RESPONSE TO FDA COMMENTS ON PEDIATRIC DEVELOPMENT PROGRAM DATED DECEMBER 06, 2021

The Sponsor acknowledges FDA Comments on PEDIATRIC DEVELOPMENT PROGRAM dated 06 DECEMBER 2021 in (**BOLD**)

ITEM 1:
Please provide a topline update on the Pediatric Development Program studies (including P203 and P204) with regards to the 03Nov2021 teleconference and the responses to Sponsor questions dated 10Nov2021 (with particular attention to Item 3). Please include updates to study milestones if applicable.

Sponsor Response:

Development Phase		
1.	**Formulation development, if applicable**	Not applicable
2.	**Nonclinical studies, if applicable**	Not applicable
3.	**Clinical Studies (Pediatric)**	
	A Phase 2/3, randomized, observer-blind, placebo-controlled study to evaluate safety, reactogenicity, and effectiveness of the mRNA-1273 SARS-CoV-2 vaccine administered as two doses in healthy adolescents 12 to <18 years of age	
	Estimated protocol submission date:	NOV 2020
	Estimated study initiation date:	DEC 2020
	Estimated study completion date:	APR 2024
	Estimated final report submission date:	JUL 2024
	A Phase 2/3, randomized, observer-blind, placebo-controlled, dose-finding, age de-escalation study to evaluate safety, reactogenicity, and effectiveness of the mRNA-1273 SARS-CoV-2 vaccine administered as two (or three) doses in healthy children 6 months to <12 years of age	
	Estimated protocol submission date:	FEB 2021
	Estimated study initiation date:	MAR 202
	Estimated study completion date:	DEC 2023
	Estimated final report submission date:	MAR 202
	Safety and effectiveness study of mRNA-1273 SARS-CoV-2 vaccine administered in healthy infants birth to <6 months of age	
	Estimated protocol submission date:	JUN 202
	Estimated study initiation date:	SEP 2022

None
2021-12-09 18:51:40

Please add a row stating 'final protocol submission date' January 2022.

Please modify the study objective to include the lower dose (50 mcg) and the study name.

None
2021-12-09 18:52:07

Please add a row stating 'final protocol submission date' February 2022.
Please modify the study objective to include the lower dose (25 mcg) and the study name.

NOne
2021-12-09 19:26:26

Given the revised dates on the other studies, please confirm whether June 2022 is still appropriate

FDA-CBER-2022-1614-3816879

	Estimated study completion date:	JUN 2024
	Estimated final report submission date:	DEC 2024

None
2021-12-09 18:58:15

Please include a paragraph to clearly indicate that the evaluation of the lower doses in these age groups will be done by amending the appropriate protocols and not as separate studies.

RESPONSE TO FDA COMMENTS ON CLINICAL DATED NOVEMBER 10, 2021

As requested by the agency the sponsor is providing topline feedback regarding CBER responses to sponsor questions for the 3 October 21 teleconference which were received on 10 November 2021 to support their PREA discussions. The full response document will be provided by 20 December to which we would respectively request the Agency's feedback regarding our proposed Adolescent and Pediatric clinical development plan.

SUBJECT: CBER Responses to sponsor questions for 11.3.21 telecon

Topline Sponsor Response:

The Sponsor responds first to comments regarding the use of mRNA-1273 in adolescents (study P203) and subsequently to use in children <12 years of age (study P204).

Adolescents 12 to <18 years

We are in receipt of agency comments regarding the use of the 100 μg dose in adolescents 12 to <18 years. Here we respond and provide context for proposed next steps, including: (Part 1) clinical evaluation of 50 μg dose in adolescents; (Part 2) consideration for continued recommendation of the 100 μg dose in adolescents considered at higher risk of severe COVID-19 for whom efficacy benefits of the broadly-studied 100 μg dose may be most appropriate; (Part 3) review of available modeling data to support the more immediate implementation of a 50 μg dose in adolescents under EUA. Key elements considered essential and sufficient to support an sBLA for a dose of 50 μg in adolescents will be proposed for CBER response.

The Sponsor acknowledges the request to conduct clinical evaluation of safety and immunogenicity of 50 μg of mRNA-1273 in adolescents 12 to <18 years and this new evaluation is described below (Part 1). Generation of new clinical data on a dose of 50 μg mRNA-1273 in adolescents will require substantial time; with the surge in infections, including the emergence of new VOC the earlier availability of 50 μg of mRNA-1273 in adolescents may be needed , we review modeling data supporting this dose in adolescents here (Part 3).

1) **Assessment of 50ug of mRNA-1273 in Adolescents**
    a. As requested by the agency, the Sponsor agrees to conduct direct clinical evaluation of safety and immunogenicity of the 50 ug dose in adolescents. Given the difficulty in enrolling naïve subjects in a clinical study while a vaccine is available, such data is not estimated to be available for 12 months, more suitable for sBLA than EUA.
    b. Clinical evaluation of approximately 300 adolescents receiving two doses of 50 ug mRNA-1273 administered 28 days apart will be performed. Blood will be collected at baseline and Day 57 (28 days post-dose 2) to allow immunobridging to the pivotal P301 clinical trial. As noted above, the immunobridging benchmark population will consist of the PP Immunogenicity Subset of P301 adults >65

years, and the noninferiority criteria specified in the P203 protocol regarding GMR and seroresponse rate will apply. Safety data will be collected (solicited AR for the 7 days after each injection; all unsolicited AE for the 28 days after each injection; SAE, MAAE, AESI and AE leading to withdrawals). Participants will be followed for 12 months post-dose 2 and a booster or third dose of 50 ug mRNA-1273 is being considered as part of the evaluation as well, which could further support the recent P203 Amendment #3 to boost participants who received 100ug primary series.

c. We acknowledge the recommendation that the study of 50 ug of mRNA-1273 be conducted as a placebo-controlled (1:1 or 2:1) with rapid cross-over to preserve recruitment and retention. However, our experience, and that of others, suggests that recruiting to placebo-controlled studies to assess safety and efficacy when authorized COVID-19 vaccines are available is extremely challenging. When a vaccine is available, even a short delay in access (i.e., cross-over at 28 days post-dose 2) is unappealing to persons potentially receptive to joining current COVID-19 vaccine studies. Similarly, conducting such a study in a region lacking vaccine authorization or access is fraught with the significant ethical concern of including a placebo arm in a region with high unmet need for COVID-19. The use of a placebo control under these circumstances is questionable and may be perceived as inconsistent with Subpart D Additional Safeguards for Children in Clinical Investigations, §50.52 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual trial participants. At present, the vast majority of adolescents will already be vaccinated, previously infected, or both, therefore the current medical need will shift towards boosters further complicating conduct of a placebo-controlled trial to assess safety or efficacy.

- *Does CBER agree that Day 57 safety and immune response data from n=~300 adolescents receiving 50 μg mRNA-1273, together with data from placebo and 100 μg mRNA-1273 recipients in study P203 (n=3700), and post-marketing data, suffice to support an sBLA for 50 μg in adolescents 12 to <18 years?*
- *In addition, while the Sponsor conducts the above described adolescent clinical development, including on-going pharmacovigilance, can CBER confirm that the primary series data is not gating for future submissions in adolescents for boosters (EUA or sBLA)?*

2) <u>Utility of 100 ug dose of mRNA-1273 in adolescents at higher risk of severe COVID-19</u>

a. Compared to other licensed COVID-19 vaccines, 100 ug of mRNA-1273 induces more durable and more potent effectiveness, evident by fewer breakthrough infections and breakthrough disease even during times that the Delta variant has prevailed.

b. In immunocompromised subjects, which are at higher risk of severe COVID-19, the mRNA-1273 vaccine has been shown to be significantly more effective than other mRNA vaccines, translating into an absolute reduction in COVID-19 hospitalization rates of 1.2% (ie 120 additional hospitalizations averted per 100.000 vaccinated subjects) (MMWR / November 5, 2021 / Vol. 70 / No. 44), largely outweighing the risk of vaccine-related myocarditis in young adult males
c. Doses other than 100 μg of mRNA-1273 introduces uncertainties regarding durability of effectiveness and potential protection against VOC such as Delta and Omicron, in particular in light of the first evidence of the decreased neutralizing response against Omicron provided by the current vaccines, the increased rates of breakthrough cases and higher infectivity of Omicron.
d. Clinical safety data of the 100 ug primary series regimen is available from more than 2400 healthy adolescents, showing an acceptable safety profile.
e. Accordingly, the sponsor considers that the 100 μg dose of mRNA-1273 is particularly appropriate for use in adolescents considered at higher risk of severe COVID-19, in whom the assurance of effectiveness and protection against VOC remains most vital.
f. Populations in this category as identified by the CDC include those with obesity, chronic lung disease (including asthma), neurologic disorders, immunosuppressed individuals, and other chronic conditions (People with Certain Medical Conditions | CDC).

- *Does CBER agree that for adolescents at higher risk of severe COVID-19, the established protection, durability and activity against VOC supports the use of the 100 ug mRNA-1273 dose?*

3) <u>Modeling Data to Support Implementation of a 50 ug dose in adolescents should the pace and severity of the pandemic justify earlier access to such a formulation</u>

a. Generation of new clinical data on a dose of 50 ug mRNA-1273 in adolescents will require substantial time –with the surge in infections, including the emergence of new VOC (including Omicron) the earlier availability of 50 μg of mRNA-1273 in adolescents may be needed. We have therefore generated modeling data supporting this dose in adolescents.
b. The Sponsor used a pharmacometric model-based interpolation to generate an inferred GMT in adolescents after a primary series of 50 μg in adolescents 12 to <18 years. A detailed review of the modeling/bracketing approach, which could be used should the profile of risk of the pandemic in adolescents change (e.g. with emergence of novel, transmissible variants) will be provided with the complete response document, including a technical report which will describe in detail data and methods used for developing the model and methods used for simulations.
c. We remain confident that the totality of evidence, including immunogenicity modeling data, together with the demonstrated safety of the higher (100 μg) primary series in 2,478 adolescents completing the full two-dose regimen, supports that the primary series of 50 μg in adolescents is safe and may be

effective in the context of a public health emergency. We intend to complete further clinical evaluations per CBER recommendations, concurrent to EUA amendment/issuance, to support an sBLA in the future.

- *Does CBER agree that the detailed pharmacometrics modeling regarding use of 50 ug of mRNA-1273 in adolescents, together with safety observed after 100 ug of mRNA-1273 could support issuance of EUA for 50 ug of mRNA-1273 under urgent pandemic conditions, e.g. to address the emergence of Omicron, while clinical trials are underway to support sBLA activities?*

Pediatrics 6 to <12 years

1) **Assessment of 25ug of mRNA-1273 in Children 6 to <12YOA**

a. As requested by the agency, the Sponsor agrees to conduct direct clinical evaluation of safety and immunogenicity of the 25 ug dose in children 6 to <12YOA (please also see Adolescent Part 1).
b. Clinical evaluation of approximately 300 children 6 to <12 years receiving two doses of 25 ug mRNA-1273 administered 28 days apart will be performed. Blood will be collected at baseline and Day 57 (28 days post-dose 2) to allow immunobridging to the pivotal P301 clinical trial. As noted above (in Adolescent section 1), the immunobridging benchmark population will consist of the PP Immunogenicity Subset of P301 adults >65 years, and the noninferiority criteria specified in the P204 protocol regarding GMR and seroresponse rate will apply.
c. Collection of safety data is planned (solicited AR for the 7 days after each injection; all unsolicited AE for the 28 days after each injection; SAE, MAAE, AESI and AE leading to withdrawals)

- *Taking into account the totality of the evidence, , including data produced with the 100 & 50 ug primary series data from P204, and post marketing safety data (US and ex-US) does the Agency agree that, should the 25 ug dose be selected, the proposed immunogenicity study would be sufficient to support an sBLA in children 6 to <12 year old population?*

2) **Benefit/Risk in Pediatric population 6 to <12 and support of an EUA**

a. A summary of the safety data collected in study P204 at the 50ug dose level in 6 to <12 year old age group, which is currently being submitted/reviewed by global Health Authorities will be included.
b. The positive benefit/risk in children 6 to <12 is supported by; 1) Unmet need/continued need; 2) Strong protection starting 14 days after a single dose during the height of a variant-induced SARS-CoV-2 infection wave (Delta); 3) Supportive safety data in P204 (~3750 exposed participants in 6 to < 12 years); 4) Differential epidemiology in rates of myocarditis in children vs. adolescents/young adults; 5) No cases of myocarditis observed in the ~ 3750 6 to

< 12 year old exposed participants in study P204 despite active solicitation and enhanced surveillance; 6) Positive benefit risk assessment

c. In addition, the recent emergence of Omicron has been associated with higher rates of infection in children, increased transmissibility, lower neutralizing capabilities of the vaccines against Omicron, and decreased vaccine effectiveness, further enhancing the public health need to vaccinate this population

- *Given the positive risk/benefit assessment of the currently selected dose of 50 ug, the commitment to explore a lower dose of 25 ug, and specifically the differential epidemiology in rates of myocarditis in children vs. adolescents/young adults, the Sponsor respectfully seeks to continue development and request EUA regulatory actions for mRNA-1273 in the pediatric 6 to <12 regardless of development status for adolescents 12 to <18, to be able meet an urgent public health need, especially in light of potential future emergence of new variants of concern. Does CBER concur?*

3) Assessment of (b) (4) and Clinical Development in Pediatrics 6m to <2 years and to 2 to <6 years

a. The Sponsor acknowledges the Agency's comments to consider changes to the clinical development plan for 6m to <2 years and 2 to <6 years and shares that plans to explore the feasibility of a (b) (4) formulation are on-going. Presently, we are evaluating the feasibility of (b) (4) 25 ug for this age population and will provide feedback in a future communication.