NON-INTERVENTIONAL (NI) STUDY INTERIM STUDY UPDATE

Post Authorization Safety Study (PASS) information

Title	Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of Spikevax in Europe
Interim report number	1.0, draft version 1.0
Date of report	27 September 2021
EU PAS register number	Protocol will be registered before start of the data collection
Active substance	COVID-19 mRNA-1273 vaccine (nucleoside modified)
Medicinal product	COVID-19 Vaccine Moderna/Spikevax
Product reference	EMEA/H/C/005791
Procedure number	MEA004.2
Marketing authorisation holder(s)	Moderna Biotech Spain, S.L. Calle Monte Esquinza 30 28010 Madrid Spain
Joint PASS	No
MAH contact	[redacted] Senior Director, Global Safety Epidemiologist, Pharmacovigilance [redacted]
Research question and objectives	The overarching research question of this study: Is the occurrence of each adverse event of special interest (AESI) among persons vaccinated with Spikevax in Europe higher than the occurrence of that AESI that would have been expected in the same population in the absence of Spikevax? Primary objective: • To assess whether vaccination with Spikevax (by dose number where feasible and for any dose) is associated with increased rates of the AESI compared with the expected rates overall and stratified by country, sex, and age group. Secondary objective:

	• To assess whether vaccination with Spikevax is associated with increased rates of the AESI compared with the expected rates in subpopulations of interest: women of childbearing age, patients who are immunocompromised, patients previously diagnosed with COVID-19 infection, patients with unstable health conditions and comorbidities, and patients with autoimmune or inflammatory disorders
Country(-ies) of study	Denmark, Italy, Norway, Spain, United Kingdom
Author	[redacted] Department of Clinical Epidemiology Aarhus University Hospital Aarhus, Denmark

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2. List of Abbreviations

Abbreviations	Definition
ACCESS	vACcine Covid-19 monitoring readinESS
AESI	Adverse Events of Special Interest
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
EMA	European Medicine Agency
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
IR	Incidence Rate
IRR	Incidence Rate Ratio
mRNA	Messenger Ribonucleic Acid
O/E	Observed to Expected
SAP	Statistical Analysis Plan
US	United States

3. Responsible Parties

Centre	Role	Address	Main Contact Person
Moderna Tx	Sponsor	Moderna Biotech Spain, S.L. Calle Monte Esquinza 30 28010 Madrid Spain	[redacted]

Aarhus University, Denmark	Lead Scientific Centre and Data Access Provider, Denmark	Dept of Clinical Epidemiology Aarhus University Olof Palmes Allé 43-45 8200 Aarhus N, Denmark	[redacted]
Julius Clinical Research	Lead Operating Centre	Julius Clinical Research Broederplein 41-43 3703 CD Zeist The Netherlands	[redacted]
Aarhus University, Denmark	Data Access Provider	As above	As above
University of Oslo, Norway	Data Access Provider	Pharmacoepidemiology and Drug Safety Research Group University of Oslo PB 1068 Blindern Oslo, Norway	[redacted]
ARS Toscana, Italy	Data Access Provider, Italy	Agenzia Regionale di Sanità della Toscana Osservatorio di Epidemiologia ARS Toscana Via Pietro Dazzi, 1 50141 Florence Italy	[redacted]
IDIAP JGolSpain	Data Access Provider, Spain	Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina Gran Via de les Corts Catalanes, 587, àtic, 08007, Barcelona	[redacted]
DSRU, UK	Data Access Provider, UK	Drug Safety Research Unit -DSRU Bursledon Hall, Blundell Lane Southampton SO31 1AA United Kingdom	[redacted]

4. Protocol Synopsis

Title

Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the COVID-19 mRNA-1273 Vaccine in Europe

mRNA-1273-P904, Protocol Version 1.2, 27 September 2021

Coordinating investigator: [redacted], Aarhus University, Denmark

Rationale and background

The novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) causes coronavirus disease 2019 (COVID-19) and has led to a global pandemic. A mass vaccination campaign is currently underway in Europe. The mRNA-1273 vaccine, currently known as Spikevax,[1] combines Moderna's mRNA (messenger ribonucleic acid) delivery platform with the stabilised SARS-CoV-2 spike immunogen.

Research question and objectives

The overarching research question of this study: Is the occurrence of each adverse event of special interest (AESI) among persons vaccinated with Spikevax in Europe higher than the occurrence of that AESI that would have been expected in the same population in the absence of Spikevax?

Primary objective:

- To assess whether vaccination with Spikevax (by dose number where feasible and for any dose) is associated with increased rates of the AESI compared with the expected rates overall and stratified by country, sex, and age group.

Secondary objective:

- To assess whether vaccination with Spikevax is associated with increased rates of the AESI compared with the expected rates in subpopulations of interest: women of childbearing age, patients who are immunocompromised, patients previously diagnosed with COVID-19 infection, patients with unstable health conditions and morbidities, and patients with autoimmune or inflammatory disorders

Study design

This study will proceed in two phases: signal detection and signal evaluation.

For the signal detection stage, population-based, country-specific historical general population background rates of the AESI estimated in the participating databases/countries from 2017-2019 will be used as estimates of the expected rates in the unvaccinated. Rates in Spikevax recipients will be compared with the historical pre-pandemic rates. All comparisons will be conducted stratified by country, and within each country further stratified on sex, and age groups.

For the signal evaluation stage, conducted as needed based on findings from signal detection, analytic approaches will be selected based on the best methodologic fit for a given AESI. It is anticipated that a combination of self-controlled designs and cohort designs using either historical or concurrent unexposed comparators will be utilised.

Population

Recipients of Spikevax will be identified between 6 January 2021 (date of the earliest approval of Spikevax in Europe) and 31 December 2022 and members of the database source population selected for

each study design, including persons providing historical rates from 2017-2019, will be eligible for inclusion in the study and will constitute the overall cohort. Subgroups of interest will include adolescents, adults, elderly individuals, patients who are immunocompromised, patients previously diagnosed with COVID-19 infection, patients with unstable health conditions and morbidities, and patients with autoimmune or inflammatory disorders (defined below). Individuals receiving more than one type of COVID-19 vaccine will be excluded.

Variables

Cohort members will be described with respect to available demographic characteristics, medical history, medication use, and receipt of other vaccines.

Outcomes of interest will include AESI primarily based on the list defined by the Safety Platform for Emergency vACcines (SPEAC) and endorsed for COVID-19 vaccine safety assessment by the WHO Global Advisory Committee for Vaccine Safety, by the EMA and by the US CDC. Other AESI may be considered if relevant signals appear during the study conduct or additional outcomes are added to the ACCESS protocol.

Data sources

This study is planned as analysis of routinely collected health data in secondary automated electronic data sources in Denmark, Italy, Norway, Spain, and the UK, selected based on availability of the required routinely collected data, including information on vaccine brand and frequency of data updates.

Study size

As of 1 June 2021, it is estimated that the participating databases together will be able to identify at least 431,216 recipients of Spikevax.

Data analysis

For signal detection, incidence rates among Spikevax vaccinees will be computed and compared using relative or absolute measures of association against appropriate (e.g., age- sex- country-specific) general population background AESI rates.

For signal evaluation using self-controlled designs, the ratio between the incidence rate estimate in the risk period and the incidence rate estimate in the control period (incidence rate ratio) will be computed using conditional Poisson regression. For parallel cohort designs, appropriate contrasts will be estimated in exposed vs. unexposed cohorts, while controlling for measured confounding. Whenever appropriate incidence rate ratios (IRRs) will be estimated with appropriate 95% confidence intervals (CIs).

Milestones

Data collection will continue through 31 March 2023 with a final study report planned by December 2023.

5. Milestones

Milestone	Planned date	Actual date	Comments
Protocol	31 Jan 2021	Dv1.0: 25 Mar 2021 Dv1.1: 19 Aug 2021	Protocol revisions were required based

		Dv1.2: 27 Sep 2021	on regulatory feedback
Start of data collection	31 Dec 2021		
End of data collection	31 Mar 2023		
Study progress report 1	30 Sep 2021	27 Sep 2021	
Study progress report 2	31 Mar 2022		
Study progress report 3	30 Sep 2022		
Study progress report 4	31 Mar 2023		
Registration in the EU PAS register	Upon approval by regulatory authorities		
Final report of study results	31 Dec 2023		

* Subject to data queues by data custodians.

6. Study status

A protocol for the Moderna study titled “Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of Spikevax in Europe” was previously prepared and submitted to applicable regulatory authorities for review. Comments were received on draft version 1.0 (submitted 30 June 2021) by the [redacted], which subsequently endorsed version 1.1 with several requests for minor revision at the next regulatory opportunity. No other regulatory authorities have provided feedback on the protocol as of 27 September 2021.

Protocol version 1.2 has been modified to address the following concerns:

- At the next regulatory opportunity, the MAH should update the RMP to reflect interim reports every 6 months.
    - The study milestones have been modified to include interim reports every six months as requested. Parallel changes to the study milestones have been proposed in RMP version 2.3.
- At the next regulatory opportunity, the MAH is requested to update the protocol to list which missing information in the RMP the study addresses.
    - Section 7 has been clarified to describe that the study will address areas of missing information including safety of use in patients who are immunocompromised, patients previously diagnosed with COVID-19 infection, patients with unstable health conditions and comorbidities, and patients with autoimmune or inflammatory disorders.

- Moreover, with regards to myocarditis/ pericarditis, the sentence indicating that "*[…] currently there is no evidence for causality*" should be removed.
    - This sentence has been removed in Section 7.
- The MAH should discuss the direction of bias mentioned in the Limitations section.
    - Hypotheses concerning the expected direction of bias have been added in Section 9.9.
- The risk of Multisystem Inflammatory Syndrome (MIS, including all age groups) should be investigated in this study. At the next regulatory opportunity, the MAH is requested to add MIS to the list of AESIs.
    - The outcome of multisystem inflammatory syndrome (including all age groups) has replaced previously separated outcomes of multisystem inflammatory syndrome in children (MIS-C) and multisystem inflammatory syndrome in adults (MIS-A).

The updated protocol is included here as an Appendix. The full Statistical Analysis Plan (SAP) is currently in development and will be shared for review prior to the planned initiation of data management (31 December 2021).

7. Next study update (31 March 2022)

Interim reports for this study will be provided every six months, with the first planned for three months after the start of data management. A final study report anticipated 31 December 2023. In advance of the next interim update (31 March 2021), we anticipate that preliminary descriptive and comparative analyses will be provided for those data access partners with the shortest approval timelines (ARS Toscana, SIDIAP, and CPRD).