VAC4EU Postauthorisation Safety Study of BIMERVAX® Vaccine in Europe

First published: 21/10/2024

Last updated: 02/07/2025

Study Planned

Administrative details

EU PAS number

EUPAS1000000321

Study ID

1000000321

DARWIN EU® study

No

Study countries

☐ Spain

Study description

The coronavirus disease 2019 (COVID-19) HIPRA vaccine BIMERVAX® is a recombinant protein-based bivalent variant vaccine intended for use as a booster in individuals 16 years of age and older who have previously received a

messenger RNA (mRNA) COVID-19 vaccine. In March 2023, the European Commission granted marketing authorisation of BIMERVAX® vaccine for use in the European Union. Marketing authorisation applications of BIMERVAX vaccine formulations adapted to other subsequent SARS-CoV-2 variants were submitted to the European Medicines Agencies (EMA) for approval. As of September 2024, approval is pending for the adapted vaccine containing the monovalent JN.1 lineage as the antigen.

This is a post-authorisation safety study (PASS) to be conducted within the Vaccine Monitoring Collaboration for Europe (VAC4EU) study network. This PASS will evaluate the risk of safety concerns and AESIs, as defined in the approved EU RMP, following immunisation in the real-world setting. The PASS has 2 components—a vaccine utilisation study and a comparative safety study—that will be conducted in a staggered-phase approach. The vaccine utilisation study will characterise individuals receiving BIMERVAX® vaccine. The comparative safety study will comprise 2 sub-studies: a cohort study and a self-controlled risk interval (SCRI) study (a subtype of the self-controlled case series design). The cohort study will evaluate the risk of adverse events due to use of BIMERVAX® vaccine booster compared with that of other COVID-19 vaccines with the same indication, whereas the SCRI study will evaluate the risk of adverse events following receipt of a BIMERVAX® vaccine booster compared with the risk of AESIs in a later period not preceded by any COVID-19 vaccination booster.

Study status

Planned

Research institutions and networks

Institutions

RTI Health Solutions (RTI-HS)

- [ ] France
- [ ] Spain
- [ ] Sweden
- [ ] United Kingdom
- [ ] United Kingdom (Northern Ireland)
- [ ] United States

First published: 21/04/2010

Last updated: 13/03/2025

Institution | Not-for-profit | ENCePP partner

Health Services Research and Pharmacoepidemiology Unit (HSRP Unit) FISABIO

- [ ] Spain

First published: 30/11/2023

Last updated: 30/11/2023

Institution | Other | ENCePP partner

EpiChron Research Group on Chronic Diseases, Aragon Health Sciences Institute (IACS)

- [ ] Spain

First published: 17/02/2017

Last updated: 02/04/2024

Institution | Educational Institution | ENCePP partner

University Medical Center Utrecht (UMCU)

Netherlands

First published: 24/11/2021

Last updated: 22/02/2024

Institution | Educational Institution | Hospital/Clinic/Other health care facility | ENCePP partner

Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina, IDIAPJGol

Spain

First published: 05/10/2012

Last updated: 23/05/2025

Institution | Educational Institution | Laboratory/Research/Testing facility | Not-for-profit | ENCePP partner

Agenzia regionale di sanità della Toscana (ARS)

☐ Italy

First published: 01/02/2024

Last updated: 12/03/2024

Institution **EU Institution/Body/Agency** **ENCePP partner**

Networks

Vaccine monitoring Collaboration for Europe (VAC4EU)

☐ Belgium
☐ Denmark
☐ Finland
☐ France
☐ Germany
☐ Italy
☐ Netherlands
☐ Norway
☐ Spain
☐ United Kingdom

First published: 22/09/2020

Last updated: 22/09/2020

Network **ENCePP partner**

Contact details

Study institution contact

Xabier García de Albéniz xgarcia@rti.org

Study contact

xgarcia@rti.org

Primary lead investigator

Xabier García de Albéniz 0000-0002-9814-2343

Primary lead investigator

ORCID number:

0000-0002-9814-2343

Study timelines

Date when funding contract was signed

Planned: 31/10/2024

Study start date

Planned: 30/09/2025

Data analysis start date

Planned: 31/03/2026

Date of interim report, if expected

Planned: 30/09/2026

Date of final study report

Planned: 30/09/2028

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

HIPRA Human Health S.L.U.

Study protocol

Protocol_PASS_6578_HIPRA_BIMERVAX_Final_V1.1_12Jan2024_clean_Redacted.pdf
(2.62 MB)

Regulatory

Was the study required by a regulatory body?

Yes

Is the study required by a Risk Management Plan (RMP)?

EU RMP category 3 (required)

Methodological aspects

Study type

Study type list

Study topic:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Drug utilisation

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

The study will comprise a vaccine utilisation study component consisting of a cohort that will be described using standard statistics. The study will also comprise a comparative safety component, consisting of both a cohort and a self-controlled risk interval design.

Main study objective:

Primary objectives:

•To characterise recipients of BIMERVAX® in relation to demographics and clinical characteristics at the time of vaccination, including the following: pregnancy status, age of childbearing potential, immunocompromised status, comorbidities, presence of autoimmune and inflammatory disorders, and interaction with other vaccines (influenza).

•To estimate the risk ratio and risk difference of prespecified AESIs comparing recipients of BIMERVAX® with recipients of other COVID-19 vaccines authorised for the booster indication, using a cohort design.

•To estimate the incidence rate ratio of selected AESIs comparing a prespecified risk period following BIMERVAX® vaccination with a later post-risk interval, using a self controlled risk interval (SCRI) design.

Study Design

Non-interventional study design

Case-only

Cohort

Study drug and medical condition

Name of medicine

BIMERVAX

Study drug International non-proprietary name (INN) or common name

COVID-19 VACCINE (RECOMBINANT, ADJUVANTED)

Anatomical Therapeutic Chemical (ATC) code

(J07BN04) covid-19, protein subunit

covid-19, protein subunit

Medical condition to be studied

COVID-19

Population studied

Short description of the study population

The eligible population for the vaccine utilisation study will be all individuals actively enrolled in each of the selected European health data sources for at least 12 months before receiving a booster dose of the BIMERVAX® vaccine within the study period. For the comparative safety studies, the main eligibility criterion will be having received a COVID-19 vaccine in the past. The study period will be from the date of availability of BIMERVAX® vaccine in each

participant country to 2 to 3 years past that date (4 years for pregnancy outcomes), pending the timing and potential seasonality of booster administration campaigns.

Age groups

All

Paediatric Population (< 18 years)

Preterm newborn infants (0 – 27 days)

Term newborn infants (0 – 27 days)

Children (2 to < 12 years)

Adolescents (12 to < 18 years)

Adult and elderly population (≥18 years)

Adults (18 to < 65 years)

Adults (18 to < 46 years)

Adults (46 to < 65 years)

Elderly (≥ 65 years)

Adults (65 to < 75 years)

Adults (75 to < 85 years)

Adults (85 years and over)

Special population of interest

Frail population

Immunocompromised

Pregnant women

Study design details

Setting

The population studied is that described in section 13. The study period will start on the first date of launch of BIMERVAX® in each country where the participating data sources are located and will end 36 months later (48 months later for pregnancy outcomes) or on the date of the latest data availability. The contributing data sources are from Spain.

Comparators

The cohort study will compare the following two vaccination strategies:

• Receive 1 dose of BIMERVAX® vaccine. Individuals can subsequently receive other COVID-19 vaccinations as per local policies

• Receive 1 dose of another COVID-19 vaccine authorised for booster use. Individuals subsequently can receive other COVID-19 vaccinations as per local policies, using any brand but BIMERVAX.

The SCRI study will compare a risk period following receipt of BIMERVAX® with a post-risk control interval when it is assumed that BIMERVAX® has no effect.

Outcomes

Safety outcomes (AESIs) include:

• Guillain-Barré syndrome

• Acute disseminated encephalomyelitis

• Transverse myelitis

• Encephalopathy

• Aseptic meningitis, meningoencephalitis

• Generalised convulsion (seizures)

• Facial nerve palsy, Bell’s palsy

• Narcolepsy

• Anosmia, ageusia

• Anaphylaxis

• Multisystem inflammatory syndrome
• Acute aseptic arthritis
• Subacute thyroiditis
• Diabetes mellitus (type 1) c
• Diabetes mellitus (any type)
• Acute cardiac injury (including microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease, arrhythmia, myocarditis/pericarditis)
• Coagulation disorders (including DVT, pulmonary embolus, cerebrovascular stroke, limb ischaemia, cerebral venous sinus thrombosis, haemorrhagic disease)
• Disseminated intravascular coagulation
• Thrombocytopenia
• Immune thrombocytopenia, thrombosis with thrombocytopenia syndrome
• Single organ cutaneous vasculitis
• Erythema multiforme
• Chilblain-like lesions
• Acute respiratory distress syndrome
• Acute kidney injury
• Acute liver injury
• Acute pancreatitis
• Appendicitis
• Rhabdomyolysis
• Death (any causes)
• Sudden death
• Spontaneous abortion, stillbirth
• Foetal growth restriction
• Preterm birth
• Major congenital anomalies
• Microcephaly

• Neonatal death
• Gestational diabetes
• Preeclampsia
• Maternal death
• Menstrual disorder

Data analysis plan

The vaccine utilisation study will summarise the variables of interest at the time of vaccination using standard measures of central tendency and of dispersion for continuous variables as well as counts and percentages for categorical variables.

The comparative safety cohort study will use matching and inverse probability weighting to adjust for the measured baseline confounders. Outcomes will be treated as time-to-event variables and will be analysed accordingly. Effect estimates will be provided as risk ratios and as risk differences scales.

The SCRI study will compare the risk of each AESI during a prespecified period following the index date (the “risk interval” during which there is a hypothesised increased risk of the outcome) with that of a self-matched “control interval,” used to assess the baseline risk of the outcome.

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Conflicts of interest of investigators

01_DeclarationofInterests-Annex5 - signed.pdf(245.48 KB)

Composition of steering group and observers

02_ENCePPCoCSteeringGroup.pdf(32.18 KB)

Signed code of conduct

03_ENCePPCoCAnnex3_DeclarationofcompliancewiththeENCePPCodeofConduct - signed.pdf(152.75 KB)

Signed code of conduct checklist

04_ENCePPCoCAnnex2_ChecklistofCodeofConduct - signed.pdf(299.42 KB)

Signed checklist for study protocols

05_ENCePPChecklistforStudyProtocol - signed.pdf(450.08 KB)

Data sources

Data source(s)

The Information System for Research in Primary Care (SIDIAP)

The Valencia Health System Integrated Database

EpiChron Cohort

Data sources (types)

Administrative healthcare records (e.g., claims)

Electronic healthcare records (EHR)

Population registry

Use of a Common Data Model (CDM)

CDM mapping

Yes

CDM Mappings

CDM name

ConcepTION CDM

CDM website

https://www.imi-conception.eu/

CDM release frequency

6 months

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

Unknown