NON-INTERVENTIONAL INTERIM STUDY REPORT 5 ABSTRACT

Title: Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine

Date: 12 March 2024

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Keywords: Pfizer-BioNTech COVID-19 vaccine; database study; active surveillance study; post-conditional approval safety study; non-interventional study.

Rationale and background: The Pfizer-BioNTech COVID-19 vaccine, tozinameran (Comirnaty®), a novel mRNA-based vaccine, has been authorised for use in several countries including the United States and European Union, for the prevention of COVID-19. Efficient and timely monitoring of the safety of the vaccine is needed. The overall goal of the study is to determine whether an increased risk of prespecified adverse events of special interest (AESIs) exists following the administration of at least one dose of the Pfizer-BioNTech COVID-19 vaccine. This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a commitment to the EMA and a Postmarketing Requirement to the Food and Drug Administration (FDA).

Research question and objectives: To determine if there is an increased risk of prespecified AESI following the administration of at least one dose of the Pfizer-BioNTech COVID-19 vaccine.

Study design: This post-authorisation active surveillance study of AESIs following administration of the Pfizer-BioNTech COVID-19 vaccine used a retrospective cohort design comparing the risk in vaccinated and unvaccinated individuals matched by the date of vaccination with data from multiple databases. Additional control for confounding was conducted using propensity score (PS) adjustment. In the final report, comparison with historical controls and a self-controlled risk interval (SCRI) design will also be used.

Setting: Data were available from six electronic healthcare data sources in Europe for the objectives of the fifth interim report: Pedianet, IT; PHARMO Institute for Drug Outcomes Research (PHARMO), NL; University of Oslo - Norwegian Health Registries (NHR), NO; EpiChron Research Group on Chronic Diseases at the Aragon Health Sciences Institute (EpiChron), ES; Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària (SIDIAP), ES and CPRD (Clinical Practice Research Datalink) Aurum (UK). As per protocol the study originally included two additional electronic healthcare data sources who could not contribute data for the fifth interim report. These were ARS Toscana (Agenzia Regionale di Sanita' della Toscana), a research institute in the Tuscany region of Italy, IT), and Health Search Database (HSD), IT.

Participating data sources: The source population was all individuals registered in the electronic healthcare data sources listed below. The study period included the following calendar time for:

- Pedianet (family paediatrician diagnoses) between 31 May 2021 and 31 December 2022
- PHARMO (general practitioner diagnoses and inpatient diagnoses) between 6 January 2021 and 30 June 2023 (and 6 January 2021 and 31 December 2022 for inpatient data)
- NHR (general practice and outpatient specialist diagnoses) between 1 January 2021 and 31 December 2022
- EpiChron (general practice and inpatient diagnoses) between 27 December 2020 and 31 July 2023
- SIDIAP (general practice and inpatient diagnoses) between 1 January 2021 and 30 June 2023

- CPRD Aurum (general practice and inpatient diagnoses) between 8 December 2020 and 21 March 2022)

Variables and data sources: Exposure was based on recorded prescription, dispensing, or administration of the Pfizer-BioNTech COVID-19 vaccine. Outcomes were identified in the data sources with algorithms based on codes for diagnoses and free text. The selected adverse events of special interest (AESIs) were based initially on the ACCESS project but the list has been extended with new AESIs and the code lists have been reviewed and tagged as narrow and possible codes on the descendant code level.

Results: Data for 17,677,132 individuals who had received ≥1 dose of Pfizer-BioNTech COVID-19 vaccine and satisfied the inclusion criteria were included in the non-matched vaccinated cohort from Italy (Pedianet: 0.08%), the Netherlands (PHARMO: 8.65%), Norway (NHR: 27.44%), Spain (EpiChron: 5.83%; and SIDIAP: 24.50%) and the UK (CPRD Aurum: 32.50%). This is an increase of 9,537,893 individuals compared with interim report 4, mainly due to the inclusion of data from CPRD Aurum.
A total of 10,665,306 (84.6%) individuals received a second dose, 4,642,445 (36.8%) received a third dose, 1,021,555 (8.1%) received a fourth dose and 7,801 (0.1%) a fifth dose of the Pfizer-BioNTech COVID-19 vaccine.
Among these individuals 12,400,847 (98.32%) were matched with an unvaccinated individual.
A total of 26,980 pregnant women who had received at least one dose of the Pfizer-BioNTech COVID-19 vaccine were included of whom 9,234 (34.23%) received the dose during their first trimester of pregnancy and 9,763 (36.19%) in their second trimester. Pregnancy data were not available from PHARMO or CPRD for this report, but they are expected to be available for the final report.
To assess baseline exchangeability of the comparator cohorts, the incidences of COVID-19 in the first 12 days after vaccination in the vaccinated and unvaccinated cohorts were compared. These incidences were similar, demonstrating that matching had achieved comparable cohorts. Despite the satisfactory matching process, the analyses in the matched cohorts were performed with additional control for confounding to evaluate the effect of the propensity score (PS) adjustment.

This interim report 5 provides a description of the characteristics and incidence rates of 37 AESIs in more than 12.4 million vaccinated individuals and more than 12.4 million unvaccinated controls. The incidence rates in the vaccinated and unvaccinated cohorts were similar for most of the AESIs.

The following 11 AESIs were discussed further in interim report 5 either at the request of EMA or because they were newly included for analysis as AESIs.

- For acute cardiovascular injury the adjusted HRs were 1.38 (95% CI: 0.73, 2.61) in Pedianet, 1.01 (95% CI: 0.99, 1.04) in NHR, 1.38 (95% CI: 1.31, 1.45) in PHARMO, 1.10 (95% CI: 1.03, 1.18) in EpiChron, 0.99 (95% CI: 0.96, 1.03) in SIDIAP, and 1.23 (95% CI: 1.18, 1.27) in CPRD Aurum.

- For arrhythmia the adjusted HRs were 1.75 (95% CI: 0.88, 3.49) in Pedianet, 1.03 (95% CI: 1, 1.05) in NHR, 1.36 (95% CI: 1.29, 1.44) in PHARMO, 1.12 (95% CI: 1.04, 1.21) in EpiChron, 0.99 (95% CI: 0.96, 1.03) in SIDIAP, and 1.27 (95% CI: 1.21, 1.33) in CPRD Aurum.

- For heart failure, the adjusted HRs were 0.77 (95% CI: 0.73, 0.82) in NHR, 1.29 (95% CI: 1.13, 1.47) in PHARMO, 0.90 (95% CI: 0.80, 1.01) in EpiChron, 0.89 (95% CI: 0.82, 0.96) in SIDIAP, and 1.02 (95% CI: 0.95, 1.09) in CPRD Aurum.

- For stress cardiomyopathy, the adjusted HRs were 0.69 (95% CI: 0.18, 2.67) in NHR, 1.49 (95% CI: 0.33, 6.69) in PHARMO, 0.85 (95% CI: 0.21, 3.47) in EpiChron, 1.51 (95% CI: 0.75, 3.04) in SIDIAP, 1.30 (95% CI: 0.53, 3.20) in CPRD Aurum.

- For coronary artery disease, the adjusted HRs were 0.99 (95% CI: 0.94, 1.04) in NHR, 1.49 (95% CI: 1.31, 1.69) in PHARMO, 0.97 (95% CI: 0.80, 1.17) in EpiChron, 1.00 (95% CI: 0.91, 1.10) in SIDIAP, 1.40 (95% CI: 1.30, 1.50) in CPRD Aurum.

- For myocarditis within 21 days, the adjusted HRs were 0.94 (95% CI: 0.46, 1.94) in NHR, 1.23 (95% CI: 0.13, 11.84) in PHARMO, 3.64 (95% CI: 0.41, 32.53) in EpiChron, 1.05 (95% CI: 0.35, 3.16) in SIDIAP, and 2.30 (95% CI: 0.94, 5.66) in CPRD Aurum.

- For cerebral venous sinus thrombosis (CVST), the adjusted HRs were 10.63 (95% CI: 0.23, 1.74) in NHR, 0.90 (95% CI: 0.06, 14.09) in EpiChron, 0.68 (95% CI: 0.11, 4.20) in SIDIAP, 0.43 (95% CI: 0.14, 1.27) in CPRD Aurum.

- For secondary amenorrhoea, the adjusted HRs were 0.91 (95% CI: 0.69, 1.21) in NHR, 1.71 (95% CI: 1.34, 2.18) in EpiChron, 0.99 (95% CI: 0.91, 1.07) in SIDIAP, and 1.24 (95% CI: 1.17, 1.30) in CPRD Aurum.

- For hypermenorrhoea, the adjusted HRs were 0.62 (95% CI: 0.08, 4.66) in Pedianet, 1.40 (95% CI: 1.23, 1.60) in EpiChron, and 1.02 (95% CI: 0.95, 1.09) in SIDIAP.

- For Bell's Palsy, the adjusted HRs were 1.15 (95% CI: 0.88, 1.50) in NHR, 0.65 (95% CI: 0.28, 1.51) in PHARMO, 0.84 95% CI: (95% CI: 0.34, 2.09) in EpiChron, 0.96 (95% CI: 0.75, 1.24) in SIDIAP, and 0.99 (95% CI: 0.75, 1.29) in CPRD Aurum.

- Glomerulonephritis was analysed for the first time in this fifth interim report. No events were identified in Pedianet, NHR or PHARMO. The adjusted HRs were 0.59 (0.22, 1.55) in EpiChron, 1.29 (0.88, 1.87) in SIDIAP and 0.88 (0.67, 1.16) in CPRD Aurum.

Discussion: The incidence rates for the majority of the 37 AESIs were generally very low in the risk intervals studied and were comparable with background incidence rates from previous studies (e.g., ACCESS) in unvaccinated cohorts.

Among the 11 AESIs that were highlighted for further discussion, the divergence in the cumulative incidences observed for several of the cardiovascular events with long risk windows (e.g., 365 days) resulted in small increases in risk in some of the data sources. These increases could be explained by a number of factors. Some of these events may have presented with mild symptoms that did not require immediate medical attention, and vaccinated individuals may have sought medical attention more frequently than those who were unvaccinated (healthy vaccinee effect). Another plausible explanation is differences in the composition of the unvaccinated cohort as follow-up progresses. Unvaccinated individuals were censored in the unvaccinated cohort if they were vaccinated and were then followed up in the vaccinated cohort from that time point. Hence, the individuals who remained in the unvaccinated cohort were those who were never vaccinated and who were possibly less likely seek medical attention at all, if it was not urgently needed. These differences may have been minimal earlier in follow-up but may have become more pronounced as follow-up progressed.

Results for CVST, Bell's Palsy and glomerulonephritis all showed no evidence of an increased risk in the vaccinated cohort based on adjusted HRs. Adjusted HRs for secondary amenorrhoea were slightly elevated in EpiChron and CPRD Aurum. For hypermenorhoea, only the adjusted HR for EpiCrhon was slightly elevated. These events, along with the cardiovascular events described above, will continue to be monitored and further refined for inclusion in the final study report.

Marketing Authorization Holder(s): BioNTech Manufacturing GmbH, Germany.

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Document Approval Record

Document Name:	C4591021 Interim 5 Study Report Abstract
Document Title:	C4591021 Interim 5

Signed By:	Date(GMT)	Signing Capacity
Younus, Muhammad	14-Mar-2024 12:31:24	Final Approval
De Bernardi, Barbara	14-Mar-2024 23:12:51	EUQPPV Approval