RESPONSE TO FDA COMMENTS ON Clinical RECEIVED ON 24 SEPTEMBER 2021

The Sponsor acknowledges FDA comments on Clinical topics (in **Bold)**

ITEM 1:

We had previously requested (please refer to our PreBLA clinical comments, dated April 28, 2021) that if symptoms recorded/reported in the COVID diaries/FAEF dataset were not due to a subject having COVID-19 (negative for COVID-19 in MB), but were instead due to a solicited event occurring within 7 days post-vaccination or an unsolicited adverse event for subjects in safety subset be summarized in CE in conjunction with events reported in FACE, or in AE; and to also provide a flag that part or all of the data was from the COVID diary. We have found that this was not implemented in the datasets submitted to the BLA. For example, subject 300-2003 was determined to be COVID-19 negative on Days 1 and 3 (as reported in MB), yet the COVID-19 symptoms reported in CE under the CECAT 'efficacy' including myalgia (mild on Day 3) and fatigue (mild on Day 3) were not included with the events under CECAT 'reactogenicity' which were reported as myalgia (mild on Day 2) and fatigue (mild on Days 1-2).

> **a. We request that the CE dataset (and FACE if that is the dataset you are using to report the ADARSUM dataset), and AE dataset be updated with this information. The FAEF should be flagged that the event is now reported in another dataset(s).**
> **b. Please comment on whether the events reported in the FAEF dataset were included in your determination of overall rates of reactogenicity events or unsolicited AEs. If not, please provide updated safety summary tables.**

Sponsor Response

a. The Sponsor would like to clarify:

In Study P301, surveillance of COVID-19 symptoms is prompted by a weekly eDiary of COVID-19 symptom log form, and is throughout the study. Such reported COVID-19 symptoms are mapped to CE domain with CECAT = "EFFICACY" that are topline records from the COVID-19 symptom log form reported by participants. Day 1 refers to the first date an event was reported by the participant, independent of injection/dosing dates. The COVID-19 symptom data (CECAT=" EFFICACY") were used to determine various efficacy endpoints to support analysis of efficacy (ADEFF, ADTTE, and ADTTEA).

Reactogenicity data were collected on and after the first and the second injection via an eDiary of reactogenicity (solicited adverse reactions), and the reference date is based on each injection date. Topline records of these data by each reference date are mapped to CE domain with CECAT=" REACTOGENICITY". Therefore, these two types of data were collected separately, of different nature, and analyses separately.

b. COVID-19 symptoms reported in COVID-19 symptom log forms are mapped into FAEF, and the topline records of COVID-19 symptoms are mapped to CE domain with CECAT=" EFFICACY". As described in response to a), these data are for surveillance of COVID-19 throughout the study via weekly prompts, and are used for efficacy endpoints. The reactogenicity data are collected by eDiary of SAR after each of the two injections.

Therefore, the events reported in the FAEF dataset were not included in analysis of reactogenicity events or unsolicited AEs.