Progress Report

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

V1.0

NON-INTERVENTIONAL STUDY PROGRESS REPORT

PASS information

Title	Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine
Protocol number	C4591021
Version identifier of the progress report	Version 1.0
Date	27 September 2021
EU Post Authorization Study (PAS) register number	EUPAS41623
Active substance	BNT162b2
Medicinal product	COVID-19 messenger ribonucleic acid (mRNA) vaccine is a nucleoside-modified ribonucleic acid (modRNA) encoding the viral spike glycoprotein S of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
Marketing Authorization Holder (MAH)	BioNTech Manufacturing GmbH
Joint PASS	No
Research question and objectives	The research question addressed by this study is: Is there an increased risk of select adverse events of special interest (AESI) after being vaccinated with the Pfizer-BioNTech COVID-19 vaccine?

	Objectives: <u>Primary study objective</u> To determine whether an increased risk of prespecified AESI exists following the administration of at least one dose the Pfizer-BioNTech COVID-19 vaccine using two approaches: (a) a cohort design comparing risk in vaccinated and non-vaccinated individuals and (b) a self-controlled risk interval (SCRI) design. <u>Secondary study objectives</u> • To estimate the incidence rates of prespecified AESI among individuals who receive at least one dose of the Pfizer-BioNTech COVID-19 vaccine using a cohort study design. • To describe the incidence rates and determine whether an increased risk of prespecified AESI exists following the administration of at least one dose the Pfizer-BioNTech COVID-19 vaccine compared with a matched comparator group with no COVID-19 vaccination within subcohorts of interest (i.e., individuals who are immunocompromised, individuals who are frail and have comorbidities, individuals diagnosed with previous COVID-19 infection, and age-specific groups) in Europe using a cohort study design and/or a SCRI design. • To determine whether an increased risk of prespecified AESI exists following the administration of at least one dose of the Pfizer-BioNTech COVID-19 vaccine compared with no COVID-19 vaccination, in pregnant people and their neonates using a cohort study design.

	• To characterise utilisation patterns of Pfizer-BioNTech COVID-19 vaccine among individuals within Europe, including estimating the proportion of individuals receiving the vaccine; two-dose vaccine completion rate and distribution of time gaps between the first and second doses; and demographics and clinical characteristics of recipients, overall and among subcohorts of interest, such as individuals who are immunocompromised, elderly, or have specific comorbidities.
Country(-ies) of study	The Netherlands (NL), Italy (IT), Spain (ES), United Kingdom (UK), Norway (NO)
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Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	BioNTech Manufacturing GmbH An der Goldgrube 12 55131 Mainz, Germany
MAH contact person	Constanze Blume

Study C4591021 is designed to monitor the safety profile of the Pfizer-BioNTech COVID-19 vaccine in European people living in the Netherlands, Italy, Spain, the United Kingdom, and Norway. This retrospective cohort design study is a non-interventional post authorization safety study (PASS) including participants vaccinated with the Pfizer-BioNTech COVID-19 mRNA vaccine as an authorized vaccine and followed up for two years for the occurrence of selected safety outcomes. People who are pregnant at time of vaccination or who become pregnant within two years of study start and their live born infants will be followed for an additional 12 months to collect information about birth outcomes and linked infant outcomes. The medically-attended safety events of interest in this study are based on the adverse events of special interest (AESI) proposed by the ACCESS project (vACcine COVID-19 monitoring readinESS). These AESIs include adverse events (AEs) previously identified with immunization in general (e.g. anaphylaxis, Guillain-Barré Syndrome [GBS]), with vaccine platforms (e.g., mRNA) relevant to COVID-19 vaccine development (such as vaccine-associated enhanced disease [VAED]), or with theoretical concerns based on immunopathogenesis. Additional AESIs may be identified as information emerges about events potentially related to COVID-19 vaccines.

The primary objective of this study is to determine whether an increased risk of prespecified AESIs exists following the administration of ⩾1 dose of Pfizer-BioNTech COVID-19 vaccine using a cohort design or a self-controlled risk interval (SCRI) design.

The secondary objectives of this study are to:

- estimate incidence rates of prespecified AESIs following the administration of ⩾1 dose of Pfizer-BioNTech COVID-19 vaccine using a cohort study design;
- describe incidence rates and assess if an increased risk of prespecified AESIs exists following the administration of ⩾1 dose of the Pfizer-BioNTech COVID-19 vaccine compared with no COVID-19 vaccination in sub-cohorts of interest, i.e., individuals who are: immunocompromised; frail; have comorbidities; with previous COVID-19 infection; and age-specific groups in Europe, using a cohort or SCRI design;
- to determine if an increased risk of prespecified AESIs exists following the administration of ⩾1 dose of the Pfizer-BioNTech COVID-19 vaccine compared with no COVID-19 vaccination in pregnant women and their neonates using a cohort study design; and
- to characterise utilisation patterns of Pfizer-BioNTech COVID-19 vaccine, including proportions who have received the vaccine; two-dose vaccine completion rates and distribution of delays between first and second doses; and demographics and clinical characteristics of recipients, overall and among sub cohorts of interest, such as individuals who are immunocompromised, elderly, or have specific comorbidities.

The initial protocol draft was submitted to the EMA on 25 February 2021 as part of the Emergency Use submission of the vaccine. Following one round of feedback from the EMA (29 March 2021), the first version of the protocol was resubmitted to EMA on 25 May 2021.

As of September 30, 2021, the study will be performed using electronic health care data from databases in Italy, the Netherlands, Norway, Spain, and UK. Table 1 summarizes the institutional review board (IRB) and governance approvals for each institution providing access to their data for use in this study.

Table 1. Status of institutional review board (IRB) and governance approval for C4591021 data access providers

Data Access Provider	Country	IRB / Governance Name	Date of Approval	Notes
Agenzia Regionale di Sanita' della Toscana (ARS Toscana)	Italy	Comitato di Indirizzo	16 July 2021	
PEDIANET	Italy	None	Not applicable	Specific approval is not required for secondary use of data.
Italian College of General Practitioners and Primary Care (SIMG)	Italy	Italian College of General Practitioners and Primary Care (Scientific Committee)	25 May 2021	
PHARMO Institute for Drug Outcomes Research (PHARMO)	Netherlands	Institutional Review Board of 'Stichting Informatie voorziening voor Zorg en Onderzoek'	16 Sep 2021	

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University of Oslo	Norway	Regional Ethics Committee (REC) south-east	15 Sep 2021	
Instituto Aragonés de Ciencias de la Salud (IACS)	Spain	Community of Aragon Research Ethics Committee (CEICA) /	2 June 2021	The case validation part has been approved verbally on 8th July 2021. Written approval for the case validation part is still pending by the Aragon Department of Health
Foundation University Institute for Primary Health Care Research Jordi Gol i Gurina (IDIAP-Jordi Gol)	Spain	IDIAP-Jordi Gol Research Ethics Committee	30 June 2021	Internal approval code: 21/147-PCV
Drug Safety Research Unit (DSRU)	UK	Clinical Practice Research Datalink (CPRD)	TBC	Following the initial application submission of the CPRD have requested on 10 August 2021 additional details and clarification to be provided. We are in the process of preparing responses and will submit the revised application by 23 August 2021. We would then anticipate approval by the end of September 2021.

As of 27 Sep 2021, all contracts with the study partners have been signed. All data access providers (DAPs) are obtaining all the necessary institutional and ethical approvals. Scientifically, the statistical analysis plan has been developed and is under review by Pfizer. DAPs are preparing the data extraction in a collaborative and harmonized manner, together with the statisticians, data managers and principal investigator (PI) and Co-PI. The next step is the finalization of the data extraction procedures which will provide the operationalized definitions, data extraction and transformation scripts for the implementation of the extraction, transformation, and loading (ETL) process, the process for converting data into a common data model.

At the time of this progress report, the study has been successfully set up and is on target to meet study milestones.

Document Approval Record

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Signed By:	Date(GMT)	Signing Capacity
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