy volunteers was therefore taken as reference for suboptimal immune response and to vaccine and immune response in MHD patients was considered optimal or sub-optimal (n=66/106, 62.3%) depending whether the titer of anti-RBD IgG was respectively superior or equal, or inferior to this value. Administration of a third dose was not limited to MHD patients with suboptimal anti-RBD IgG titers, and 19 MHD patients with optimal IgG response also accepted a third vaccine dose. The authors found, that although, the safety of the third dose of BNT162b2 vaccine was excellent and comparable to that of the 2-dose schedule with no critical local or systemic side-effect reported, the tolerance was worst in patients with already optimal humoral response, who did not improve significantly their immune response against the spike protein of SARS-Cov-2 after this additional injection. In contrast, after a third dose, 2/3 of MHD patients with suboptimal response after two doses experienced an increase of anti-RBD-IgG titer up to optimal level and/or the appearance of spike-specific CD8+ T cells.

One case-series, published by Werbel et al. reported one case of organ rejection. One heart transplant recipient had biopsy-proven, antibody-mediated rejection 7 days after the third dose of vaccine in the setting of acute volume overload. The patient did not experience an increase in the titer of antibodies against the spike protein, heart function remained normal, and immunosuppressive intensification was not initiated. The vaccine is not specified in the publication and no further clinical information is available. The objective of the trial was to describe antibody responses and vaccine reactions in recipients of solid organ transplants who had a suboptimal response to standard vaccination and subsequently received a third dose of vaccine. The definition for suboptimal immune response is not specified in the publication. Overall, 30 patients reported a third vaccination, but only 3 of them received three doses of Spikevax. Taking the risk of poor outcome after COVID-19 infection in the severely immunocompromised patients into account this single case of organ rejection with only very limited clinical information available would not alter the benefit-risk assessment of a third dose.

The very limited safety data in the publications do not reveal any safety concern with regard to a third dose of mRNA SARS-CoV-2 vaccines in severely immunocompromised individuals.

In MSSR #8 (provided on 15 September 2021), a subsection was provided for third dose of Spikevax. Here 2 cases of myocarditis were recorded after a third dose.

One case occurred in a 30-39-year-old patient with past medical history included recurrent urinary infections and Stem cell transplant in 2020. Concurrent medical conditions included chromosomal

disorder since July 2020 and Immunodeficiency. On Day 0, the patient received first dose of Spikevax; on Day 28, received second dose of Spikevax, and on Day 122, received third dose of Spikevax. Five days later the patient was diagnosed with Pericarditis and Myocarditis. Laboratory results showed elevated troponin and EKG with diffuse ST elevation without defined territory. No other information was provided.

The second case was a 50-59 years old with concurrent medical history of essential hypertension and hyperlipidaemia, and concomitant medications of lisinopril and rosuvastatin, who the same day after receiving the third dose of Spikevax experienced left arm tingling, left shoulder pain, then chest pain that became severe enough the patient had to pull to the side of the road. Had diaphoresis, dyspnoea, pre-syncope. The patient received a first Comirnaty dose on Day 0 then a second Comirnaty dose on Day 26 and had a booster dose with Spikevax on Day 220. The patient had full cardiac workup, d-dimer, chest x-ray but results were not provided, Patient had a cardiac catheterisation which was normal. No relief in symptoms with narcotics, nitroglycerin, etc. Post catheterisation, given ketorolac with significant relief. Diagnosed with Pericarditis. No other information was provided. This case is classified as Level 4 diagnostic according to the Brighton Collaboration case classification. Considering the time to onset, a myocarditis related to vaccination is unlikely.

Currently, it is not possible to estimate whether there is an increased risk of developing myocarditis or pericarditis after a 3-dose schedule compared with a 2-dose schedule.

In summary, the subsequently submitted information do not provide safety information for a third dose of Spikevax in individuals with immunosuppression not related to SOT. The very limited safety data so far do not raise safety concerns with regard to a third dose of mRNA SARS-CoV-2 vaccines in severely immunocompromised individuals.

Immunogenicity

Upon request the MAH referenced four further publications, which report immunogenicity results following a third dose of Spikevax in immunocompromised patients or patients with autoimmune and inflammatory diseases (Werbel et al. 2021, Benotmane et al. 2021, Westhoff et al. 2021, Connolly et al. 2021).

Werbel et al. 2021 evaluated the immune response in SOT recipients following a third dose of Spikevax after completion of the initial 2-dose vaccination regimen. In this case series, however, only three out of 30 patients received three doses of Spikevax within 60-101 days, while the others received different combinations of COVID-19 vaccines. Two different serological assays were used to determine the antibody responses in SOT patients, but no comprehensive information is available, which one was used for these subjects. The concentrations given suggest, that one of the two low responders developed a strong antibody response, while the other did not respond.

Benotmane et al. investigated the immune response following a third dose of Spikevax in 159 kidney transplant recipients having received mRNA vaccines in the primary vaccination series. This study found that a third dose of Spikevax induced a serologic response (anti-RBD-antibodies) in 49% of kidney transplant recipients who did not respond after two doses. However, no analysis according to the vaccine used for the initial 2-dose vaccination series is provided. Interestingly, it was reported that patients taking tacrolimus, mycophenolate, and steroids were less likely to develop anti–SARS-CoV-2 antibodies than those treated with other regimens.

Westhoff et al. evaluated the immune response in 10 renal transplant recipients having received a heterologous vaccination regimen, i.e. Spikevax was given as a third dose only.

In the publication of Connolly et al. (case series) 18 patients with autoimmune and inflammatory diseases received each a third dose of a COVID-19 vaccine (either heterologous or homologous

regimens employing mRNA and vector-based vaccines). Out of these 18 patients only 3 patients received three doses of Spikevax. One patient had myositis and 2 had autoimmune hepatitis and all of them were on immunosuppressant therapy (combination or monotherapy). Anti-spike antibodies, evaluated by the Roche Elecsys anti-RBD pan-Ig were found low to high positive (anti-RBD concentration: 2.7 U/ml, 260 U/ml and 825.8 U/ml respectively) after completion of the initial vaccine series and developed high antibody concentrations of >2500 U/ml after the third dose. The time interval between the second and the third dose was 85-96 days.

In conclusion, information on the immunogenicity following a 3-dose Spikevax vaccination regimen in immunocompromised subjects other than solid organ transplant recipients is very scarce and has no added value for the benefit-risk assessment.

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

8. Overall conclusion and impact on the benefit-risk balance

The MAH seeks approval of a third dose of Spikevax (also referred to as mRNA-1273) in the primary vaccination schedule for immunocompromised individuals, based on limited published data from one clinical trial (PREVent-COVID) conducted in solid organ transplant recipients in Canada. The study results were published by Hall et al., 2021.

No data are currently available from the ongoing post authorisation Phase 3b study initiated by the MAH in solid organ transplant recipients and healthy controls to assess the safety and immunogenicity of Spikevax in immunocompromised adults aged 18 years and older as agreed during the initial approval in the RMP.

Immunogenicity

The PREVent-COVID-19 study is a randomised, placebo-controlled, double blind study of transplant recipients. 120 adult solid organ transplant (SOT) recipients who were stable outpatients with functioning allograft and who have already received both doses of Spikevax at 0 and 1 months have been enrolled in the study to either receive a third dose of Spikevax or placebo, respectively.

Immunogenicity of Spikevax in immunocompromised (IC) patients was assessed by two serological assays. Although the trial was not planned with the usual standards of pivotal trials, it was conducted and analysed seemingly in an acceptable manner. The data reported suggest that a third dose of Spikevax is able to elicit a pronounced antibody response in a substantial number of IC patients at risk for severe COVID-19 (a significant rise in antibodies was observed with 55% of the IC patients showing at least an antibody titer of 100 U/ml, compared to 17.5% in the placebo group). And data from routine vaccination of healthcare workers with a standard 2-dose regimen suggest that the level of anti-receptor-binding domain (RBD) antibody response achieved in IC patients following a third dose of Spikevax is in the same range as in the healthy population post-second dose. However, as no immune correlate of protection exists so far to infer vaccine efficacy, the interpretation of the available immunogenicity results based on anti-RBD antibody responses is limited. The assay does not measure the antibody response to the full-length spike protein, nor does it provide information on the neutralising capacity of the immune response. Results provided on the neutralising antibody responses in IC patients following a third dose were not determined with a standard cell-based assay but a

semiquantitative surrogate assay. This surrogate assay has various flaws and limitations and the results provide no additional value to conclude on the benefit of a third dose.

No data are available on the duration of the antibody response in IC patients following a third dose or whether the immune response elicited by a third dose correlates with a higher chance to prevent serious disease.

In conclusion, the limited published data on the immunogenicity in solid organ transplant recipients cannot provide direct estimates of the protective benefit of a third dose of Spikevax in patients under immunosuppressant therapy.

No immunogenicity data are available on other cohorts of immunocompromised patients, i.e. with specific medical therapies or due to hereditary immunodeficiencies. B cell targeted therapies have a strong but selective impact on antibody responses that might not be overcome by additional doses for primary immunisation.

Safety

The limited dataset in this application do not indicate any specific safety concern. The observed reactogenicity and the observed adverse events were comparable to what is reported in healthy subjects.

The MAH provided a high-level overview of the available literature on the safety of a third dose of Spikevax as part of a primary series in immunocompromised individuals. All published literature refers to solid organ recipients and no safety data for Spikevax in patients with other types of immunodeficiency is available.

Thus, no safety data are available from other immunocompromised populations such as patients with auto-immune or auto-inflammatory diseases, or patients under medical treatment other than the regimen used in transplant patients, known to result in immune suppression.

Benefit-risk

Based on general experience with vaccines, an increased antibody titre induced by a third dose may be associated with increased protection from the disease. Based on the very limited immunogenicity data the extent of the benefit of a third dose in immunocompromised patients cannot be estimated. For some types of immunocompromise, even a third dose within the primary series is unlikely to provide any benefit.

No safety concerns are anticipated. There is uncertainty regarding the safety in different types of immunodeficiency.

Overall, a third dose within a primary series could be justified based on individual benefit-risk considerations. A third dose of Spikevax (0.5 mL) may only be given to severely immunocompromised individuals, who have a high risk of severe disease due to a diminished antibody response following a 2-dose regimen. The third dose should be given as part of the primary series and the time interval between the second and the third dose should be at least 28 days.

The benefit-risk balance of Spikevax remains positive.

9. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2 and 4.4 of the SmPC in order to introduce a third dose of Spikevax in the primary vaccination schedule for individuals 12 years of age and older who are severely immunocompromised, based on published literature data; the Package Leaflet is updated accordingly. The MAH took the opportunity to make minor administrative and editorial corrections throughout the product information.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB are recommended.

10. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

SmPC new text

A third dose may be given at least 28 days after the second dose to individuals who are severely immunocompromised. The recommendation to consider a third dose (0.5 mL) is based on limited serological evidence with patients who are immunocompromised after solid organ transplantation.

For more information, please refer to the Summary of Product Characteristics.

Please refer to Scientific Discussion 'Spikevax/H/C/005791/II/31'