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Randomised trial optimising COVID-19 vaccination in patients with chronic health conditions and a poor response to standard vaccination

Submission date
16/07/2021

Recruitment status
No longer recruiting

Registration date
26/07/2021

Overall study status
Completed

Last Edited
30/01/2025

Condition category
Infections and Infestations

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
COVID-19 is a condition caused by the coronavirus (called SARS-CoV-2) that was first identified in late 2019. This virus can infect the respiratory (breathing) system. Some people do not have symptoms but can carry the virus and pass it on to others. People who have developed the condition may develop a fever and/or a continuous cough among other symptoms. This can develop into pneumonia. Pneumonia is a chest infection where the small air pockets of the lungs, called alveoli, fill with liquid and make it more difficult to breathe.
Nearly 32 million people in the UK have received two doses of the COVID-19 vaccine. Research shows that this prevents infection in over 90% of people. However, these vaccines were tested in healthy people. Recent research in individuals with chronic health problems or cancer suggests that 30% are generating low antibody or T-cells (a type of white blood cell which fights infection) levels after two doses of the Pfizer or AstraZeneca COVID-19 vaccines. This raises the question of the potential benefit of a third dose (re-boost) of the vaccine in these vulnerable patients. A re-boost strategy has been successfully used for other vaccines but the limited research performed to date for COVID-19 has given variable results, so additional research is needed. This study aims to find out whether a re-boost vaccine strategy can induce an immune response in clinically vulnerable patients who have not produced an adequate antibody response after two doses of the COVID-19 vaccine.

Who can participate?
Patients aged 18 and over who have not produced an adequate antibody response after two doses of COVID-19 vaccine and have one of the following diseases:
1. Breast or lung cancer
2. Certain types of blood cancer
3. Immune-mediated rheumatic diseases (e.g. rheumatoid arthritis)
4. Chronic kidney disease
5. Chronic liver disease
6. Inflammatory bowel disease on immune suppressive therapy

7. Stem cell transplant
8. Primary immunodeficiency (a group of disorders characterized by poor or absent immune function)

What does the study involve?
Participants will be randomly allocated to receive an additional dose of Pfizer or Moderna COVID-19 vaccine (the main study) or, for a sub-set of patients with blood cancer, the Pfizer or Moderna or Novavax vaccine. Blood samples will be collected before and 21 days after the re-boost vaccine and the level of antibodies and T-cells determined. Patients will be followed up for 3 months to see if they go on to develop COVID-19.

What are the possible benefits and risks of participating?
There may be no direct benefit to the participants from taking part in this study. The information gained from this study may help to improve the way in which patients with chronic health conditions and cancer are vaccinated for coronavirus in the future. Participants may need to go to hospital more frequently to have the blood samples taken. How many extra visits are needed will depend on the patient's condition and how frequently they are currently being seen by their doctor. Where possible the study doctor and research nurse will try to limit the number of extra visits needed. Having blood taken may cause some discomfort, bleeding or bruising where the needle enters the body and, in rare cases, light-headedness and fainting.

Where is the study run from?
The Cancer Research UK Clinical Trials Unit at the University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
May 2021 to August 2024

Who is funding the study?
UK Research and Innovation (UK)

Who is the main contact?
OCTAVE DUO Trial Office
OCTAVE-DUO@trials.bham.ac.uk

Contact information

Type(s)
Public

Contact name
Mrs Ana Hughes

Contact details
Cancer Research UK Clinical Trials Unit
Institute of Cancer & Genomic Sciences
University of Birmingham
Edgbaston
Birmingham
United Kingdom

B15 2TT
+44 (0)121 4143100
octave-duo@trials.bham.ac.uk

Type(s)
Public

Contact name
Prof Iain McInnes

ORCID ID
https://orcid.org/0000-0002-6462-4280

Contact details
University of Glasgow
Wolfson Medical School Building
University Avenue
Glasgow
United Kingdom
G12 8QQ
+44 (0)141 332378
Iain.McInnes@glasgow.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2021-003632-87

Integrated Research Application System (IRAS)
302634

Protocol serial number
RG_21-112

Study information

Scientific Title
A Phase III, multicentre, randomised trial comparing SARS-CoV-2 re-boost vaccine strategies in immunocompromised patients

Acronym
OCTAVE DUO

Study objectives
To determine across a range of immune-mediated/immunosuppressive diseases whether re-vaccination with Pfizer or Moderna vaccines will increase the magnitude of SARS-CoV-2 immune responses in patients with no or low antibodies after two prior vaccine doses

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 22/07/2021, London – Fulham Research Ethics Committee (Health Research Authority, Skipton House, 80 London Road, London, SE1 6LH, UK; +44 (0)20 7972 2545; fulham.rec@hra.nhs.uk), REC ref: 21/HRA/3072

Primary study design
Interventional

Study design
Phase III multi-centre multi-disease open-label randomized trial

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Patients with 1) solid cancer; 2) lymphoid malignancies; 3) immune-mediated rheumatic diseases; 4) end stage kidney disease; 5) liver disease; 6) inflammatory bowel disease on immune suppressive therapy; 7) haematopoietic stem cell transplant; and 8) primary immunodeficiency who have received two doses of SARS-CoV-2 vaccine but have proven inadequate response to the SARS-CoV-2 vaccine

Interventions
For the main study randomised comparison, patients will randomised using a minimisation program (developed by the CRCTU) in a 1:1 ratio. Patients will be randomised to receive:
Arm 1: Pfizer SARS-CoV2 Vaccine
Arm 2: Moderna SARS-CoV2 Vaccine

For the sub-study randomised comparison, patients will be randomised using a minimisation program in a 1:1:1 ratio. Patients will be randomised to receive:
Arm 1: Pfizer SARS-CoV2 Vaccine
Arm 2: Moderna SARS-CoV2 Vaccine
Arm 3: Novavax SARS-CoV2 Vaccine

The dose of Pfizer vaccine is 30 µg contained in 0.3 ml of the diluted vaccine given intramuscularly.
The dose of Moderna vaccine is 0.5 ml, containing 100 micrograms of messenger RNA (mRNA), given intramuscularly.
The dose of Novovax vaccine is 5 µg recombinant spike protein with 50 µg Matrix-M1 adjuvant (0.5 ml). A dose of 5 µg recombinant spike protein with 50 µg Matrix-M1 adjuvant (0.5 ml) will be given intramuscularly.

Where possible participants will be followed up in accordance with standard clinical practice for the relevant disease cohort and data will be collected retrospectively from clinic records 3 months after re-boost vaccination. Where participants do not attend for a routine clinic visit, data may be collected following an additional telephone follow-up call.

Intervention Type
Biological/Vaccine

Phase

Phase III

Drug/device/biological/vaccine name(s)
Pfizer SARS-CoV-2 Vaccine BNT162b2, Moderna SARS-CoV-2 Vaccine, Novavax COVID-19 Vaccine NVX-CoV2373

Primary outcome(s)
1. Anti-spike SARS-CoV-2 antibody and T cell responses to SARS-CoV-2 peptides following Pfizer and Moderna re-boost vaccinations will be measured before the re-boost vaccination was given and will be compared with those achieved at day 21 post dose:
1.1. Anti-spike SARS-CoV-2 antibodies following re-boost vaccination will be measured using the Roche platforms by the Public Health England (PHE) Laboratories at Porton Down. The Roche assays will measure the presence and amount of serum antibodies to both the spike (S) and the nucleocapsid (N) antigens of SARS-CoV-2. This assay will enable the discrimination of antibody responses to SARS-CoV-2 that results from vaccination and/or SARS-CoV-2 infection.
1.2. T cell responses to SARS-CoV-2 peptides following re-boost vaccination will be measured using the Oxford Immunotec modified T-spot discovery SARS-CoV-2 assay. This IFNγ ELISpot assay will provide insights into the participants' reactivity to SARS-CoV-2 s1, s2, nucleocapsid and membrane peptides.

Key secondary outcome(s)
1. In a sub-set of participants with lymphoid malignancies, measure the change in vaccine-specific immunogenicity in response to vaccination (as defined for the primary outcome) with Pfizer, Moderna or Novavax vaccines.
2. In all patient groups, we will assess the capacity of re-boost vaccine-induced SARS-CoV-2 antibodies to neutralise/block SARS-CoV-2 infection using IgG (pseudo)neutralisation assays (CE marked Menarini Diagnostics surrogate neutralisation assay) and measured in samples collected before the re-boost vaccination was given and compared with those achieved at day 21 post-dose.

Completion date
20/08/2024

Eligibility

Key inclusion criteria
1. Aged ≥18 years
2. Have an inadequate response to two doses of SARS-CoV-2 vaccine measured at least 14 days after receipt of the second vaccine, defined by SARS-CoV-2 spike antibody response. An inadequate response is defined as:
2.1. Antibody non-response: SARS-CoV-2 anti-spike antibodies below the level of detection using the PHE Roche platform [or equivalent] ≤8 AU/ml, or
2.2. Antibody low-response: SARS-CoV-2 anti-spike antibodies >8 and <400 AU/mL using the Roche platform [or equivalent])
2.3. There is no agreed international/WHO cut off for titres of AU following vaccination and serologic assessment. As such, the low responder status for OCTAVE-DUO eligibility is by definition arbitrary. We have examined the serology levels obtained in the OCTAVE study, compared with PITCH (health care workers without vulnerable conditions) and elected to choose a titre that equates to approximately 30% of the OCTAVE population – this equates to approx. 400 AU hence this selection for this part of the eligibility criteria. Since in practice all vulnerable groups will receive a re-boost in due course, by choosing the lowest tertile for evaluation of

enhancement of response, we are maximising the pragmatic value of the study in terms of policy advice, and determination of the magnitude of the immune response, representing our primary outcome. Moreover, we are thereby ensuring rapid and representative recruitment from the variety of vulnerable patient groups in the study protocol.
3. Anticipated life expectancy of 6 months or greater.
4. Fall into one (or more) of the following patient cohorts who will meet disease-relevant classification, disease state, and staging according to established international standards:
4.1. Diagnosed with any of the following solid cancers:
4.1.1. Breast
4.1.2. Lung
4.2. Diagnosed with any of the following lymphoid malignancy categories:
4.2.1. Aggressive B-NHL
4.2.2 Chronic lymphocytic leukemia (CLL)
4.2.3. Hodgkin Lymphoma
4.2.4. Indolent B NHL (except CLL and small lymphocytic lymphoma [SLL])
4.2.5. Myeloma
4.3. Diagnosed with the following rheumatic/inflammatory conditions:
4.3.1. Rheumatoid arthritis
4.3.2. Psoriatic arthritis
4.3.3. Seronegative arthritis
4.3.4. Spondyloarthritis
4.3.5. ANCA-associated vasculitis
4.3.6. Systemic lupus erythematosus (SLE)
4.3.7. Psoriasis
4.3.8. Crohn's disease/ulcerative colitis
4.3.9. Autoimmune hepatitis
4.4. Diagnosed with the following chronic renal conditions:
4.4.1. End-stage kidney disease secondary to any cause
4.4.2. Renal transplant following end-stage kidney disease
4.5. Diagnosed with the following chronic liver conditions:
4.5.1. Liver cirrhosis
4.5.2. Liver transplantation
4.6. Chronic liver disease (of any stage) on immune suppressive therapy
4.6.1. Diagnosed with gastrointestinal disease and on immune suppressive therapy
4.7. Diagnosed with primary antibody deficiency: defined as any patient who is on immunoglobulin replacement therapy or any patient with an IgG <4g/l and on prophylactic antibiotics.
4.8. Haematopoietic stem cell transplant:
4.8.1. Previously treated with autologous or allogenic haematopoietic stem cell transplant for any indication and with any conditioning regimens and intensities
4.8.2. Previously treated with CAR-T cell therapies
5. Participant is willing and able to comply with trial requirements.
6. For the randomised sub-study only, female participants of childbearing potential* must be willing to ensure that they or their partner use acceptable effective contraceptive methods until 3 months after the re-boost immunisation. See Section 7.4 for the definition of child-bearing potential and the definition of acceptable effective contraceptive methods.
* Defined as a fertile woman, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Postmenopausal is defined as no menses for 12 months without an alternative medical cause.

Participant type(s)

Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
804

Key exclusion criteria
1. Receipt of any vaccine within 30 days before trial entry, with the exception of a SARS-CoV2 vaccine which is allowed ≥14 days prior, or a flu vaccination which is allowed ≥7 days prior
2. For aggressive B-NHL or Hodgkin lymphoma only, participants on active systemic treatment or within 4 weeks of completion of systemic treatment
3. Any known contraindications as specified in the applicable product information (see Section 7.1) including but not limited to:
3.1. Known allergy or hypersensitivity to any of the trial IMPs or any of the trial drug excipients
3.2. History of anaphylaxis
4. In the judgement of the Investigator the patient is unsuitable to participate in the trial or is unlikely to comply with trial procedures
5. For the randomised sub-study only, patients who are pregnant at trial entry or planning to become pregnant within 3 months after re-vaccination

Date of first enrolment
26/07/2021

Date of final enrolment
31/03/2022

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Queen Elizabeth Hospital
University Hospitals Birmingham NHS Foundation Trust

Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2TT

Study participating centre
Gartnavel Royal Hospital
NHS Greater Glasgow and Clyde
1055 Great Western Road
Glasgow
United Kingdom
G12 0XH

Study participating centre
St. James's University Hospital
Leeds Teaching Hospitals NHS Trust
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
St Mary's Hospital
Imperial College Healthcare NHS Trust
South Wharf Road
London
United Kingdom
W2 1BL

Study participating centre
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Study participating centre
Cambridge University Hospitals NHS Foundation Trust
Cambridge Biomedical Campus

Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Southampton General Hospital
University Hospital Southampton NHS Foundation Trust
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
Kings College Hospital
King's College Hospital NHS Foundation Trust
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
Northern General Hospital
Sheffield Teaching Hospitals NHS Foundation Trust
Herries Road
Sheffied
United Kingdom
S5 7AU

Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type

Government

Funder Name
UK Research and Innovation

Alternative Name(s)
UKRI

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request. The CRCTU is committed to responsible and controlled sharing of anonymised clinical trial data with the wider research community to maximise potential patient benefit while protecting the privacy and confidentiality of trial participants. Data anonymised in compliance with the Information Commissioners Office requirements, using a procedure based on guidelines from the MRC Methodology Hubs, will be available for sharing with researchers outside of the trials team within 6 months of the primary publication. More detailed information on the CRCTU's Data Sharing Policy and the mechanism for obtaining data can be found on the CRCTU website: https://www.birmingham.ac.uk/research/activity/mds/trials/crctu/index.aspx.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/06/2024	20/08/2024	Yes	No
HRA research summary			28/06/2023	No	No
Plain English results			28/01/2025	No	Yes
Plain English results	version 1.0	16/12/2024	30/01/2025	No	Yes
Protocol file	version 5.0a	19/11/2021	11/04/2022	No	No