BEILAGE 2

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2021-01-12 (mit Zeitstempel)

201.3534

RECOMMANDÉ
Moderna Switzerland GmbH
c/o Katja Schott, Walder Wyss AG
Aeschenvorstadt 48
4051 Basel

Berne, le 12.01.2021

N° d'AMM : 68267 - COVID-19 Vaccine Moderna dispersion for injection
N° de demande : 102643108
Votre demande d'autorisation du 09.11.2020

Décision d'approbation

Madame, Monsieur,

En date du 09.11.2020, vous nous avez transmis les documents requis pour l'autorisation du médicament COVID-19 Vaccine Moderna dispersion for injection, COVID-19 mRNA Vaccine. Par courrier du 30.11.2020 (LoQ nonclinical no 1), 23.12.2020 (LoQ nonclinical no 2, quality no 1 and risk management no 1) et 30.12.2020 (LoQ clinical no 1), Swissmedic vous a adressé les listes de questions. Le 07.12.2020 (answer to LoQ nonclinical no 1), le 30.12.2020 (answer to LoQ risk management no1, nonclinical no 2), le 31.12.2020 (answer to LoQ quality no1) et le 06.01.2021 (answer to LoQ clinic no 1), vous nous avez adressé vos réponses à nos listes de questions. Le 09.01.2021 Swissmedic vous a fait parvenir une lettre intitulée «*Provisional interim assessment – invitation/opportunity to take a stand*». Dans cette lettre, vous avez notamment été informés que Swissmedic considérait la documentation transmise jusqu'à cette date comme insuffisante pour l'octroi d'une autorisation ordinaire de mise sur le marché conformément à l'art. 11 de la loi sur les produits thérapeutiques[1] (LPTh), mais qu'elle envisageait l'octroi d'une autorisation à durée limitée sur la base de l'art. 9a LPTh. En même temps, vous avez été informés sur les charges spécifiques jugées nécessaires pour l'octroi d'une autorisation à durée limitée de votre préparation sur la base du dossier d'autorisation de mise sur le marché évalué jusqu'à ce moment dans le cadre de la « Rolling submission ». Enfin, votre attention a été attirée sur le fait que, compte tenu de la situation particulière de risque due à l'épidémie actuelle de Covid 19, Swissmedic est obligé de fixer des délais très courts pour la présentation de vos objections respectives dans le cadre du droit d'être entendu. Le 10.01.2021 vous nous avez soumis votre réponse à notre lettre du 09.01.2021 ainsi que vos projets pour l'information professionnelle et l'information destinée aux patients.

[1] RS 812.21

Swissmedic vous a ensuite fait part le 11.01.2021 de la décision qu'il entendait rendre. Vous nous avez adressé à la même date une prise de position au sujet de cette dernière. Swissmedic a examiné vos documents à la lumière des exigences légales en termes de sécurité, d'efficacité et de qualité et est parvenu aux conclusions suivantes.

Évaluation :
La demande d'autorisation du médicament COVID-19 Vaccine Moderna dispersion for injection déposée le 09.11.2020 peut être approuvée dans la mesure où conformément à l'art. 9*a* de la loi sur les produits thérapeutiques[2] (LPTh) en relation avec l'art. 21, al. 1 de l'Ordonnance sur l'autorisation simplifiée de médicaments et l'autorisation de médicaments fondée sur une déclaration[3] (OASMéd) l'autorisation pour le médicament COVID-19 Vaccine Moderna dispersion for injection est octroyée pendant une période limitée allant jusqu'au 11.01.2023.

Plan d'investigation pédiatrique
Swissmedic n'a pas effectué de propre examen scientifique du plan d'investigation pédiatrique présenté.
L'"Opinion of the Paediatric Committee on the agreement of a Paediatric Investigation Plan and a deferral" du 30.11.2020 de l'Agence européenne des médicaments (EMA) concernant le plan d'investigation pédiatrique (PIP) portant le numéro EMEA-002893-PIP01-20 est reprise.

SwissPAR
Swissmedic publiera un Swiss Public Assessment Report (SwissPAR) après l'entrée en force de la décision exécutoire relative à la demande de mise sur le marché de COVID-19 Vaccine Moderna dispersion for injection. En plus du SwissPAR, Swissmedic publie un Public Summary SwissPAR compréhensible pour les non-initiés (voir Guide complémentaire *SwissPAR HMV4*). Compte tenu de la situation exceptionnelle actuelle et de la menace qui en découle pour la santé publique, nous ne préparerons les public Assessment Reports qu'à une date ultérieure. Par conséquent, le SwissPar sera publié avec un certain retard après que nous vous aurons donné la possibilité de commenter les pEBs.

Vous trouverez également en annexe les textes suivants, revêtus de notre cachet d'approbation :

- Cartonnage
- Étiquette
- Information destinée aux patients
- Information professionnelle sur le médicament

En règle générale, les textes du médicaments (information destinée aux professionnels, aux patients etc.) doivent être disponibles dans une des langues officielles nationales suisses et ceci avant la mise sur le marché du produit en Suisse. Cependant, compte tenu de la situation de pandémie, nous pouvons accepter pour le moment les versions en langue anglaise ci-

[2] RS 812.21
[3] RS 812.212.23

jointes. Nous vous demandons de nous envoyer les textes de médicament mentionnés dans une langue nationale suisse (allemande et/ou française) dans les plus brefs délais. En raison de la situation pandémique, nous acceptons pour l' instant des emballages approuvés par l'EMA.

Le titulaire de l'autorisation est tenu par la loi d'adapter l'information sur son médicament, en permanence et spontanément, à l'état des connaissances scientifiques et techniques (art. 28 de l'ordonnance sur les médicaments[4], OMéd) et d'en transmettre la version approuvée ainsi que ses versions traduites exigées par la législation sur les produits thérapeutiques à l'institution prévue à l'art. 67, al. 3 de la loi sur les produits thérapeutiques[5] (LPTh) pour publication au plus tard à la première mise sur le marché du médicament (art. 29 OMéd).

Compte tenu de ces considérations et conformément à l'art. 9*a*, à l'art. 16, al. 1 et al. 2, let. a, à l'art. 67, al. 1 LPTh, à l'art. 68, al. 1, let. e OMéd, à l'art. 18, à l'art. 21, al. 1 et al. 2 et à l'art. 21*a* de l'ordonnance sur l'autorisation simplifiée de médicaments et l'autorisation de médicaments sur annonce[6] (OASMéd), ainsi qu'en application de l'art. 3, al. 1 et de l'art. 4, en relation avec l'annexe 1, ch. I, ch. 2.1 de l'ordonnance de l'Institut Suisse des produits thérapeutiques sur ses émoluments[7] (OE-Swissmedic),

la décision suivante est prise :

1. La demande d'autorisation du médicament COVID-19 Vaccine Moderna dispersion for injection déposée le 09.11.2020 est partiellement approuvée. L'autorisation du médicament COVID-19 Vaccine Moderna dispersion for injection, est octroyée pendant une période limitée allant jusqu'au **11.01.2023.**

a) Le médicament COVID-19 Vaccine Moderna dispersion for injection est autorisé pendant une période limitée pour les indications / possibilités d'emploi «COVID-19 Vaccine Moderna is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older» dans la catégorie de remise B.

b) Recommandation posologique : voir l'information sur le médicament (information professionnelle et information destinée aux patients) approuvée jointe en annexe.

2. L'information sur le médicament (information professionnelle et information destinée aux patients) approuvée et les textes d'emballage approuvés sont joints en annexe et font partie intégrante de la présente décision.

3. Les émoluments sont fixés à **80'000.00 francs** (annexe 1, ch. I, ch. 2.1 OE-Swissmedic) et sont à la charge de Moderna Switzerland GmbH.

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[4] RS **812.212.21**
[5] RS **812.21**
[6] RS **812.212.23**
[7] RS **812.214.5**

4. CHARGES :

Si vous voulez une traduction du texte ci-dessous, veuillez s'il vous plaît contacter constanze.fritzsche@swissmedic.ch

a. Charges relatives à la qualité

The definition of the drug substance does not conform to the Swissmedic definition. Only the mRNA CX-024414 is considered the drug substance of COVID-19 mRNA Vaccine (nucleoside modified).
As for the time being, only a temporary authorisation for the drug product can be issued, we accept the proposed definition. In case a full authorisation is requested at a later stage, the applicant is expected to align the definitions of excipients, drug substance and drug product.

1. S.2.2.3 CX-024414: In the response to question 10 of the LoQ Quality, the applicant states that a Hold Time qualification will be performed. A qualification of Hold Times is expected for the [redacted] drug substances intermediates CX-024414[redacted] and mRNA-1273 LNP. This qualification should cover the combination of manufacturing times and hold times. The results of this Hold Study shall be submitted not later than 31-MAR-2021.

2. S.2.3: The manufacturer should define his own in-house specifications for raw materials (which may be derived from those of the vendor) and assess the raw materials against those. Only a single set of harmonized specifications should be provided for each raw material. Update the raw material specification not later than 31-JUL-2021.

3. 3.2.S.4.1 / 3.2.P.5.1: The calculated statistical intervals results are not always taken into consideration to redefine the specifications (e.g.: Polydispersity). Furthermore, the statistical analysis of specification do not take into account results that are smaller than LOQ or greater than 99%. A conservative approach would be to use the LOQ or 99% as a value to calculate the impacted specifications.
   Based on the batch data of the PPQ batches manufactured at Lonza Visp and Rovi, we expect a reassessment and tightening of the following specification parameters by 30-JUN-2021:
   - Residual DNA Template
   - %5' Capped
   - % PolyA Tailed RNA
   - Residual DNA Template
   - Polydispersity
   - LNP size
   - Content of the four lipids
   - Lipid impurities
   - Post-Main Peak impurities by RP-HPLC

4. P.3.3: In the answer to question 49 of the LoQ Quality, the applicant states that there are no technical reasons to limit the number of LNP batches that may be combined. LNP

bags from different batches are combined simply to use up material leftover due to mismatch between LNP batch size and DP batch size.
Batches from different scales should only be pooled after the new process is validated.

5. S.2.2 / S.2.5 drug substances intermediates CX-024414[redacted] and mRNA-1273 LNP: Applicant should provide a list of process parameter target value with the associated NOR and PAR, and their criticality classification for every manufacturing process description. There is a discrepancy between the In-Vitro Transcription Non-critical Process Parameters range defined in the protocol PV-VL-RPT-0001 and those defined in 3.2.S.2.2 "Description of the Manufacturing Process and Process Controls {CX-024414}" (e.g. DNAse reaction duration range is larger in the PPQ report, Oligo dT chromatography flow rates are not listed). Please ensure that the parameters used in all the PPQ runs are compliant with the predefined parameters and their NORs and if necessary, they should be corrected is the next eCTD sequence.

6. P.3.3: The PAR "Cumulative Processing duration" for the drug product manufacturing is defined as ≤ 336 hours out of frozen conditions (= 96 hours + 240 hours), with no more than 96 hours under TOR conditions. This is not supported by the studies listed in the tables 14 and 15. 96 hours at CRT and 240 hours at 2°-8°C were not tested cumulatively but in two separate studies. Please reduce the max. processing duration or demonstrate the cumulative duration of 336 hours with no more than 96 hours TOR. This should be corrected is the next eCTD sequence.

7. P.3.5: Sterile filter validation should be supplemented with data and discussion on potential sorption of solution components to the filters and extractable and leachables from the filters. This information shall be submitted by 31-MAR-2021.

8. P.7: The document [redacted] which supports the use of the stoppers as closure for multiple-dose product vials is not available. This document shall be submitted by 31-MAR-2021.

9. P.3.5: The following issues should be corrected in the PPQ protocols from Rovi. The corrected protocols shall be submitted by 31-MAR-2021:
   a. P.3.5: Filling hold time (time between sterile filtration and capping of the vial) should not exceed 36 hours for aseptic filling process
   b. Deviations (exception register) in the method transfer reports from Rovi are not all approved by Quality Assurance. For [redacted], the register is not attached
   c. Verification of the Bioburden determination test method at Rovi is not described. The verification report of the Endotoxin test methods is not attached
   d. Leachable and extractable assessment for the drug product: Actions for risk mitigation of high-risk process consumables are ongoing and should be reported as soon as available

10. Following differences have been observed between the US and EU manufacturers and shall be corrected in the next eCTD sequence:

a. S.2.3.3.3 Enzymes are of biological origin. Please correct the US manufacturing chapter 3.2.S.2.3.3.3
b. S.2.3.3.3 Some of the Certificate of Analysis from New England BioLabs enzymes do not list the batch number, the results of testing nor a Pass/Fail results. Please correct.
c. S.2.3.5.1.2 There is a difference between the US and the Lonza Visp leachable risk assessment for medium risk consumables even though the manufacturing process is identical. Please clarify and correct if necessary.
d. S.2.3.2 for the pre-packed [redacted] Resin, a BSE/TSE Certificate is required by Lonza Visp but not by the US manufacturers. Please clarify and correct if necessary
e. S.2.3 Mixer Zephyros [redacted] in the documentation from Lonza Visp. Please clarify and correct if necessary.
f. S.7.1 Stability Protocol for GMP CX-024414 Aramus bags should include a test for purity, product-related impurities, %polyA Tail and total RNA content for the time point 6 months at 5°C ± 3°C to be consistent with the stability protocol of the PETG bottles

11. S.2.3.1 Provide an overview of the plasmid manufacturing process and release testing at [redacted]. This overview shall be submitted by 31-MAR-2021.

12. P.2.3: Characterisation studies of selected batches of the drug product are ongoing, a master comparability protocol has been provided. PPQ batches manufactured at Lonza Visp (Scale B-initial and Scale B-final) and Rovi (Scale B, 65'000 vials) should be included in the studies.
The study report shall be submitted by 30-JUN-2021.

13. S.2.5 / P.3.5: The following PPQ Reports must be provided as soon as they are available, but not later than 30-JUN-2021:
a. Lonza Visp Scale B-initial and Scale B-Final
b. Rovi Scale B, 65'000 vials

14. S.4.2.2 The Sanger sequencing method described for Lonza does not correspond to the one used by [redacted] (contract labor for Lonza). Please update the method description accordingly in the next eCTD Sequence.

15. 3.2.P.5.3: Analytical Procedure UPLC-CAD: Detection and quantitation limit for other lipids and individual impurities have to be evaluated by 30-SEP-2021.
Forced degradation study: A typical chromatogram of "a degradant solution" has been shown, but no quantitative results of these solutions have been reported. Please demonstrate that the proposed method has adequate stability-indicating properties. Mass balance of these samples should be calculated.

16. 3.2.S.7 / 3.2.P.8: Please submit updated sections 3.2.S.7.3 and 3.2.P.8.3, including first data of PPQ batches manufactured at Lonza Visp / Rovi, as soon as available, but not later than 31-AUG-2021. The stability commitment should be updated.

The following additional documentation for the **Novel Excipient SM-102** shall be submitted by 01-JUL-2021:

17. More data on the tests purity and assay of SM-102. The limits of the tests purity and assay should be further tightened accordingly.

18. Impurities should be specified and limits should be implemented.

19. The expression Action limit should be replaced by an expression that is consistent with ICH Q3A.

20. The limit for the test Related impurities (Corden Pharma Colorado), Report all impurities should be tightened.

21. The limit for the test Related impurities (Corden Pharma Colorado), Identified and unidentified impurities, and Total impurities should be tightened.

22. A discussion on fate and purge of the impurities should be submitted.

23. The control strategy for benzene should be submitted.

24. A comparison of the experimental results of the elemental analysis with the theoretical values should be submitted.

25. A classification of the impurities in line with ICH M7 should be submitted.

26. The control strategy for the impurity undecyl-6-bromohexanoate (starting material) should be submitted.

27. Data on the robustness of the UPLC method for assay, identity and purity should be submitted.

28. The final report of the ongoing stability studies should be submitted.

29. A risk evaluation on the potential presence of nitrosamine impurities in the novel excipient SM-102 should be submitted according to Questions and answers on "Information on nitrosamines for marketing authorisation holders" (EMA/CHMP/428592/2019 Rev. 3, question 13). The risk evaluation will have to be adequately documented and, if applicable, supported by confirmatory testing in case a possible risk of presence of nitrosamines has been identified.

Please acknowledge that the documentation submitted for the novel excipient SM-102 is not considered to represent a *Drug Master File* in the sense of CHMP/QWP/227/02 Rev 4. Nevertheless, relevant changes to the scientific documentation, concerning e.g. the manufacturer of the novel excipient, the manufacturing process, specifications, retest period, or analytical procedures, have to be notified to the MA holder and National Competent Authority.

The following additional documentation for the **Novel Excipient PEG2000-DMG** shall be submitted by 01-JUL-2021:

30. The specifications for the starting materials [redacted] should be submitted.

31. Additional results for the test Purity should be submitted. The limits have to be tightened accordingly.

32. Limits for the tests Content of Monomyristoylglycerol-PEG2000 (%), Content of Other PEG derivatives (%), Content of Free Fatty Acid (%) and Content of Unknown (%) are missing. The limits should be submitted.

33. Additional results for the test Moisture (%) should be submitted. The limits have to be tightened accordingly.

34. The control strategy for benzene should be submitted.

35. A risk evaluation on the potential presence of nitrosamine impurities in the novel excipient PEG2000-DMG should be submitted according to Questions and answers on "Information on nitrosamines for marketing authorisation holders" (EMA/CHMP/428592/2019 Rev. 3, question 13). The risk evaluation will have to be adequately documented and, if applicable, supported by confirmatory testing in case a possible risk of presence of nitrosamines has been identified.

Based on the preliminary stability data available so far, **a shelf-life of seven (7) months at the recommended storage condition -15°C to -25°C can be assigned to the drug product.** This period can include up to 30 days storage at 2°C to 8°C and up to 12 hours at 8°C to 25°C at the vaccine point of care site for dose preparation.

b. Charges relatives à la Préclinique

1. A study in rhesus macaques (NHPs) is underway to evaluate antibody levels over the course of 1 year and protection from high-dose SARS-CoV-2 challenge 6 months and 1 year after vaccination with 100 µg mRNA-1273. The final report has to be submitted to Swissmedic **by the end of 2021.**

2. No report with respect to ADME of the modified mRNA was submitted. Data from cell-based experiments were summarised where no differences in mRNA half-life between unmodified mRNAs and the same sequences fully substituted with N1-methyl-pseudouridine was detected. These data shall be submitted as a full report to Swissmedic **as soon as possible**.

3. ADME studies with respect to the new excipients SM-102 and PEG2000-DMG have not been performed. Data on SM-86, a lipid very similar to SM102, was summarised in a draft report. A finalised report shall be submitted to Swissmedic **as soon as possible**. With respect to PEG2000-DMG, Moderna referred to Onpattro, where a structural analog was evaluated. This can be accepted and **no further action is required** with respect to PEG2000-DMG at the present point in time.

4. A qualification report with respect to the bDNA assay will be finalised and has to be submitted to Swissmedic **by the end of Q1 2021**.

5. Moderna performed a characterisation of the antigen expression in cells at the injection site, in the draining lymph nodes, spleen and in systemic circulation (liver, lung, any other tissues?). These data have to be summarised in a separate report and submitted to Swissmedic **by the end of January 2021**.

c. Charges relatives à la Clinique/Risk Management

Risk Management:

1. Potential options for a broader European PASS including similar populations with similar demographic attributes as the Swiss population should be investigated. Submission of a protocol: upon availability.

2. An EU Risk Management Plan for mRNA-1273, version 0.1, dated 10 December 2020, has been submitted for evaluation to Swissmedic. The Applicant is asked to submit a signed and dated main version of the RMP. Submission: Two months after approval

3. A RMP summary must be submitted to Swissmedic within 60 calendar days after approval (Submission via portal, CD by post or eCTD).

4. Interim reports and final study reports of all on-going and planned additional pharmacovigilance activities and study protocols have to be submitted as indicated in the RMP. Submission: upon availability

5. Validated Safety Signals identified through the sponsor's safety governance process have to be reported to Swissmedic monthly.

6. All PSUR / PBRER submitted to the EMA must also be brought to Swissmedic's attention.

7. An "Opinion of the Paediatric Committee on the agreement of a Paediatric Investigation Plan and a deferral EM EA-002893-PIP0 1-20", EMA/PDCO/529326/2020; Amsterdam, 30 November 2020 was submitted. However, the final decision of the EMA is still pending. The Applicant has to submit the final European Medicines Agency decision on the agreed paediatric investigation plan (PIP) upon availability.

Clinique:

New SARS-CoV-2 variants:
According to Moderna's response to Swissmedic's clinical LoQ, assessment of SARS-CoV-2 neutralization against both the UK and South African strains from mRNA-1273 vaccinated NHPs and clinical trial participant polyclonal sera are currently being evaluated. Moderna expects to have results by mid to late January.

1. Please submit these results once available, as delineated in your response dated January 10, 2021.

2. Swissmedic also recommends that Moderna monitor the possibility of lack of efficacy of the vaccine towards current and future viral variants by using human vaccine recipient sera in live virus neutralization assays (see Lauring AS, Hodcroft EB, JAMA online 6.1.2021; Weissmann D et al, Cell Host & Microbe 29, 1-9 January 2021). Can Moderna please provide details on the different types of SARS-CoV-2 neutralization assays used in their current assessment of vaccine efficacy against variant strains? **The answer can be submitted together with the answer to question 1 above.**

PEG compounds and anaphylaxis

Anaphylactic reactions have been identified as an important medical risk in the Risk Management Plan and are being monitored under enhanced pharmacovigilance activities. It will be monitored as part of the EU PASS study, the US post approval safety study, and ongoing monitoring in the Phase 1, 2, and 3 clinical studies.

3. Right now the labeling for Switzerland requires a monitoring time of at least 15 minutes after each dose. In case of future severe allergic reactions occurring later than 15 minutes after dosing, Moderna is asked to submit a change in the professional information proposing a longer monitoring time. The new monitoring time should be based on the timing of the cases post-authorization.

4. A change in labeling may also be necessary in case of identification of specific risk factors for these hypersensitivity reactions, such as history of certain types of food or other allergies. Based on the information that will become available, the professional information should be adjusted as appropriate, e.g. additions to the warnings and precaution section.

Conditions that have to be met prior to a regular marketing authorization

The following studies must be completed and evaluated by Swissmedic before a regular marketing authorization can be granted.

- Phase 1 study 20-0003

- Phase 2a study P201
- Phase 3 study P301

Phase 1 study 20-0003 and phase 2a study P201

5. Please submit the phase 1 interim study report **as soon as available (March/April 2021).**

6. The phase 1 CSR should be submitted to Swissmedic as soon as it is available.

7. The interim and complete study reports of study P201 should be submitted once available.

Phase 3 study P301

8. For the ongoing phase 3 study P301, **please submit the interim study report as soon as available.**

9. In order to confirm the efficacy and safety and immunogenicity of COVID-19 Vaccine Moderna, please submit the final Clinical Study Report for study P301. **Deadline for CSR: December 2022.**

10. Immune correlates of protection: Moderna is planning a study to define immune correlates of protection in a subset of serum samples from the P301 pivotal efficacy trial and is expecting a report no later than July. Please submit the report when ready.

d. Charges générales

1. Un rapport périodique sur la sécurité du médicament (PSUR/PBRER) doit être envoyé à Swissmedic après l'octroi de l'autorisation en application de l'art. 60 OMéd.

2. Pour toute importation en Suisse, il faut vérifier si une demande d'autorisation d'importer à l'unité doit être déposée (voir l'art. 44 de l'ordonnance sur les autorisations dans le domaine des médicaments[8] [OAMéd]).

3. Conformément à l'art. 18 OEMéd, le médicament COVID-19 Vaccine Moderna dispersion for injection doit faire l'objet d'une libération officielle des lots.

4. Toutes les charges éventuelles du document «Opinion of the Paediatric Committee on the agreement of a Paediatric Investigation Plan and a deferral» du 30.11.2020 de l'Agence européenne des médicaments (EMA) concernant le plan d'investigation pédiatrique (PIP) portant le numéro EMEA-002893-PIP01-20 et soumis à Swissmedic dans le cadre de la présente demande doivent être satisfaites. Si une version du PIP

[8] RS 812.212.1

plus récente, modifiée et approuvée par l'EMA est disponible, les charges et les délais qui y figurent s'appliquent.
Le requérant est tenu d'adresser à Swissmedic, en continu et dans les meilleurs délais, des demandes relatives à l'intégration des résultats d'études concernant le plan d'investigation pédiatrique dans l'information sur le médicament suisse.

Swissmedic comments and recommendations:

Préclinique

1. Swissmedic considers the determination of anti-mRNA-1273 antibodies after prime-boost vaccination as very important. It is **highly recommended** to establish an assay and to evaluate the potential for the induction of anti-mRNA-1273 antibodies.

2. Swissmedic agrees that the risk of reverse transcription of modified mRNA by LINE-1 encoded RT and subsequent integration into the genome is very small. However, the public interest in the paper published by the Jaenish lab is not to underestimate. Swissmedic **recommends** that Moderna addresses the risk whether reverse transcriptases (LINE-1, HIV) can convert N1-methyl-pseudouridine-modified mRNA into DNA.

Clinique

Duration of protection and potential boosting doses

1. Moderna is considering additional boosting doses of mRNA-1273 within ongoing clinical trials to assess safety and immunogenicity endpoints. Given that at this point the duration of protection and the potential need for boosting doses is unknown, Swissmedic would like Moderna to keep Swissmedic informed through submission of protocol amendments and SAPs.

Asymptomatic disease

2. Within the context of the phase 3 study, Moderna plans to evaluate the extent of protection provided by the vaccine against asymptomatic disease. The protocol does not describe any plan to test for the induction of mucosal immunity. Nevertheless, this is recommended, as the induction of secretory IgA in upper respiratory secretions might be relevant to the prevention of asymptomatic spread of SARS CoV-2. Swissmedic has taken note of Moderna's response dated January 10, 2021.

3. Moderna has planned to test immunogenicity prior to first dose, prior to second dose, then on days 7, 14, 21, 28, 180 and 365 post-dose two. One of the aims is to look for asymptomatic infection in vaccinated people (who had no binding antibodies prior to doses one and two, but developed antibodies later without showing symptoms of disease). Swissmedic highly welcomes this approach and finds it to be a very important part of mid- or even long-term monitoring of performance of a COVID-19 vaccine. In principle, longitudinal serosurveillance studies can reveal infections (defined as significant antibody level changes in consecutive serum specimens) if specific and

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sensitive assays are being used. This approach has been demonstrated to be successful for various organisms, e.g. Bordetella pertussis [Pertussis surveillance by small serosurveys of blood donors - PubMed (nih.gov)]. To detect asymptomatic infections requires close monitoring of clinical signs and symptoms by the surveillance participants, e.g. in form of a standardized diary, ideally but not necessarily accompanied by active surveillance (questionnaire sent to participants every 2-4 weeks, for example). This will allow to also discover symptomatic infections and distinguish them from asymptomatic infections. To determine whether the vaccine can prevent asymptomatic disease, a control group comprising unvaccinated individuals with similar risk of exposure to SARS-CoV-2, ideally from the same study (i.e. amendment 6 for the phase 3 study), or alternatively matched individuals from the same community, is needed. In the absence of such a control group, one can still determine how many vaccinees do develop asymptomatic infections but interpretation of the results will be difficult and challenging. A caveat is the fact that an asymptomatic infection does not necessarily mean that the affected individual will also *transmit* SARS-CoV-2 to other contact persons. In order to analyse transmission, one would be well advised to not only monitor the vaccinated study participants but also their close contact persons, e.g. household members. Whether this is feasible needs to be discussed and assessment of the COVID-19 immunization status as well as monitoring of clinical signs and symptoms in those contact persons needs to be implemented. Regarding timing of the serum specimens to be taken, 180 and 365 days post-dose two is not frequent enough for a detailed analysis regarding the dynamics of potential waning immunity. Two ways to optimize this could be:

a) If laboratory capacities allow, one should seriously consider more frequent time points for serum collection, e.g. monthly intervals. This would require willingness to do so by the study participants.

b) Alternatively, if laboratory capacities are tight and/or compliance of the participants is an issue, one could randomize each study participant to 1 or 2 extra time points for blood collection with an approximate 1 month interval, *in addition to 180 and 365 days* post-dose 2. Subgroups into which the study participants would be randomized could be as follows (time points for serum collection, days after dose 2, **monthly intervals highlighted bold**): Subgroup 1: Days **150, 180** and 365 Subgroup 2: Days **180, 210** and 365 Subgroup 3: Days **180, 210, 240** and 365 Subgroup 4: Days 180, **240, 270** and 365 Subgroup 5: Days 180, **270, 300** and 365 Subgroup 6: Days 180, **300, 330 and 365** Subgroup 7: Days 180, **330 and 365**.

With a large enough number of study participants, this would give a more precise picture than solely relying on days 180 and 365 with a 6 month interval where significant antibody value changes could be missed. Depending on the results of year 1, this could be extended to year 2 of the ongoing study.

Swissmedic has taken note of Moderna's response dated January 10, 2021, in particular that the Sponsor is working to collect more frequent serology timepoints for asymptomatic infection at a subset of clinical sites (~10) and will provide additional information on these plans once available.

Duration of protection, persons at risk and rates of hospitalizations /deaths

4. Amendment 6 plans for the fact that the phase 3 trial will only remain partially blinded as placebo participants may wish to get vaccinated. Moderna, however, tries to maximize the number of subjects who will remain in the study for two years.
The opportunity to offer to study participants a) the choice to remain blinded or be unblinded, followed by b) offering the choice to receive active vaccination with mRNA-1273 and possible vaccination against COVID-19 (with a different product?) to those who will be unblinded and then know they had originally received placebo, is ethically sound. It will be interesting to see how many study participants agree to remain blinded (rather few I would guess) and, of those unblinded and belonged to the placebo group, how many will decide to decline the offer to receive active vaccination against COVID-19 and therefore remain unvaccinated. Because, the ability to answer the open question of duration of protection will heavily rely on an unvaccinated control group (blinded and/or unblinded). Alternatively, this question as well as that regarding protection of persons most at risk could also be answered by performing a household contact study where household members who acquire COVID-19 disease as the primary case will expose study participants to SARS-CoV-2. Such a study would allow calculating attack rates in the exposed study participants and comparing the attack rates in immunized and unimmunized study participants. Depending on the time interval of such household exposure since dose 2 of the vaccine in the trial, dynamics of waning immunity can be analyzed if enough cases occur.
The effect on rates of hospitalization and deaths can be determined similarly under the plans outlined in amendment 6 and a household contact study as outlined above.
Additional comment: From an academic point of view, exposure studies would be highly interesting during the post-licensure phase where performances of different COVID-19 vaccine product could be compared directly, e.g. during outbreak situations. We have done such a study with varicella vaccines in the past [Comparative varicella vaccine effectiveness during outbreaks in day-care centers - PubMed (nih.gov)].
Swissmedic has taken note of Moderna's response dated January 10, 2021: With regards to a household contact study, Moderna is engaged with key stakeholders to develop the specific questions to understand transmission from close household contacts to study participants (potentially through e-Diary) and will provide additional information on these plans once available.

Auto-immunity

5. The widespread distribution of SARS CoV-2 spike protein encoding mRNA may also occur in humans and may pave the way to various organ-specific autoimmune disorders. Such disorders usually have a long pre-symptomatic phase in which only organ-specific autoantibodies are found. It would be informative if the sponsor would provide data on auto-antibodies in a significant number of vaccinated and unvaccinated subjects (ANA, anti-dsDNA, liver, neural tissues, muscle, neuromuscular junction, thyroid, pancreas, joints, blood vessels, red blood cells etc.).
Swissmedic has taken note of Moderna's response dated January 10, 2021: Moderna is assessing the feasibilty of investigator-sponsored proposals and will provide updated information to Swissmedic as it becomes available.

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Les émoluments sont fixés à **80'000.00 francs** (annexe 1, ch. I, ch. 2.1 OE-Swissmedic) et sont à la charge de Moderna Switzerland GmbH.

La facture vous sera adressée par courrier séparé.

Les émoluments dus pour l'examen des charges se fondent sur la version actuelle de l'OE-Swissmedic et seront facturés par courrier séparé lorsque la charge sera levée à Moderna Switzerland GmbH . Si des adaptations de l'information sur le médicament sont également requises dans le cadre de la satisfaction de charges énoncées dans la décision d'approbation de la demande d'autorisation, les textes adaptés de l'information sur le médicament peuvent être soumis en même temps que les documents attestant de la satisfaction des charges. L'examen supplémentaire des textes de l'information sur le médicament est alors facturé selon le temps consacré à la réalisation de cette tâche. Y font exception les adaptations de l'information sur le médicament en fonction du résultat d'une procédure en lien avec un PSUR ou une PASS. Ces adaptations doivent être envoyées sous la forme d'une demande séparée C.I.3 et sont facturées forfaitairement.

Veuillez recevoir, Madame, Monsieur, nos salutations distinguées.

Swissmedic, Institut suisse des produits thérapeutiques

Gerda Baeriswyl
Zentraler Versand / Envoi centralisé

Votre interlocuteur :
Ihr Kontakt:
Abteilung Inspektorate und Bewilligungen, Einheit Transplantate
Dr. Constanze Fritzsche, +41 58 462 02 81

Annexes:

- Textes approuvés de l'information sur le médicament
- Textes d'emballage approuvés

Voies de droit

La présente décision peut faire l'objet d'un recours dans un délai de 30 jours suivant sa notification. Le recours doit être adressé au Tribunal administratif fédéral, Case postale, 9023 St-Gall (art. 31 et 33, let. e de la loi fédérale du 17 juin 2005 sur le Tribunal administratif fédéral ; RS 173.32).
Le mémoire de recours doit indiquer les conclusions, motifs et moyens de preuve et porter la signature du recourant (ou de la recourante) ou de son mandataire ; la décision attaquée ainsi que les pièces invoquées comme moyens de preuve doivent être jointes au recours (art. 52 de la loi fédérale du 20 décembre 1968 sur la procédure administrative ; RS 172.021).