Study design concept

Study code	D8111R00003/ D8111R00004
Date	10 Dec 2020
Version	Draft 1.4

A Phase IV Enhanced Active Surveillance Study of People Vaccinated with AZD1222

AstraZeneca team/function leading study: Biopharmaceuticals Medical

Therapy area: R&I

Product: AZD1222

Development phase of the product:

[ ] Not applicable [ ] Pre-development [ ] In development (please indicate the phase): IV

[x] Marketed

Study category: Observational, Non-Drug Interventional

Is this study linked to a previously approved project or study? NO

Is this a regulatory post-market commitment (e.g. post-authorization safety study)? YES

What is the probability of having an impact on the label or being used as supportive data in a regulatory filing dossier?

[ ] Low [ ] Medium [x] High

Risk assessment – to be completed by Evidence Review Team Lead (ERT Lead):
[ ] Low [X] High

RESPONSIBLE PARTIES

Name	Professional title	Role in study	Affiliation	Email address
[redacted]				

1. RATIONALE

The COVID-19 pandemic has caused major disruption to healthcare systems with significant socioeconomic impacts. A safe and effective vaccine for COVID-19 prevention would have significant global public health impact. AZD1222 is a ChAdOx1 vectored vaccine against SARS-CoV-2, currently in phase III clinical development. Approval for Conditional or Emergency Use is expected in the coming months, and regulatory reviews for full approval will take place following this. Once AZD1222 will start being administered to the public, a passive safety reporting system will be initiated. In the immediate period after the emergency regulatory approval or equivalent, it is expected that high risk and special populations as defined by government and regulatory agencies will be prioritized for an early access to vaccine. These populations/uses are classified as missing information in the AZD1222 RMP and include use in pregnant and breastfeeding women, use in subjects with severe immunodeficiency, use in subjects with severe and/or uncontrolled underlying disease and use with other vaccines. Hence, the AZD1222 risk-benefit profile in these populations/uses will need to be further established through a series of post-authorization safety studies.

This Enhanced Active Surveillance study proposal aims to enroll and collect safety and tolerability data from volunteers vaccinated with at least one dose of the AZD1222 in the real world setting. In addition, a dedicated pregnancy sub-study will provide information on outcomes of AZD1222 exposure in (or shortly prior to) pregnancy among women who become inadvertently pregnant prior to or after vaccine administration.

An active surveillance study will be part of a programme of four post authorisation safety studies also including a large secondary data observational study to evaluate the risk of AESIs and other safety concerns (as per the RMP) over a long term period after exposure and also in the above-mentioned populations/uses with missing information. This particular primary data collection surveillance study is considered to be an important part of the overall post-authorization safety programme for the following reasons:

- Safety data collected including subject reporting data near ‘real time’ in comparison to the secondary data studies;
- Increased ability to confirm AESIs/safety concerns with adjudication committee reviewing cases not available in secondary database studies;
- Concrete data on exposure including batch # and timings of vaccination (X2);
- Denominator data will be available;
- Secondary data availability have substantive lag times outside the UK and US contributing to longer delivery of secondary analysis;
- Accuracy of exposure in secondary databases has not been fully determined for EU countries;
- Staged or stepwise distribution of COVID-19 vaccines including AZD1222 may lead to the number of vaccinees growing at an incrementally slower pace in secondary data throughout 2021 and 2022 as compared with primary data collection targetting vaccination centres.

This Study Design Concept is a master document to be adapted for operationization in two separate studies, one conducted in EU/UK and the other in the US.

2. OBJECTIVES AND HYPOTHESES

Primary objective(s)	**Outcome measure**	**Hypothesis tested (if relevant)**
Assess the safety and tolerability of at least one dose of the AZD1222 in adults ≥ 18 years of age for a predefined period (eg, 3 months) after vaccination with fist dose of AZD1222	Incidence of medically-attended AEFIs (Adverse Events Following Immunization), SAEs,pre-defined AESIs (Adverse Events of Special interest), and safety concerns (as defined in the RMP)	Not applicable
Secondary objective(s)	**Outcome measure**	**Hypothesis tested (if relevant)**
Assess the longer term safety and tolerability of at least one dose of the AZD1222 in adults ≥ 18 years of age for 12 months after vaccination with first dose of AZD1222	Incidence of SAEs, pre-defined AESIs and safety concerns after vaccination with AZD1222	Not applicable
In a pregnancy sub-study:		
Estimate the frequency of selected adverse pregnancy outcomes in women receiving at least one dose of the AZD1222 vaccine during pregnancy or up to a predefined period (eg, 60 days) before estimated date of conception	Prevalence of spontaneous abortions, stillbirths, and preterm births	Not applicable
Estimate the frequency of selected adverse foetal/neonatal outcomes at birth and up to at least 6 months of life in infants from pregnancies in which the mothers received at least one dose of the AZD1222 vaccine during pregnancy or up to a predefined period (eg, 60 days) before estimated date of conception	Prevalence of major congenital malformations and small for gestational age	
Exploratory objective		**Hypothesis tested (if relevant)**
Quantify the health-related quality-of-life (HRQoL) and healthcare resource utilization (HCRU) following vaccination with AZD1222	Vaccine-related and all cause HCRU	Not applicable
In a pregnancy sub-study:		
Estimate the frequency of selected adverse pregnancy outcomes in the external comparator cohort unexposed to any COVID-19 vaccine	Prevalence of spontaneous abortions, stillbirths, and preterm births	
Estimate the frequency of selected adverse foetal/neonatal outcomes at birth and up to at least the 6 months of life in infants from an external comparator of mothers who were unexposed to any COVID -19 vaccine	Prevalence of major congenital malformations and small for gestational age	
Safety objective(s)	**Outcome measure**	**Hypothesis tested (if relevant)**
See primary and secondary objectives	See primary and secondary objectives	

		Not applicable

3. METHODOLOGY

3.1 Study design

The study will be a single arm cohort study of ~30 000 adult volunteers drawn from the general population in the EU (inclusion of the UK is considered) and USA, who seek to receive the AZD1222 vaccine. Operationalization through two separate studies based on linked protocols locally adapted is proposed. Volunteers will be enrolled after being immunized with at least one dose of AZD1222 in a real world vaccination settings ("study sites") after the date of market emergency use authorisation or equivalent regulatory approval with the goal to estimate the frequency of events related to safety and tolerability, including pregnant women. A separate study in the UK enabling an expedited start shortly after the AZD1222 availability is considered.

Two separate linked protocols with be developed and initiated in a staggered manner, starting with an EU protocol (UK site feasibility is being considered) and a separate aligned US protocol. Each of the two protocols will aim to recruit about 15,000 volunteers. The data will be reported separately for each study and aggregated for the entire population across two studies, preferably at the individual patient data level.

To support safety signal evaluation observed-to-expected analyses, stratified by age and gender will be conducted using background incidence rates obtained from one or more of the following sources: the published literature, secondary database analyses (eg, EUPAS37273 Background rates of Adverse Events of Special Interest for monitoring of COVID-19 vaccines) and AZD1222 clinical trials safety database. All reported events will be monitored and evaluated for seriousness and relatedness to AZD1222. Clinical validation or adjudication of AESI cases/safety concerns will be conducted.

All participants will be asked to consent for access to their medical records (paper or electronic) to further evaluate events categorized as SAEs,AESIs or safety concerns. Access to medical records could be also needed to allow confirmation of pre-specified events by independent adjudication committee.

In a pregnancy sub-study, all participants who become pregnant or aware of their pregnancy up to a predefined period (eg, 60 days) prior vaccination with AZD1222 will create a dedicated sub-cohort. Women will be recruited into the study at the time of vaccination or soon afterward, and will be followed until the end of their pregnancy (i.e, abortion, stillbirth, or live birth). Live-born infants will be followed for up to at least 6 months after birth to document any major congenital malformations (MCMs) diagnosed after birth. Data from this sub-study may be merged with a separate pregnancy registry. An external comparator cohort from existing health care data sources including women with pregnancies in the same time frame, will be analyzed to provide a context for interpreting the results from this prospective registry.

3.2 Study population (Main cohort)

Volunteers from resident population of adults in the EU, UK, and USA who seek to receive at least one dose of the AZD1222 vaccine after the date of conditional use approval, emergency use approval or equivalent regulatory approval.

3.2.1 Inclusion criteria (Main cohort)

Adults aged 18 years and above

3.2.2 Exclusion criteria (Main cohort)

Participants are excluded from the study, in alignment with vaccination general best practice, particularly if any of the following criteria apply. Further review of these criteria will be applied at the protocol writing stage:

- History of allergy to any component of the vaccine
- Significant infection or other acute illness, including fever > 100 °F (> 37.8 °C) on the
- day of vaccination with AZD1222
- Recurrent severe infections and use of immunosuppressant medication within the past 6 months (≥ 20 mg per day of prednisone or its equivalent, given daily or on alternate days for ≥ 15 days within 30 days prior to administration of study intervention)
- Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture
- Current receipt of, or planned receipt of investigational products indicated for the treatment or prevention of SARS-CoV-2 or COVID-19
    - Note: For participants who become hospitalized with COVID-19, receipt of licensed treatment options and/or participation in investigational treatment studies is permitted
- Not able or willing to consent to study enrollment or to provide permission to access medical records, including electronic medical records if available.

3.3 Study population (Pregnancy sub-study)

Women who receive at least one dose of the AZD1222 vaccine at any time while they are pregnant or who become pregnant within a pre-defined period (eg, 60 days) after being vaccinated will be eligible for inclusion in the vaccine exposed cohort. Only women without prior knowledge of foetal or pregnancy outcome at the time of recruitment will be eligible for inclusion.

The external comparator cohort will include women identified in existing health care data sources with the follow-up period as the treated cohort.

3.3.1 Inclusion criteria (Pregnancy sub-study)

AZD1222 Vaccinated Cohort

- Women between the ages of 18 and 45 on the estimated date of conception (EDC).
- Vaccination with at least one dose of the AZD1222 within a predefined period (eg, 60 days) prior to the EDC or any time during pregnancy.

External Comparator Cohort

- Women between the ages of 18 and 45 on the estimated date of conception (EDC).

3.3.2 Exclusion criteria (Pregnancy sub-study)

AZD1222 Vaccinated Cohort

- Women with knowledge of pregnancy outcome at the time of recruitment.
- Women with prenatal pathologic testing prior to recruitment.

External Comparator Cohort

- Women with any COVID-19 vaccination before the first identified prenatal visit (where feasible to extract).

3.4 Data source

Data collection will occur at study sites, through a dedicated call centre and through the use of a validated digital patient solution allowing consent, enrolment and data collection using a web-portal and/or smartphone application. The applicationwill be downloaded by volunteers on the day of the first dose administration. The digital solution will be used to complement study eCRF and collect information about baseline characteristics, study outcomes and study variables, from informed consent through the end of the 12-month follow up period. The digital solution will be deployed in multiple countries on Apple, Android and web based operating systems, and requiring minimal bandwith.

To maintain a naturalistic design and facilitate contextualization with real world evidence cohorts, only a small number of reminders will be set up in the App. It is proposed, subject to operational feasibility and further scientific review during protocol development, to use the following schedule: 24, 96 hours and 7 days after each dose, 28 days after the last dose, 3 months after the last dose and then periodically during the rest of the 12 months follow up period**.** Additional information will be provided to the subjects through the year in order to maintain engagement through the follow up period.

Study sites will be set up in real world settings where vaccine will be administered in individual countries, preferably GP/primary care practices. Relevant volunteers' characteristics and outcomes will be collected through these sites after the time of emergency use in countries in the EU and the USA. Data will be collected at time of the first and second dose administration.

In total, 15,000 volunteers are planned to be recruited in the EU (planned to be enriched with UK sites) and about 15,000 in the USA providing an overall population of ~30 000 volunteers.

The comparator cohort, to produce observed-to-expected analyses, will be identified within existing health care data sources (eg, national registries, electronic health records, administrative claims data, clinical trial reports, published data).

Pregnancy sub-study

Pregnant women may be recruited for the AZD1222 exposed cohort at the time of vaccination or afterwards, dependent on where the vaccine was administered, the approach to recruitment and when pregnancy status becomes known relative to the timing of the vaccination. Additional informed consent will be obtained at the time of recruitment. Structured questionnaires will be the source of

data on the estimated date of conception, reproductive history, , medications used and morbidities during pregnancy, pregnancy outcomes, and infant outcomes.

The comparator cohort will be identified within existing health care data sources (eg, national registries, electronic health records, administrative claims data). Where feasible to ascertain, women who have not had a COVID-19 vaccination prior to the first prenatal visit will be eligible for inclusion. Data on estimated date of conception, demographics, reproductive history, morbidities, medications used during pregnancy, pregnancy outcomes, and infant outcomes will be derived from the health care data sources using diagnosis, procedure, medication, and medical encounter codes.

3.5 Study assessments (primary data collection) or variables and epidemiological measurements (secondary use of data)

At enrollment & AZ1222 dose 1

- Informed consent and contact information, including next of kin, in case of apparent loss to follow-up:
- Baseline characteristics [at vaccination or specified if otherwise]
    - Demographics: age, sex, socioeconomic status, residence location and work location, job, if applicable
    - COVID-19 preventive behaviours of volunteer and household members [prior 3 months]
    - Selected comorbidity [ever] and comedication [prior 12 months] including
        - Risk of COVID-19 complication: healthy, immunocompromised, severe and/or uncontrolled underlying disease
        - Prior vaccinations including COVID19
    - Health-Care Resource Utilization [prior 12 months]
- Exposure: AZ1222 dose 1

At AZ1222 dose 2 administration

- Exposure: AZ1222 dose 2
- Changes in COVID-19 preventive behaviours, risk of COVID-19 complication, comorbidity and comedications
- Study outcomes – see below

Assessment At Predefined time points (subject of operational feasibility and further scientific review at protocol development): eg, 24, 96 hours, 7 days after any dose, 28 days after the last dose, every two months during the rest of the follow up period

- Changes in COVID-19 preventive behaviours, risk of COVID-19 complication, comorbidity and comedications

- Characterization of population as missing information in the RMP : pregnancy, lactation, severe immunodeficiency, severe and uncontrolled underlying disease

- Outcomes

    - Safety. All safety events will be handled according the AstraZeneca policies and standard operation procedures for clinical trials

    - All AEs are considered to be unsolicited AEs (collected by 'open question' through app) – and flagged to the patients HCP via an HCP dashboard

    - The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

    - SAEs will be recorded from the time of signature of the informed consent form through the last participant contact.

    - AEs will be reported by the participant

        - All AEs spontaneously reported by the participant: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded **in the eCRF**. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

    - Medically attended AEFIs will be recorded from Day 1, post treatment, through the pre-defined period (eg, 3 months) after vaccination with the first dose.

    - AESIs will be recorded from Day 1, post treatment, through the last participant contact.

        - Medically Attended Adverse Events Following Immunization (AEFI): are defined as AEs leading to medically-attended visits that were non-routine visits to a health-care professional, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. AEs, including abnormal vital signs, identified on a routine study visit or during the scheduled illness visits will not be considered MAAEs.

        - Adverse Events of Special interest AESIs are events of scientific and medical interest specific to the further understanding of study intervention safety profile and require close monitoring and rapid communication by the investigators to the Sponsor. An AESI can be serious or non-serious. All AESIs will be recorded **in the eCRF**. Serious AESIs will be recorded and **reported** (Note: a subset of AESIs are also considered safety concerns as per the RMP)

    - **Reporting of Serious Adverse Events:** All SAEs have to be reported, whether or not considered causally related to the study intervention, or to the study procedure(s). All SAEs will be recorded in **the eCRF.**

        If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate Sponsor representatives within one day

ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform Sponsor representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated Sponsor representative.

If the EDC system is not available, then the investigator or other study site staff reports an SAE to the appropriate Sponsor representative by telephone or other method.

- Exploratory outcomes may include (subject of feasibility assessment):
  - Quality of life and Patient Reported Outcomes
    - EQ-5D; To describe self-perceived health status and health-related quality of life
    - Covid 19 anxiety and depression; Bespoke questionnaire
    - Work loss due to COVID-19 sickness; work loss days due to not being sick to COVID-19 (2 questions (days))
    - Activity/sport/leisure loss; Bespoke questionnaire
    - COVID-19 Symptom questionnaire among those who experience COVID-19 infection !
  - Health resource utilization
    - All cause and COVID-19 related hospital/non-hospital HCRU: to be specified at the protocol development stage

<u>Pregnancy sub-cohort</u>

For the AZD1222 exposed cohort, data collection will be through structured questionnaires at 4 time points: enrolment (after informed consent), 6 weeks post enrolment, 8 weeks post estimated date of birth, 24 weeks post date of birth.

- Outcomes: For the prospective AZD1222 cohort, COVID-19 infection and pregnancy outcomes (ie, spontaneous abortion, still birth, live birth) and infant outcomes (ie, MCM, SGA) will be collected through questionnaires at the 6-week post enrolment and 8-week post estimated birth date. Additional MCM data will be collected at the 24-week post birth date. The specific time point

for the final assessment might be revised to align with other COVID-19 vaccine pregnancy safety registries .

3.6 Study limitations

The strength of the COVID-19 pandemic, availability of other vaccines and the social and political environment at each location will impact recruitment and follow-up of vaccinated volunteers. The uncertainty of the situation and the highly dynamic environment can hinder enrollment forecasts.

Potential differences in covid strains/mutations may not be known however can have a variable effect on outcomes, so does differences in exposure patterns.

While an internal comparison (ie, a cohort unexposed to any COVID-19 vaccine) is preferrable, it was deemed not feasible for the following reasons 1)it would be unethical to include volunteers that could be discouraged from taking a COVID-19 vaccination 2)volunteers who opt out of an un-exposed cohort may have different risks for the outcomes 3)final recruited cohorts (exposed and un-exposed) may exhibit different characteristics resulting in different risks for the outcomes and 4)having an additional cohort will prolong study delivery timeliness.

It is unclear how efficient an observed-to-expected ecological design can be used in COVID times given the major impact of COVID itself on general healthcare seeking behavior. Changes over time are likely to be related to the local rates of COVID and the resulting access to care, with better access and routine disease diagnosis as the local rates of COVID decrease. Paradoxically, increased outcomes may then be observed as vaccination coverage increases and COVID rates decrease. Time trends may be challenging to interpret in this changing healthcare use environment confounded by vaccine and other treatment/prevention measures. Further, AESIs with high attributable % (or etiologic fraction; AR) to the vaccine might be much more relevant to consider for an ecological comparative design (observed-to-expected) than AESIs with low AR % (such as diabetes) for which confounding will be more difficult to control.

Pregnancy sub-study

A limitation of prospective pregnancy registries is that any spontaneous abortions that occur prior to recruitment will not be identified. Gestational age at the time of recruitment will be considered in the analyses and interpretation of results.

While an internal comparison (ie, a cohort unexposed to any COVID-19 vaccine) is preferrable, it was deemed unlikely to be feasible for several reasons (similar to the main study): it would be unethical to include pregnant women that would be discouraged from taking a COVID-19 vaccination, unvaccinated women could not be recruited at the time of delivery with the same risk of adverse pregnancy outcomes as women recruited earlier in pregnancy, women who opt out of COVID-19 vaccination during pregnancy may havea different risk of adverse pregnancy outcomes, and unvaccinated women would be at a higher risk of COVID-19 infection which may in turn have an adverse effect on the pregnancy.

The comparator cohort derived from some of the data sources (eg, administrative claims) will have more limited time and data in the preconception period.

Because the data in health care databases are not collected for research purposes, the information for the comparator cohort may be more prone to misclassification.

The patient characteristics of the AZD1222 exposed cohort and comparator cohort might be different for factors that could affect pregnancy or infant outcomes (eg, age). While we do not propose conducting direct comparisons, we could standardize the outcome estimates to account for a limited number of cohort differences. This will be described in the protocol and statistical analysis plan.

4. STATISTICAL METHODS

4.1 Sample size and statistical power; precision assessment

The study is descriptive in nature. For sample size of 30,000 volunteers, if no event observed, one can rule out (at 95% confidence) events occuring with a frequency of 1 in 10,000.

No formal statistical testing is foreseen. Distribution of volunteer characteristics at baseline will be described through point estimates (mean, median, rates or proportions) and the corresponding variability (interquantile range, 95% confidence intervals).

Pregnancy sub-study

The size of the prospective cohort will be determined, in part, by the uptake of vaccination with AZD1222 among pregnant women. We have calculated the precision (95% confidence limits) around prevalence estimates for different prospective cohort sizes for outcomes with different prevalence estimates. Data used for the expected prevalence of MCMs, spontaneous abortions, and still births in the unexposed cohort are described below

Table 1. Upper and lower 95% confidence limits of prevalence estimates, under different sample sizes and estimates of the prevalence of different outcomes

Outcome prevalence	Number exposed to AZD1222	Expected Number of Events	Prevalence	95% confidence limits*	
				Lower	Upper
3% (MCMs)	400	12	0.03	0.017	0.052
	600	18	0.03	0.019	0.047
	800	24	0.03	0.020	0.044
	1,000	30	0.03	0.021	0.043
12% (spontaneous abortions)	400	48	0.12	0.092	0.156
	600	72	0.12	0.096	0.148
	800	96	0.12	0.099	0.144
	1,000	120	0.12	0.101	0.142
0.5% (stillbirths)	400	2	0.005	0.001	0.018
	600	3	0.005	0.002	0.015
	800	4	0.005	0.002	0.013
	1,000	5	0.005	0.002	0.012

*Estimated using approximate confidence intervals

MCM = major congenital malformation

Calculations done in EpiSheet (Rothman 2015).

4.2 Statistical considerations

The cumulative incidence of medically-attended AEFIs and AESIs will be computed as the proportion of participants who reported an event among all AZD1222-vaccinated participants who completed each study-defined follow-up interval, including the full study period.

All events reported, regardless of seriousness, will be tabulated. Serious adverse events, AEFIs and AESI will also be tabulated separately.

Where feasible, incidence rates will be calculated. Data will be stratified by age category agreed with the regulatory authority (eg, 6 months to 5 years, 6 to 12 years, 13 to 17 years, 18 to 65 years, > 65 years). Participants will be classified according to their risk of complication from COVID-19, eg, healthy, immunocompromised, severe and/or uncontrolled underlying disease. Definitions of these populations will be refined based on feedback from regulators. Pooling of participant data across multiple geographies is proposed. Frequent interim reports will be scheduled. Proposed schedule of reports are to be finalized in the study protocol, for illustration:

- At month 1 after first enrolment or after enrolment of the first 1,000 subjects with at least 30 days post-first dose, whichever comes first

- At month 3 after first enrolment or after enrolment of the first 5,000 subjects with at least 30 days post-first dose, whichever comes first

- At month 6 after first enrolment or after enrolment of the first 10,000 subjects with at least 30 days post-first dose, whichever comes first

- After enrolment of the first 15,000 subjects with at least 30 days post-first dose

Alternative interim reporting schedule may be proposed at protocol development stage if other designs are used, i.e. based on the number of events.

To support safety signal evaluation, observed-to-expected analyses will be conducted. As this will be the first year of the implementation of enhanced surveillance activities, it is planned to compare the observed events reported in this study with the expected events frequencies from external sources, detailed in previous sections.
Observed-to-expected analyses will be performed for AESIs and fatalities. In order to take the age distribution of the study population into account, an age-stratified expected number of cases will be calculated. For a comparison with expected rates based on background incidence rates reported, risk windows, defined as the time period in days following vaccination during which a reported AESI may be assumed to be related to vaccination, will be defined for each event type. Counts of AESIs that occurred within the pre-specified risk window will be compared against expected values using approaches like sequential testing including a Maximized Sequential Probability Ratio Test (maxSPRT).

Data will reported for each of the two EU/UK and US linked protocols and also for an overall total population across the two studies.

Pregnancy sub-study

Descriptive analyses will be used to describe patient characteristics of the the AZD1222 exposed and comparator cohorts, including demographics, medication use, morbidities, and reproductive history. These measures will include counts, percentages, mean, standard deviation, 95% CI, median, interquartile range, minimum, and maximum.

Pregnancy outcome measures by cohort will include: prevalence of pregnancies that resulted in live births, spontaneous abortions, and stillbirths, stratified by country and summarised across countries (if appropriate) and 95% confidence intervals will be estimated.

Infant outcome measures by cohort will include: prevalence of live births that were SGA or had an MCM, stratified by country and summarised across countries (if appropriate) and 95% confidence intervals will be estimated.

Pregnancy and infant utcome measures may be stratified by COVID-19 infection during pregnancy, age at conception, or other relevant patient characteristics.

5. TIMELINES AND OPERATIONAL INFORMATION

Milestones	**Planned dates**
Study design concept approved	December 11 2020
External service provider/contract research organization selected (if relevant)	January 08 2021 or earlier
Study protocol approved	March 01 2021 or earlier
First subject/patient in (or database start date)	May 01 2021 or earlier
Last subject/patient in (or database end date)	TBD
Last subject/patient last visit	TBD
Final database lock	TBD
Clinical study report approved	TBD
Operational information	**Details**
Approximate study budget	TBD
Budget holder(s), including cost-sharing	*TBD, GPT*
Delivery model (internal – Global Medical Affairs, Marketing Company, Site Management and Monitoring – or external) <<IF EXTERNAL: LIST POTENTIAL SERVICES PROVIDERS>>	
Planned data re-use	TBD

Approach towards patient centricity (e.g. engagement with patient groups related to study)	TBD
International coordinating investigator or executive steering committee	*TBC* YES

6. REFERENCES

Rothman KJ. Episheet—spreadsheets for the analysis of epidemiologic data. 4 October 2015. Available at: http://www.krothman.org/episheet.xls Accessed 21-November-2020.