EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/472994/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

COMIRNATY

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

Procedure No. EMEA/H/C/005735/II/0062

Marketing authorisation holder (MAH): BioNTech Manufacturing GmbH

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	
Description	**Date**
Start of procedure	13 Sep 2021
CHMP Rapporteur Assessment Report	23 Sep 2021
CHMP members comments	29 Sep 2021
Updated CHMP Rapporteur Assessment Report	01 Oct 2021
Opinion	04 Oct 2021

Procedure resources	
Rapporteur:	Filip Josephson

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, BioNTech Manufacturing GmbH submitted to the European Medicines Agency on 19 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 Comirnaty as part of 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.

2. Introduction

In a correspondence to New England Journal of Medicine, Kamar et al (Kamar N, Abravanel F, Marion O, et al. Three doses of an mRNA COVID-19 vaccine in solid-organ transplant recipients. N Engl J Med 2021;385:661-2. DOI: 10.1056/NEJMc2108861) reported findings from a retrospective study of administration of a 3rd dose of Comirnaty in solid-organ transplant recipients who had received 2 doses, 1 month apart.

The marketing authorisation holder (MAH) submitted a variation to include information regarding a 3rd vaccination dose in immunocompromised patients in Sections 4.2, 4.4, 4.8 and 5.1 of the EU SmPC, to align the EU SmPC with information included in United States Emergency Use Authorization (EUA) Fact Sheets.

3. Clinical Efficacy aspects

A weak immune response to two doses of vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been observed in the immunosuppressed recipients of solid-organ transplants. Severe cases of COVID-19 have been reported in transplant recipients who had received two doses of vaccine.[3] These reports prompted the French National Authority for Health to recommend the use of a third dose in immunosuppressed patients.

According to French law, because the data reported by Kamar et al was an anonymous retrospective study, institutional review board approval was not required.

The author of the publication has kindly provided a table of data to confirm the publication. As there was no study protocol the publication is more of a case series than a clinical study.

3.1. Methods – analysis of data submitted

The basis of this application is a retrospective case series. There is no study protocol.

The levels of antibodies to SARS-CoV-2 spike protein were assessed in all the patients at one-month post dose 3, with the use of the Wantai enzyme-linked immunosorbent assay (Beijing Wantai Biological Pharmacy Enterprise).

Wantai microplate ELISA that detect total anti-SARS-Cov-2 antibodies (IgG, IgM and IgA) (WANTAI SARS-CoV-2 Ab ELISA). Semi-quantitative results are expressed as signal-to cut-off ratio (S/C0). Patients were defined as positive if S/Co> 1.1.

Samples with a S/C0> 47 were retested after dilution. Using this assay, the research group has previously reported a 100% specificity and 100% sensitivity in immunocompetent patients tested at 2 to 14 days post symptom-onset and at 15 to 45 days post symptom-onset, suggesting it as the ability to detect low level of antibodies.

The operative characteristics are published in:

Abravanel F, Miédouge M, Chapuy-Regaud S, Mansuy J-M, Izopet J. Clinical performance of a rapid test compared to a microplate test to detect total anti SARS-CoV-2 antibodies directed to the spike protein. J Clin Virol 2020; 130: 104528.

This ELISA test bases on the spike antigen of SARS-CoV-2. The immunoassay was used to test 30 negative sera collected in 2019 at Toulouse hospital and 69 serum collected from PCR-confirmed SARS-CoV-2 infected patients. The COVID-19 infected patients provided 40 samples collected 2–14 days post symptom-onset (group 1) and 29 collected 15–45 days post symptom-onset or after contact with a positive case, including 3 asymptomatic patients (group 2). All 30 negative samples tested negative with the assay, corresponding to 100 % specificity (confidence interval 95 %, (CI 95 %): 82.1–100 %). The overall sensitivity of the ELISA test was 100 % (69/69) (CI 95 %: 88.2–100 %, $p < 0.01$) (Table 1). The ELISA test was 100 % sensitive (40/40) (CI 95 %: 84.5–100 %, $p = 0.01$). Similarly, the ELISA test was 100 % sensitive (29/29) (CI 95 %: 81.8–100 %, $p = 0.49$) when tested on the 29 group 2 samples. The 2 group 2 samples that tested negative with the Wantai rapid test had low index values (< 8) when tested with the Wantai ELISA assay and these samples were from 2 of the 3 asymptomatic patients. The research group therefore find that the Wantai ELISA assay has excellent specificity and sensitive.

Serological results for patients with a PCR-confirmed SARS-CoV-2 infection.

	All samples N = 69	samples collected < 14 days post-onset n = 40	samples collected > 14 days post-onset n = 29
Wantai Rapid test			
Positive	60	33	27
Negative	9	7	2
Wantai ELISA			
Positive	69	40	29
Negative	0	0	0

The method used to detect antibodies are commercially available test kits. The results should not be compared to the results from clinical studies perfomed by the MAH, using in-house methods. There is currently no immune correlate of protection established in healthy subjects or in immunocompromised subjects.

Conduct of the study and study population

When the vaccination campaign started (7 January 2021), all transplant-patients in Toulouse were invited to be vaccinated. Due to weak immunogenicity of 2 doses of mRNA based anti-SARS-CoV-2

vaccines, the French National Authority for Health recommended (4 April 2021) the use of a third dose in immunosuppressed patients. This dose was to be given at least one month after the second dose or as soon as possible, in patients in whom the second dose had been administrated more than one month before this latter recommendation. Hence, all seropositive or seronegative transplant patients were invited to receive the third dose.

According to the recommendations of the Francophone Society of Transplantation, anti-SARS-CoV-2 spike protein antibodies were monitored before and after vaccination. Furthermore, the French authorities recommended that anti–SARS-CoV-2 serology be performed in immunosuppressed patients. Therefore, all study patients were also invited to perform a serology according to the national recommendations. Serology was performed at one month after the third dose according to the publication.

In the published letter retrospectively the outcome of the first 101 consecutive patients who have been given 3 doses and who have had their anti–SARS-CoV-2 spike protein antibodies assessed was collected. According to French law, anonymous retrospective studies do not require institutional review board approval.

3.2. Results

The case series consists of 101 consecutive solid-organ transplant recipients (mean [±SD] age, 58±2 years; 69% were men) who were given three doses of the messenger RNA vaccine Comirnaty (BNT162b2, Pfizer–BioNTech). The group included 78 kidney-transplant recipients, 12 liver-transplant recipients, 8 lung-transplant or heart-transplant recipients, and 3 pancreas-transplant recipients (Table 1).

The first two doses were given 1 month apart, and the third dose was administered approximately 2 months after the second dose (median 63 days range:35-83 days). The time between transplantation and the initiation of vaccination was 97±8 months. Immunosuppression was due to the use of glucocorticoids (in 87% of patients), calcineurin inhibitors (in 79% of patients), mycophenolic acid (in 63% of patients), mammalian target of rapamycin inhibitors (in 30% of patients),and belatacept (in 12% of patients). (Table 1)

The prevalence of anti-SARS-CoV-2 antibodies was 0% (0 of 101 patients) before the 1st dose, 4% (4 of 101 patients) before the 2nd dose, 40% (40 of 99 patients) before the 3rd dose and 68% (67 of 99 patients) 4 weeks after the 3rd dose.

Among the 59 patients who had been seronegative before the 3rd dose, 26 were seropositive at 4 weeks after the 3rd dose. All 40 patients who had been seropositive before the 3rd dose were still seropositive 4 weeks later; their antibody titers increased from 36±12 before the 3rd dose to 2676±350 one month after the 3rd dose ($p<0.001$).

The research group compared responders to non-responders after 3-doses vaccine (table 1). Non-responders were older, had a lower total lymphocyte count, a lower CD4-positive Tcell count, a lower CD19-positive count, and a lower estimated glomerular filtration rate before vaccination compared to responders. The proportion of patients given belatacept was higher among non-responders.

Table 1 (supplementary appendix to publication). Clinical and biological characteristics of solid organ transplant recipients according to humoral response one month after three doses of mRNA-based vaccine.

	Anti-SARS-CoV2 positive patients (*N*=67)	Anti-SARS-CoV2 negative patients (*N*=32)	*p*-value
Sex ratio (M/F)	2.2 (46/21)	2.6 (23/9)	0.745
Age (years, mean ±SEM)	54 ±2	65 ±3	**<0.001**
Type of organ transplant, n (%)			0.491
- Kidney	51 (76)	25 (78)	
- Liver	9 (13)	3 (9)	
- Thoracic organs	4 (6)	4 (13)	
- Pancreas	3 (4)	-	
History of rejection in the year preceding vaccination, n (%)	2 (3)	1 (3)	1
Time between vaccine and transplantation (months, mean ±SEM)	99 ±10	94 ±16	0.793
No induction therapy, n (%)	26 (39)	14 (44)	0.667
Induction therapy, n (%)	41 (61)	18 (56)	
- Anti-IL2 receptor blockers	26 (63)	9 (50)	
- Polyclonal antibodies	14 (34)	8 (44)	
- Others	1 (2)	1 (6)	
Type of immunosuppressive regimen, n (%)			
- Calcineurin-inhibitors	55 (82)	23 (72)	0.245
○ Tacrolimus	51 (93)	22 (97)	
○ Ciclosporin A	4 (7)	1 (3)	
- Anti-metabolite	41 (61)	24 (75)	0.176
○ Mycophenolic acid	40 (98)	24	
○ Azathioprine	1 (2)	-	
- mTOR inhibitors	22 (33)	7 (22)	0.262
- Steroids	58 (87)	28 (88)	1
- Belatacept	5 (7)	7 (22)	0.052
Neutrophils count before vaccination (/mm^3, mean ±SEM)	5459 ±252	5600 ±664	0.810
Lymphocytes count before vaccination (/mm^3, mean ±SEM)	1561 ±123	1173 ±114	**0.049**
CD4+ T-cells count before vaccination (/mm^3, mean ±SEM)	n=59 529 ±37	n=30 339 ±38	**0.002**
CD8+ T-cells count before vaccination (/mm^3, mean ±SEM)	n=59 440 ±38	n=30 358 ±48	0.201
CD19+ B-cells count before vaccination (/mm^3, mean ±SEM)	n=59 182 ±83	n=30 89 ±33	**0.003**
NK cells count before vaccination (/mm^3, mean ±SEM)	n=59 235 ±18	n=30 216 ±33	0.582
eGFR before vaccination (mL/min/1.73m²)	60 ±3	45 ±4	**0.005**

According to the correspondence, none of the patients had developed COVID-19 after receiving the 3rd dose of Comirnaty. The duration of follow-up is unknown. Therefore, this is non-informative.

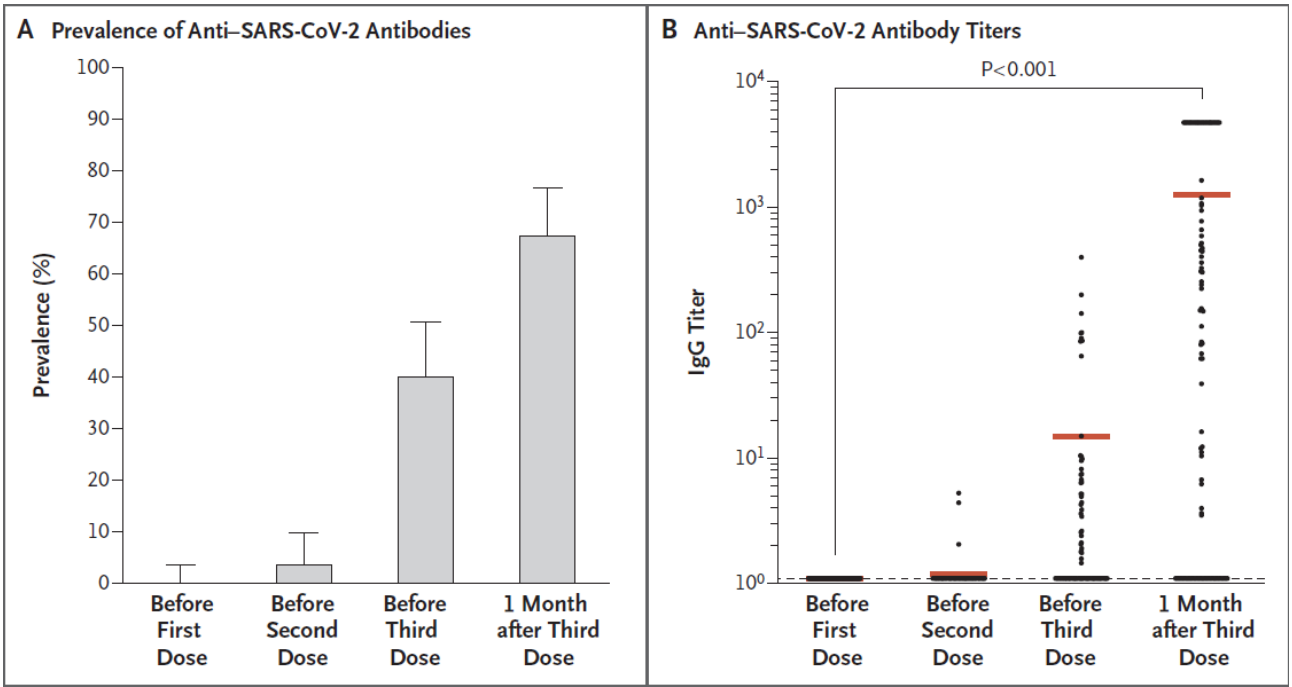

Figure 1. Immunogenicity.

Panel A shows the prevalence of anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies before and after vaccination in the study population. Panel B shows anti–SARS-CoV-2 antibody titers before and after vaccination in the study population.

3.3. Discussion of efficacy

The current submission aims to include data in the SmPC regarding immunocompromised subjects. It is agreed that this is a group at increased risk of severe COVID-19.

The current submission contains data from a publication of a case series of vaccinated subjects who had previously undergone a solid organ transplant. Antibodies were measured using a commercially available kit which measures binding antibodies in contrast to the methods used in clinical trials performed by the MAH which measure neutralising antibodies. Results are therefore not directly comparable to the already available serology results from healthy subjects.

Serostatus was determined at one month after the third dose. Semi-quantitative results are expressed as signal-to cut-off ratio (S/C0). Patients were defined as positive if S/Co> 1.1. This metric has no relation to any immune correlate of protection, which has not been defined either for healthy subjects or for the immunocompromised.

The data indicate that an additional dose given to immunocompromised subjects increases the frequency of sero-responders, as defined above. The clinical relevance of the increased frequency is unknown as no efficacy data are available. However, given the medical need for protection it is a reasonable assumption that a third dose could be given to this vulnerable group. It seems to be already the case in clinical practice in several countries including France.

Based on previous experience of vaccination of adolescents the results can be extrapolated to subjects down to 12 years of age with similar immunosuppression. Immune responses are not expected to be lower in adolescents compared to adults.

The practice of Kamar et al 2021 are considered illustrative of what may be considered reasonable clinical management.

Overall, a third dose could be justified based on individual benefit-risk considerations and may be given to individuals who are severely immunocompromised. The time interval between the second and the third dose should be at least 28 days.

4. Clinical Safety aspects

4.1. Methods – analysis of data submitted

The provided submission does not state how safety data was collected.

4.2. Results

No reactogenicity data were provided. The only safety information available is the statement of the authors that no serious adverse reactions occurred, and that no acute reactions were reported until the publication date. The duration of follow-up is unknown.

4.3. Discussion

The safety information provided is very limited. The only available information is that no SAE occurred within an unspecified period after a third dose was given to 101 solid organ transplant recipients. The safety profile of a third dose in this populations is likely acceptable.

5. Changes to the Product Information

As a result of this variation, sections 4.2 and 4.4 of the SmPC are updated to introduce a third dose of Comirnaty 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 suggested additions to the SmPC are not agreed as discussed above. We suggest the following statement in section 4.2:

Immunocompromised population
A third dose may be given at least 28 days after the second dose in patients not anticipated to achieve a sufficient vaccine response due to profound immunosuppression (see section 4.4.)

The MAH is invited to comment on this proposal.

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

7.1. Other concerns

Clinical aspects

The suggested additions to the SPC are not agreed as discussed above. We suggest the following statement in section 4.2:

Immunocompromised population
A third dose may be given at least 28 days after the second dose in patients not anticipated to achieve a sufficient vaccine response due to profound immunosuppression (see section 4.4.)

The MAH is invited to comment on this proposal.

Summary of the MAH's response. The MAH finds it important to make sure the SmPC is clear that the data to support this was not generated by the company.

Assessment of the MAH's response. The MAH position is understood and can be accepted provided that the wording is in agreement with SmPC guidelines.

Conclusion. Issue resolved.

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 current submission aims to include a recommendation for a third dose in immunosuppressed subjects, along with data on serological response in subjects on immunosuppressive treatment after solid organ transplant. This is a group at increased risk of severe COVID-19.

The variation is based on a case series of vaccinated subjects who had undergone a solid organ transplant previously, and who received a third dose of Comirnaty one month after the second dose (Kamar et al, 2021). Some of these patients were sero-responders after two doses; some were not.

Anti-Sars-Cov2 antibodies were measured before a third dose, and 4 weeks after the third dose. A commercially available kit which measures binding antibodies was used, in contrast to the methods used in clinical trials performed by the MAH which measure neutralising antibodies. Results are therefore not directly comparable to the already available serology results from healthy subjects. Furthermore, it should be noted that sero-response was conventionally defined, as there is no immune correlate of protection established for healthy subjects or for patients with various immunocompromised conditions.

The data indicate that an additional dose given to immunocompromised subjects increases the frequency of sero-responders from 40% prior to dose three, to 68% one month after the third dose. The clinical relevance of the increased frequency is unknown as no efficacy data are available. However, given the medical need for protection against COVID-19 in these vulnerable patients, it is a reasonable assumption that a third dose given to this group may increase protection against COVID-19, at least in some patients.

Based on previous experience of vaccination of adolescents the results can be extrapolated to subjects down to 12 years of age with similar immunosuppression. Immune responses are not expected to be lower in adolescents compared to adults.

The safety information provided is very limited. The only available information is that no SAE occurred within an unspecified period after a third dose was given to 101 solid organ transplant recipients, and that no acute rejections occurred.

The practice of Kamar et al 2021 is considered illustrative of what may be considered reasonable clinical management.

Overall, a third dose could be justified based on individual benefit-risk considerations and it may be given to individuals who are severely immunocompromised. The time interval between the second and the third dose should be at least 28 days. Inclusion of the data in sections 4.4, 4.8 and 5.1. is not supported, due to the limited nature of this data.

More information on the safety and immunogenicity of the vaccine in immunocompromised subjects (including assessment of antibody responses and cell-mediated responses) will be collected in the remit of the studies BNT162-01 Cohort 13, ACCESS/VAC4EU, C4591011, C4591012 and C4591018 as detailed in the currently approved RMP.

The benefit-risk balance of Comirnaty 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 Comirnaty for individuals 12 years of age and older who are severely immunocompromised, based on published literature data; the Package Leaflet is updated accordingly.

☒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 of Comirnaty may be given at least 28 days after the second dose to individuals who are severely immunocompromised based on limited serological evidence from a case series in the literature from the clinical management of patients with iatrogenic immunosuppression after solid organ transplantation.

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