Study Synopsis:

VidPrevtyn Beta® Vaccine Effectiveness against hospitalisation due to SARS-CoV-2 infection - a secondary database study in the UK

1 BACKGROUND

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is responsible for the current global coronavirus disease 2019 (COVID-19) pandemic. Most individuals infected with the virus have mild-to-moderate respiratory symptoms; however, some individuals have severe symptoms requiring medical attention, hospitalisation and in some cases a fatal outcome. On the week of 17 May 2023, 2,438 people in England had been admitted to hospital due to COVID-19, with 81 individuals requiring mechanical ventilation[1].

Since the start of the pandemic, vaccine development and national roll-out programmes have been the priority worldwide. The availability of vaccines has slowed transmission and reduced the burden on healthcare systems; however, vaccine effectiveness (VE) wanes over time, which can be accelerated by new viral variants becoming predominant.

In England, the vaccination guidelines as set out by the Joint Committee on Vaccination and Immunisation (JCVI) as of 27 January 2023[2] state that:

- Adults over 75+ years, residents in care homes and individuals aged 5 years and over who are immunocompromised will be offered a spring 2023 booster dose.
- Some people, including those aged 50 years or over, those at higher risk or who are pregnant, and frontline health and social care workers, will be offered a seasonal booster (autumn 2023 booster campaign details to be set out in June 2023).

VidPrevtyn Beta is the 7th vaccine to be authorised by Medicines and Healthcare products Regulatory Agency (MHRA) for COVID-19 in ages 18 and older. On March 7th, 2023, the JCVI has confirmed its advice for a 2023 spring coronavirus (COVID-19) booster programme[3]. The committee has since advised that a spring booster dose should be offered to: adults aged 75 years and over, residents in a care home for older adults, individuals aged 5 years and over who are immunosuppressed. Eligible individuals will be offered the vaccine around 6 months after their previous dose. VidPrevtyn Beta is currently not intended for use in the peadiatric population.

Contingent on a feasibility assessment, Sanofi will monitor the benefit of its product in real life setting and will conduct a booster vaccine effectiveness study.

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[1] https://coronavirus.data.gov.uk/details/healthcare?areaType=nation&areaName=England [accessed 13 June 2023]

[2] https://www.gov.uk/government/publications/covid-19-vaccination-programme-for-2023-jcvi-interim-advice-8-november-2022/jcvi-statement-on-the-covid-19-vaccination-programme-for-2023-8-november-2022 [accessed 20 March 2022]

[3] https://www.gov.uk/government/news/most-vulnerable-to-be-offered-spring-covid-19-booster

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE[4]

1. Estimate the vaccine effectiveness of VidPrevtyn Beta against hospitalisation due to COVID-19 with laboratory-confirmed SARS-CoV-2 infection in patients who have received at least one dose of VidPrevtyn Beta as their last booster, compared with patients who have not received a booster dose within the same vaccination campaign period

2.2 SECONDARY OBJECTIVES

1. Estimate the vaccine effectiveness of VidPrevtyn Beta against death due to COVID-19 with laboratory-confirmed SARS-CoV-2 infection in patients who have received at least one dose of VidPrevtyn Beta as their last booster, compared with patients who have not received a booster dose within the same campaign period

2. Estimate the relative vaccine effectiveness of VidPrevtyn Beta against hospitalisation due to COVID-19 with laboratory-confirmed SARS-CoV-2 infection in patients who have received at least one dose of VidPrevtyn Beta as their last booster, compared with patients who have received an mRNA booster as their last dose within the same campaign period

2.3 EXPLORATORY OBJECTIVES[5]

1. Estimate the vaccine effectiveness of VidPrevtyn Beta against hospitalisation due to COVID-19 with laboratory-confirmed SARS-CoV-2 infection in patients who have received at least one dose of VidPrevtyn Beta as their last booster, compared with patients who have not received a booster dose within the same campaign period, stratified by:
   - Age groups
   - Gender
   - COVID-19 vaccination history
     - Compare by heterologous vs homologous (platform) history of vaccination
     - Compare by number of previous COVID-19 vaccine doses received
   - Subgroups of special interest (e.g. pregnant women, immunocompromised patients, frail patients with unstable health conditions and co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders), patients with autoimmune or inflammatory disorder)[6]

[4] *Objectives may be adapted in the final study protocol following the feasibility assessment and sample size calculations.*

[5] *Exploratory objectives to be considered if sufficient sample size is met.*

[6] Short-list of sub-groups of special interest to be identified once sample size from NHS-SDE is confirmed

3 STUDY DESIGN

Study design:

Retrospective database matched cohort study using National Health Service (NHS) Digital Secure Data Environment (SDE)

Rationale for cohort study design:

- Allows for evaluation of the effect of the exposure on multiple outcomes and sub-groups
- Allows for exploration of the effect of time on the outcome (e.g. investigation on duration of protection)
- Can provide event rate estimations, absolute risk reduction and number needed to vaccinate
- Option to add a nested case-control within a cohort study for sensitivity analysis or exploration of results

Study population:
Individuals aged 18 years or older who are eligible to receive a VidPrevtyn Beta vaccination as per MHRA and JCVI guidelines and captured within the SDE database.

3.1 DATABASE

In response to the COVID-19 pandemic, the NHS SDE for England was set up to provide researchers with secure, remote access to linked, personal-level electronic health record data from national health settings (including historical data). This database links; General Practice Extraction Service (GPES); COVID-19 Second Generation Surveillance System (SGSS); National Immunisation Management System (NIMS); Hospital Episode Statistics (HES); Office of National Statistics/Personal Demographic Service (ONS/PDS); and Intensive Care National Audit and Research Centre (ICNARC) databases.

3.2 SELECTION AND ENROLLMENT OF PARTICIPANTS

Inclusion criteria:

- All individuals aged 18+ and eligible to receive a VidPrevtyn Beta vaccine.

Exclusion criteria:

- Individuals under the age of 18
- Individuals in the unboosted cohort with no record of a primary vaccination series

Primary outcome:

- Hospitalisation due to COVID-19 as a primary cause, with a laboratory confirmed SARS-CoV-2 PCR test.

Secondary outcome:

- COVID-19 listed as a cause of death on the death certificate

Exposure:

- VidPrevtyn Beta as a last COVID-19 booster dose[7]
- mRNA vaccine as a last COVID-19 booster dose[7]

3.2.1 Variables

Relevant variables will be extracted from the following linked databases through the SDE database:

- GPES: primary care data including personal characteristics, demographic data, and comorbidities.
- SGSS: PCR testing data from pillar 1 (hospital labs). Note: this data includes information on those that test positive and negative, the reason for the PCR test and symptom onset date.
- NIMS: nationwide vaccination status data that includes information on batch number, vaccine type, date of vaccination, identification of risk status for severe disease.
- CHESS: COVID-19 hospitalisation data.
- HES OP, APC, DID, and ACC: outpatient, inpatient, critical care and diagnostic scans hospital claims data.
- ONS/PDS: death data.
- Note: if additional data on utilisation of intensive care (e.g. HDU/ICU admission) is required there is also the option to link to ICNARC.

3.3 STUDY PERIOD

International regulators have recently published a report following a meeting of the International Coalition of Medicines Regulatory Authorities (ICMRA). Guidance states that vaccine formulations used in the upcoming winter 2023 season in the northern hemisphere should include only one virus strain and be based on the XBB family of Omicron subvariants (such as XBB.1.5)[8]. Sanofi is therefore faced with two potential scenarios: VidPrevtyn Beta is continued to be offered to at-risk populations within the UK during the Fall 2023 vaccination campaign. Alternatively, the recommendation for VidPrevtyn Beta may be reduced to second intention in the UK (as is currently the case in France) or removed entirely. Pending JCVI guidance on the winter season COVID-19 vaccination campaign, we outline two study period scenarios to manage this uncertainty in VidPrevtyn uptake.

[7] Index date will be 14 days after exposure to the vaccine of interest. A 14 day window is to allow the immune system to mount an immune response following inoculation with the vaccine of interest, this follows the exposure definition as defined by the ECDC. https://www.ecdc.europa.eu/sites/default/files/documents/Core-protocol-for-ECDC-studies-of-COVID-19-vaccine-effectiveness-against-hospitalisation-with-SARI.pdf [accessed 14 June 2023]

[8] https://icmra.info/drupal/covid-19/8may2023

3.3.1 In the case that the JCVI maintains recommendation for VidPrevtyn Beta as a COVID-19 booster in the UK

The enrolment period for this study will be from 1 March 2023 to 31 December 2023. The analysis will then be conducted on the exposed and non-exposed subjects followed-up for 3 months. An extended analysis will be conducted on a follow-up period of 6 months.

3.3.2 In the case that the JCVI no longer recommends VidPrevtyn Beta in the UK

The enrolment period for this study will be from 1 March 2023 to the date of recommendation change in the UK (update expected in June 2023). The analysis will then be conducted on the exposed and non-exposed subjects followed-up for 3 months. An extended analysis will be conducted on a follow-up period of 6 months.

3.4 FEASIBILITY ASSESSMENT

Sanofi will develop a full protocol and conduct sample size calculations. Given that the hospitalisation due to COVID-19 is becoming a rarer outcome, a feasibility assessment will be performed. This feasibility assessment will be conducted by monitoring VidPrevtyn Beta uptake in England and monitoring the force of infection of SARS-CoV-2 and COVID-19 related hospitalisations. Modelling projections will be used to estimate the number of cases likely to be accrued within the study period and understand the chance to meet a sufficient sample size to obtain a robust and precise estimate of VE within a reasonable window of time.

4 STATISTICAL ANALYSIS

4.1 SAMPLE SIZE

Sample size estimates were calculated for 80% power and an alpha of 5% with the assumption of 1:2 matching for VidPrevtyn boosted to un-boosted. According to the ONS COVID-19 latest insights about 10 in 100,000 people per week were hospitalized with COVID-19 in March[9]. Of those, about 30% were being treated primarily for COVID-19. Therefore, about 36 per 100,000 people are estimated to be hospitalized primarily for COVID-19 over the three-month follow-up period and 72 per 100,000 people over the 6-month follow-up period for this study. The table below shows sample size estimated for a range of vaccine effectiveness (VE) values for both three and six months of follow-up. If VidPrevtyn Beta has a VE of 30% then a total sample of 616,647 patients will be required, 205,549 of which will need to have received the vaccine for a follow-up of six months. If VidPrevtyn Beta has a VE of 30% then a total sample size requirements drop to 126,960 patients, 42,320 of which will need to have received the vaccine for a follow-up of six months.

Sample Size Estimates

[9]https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/coronaviruscovid19latestinsights/hospitals

Follow-up period	VE	Sample size (total)	VidPrevtyn boosted	Un-boosted
6 months	30%	616647	205549	411098
	40%	326466	108822	217644
	50%	195882	65294	130588
	60%	126960	42320	84640
3 months	30% 40% 50% 60%	1233684 653133 391881 253998	411228 217711 130627 84666	822456 435422 261254 169332

4.2 MATCHING CRITERIA[10]:

Individuals vaccinated with VidPrevtyn will be matched on age (year of birth) and sex using a matching ratio of 1:5 to those who were not vaccinated (i.e. during the same vaccine campaign) with any COVID-19 vaccine booster dose.

In the second step, other covariates and potential confounders, such as Charlson Comorbidity Index (CCI), previous COVID-19 infections, and the number of severe COVID-19 risk factors as listed on the CDC website will be included in the propensity score (PS) model. Further matching on PS will be considered for individuals vaccinated with VidPrevtyn and their matched counterparts. The balance between the two cohorts after PS matching will be evaluated using standardized differences of baseline characteristics. PS matching can lead to a reduction of the sample size. Therefore, if the sample size is limited, inverse probability of treatment weighting (IPTW) can be considered.

4.3 METHODS

Cox proportional Hazards modelling will be performed to calculate the Hazard Ratio (HR) of COVID-19 related hospitalization or COVID-19 related death following PS matching method as defined in the protocol. The Cox model estimates a survival function that predicts the probability that the event of interest (in this case COVID-19 related hospitalization or COVID-19 related death) will occur at a given time (t) for given values of covariates (e.g., VidPrevtyn Beta booster vaccination status). In this study, the Cox model estimates the hazard rate of the events of interest in the populations or subgroups being compared and calculates a hazard rate ratio which indicates how much more or less likely one group is to experience the event compared to the other group. Vaccine effectiveness (VE) will be calculated per each outcome using the following formula:

$$VE=1- HR$$

Corresponding 95% confidence intervals (CI) will be estimated around VE estimates.

[10] Definitions to be defined explicitly in the full protocol.

Analyses will be performed for the entire sample, as well as stratified by a selected set of measures in exploratory analyses. These measures may include, age group, time since last vaccine dose (and inbetween doses if more than one dose), immunocompromised status (immunocompromising condition or taking immunosuppressant therapy); groups at a greater risk of poor COVID-19 outcomes (e.g., immunosuppressed, liver cirrhosis, Down's syndrome, diabetes mellitus), pregnancy status.

4.4 SENSITIVITY ANALYSES

The above analyses will be repeated with COVID-19 hospitalizations defined as hospitalization with COVID-19 as a primary or secondary cause, with a laboratory confirmed SARS-CoV-2 PCR test.