To the European Medicines Agency

Documents Access and Publication Department

Attention: Isabella Ronci

**ASK-113461 Clarification of Freedom of Information Request - Your Feedback is requested**

Münster, June 9, 2022

Dear Ms Ronci,

thank you for providing more information on the access to documents procedure. For clarification, our access to documents request aims at the transparency of regulatory oversight of a mandated post-authorisiation safety study on the Pfizer/BioNTech vaccine BNT-162b2 (Comirnaty®) in pregnant women.

The information you cited on study C4591015 from the Comirnaty® assessment report of February 2021 is outdated. Study C4591015 is a mandated post-authorisation safety study under conditional marketing authorisation. All post-authorisation obligations apply in a legally binding manner and are evaluated by the EMA. The requirements are codified in Risk Management Plans written by the manufacturer and agreed upon with the regulator before authorisation, and they form an enforceable feature of the authorization. https://ec.europa.eu/commission/presscorner/detail/en/qanda_20_2390. 41231

We tracked the registered history of changes related to this particular study, first registered on February 11, 2021 at:

Study to Evaluate the Safety, Tolerability, and Immunogenicity of SARS CoV-2 RNA Vaccine Candidate (BNT162b2) Against COVID-19 in Healthy Pregnant Women 18 Years of Age and Older –

https://clinicaltrials.gov/cT2/show/NCT04754594

Overall, 17 changes to the protocol are documented and can be downloaded from the clinicaltrials.gov website, those with an impact on study integrity are listed below:

On March 5, 2021 the trial started active recruitment at 16 trial sites in the U.S. with a planned size of **4000** pregnant women between **24-34** weeks of gestation, of which **350** women between **27-34** weeks of gestation would be enrolled first for the phase 2 portion of the trial.

On March 30, 2021, recruitment extended to 40 sites in the U.S., planned size: 4000 pregnant women.

On May 27, 2021, active recruitment remaining at 40 sites, planned size still **4000** women; but anticipated enrollment changed to only **700.**

On July 19, 2021, active recruitment extended to 76 sites in and outside the U.S. (Brazil, South Africa, Spain, UK) planned size**:** **700** pregnant women between **24-34** weeks of gestation, of which **200** women between **27-34** weeks of gestation would be enrolled first for the phase 2 portion of the trial.

On August 16, 2021, active recruitment extended to 80 sites in and outside the U.S. (Brazil, South Africa, Spain, UK) planned size: **700** pregnant women between **24-34** weeks of gestation, of which **200** women between **27-34** weeks of gestation would be enrolled first for the phase 2 portion of the trial.

September 13, 2021, active recruitment extended to 81 sites in and outside the U.S. (Brazil, South Africa, Spain, UK) planned size: **700** pregnant women between **24-34** weeks of gestation, of which **200** women between **27-34** weeks of gestation would be enrolled first for the phase 2 portion of the trial.

September 29, 2021, recruitment extended to 83 sites in and outside the U.S. (Brazil, South Africa, Spain, UK) planned size: **700** pregnant women between 24-34 weeks of gestation, of which **200** women between **27-34** weeks of gestation would be enrolled first for the phase 2 portion of the trial.

October 27, 2021, **active recruitment** by **83 sites** in and outside the U.S. (Brazil, South Africa, Spain, UK) planned size**:** **700 p**regnant women between 24-34 weeks of gestation, of which **200** women between **27-34** weeks of gestation would be enrolled first for the phase 2 portion of the trial. One site in the U.S. listed twice, and one site in Spain switched status to active, not recruiting.

On November 16, 2021 **recruitment stopped** at enrollment of only **343** participants ; listed trial sites are **84, but the above mentioned Spanish site no longer listed.**

Last entry: May 15, 2022 enrollment: **348 (!),** 84 trial sites listed, two new sites in Spain although trial status since November 16, 2021 unchanged (active, not recruiting).

The BNT162b2 Risk Management Plan Update February 2022, states on Page 40 :

**“ • C45910153 : A phase 2/3 placebo-controlled, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of SARS-CoV-2 RNA vaccine candidate (BNT162b2) against COVID-19 in healthy pregnant women 18 years of age and older. A total of 348 (209 in phase 2 and 139 in phase 3) pregnant women at 24 to 34 weeks gestation were randomised in a 1:1 ratio to vaccine or placebo. • “**

**“Footnote 3: Enrolment of participants into study C4591015 was stopped on 25 October 2021 due to recruitment challenges as a result of global recommendations for COVID-19 vaccination in pregnant women and the increased availability of COVID-19 vaccines. Participants already enrolled will continue follow up evaluations until study end as planned. “**

The RMP update of February 2022 provided by Pfizer is not consistent with the documented protocol changes nor compatible with GCP standards. Of the 4000 women between weeks 24-34 of their pregnancy originally planned to be enrolled, merely **209 out of 350 women**

are left in the **Phase II study** contributing safety information on Comirnaty® vaccine use only between weeks **27-34** of pregnancy. The phase III study planned to provide safety information on Comirnaty@ between weeks **24-34 (Phase III)** is left with a number of only **139 out of 4000 originally planned** study participants. How many, if at all, of those 139 participants will be included between weeks 24-27 in the phase III portion of the trial? The rationale for recruitment of the few remaining women at **84 far apart trial sites, studying, on average, only 4-5 women per site**, is unclear. Furthermore, enrollment procedures, selection criteria, randomization schemes, allocation to study groups and achievement of study aims are totally unclear.

Our actual access to documents request therefore, includes:

1. *anonymized individual participant data (IPD) of all participants of study **C4591015** from the time of screening (i.e. before randomization), through group allocation (vaccine versus placebo) and follow-up, explicitly including those women who withdrew (or were withdrawn) after receiving only one dose and to all screened and/or enrolled participants of centers eliminated from the trial site list including all respective case report forms (CRFs)*

2. *PRAC Rapporteur's preliminary AR EMEA/H/C/005735/II/0087*

3. With respect to supplementary information, we are interested in Section B/0110 C.I.z – "Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products – Other variation 15/02/2022 28/02/2022 SmPC and PL To update section 4.6 of the SmPC and section 2 of the PL to implement the recommendation on vaccination with Comirnaty in pregnant and breastfeeding women as requested by the CHMP."

   With respect to PSUSA/00010898/202112, or PSUSA/00010898/202206, we are not in the position to know which of the two, if any, would contain information on study C4591015. Therefore, we would kindly ask for your help by searching those documents exclusively for C5491015 and inform us about the result.

   With many thanks and kind regards

   Ulrich Keil

   Angela Spelsberg