# A Post-Authorisation/Post-Marketing Observational Study to Evaluate the Association Between Exposure to AZD1222 and Safety Concerns, Using Existing Secondary Health Data Sources

Progress Report: Final

**11 October 2021**

Prepared for

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# ABBREVIATIONS

| | |
|---|---|
| ARS | Agenzia Regionale di Sanità Della Toscana (Regional Health Agency of Tuscany) |
| AZ | AstraZeneca AB |
| COVID-19 | coronavirus disease 2019 |
| CPRD | Clinical Practice Research Datalink |
| DAP | database access partner |
| DSRU | Drug Safety Research Unit |
| ECDC | European Centre for Disease Prevention and Control |
| EMA | European Medicines Agency |
| EU | European Union |
| EU-PAS | European Union Electronic Register of Post-Authorisation Studies |
| FAIR | Findable accessible interoperable and re-usable |
| FISABIO | Foundation for the Promotion of Health and Biomedical Research of Valencia Region |
| HES | Hospital Episodes Statistics |
| IDIAP | Institut Universitari D'Investigació en Atenció Primària Jordi Gol |
| IRB | institutional review board |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| mRNA | messenger ribonucleic acid |
| PASS | post-authorisation safety study |
| PHARMO | Database Network of the PHARMO Institute for Drug Outcomes Research |
| RTI-HS | RTI Health Solutions |
| SIDIAP | Information System for Research in Primary Care |
| TBD | to be determined |
| UK | United Kingdom |
| UMCU | University Medical Center Utrecht |
| VAC4EU | Vaccine Monitoring Collaboration for Europe |
| VID | Valencia Health System Integrated Database |

# 1 POST-AUTHORISATION SAFETY STUDY OF AZD1222

AZD1222 is a vaccine developed to prevent coronavirus disease 2019 (COVID-19). The vaccine received emergency use authorisation in the United Kingdom (UK) on 30 December 2020 and conditional approval by the European Commission on 29 January 2021.

As part of the marketing authorisation, AstraZeneca AB (AZ) was asked to conduct a post-authorisation safety study (PASS, study number D8111R00006) to examine the safety of AZD1222. The protocol (version 3.0 dated 7 July 2021) was endorsed by the European Medicines Agency (EMA) on 22 July 2021 and by the Medicines and Healthcare Products Regulatory Agency (MHRA) (Version 2.0 dated 11 June 2021) on 9 July 2021. The protocol was finalised using the version of the RMP under review by PRAC at the time of protocol sign-off (Version 3).

The aim of this progress report is to present the progress made by the participating research teams and data sources; to confirm that the data extractions, data analysis, and other study activities are being conducted as planned; and to discuss the impact of the changes in the uptake of the vaccine on the study and whether the inclusion of other databases should be explored.

# 2 STATUS OF THE PARTICIPATING RESEARCH PARTNERS AND DATA SOURCES

As of 11 October 2021, the AZD1222 study will be performed using 5 electronic health data sources: the Clinical Practice Research Datalink (CPRD) Aurum (UK), the Valencia Health System Integrated Database (VID) (Valencia, Spain), the Information System for Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària) (SIDIAP) database (Catalonia, Spain), the Agenzia Regionale di Sanità Della Toscana (Regional Health Agency of Tuscany) (ARS) database (Italy), and the PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research (PHARMO) (Netherlands). The actual numbers of patients with at least 1 dose of AZD1222 captured in each data source are presented in Table 1 and in Table 2. For contextualisation, the estimated distribution of vaccines in the geographic area and the population of each data source is provided in Table 1.

**Table 1. Number of Unique Subjects With at Least One Dose of AZD1222 Captured, by Data Source**

| Data source | Approximate current enrolled population (millions) | Cumulative distribution estimates for each data source, based on ECDC and UK MHRA vaccine country distribution (doses)[a] | Number of vaccinated individuals with AZD1222 recorded in the database |
|---|---|---|---|
| CPRD Aurum, UK[b] | 13.4 | 5,059,200 first doses<br>4,916,400 second doses | 4,130,926 first doses and approximately 1,403,816 second doses (as of the June 2021 database release) |
| VID (FISABIO), Valencia, Spain[c] | 5 | 1,033,945 | 507,846 first doses and 439,613 second doses (as of 26 September 2021) |
| SIDIAP (IDIAP), Catalonia, Spain[d] | 5.8 | 1,219,275 | 609,672 subjects with at least one dose administered (as of 30 June 2021) |
| ARS Toscana, Italy[e] | 3.6 | 717,160 | 319,847 first doses and 61,641 second doses (data updated on 4 August 2021, including all doses given up to 31 May 2021) |
| PHARMO, Netherlands[f] | 1.4 | 228,768 | 84,646 first doses (as of the June 2021 database release) |

ARS = Agenzia Regionale di Sanità Della Toscana (Regional Health Agency of Tuscany); AZ = AstraZeneca AB; CPRD = Clinical Practice Research Datalink; ECDC = European Centre for Disease Prevention and Control; EU = European Union; FISABIO = Foundation for the Promotion of Health and Biomedical Research of Valencia Region; IDIAP = Institut Universitari D'Investigació en Atenció Primària Jordi Gol; MHRA = Medicines and Healthcare Products Regulatory Agency; PHARMO = PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research; SIDIAP = Information System for Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària); UK = United Kingdom; VID = Valencia Health System Integrated Database.

[a] Number of doses for EU data sources were estimated using ECDC distribution data per country as of 14 September 2021 multiplied by the proportion of the national population covered in each database. This number also assumes that vaccine distribution in the country is uniform and that all distributed vaccines will be administered (https://qap.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab). For the CPRD Aurum, the estimates are based on vaccine distribution in the UK. See footnote b.

[b] The CPRD Aurum contains information on approximately 13.4 million inhabitants in England and Northern Ireland, representing 20.0% of the 66.8 million individuals in the UK population. As of 22 September 2021, an estimated 24.8 million first doses and 24.1 million second doses of AZD1222 had been administered in the UK (https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting).

[c] VID: 10.6% coverage for the Valencia region, among the 9,754,197 total AZ doses administered in Spain as of 14 September 2021, resulting in an estimated 1,033,945 doses potentially distributed in the VID population.

[d] SIDIAP: 12.5% coverage for the Catalonia region, among the 9,754,197 total AZ doses administered in Spain as of 14 September 2021, resulting in an estimated 1,219,275 doses potentially distributed in the SIDIAP population.

[e] ARS Toscana: 6% coverage for the Tuscany region, among the 11,952,659 total AZ doses administered in Italy as of 14 September 2021, resulting in an estimated 717,160 doses potentially distributed in the ARS Toscana population.

[f] PHARMO: 8.1% coverage among the 2,824,297 total AZ doses administered in the Netherlands as of 14 September 2021, resulting in an estimated 228,768 doses potentially distributed in the PHARMO Network General Practitioners population.

**Table 2. Number of Unique Subjects With at Least One Dose of ADZ1222 Captured, by Data Source: Vaccines per Quarter and by Age Group**

| | CPRD Aurum (UK) | VID (FISABIO) (Valencia, Spain) | SIDIAP (IDIAP) (Catalonia, Spain) | ARS Toscana (Italy) | PHARMO (Netherlands) |
|---|---|---|---|---|---|
| Date end of data availability | June 2021 | 26 September 2021 | 30 June 2021 | 31 March 2021 | June 2021 |
| Total | 4,130,926 | 507,846 | 609,672 | 319,847 | 84,646 |
| **Calendar quarter at vaccination date** | | | | | |
| Q1 2021 | 3,633,157 | N/A | 234,495 | 130,977 | 52,423 |
| Q2 2021 | 497,769 | N/A | 375,177 | 188,870 | 32,223 |
| Q3 2021 | N/A | N/A | N/A | N/A | N/A |
| Q4 2021 | N/A | N/A | N/A | N/A | N/A |
| **Age at vaccination date (years)** | | **18-65 years: 505,720**<br>**> 65 years: 2,126** | | | |
| 0-19 | 17,486 | 1.125[a] | 2,019[b] | 22 | 1,470 |
| 20-29 | 209,255 | 29.048[a] | 26,964 | 4,301 | 1,993 |
| 30-39 | 331,379 | 44.585[a] | 37,195 | 13,087 | 2,182 |
| 40-49 | 759,324 | 66.564[a] | 53,321 | 31,093 | 3,417 |
| 50-59 | 1,168,580 | 54.695[a] | 60,241 | 32,789 | 5,698 |
| 60-69 | 856,408 | 341.233[a] | 429,781 | 72,625 | 67,923 |
| 70-79 | 585,222 | 236[a] | [redacted] | 153,341 | 824 |
| 80 or more | 203,272 | 30[a] | [redacted] | 12,589 | 1,139 |

ARS = Agenzia Regionale di Sanità Della Toscana (Regional Health Agency of Tuscany); CPRD = Clinical Practice Research Datalink; FISABIO = Foundation for the Promotion of Health and Biomedical Research of Valencia Region; IDIAP = Institut Universitari D'Investigació en Atenció Primària Jordi Gol; PHARMO = PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research; SIDIAP = Information System for Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària); UK = United Kingdom; VID = Valencia Health System Integrated Database.

[a] The Number of vaccinees by age groups could not be obtained directly from the VID data source. Data by age groups presented in the table were estimated using data on age distribution in the Valencia region from FISABIO as of 6 October 2021 (https://coronavirus.san.gva.es/es/web/vacunacion/informacion-vacunal).

[b] Among the 0-19 years age group, there were 1,358 vaccinated patients aged 19 years, 639 vaccinated patients aged 18 years, and 22 vaccinated patients aged less than 18 years.

Specific details regarding all start-up activities conducted by each data access partner (DAP) at research partner organisations and data sources, as applicable, are included in the following subsections.

## 2.1 RTI Health Solutions, Spain

RTI Health Solutions (RTI-HS) will be the coordinating centr of the AZD1222 PASS.

The contract between RTI-HS and AZ was executed on 7 September 2021

The application to the institutional review board (IRB) was submitted on 4 October 2021 and approved on 6 October 2021.

## 2.2 CPRD Aurum (DSRU), United Kingdom

The research partner for CPRD Aurum data source is the Drug Safety Research Unit (DSRU).

The contract between DSRU and RTI-HS is under legal review as of 11 October 2021.

The application to the CPRD Research Data Governance process will be submitted by 8 October 2021. A response is expected by 15 November 2021.

The next version of CPRD Aurum, with primary care data captured up to end of October 2021, is expected to be released in November 2021. Therefore, the data extraction for the first interim report, planned for the end of November 2021, is considered feasible.

Current linkages (Set 21) for Hospital Episodes Statistics (HES) Admitted Patient Care and HES Outpatient contain data up to 31 October 2020. The HES's Accident and Emergency database contains data up to 31 March 2020. The Office of National Statistics death registration contains data up to 16 November 2020, and the Public Health England's COVID-19 Hospitalisation in England Surveillance System contains data up to 29 September 2020.

The release date for linkages in Set 22 has not yet been announced by the CPRD. Set 22 is expected to contain HES Admitted Patient Care and Outpatient data up to 31 March 2021 and may be linked to the Intensive Care National Audit and Research Centre data on COVID-19 intensive care admissions.

Once the monthly updates of the Pregnancy Register (expected to be initially produced on an ad hoc basis at the end of 2021, with regular monthly updates beginning in approximately April 2022) and the Mother-Baby linkage data sets (under CPRD development) with CPRD Aurum become available, the databases can be used to identify the number of vaccinations given during pregnancy.

As of 31 May 2021 (June 2021 database release), the CPRD Aurum contained data on 4,130,926 individuals who have received at least 1 dose of AZD1222.

## 2.3 VID (FISABIO), Valencia, Spain

The research partner for the VID data source is the Foundation for the Promotion of Health and Biomedical Research of Valencia Region (FISABIO).

The contract between VID and RTI-HS is under legal review as of 11 October 2021.

The application to FISABIO's Ethics Committee was submitted on 17 September 2021. A response is expected by 7 October 2021.

The data extraction for the first interim report, planned for the end of November 2021, is considered feasible. The available data will include general practice data up to July through September 2021 and hospitalisation data up to May 2021.

As of 26 September 2021, the VID contained data on 507,846 patients who have received at least 1 dose of AZD1222.

## 2.4 SIDIAP (IDIAP), Catalonia, Spain

The research partner for the SIDIAP data source is the Institut Universitari D'Investigació en Atenció Primària Jordi Gol (IDIAP).

The contract between SIDIAP and RTI-HS is under legal review as of 11 October 2021.

The application to the SIDIAP Scientific Committee was evaluated and approved on 9 September 2021. The application to IDIAP's Ethics Committee was submitted on 13 September 2021 and approved on 4 October 2021.

The data extraction for the first interim report, planned for the end of November 2021, is considered feasible. The data available will include Primary Care and Hospital Discharge data up to 30 June 2021.

As of 30 June 2021, the SIDIAP contained data on 609,672 patients who have received at least 1 dose of AZD1222.

## 2.5 ARS Toscana, Italy

The research partner for the ARS Toscana data source is the ARS Toscana Institute.

The contract between ARS Toscana Institute and RTI-HS is under legal review as of 11 October 2021.

The internal governance at ARS Toscana approved the study on 16 July 2021.

The data extraction for the first interim report, planned for the end of November 2021, is considered feasible. All data banks will be updated up to at least the beginning of September 2021, including complete data up to approximately July 2021 (the exact completeness of the data will be known once the data are available).

As of data extracted on 4 August 2021 (complete data up to 31 May 2021), The ARS Toscana contained data on 319,847 patients who have received at least 1 dose of AZD1222.

## 2.6 PHARMO, Netherlands

The research partner for the PHARMO data source is the PHARMO Institute for Drug Outcome Research.

The contract between PHARMO and RTI-HS is under legal review as of 11 October 2021.

The application to the IRB of Stichting Informatie voorziening voor Zorg en Onderzoek was submitted on 13 September 2021. Response is expected by 25 November 2021.

The PHARMO Database Network contains data from different primary and secondary healthcare settings, linked at the patient level. These linkages between databases are updated on a yearly basis. The data extraction for the first interim report, planned for the end of November 2021, is considered feasible. For the first and second interim reports, the extraction will contain data from the General Practitioners Database, which is more frequently updated. The General Practitioners Database contains data up to June/July 2021 (first interim) and up to December 2021 (second interim) on vaccines, primary care reported outcomes, and prescription information that can be used to assess baseline co-medication. For the third interim report and final report, the linkage will be available with the remaining part of the PHARMO Database Network. These extractions also will contain data from the Hospital and Outpatient Pharmacy Database; this database has a 1-year lag time.

As of 22 June 2021, The PHARMO Database Network contained data on 84,646 patients who have received at least 1 dose of AZD1222.

## 2.7 UMCU, Netherlands

A research partner for the AZD1222 PASS will be University Medical Center Utrecht (UMCU). UMCU will provide scientific input throughout the project, will develop the data management plan, and will be responsible for programming analysis alongside RTI-HS (i.e., double programming and quality control).

The contract between UMCU and RTI-HS is under legal review as of 11 October 2021.

## 2.8 VAC4EU

A research partner for the AZD1222 PASS will be Vaccine Monitoring Collaboration for Europe (VAC4EU). VAC4EU will facilitate collaboration and distributed analytics to its members. VAC4EU will provide infrastructures during the study, including set up of a study-specific SharePoint, a digital research environment (Azure) for the conduct of the analysis, and a findable accessible interoperable and re-usable (FAIR) catalogue

(i.e., meta-data describing the DAP organisation, the data sources, and databases the DAP has access to).

The contract between VAC4EU and RTI-HS is under legal review as of 11 October 2021.

# 3 IMPACT OF THE CHANGES IN THE UPTAKE OF THE VACCINE ON THE STUDY

Table 3 describes the different restrictions on the use of AZD1222 in the countries or regions of interest to this study.

Although the restrictions for the use of AZD1222 affected the number of newly vaccinated individuals, as of September 2021 almost 5.7 million patients have received at least 1 dose of AZD1222, according to the participating data sources (Table 1). According to version 3.0 of the study protocol, the rarest adverse event of interest included in the analysis was anaphylaxis. Assuming a background rate of 6 person-years per 100,000 person-years, 6 days at risk (3 days per dose), and a study size of 5 million vaccinated individuals, we anticipate there is a 59% probability that the upper bound of the observed incidence rate ratio would be below 3.0. For the most common adverse events of interest, the inclusion of a further 5 million vaccinated individuals would allow the upper bound of the 95% confidence interval to fall below 1.5, assuming there is no increased risk associated with the vaccine.

The restrictions on AZD1222 across countries and regions also has impacted the age, sex, and comorbidity distributions for newly vaccinated individuals. In order to find comparable controls for the cohort study, the study will match vaccinated individuals by age, sex, and calendar year of vaccination with a contemporaneous unvaccinated control cohort. Differences in age and potentially different distributions of baseline variables will be addressed by adjusting propensity scores. However, in the event that there are not enough comparators or there is not sufficient follow-up time, we will consider the use of historical unvaccinated controls. At the time of the first interim report, the number of available controls will be estimated, and a final decision will be made on whether contemporaneous or historical controls will be used.

**Table 3. Restrictions, by Data Source**

| | CPRD Aurum (UK)[a] | VID (Valencia, Spain) | SIDIAP (Catalonia, Spain) | ARS Toscana (Italy) | PHARMO (Netherlands) |
|---|---|---|---|---|---|
| Date of AZD1222 approval | 30 Dec 2020 | 29 Jan 2021 | 29 Jan 2021 | 1 Feb 2021 | 29 Jan 2021 |
| Date of the first dose administration | 4 Jan 2021 | 9 Feb 2021 | 9 Feb 2021 | 2 Feb 2021 | 12 Feb 2021 |
| Indication age at approval in the country | Age ≥ 18 years | Age ≥ 18 years | Age ≥ 18 years | Age ≥ 18 years | Age ≥ 18 years |
| Description of the restrictions in the country | ▪ April 2021: AZD1222 vaccine not provided to adults under 30 years of age. AZD1222 vaccine not the preferred vaccine for pregnant women of any age who are coming for their first dose.<br>▪ May 2021: AZD1222 vaccine not provided to adults under 40 years of age.<br>▪ The mRNA-based COVID-19 vaccines are the first choice for a booster dose (third jab). However, the AZD1222 vaccine | ▪ Vaccination began in Feb in groups of individuals providing essentials for the population and who are between 18 and 55 years of age.<br>▪ 16 Mar 2021: Suspended vaccination with AZD1222.<br>▪ 23 Mar 2021: To be used only in individuals ≥ 60 years.<br>▪ 30 Mar 2021[b]: Restrictions for individuals who are under age 55 years is eliminated. | ▪ 16-23 Mar 2021: Suspended vaccination with AZD1222.<br>▪ 23 Mar 2021: To be used only in patients ≥ 60 years.<br>▪ 30 Mar 2021[b]: Restrictions for individuals who are under age 55 years is eliminated.<br>▪ 20 Apr 2021[b]: To be used only in patients aged between 60-69 years.<br>▪ 11 May 2021[b]: Extended the dose | ▪ 23 Feb 2021: To be administered to individuals aged 18-65 years, excluding extremely vulnerable individuals.<br>▪ 8 Mar 2021: Administration allowed in individuals older than 65 years of age.<br>▪ 15-19 Mar 2021: Suspended vaccination with AZD1222.[b]<br>▪ 7 April 2021: Preferential use in individuals > 60 years old.[b] | ▪ 8 Apr 2021: Only for persons aged ≥ 60 years.<br>▪ 14 March 2021: Suspended vaccination with AZD1222.[b]<br>▪ 18 March 2021: Use only in individuals aged 60-64 years and healthcare staff.[b]<br>▪ 23 March 2021: Use only in individuals aged 60-75 years and healthcare staff.[b]<br>▪ 2 Apr 2021: Suspended |

| | CPRD Aurum (UK)[a] | VID (Valencia, Spain) | SIDIAP (Catalonia, Spain) | ARS Toscana (Italy) | PHARMO (Netherlands) |
|---|---|---|---|---|---|
| | may be used as a booster dose and may be an option for those who have had the AZD1222 vaccine as their first 2 doses and/or cannot receive mRNA-based COVID-19 vaccines. | ▪ 20 April 2021[b]: To be used only in patients aged between 60-69 years.<br>▪ 11 May 2021[b]: Extended the dose interval up to 16 weeks.<br>▪ 22 June 2021[b]: Individuals under 60 years of age: Second dose with mRNA vaccine is allowed in individuals who had received the first dose of AZD1222 Individuals between 60-69 years of age: Second dose with AZD1222 is allowed. | interval up to 16 weeks.<br>▪ 21 May 2021: If individuals aged < 60 years had first dose of AZD1222, signed informed consent needed for a second dose of AZD1222.<br>▪ 22 June 2021[b]: Individuals under 60 years of age: Second dose with mRNA vaccine is allowed in individuals who had received the first dose of AZD1222. Individuals between 60-69 years of age: Second dose with AZD1222 is allowed. | ▪ 11 Jun 2021: To be used only in individuals ≥ 60 years. If individuals were < 60 years and had first dose of AZD1222, an mRNA vaccine should be administered within 8-12 weeks as the second dose.<br>▪ 18 June 2021: Patients aged ≥60 years who refuse crossing to an mRNA vaccine for the second dose can receive AZD1222 for the second dose.<br>▪ | vaccination with AZD1222.[b]<br>▪ 9 Apr 2021: Restarted vaccinations in individuals aged 60-75 years.[b] |

ARS = Agenzia Regionale di Sanità Della Toscana (Regional Health Agency of Tuscany); AZ = AstraZeneca AB; COVID-19 = coronavirus disease 2019; CPRD = Clinical Practice Research Datalink; mRNA = messenger ribonucleic acid; PHARMO = PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research; SIDIAP = Information System for Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària); UK = United Kingdom; VID = Valencia Health System Integrated Database.

[a] Additional information regarding the vaccine roll-out programme can be found here: https://www.gov.uk/government/publications/uk-covid-19-vaccines-delivery-plan/uk-covid-19-vaccines-delivery-plan; https://www.gov.uk/government/publications/priority-groups-for-coronavirus-covid-19-vaccination-advice-from-the-jcvi-30-december-2020/joint-committee-on-vaccination-and-immunisation-advice-on-priority-groups-for-covid-19-vaccination-30-december-2020#vaccine-priority-groups-advice-on-30-december-2020.

[b] Information at national level provided by AZ affiliates.

# 4 EXPLORATION OF OPENSAFELY AS A POSSIBLE DATA SOURCE FOR THE AZD1222 PASS

Previous communications between RTI-HS and researchers at OpenSAFELY (located at Oxford University in the UK) suggested the database could, in principle, be made available for a pharmaceutical-sponsored PASS, under the condition the marketing authorisation holder is willing to accept the terms of agreement for OpenSAFELY.

After further review, the marketing authorisation holder has decided that the terms of agreement for OpenSAFELY do not adequately meet the requirement of the marketing authorisation holder in terms of the need to protect intellectual property and therefore, has decided **not** to include that database in this study.

# 5 COMPLETED AND ONGOING ACTIVITIES

- The contract between AZ and the coordinating centre RTI-HS was executed on 7 September 2021. Contracts with research partners are under review as of 11 October 2021.
- Study start-up activities were initiated on 7 September 2021.
- The AZD1222 PASS kick-off meeting between RTI-HS and AZ was held on 7 September 2021. The AZD1222 PASS kick-off meeting for all research partners (RTI-HS, DSRU, FISABIO, IDIAP, ARS Toscana, PHARMO, UMCU, and VAC4EU) was held on 13 September 2021.
- Periodic meetings have been set up with the research team, starting on 27 September 2021.
- The AZD1222 PASS study and the endorsed protocol was registered in the European Union Electronic Register of Post-Authorisation Studies on 7 October 2021 (EUPAS43556) within the recommended timeline, i.e., no later than 6 months after endorsement (22 January 2022) and before start of data collection (November 2021) (http://www.encepp.eu/encepp/viewResource.htm?id=43565).
- Approvals from IRBs have been granted for SIDIAP (IDIAP) and ARS Toscana. Remaining approvals for CPRD (DSRU), VID (FISABIO), PHARMO (PHARMO Institute for Drug Outcome Research) and RTI-HS are expected by the end of November 2021.
- The statistical analysis plan is under development and will be submitted to the EMA and MHRA as planned November 2021.
- The data management plan is under development and will be ready at the time of the first data extraction, planned by November 2021.
- The research team is initiating data extraction preparation in a collaborative and harmonised manner.

# 6 NEXT STEPS

- The statistical analysis plan will be submitted to the EMA and the MHRA by the end of November 2021.
- The start of data collection, planned by the end of November 2021, is considered feasible. Finalisation of the data extraction procedures will provide operationalised definitions, data extraction, and transformation scripts for the implementation of the extraction, transformation, and loading process, i.e., the process for converting data into a common data model. Discussions between data access providers, UMCU, and RTI-HS regarding study-specific development and application of the VAC4EU common data model started in September 2021.
- The first interim report is planned to be submitted to the EMA and the MHRA by the end of April 2022.
- The second interim report is planned to be submitted to the EMA and the MHRA by the end of October 2022.
- The third interim report is planned to be submitted to the EMA and the MHRA by the end of April 2023.
- The final report is planned to be submitted to the EMA and the MHRA by the end of October 2023.

# 7 MILESTONES

At the time of the writing of this progress report, the study has been initiated and is on target to meet study milestones. There are no changes to the milestones from the endorsed protocol, listed in Table 4.

**Table 4. Milestones for AZD1222 PASS (Protocol Version 3.0, 7 July 2021)**

| Milestone | Anticipated date | Actual date |
|---|---|---|
| Protocol submission | 1 April 2021 | 1 Apr 2021 |
| Protocol endorsement by EMA/MHRA | TBD (expected July 2021) | 22 Jul 2021/ 9 July 2021 |
| Registration in the EU PAS Register | No later than 6 months after EMA protocol endorsement and before start of data collection | Registered on the 7 Oct 2021 (EUPAS43556) |
| Statistical analysis plan submission | 4 months after protocol endorsement (expected November 2021) | Ongoing<br>As planned, the statistical analysis plan will be submitted in November 2021 |

| Milestone | Anticipated date | Actual date |
|---|---|---|
| Start of data collection[b] | 4 months after protocol endorsement (expected November 2021-first interim analysis) | Ongoing<br>As planned, data collection will be performed in November 2021 |
| End of data collection[c] | 20-21 months after protocol endorsement (expected March/April 2023 - final report) | Planned |
| Progress report | 3 months after protocol endorsement (expected October 2021) | Submitted October 2021 |
| Interim report 1 | 9 months after protocol endorsement (expected April 2022) | Planned |
| Interim report 2 | 15 months after protocol endorsement (expected October 2022) | Planned |
| Interim report 3 | 21 months after protocol endorsement (expected April 2023) | Planned |
| Final report of study results | 27 months after protocol endorsement (expected October 2023) | Planned |

EMA = European Medicines Agency; EU-PAS = European Union Electronic Register of Post-Authorisation Studies; MHRA = Medicines and Healthcare Products Regulatory Agency; TBD = to be determined.

Notes: The schedule is dependent on ethics/scientific committee approvals and approvals for data extraction in each data source.

Start of data collection: The date from which information on the first study subject is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts [IR Art 37(1)]. Simple counts in a database to support the development of the study protocol, e.g., to inform the sample size and statistical precision of the study, are not part of this definition.

End of data collection: The date from which the analytical data set is completely available [IR Art 37(2)].

Analytical data set: The minimum set of data required to perform the statistical analyses leading to the results for the primary objective(s) of the study.